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Nikhil Thapar
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Pediatric Neurogastroenterology

Gastrointestinal Motility Disorders and Disorders of Gut Brain Interaction in Children

Third Edition

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To my parents with love.

Christophe Faure

To my parents for their unconditional support and love.

Carlo Di Lorenzo

To my beloved parents, Baldev and Brijender Thapar—so blessed by your unending love. You will forever be my guiding light and inspiration.

Nikhil Thapar

To our patients and all the children afflicted by motility and sensory digestive disorders.

Christophe Faure
Carlo Di Lorenzo
Nikhil Thapar

Foreword

Neurogastroenterology is the subdiscipline of gastroenterology that focuses on disease states characterized by neuromuscular or sensory dysfunction of the gastrointestinal tract. It comprises disorders which are among the most common encountered in clinical practice, defined by a constellation of symptoms in the absence of a measurable diagnostic marker upon routine laboratory, endoscopic, or radiological evaluation. It has been estimated that up to half of the patients seen in adult gastroenterology practice suffer from Disorders of Gut-Brain Interaction, as they are now commonly referred to.

Over three decades of patient cohort studies and pathophysiological, diagnostic, and therapeutic research have unraveled a complex interplay of varied disease mechanisms that contribute to the clinical manifestations in individual patients. A variable combination of disordered motility, visceral hypersensitivity, altered responses to luminal contents, gut microbiota composition, low-grade inflammation, and altered central nervous system processing of incoming signals from the gastrointestinal tract determines symptom presentation and disease impact in a highly individualized pattern.

Once considered mainly psychosomatic in origin, the integrated biopsychosocial disease concept, promoted by the Rome Foundation for Functional Gastrointestinal Disorders, has allowed recognition of Disorders of Gut-Brain Interaction as true disorders, with major impact on the individual, society, and the healthcare system.

Early in this process, experts around the world realized that these disorders are also highly prevalent in pediatric medicine, where they constitute an at least equally large diagnostic and management challenge. Already in the second update of the "Rome Foundation Consensus," published in 1999, a separate chapter defined criteria for gastrointestinal disorders in infancy, childhood, and adolescence. Since then, pediatric neurogastroenterology and functional disorder knowledge has evolved in parallel with its adult counterpart into a subdiscipline which offers broad clinical diversity, stimulating supportive techniques (especially motility studies), and an exciting and rapidly evolving multifaceted scientific basis.

However, clinical neurogastroenterology mainly requires a creatively thinking physician who integrates multiple aspects to develop a personalized approach for each individual patient. Indeed, while the disease pathophysiological concept is now truly multifaceted, the presence of most of the underlying abnormalities is not tested in routine or even in advanced clinical management, and disease mechanism studies mostly belong to the clinical research arena. Historically, abnormal motility was the first and best studied pathophysiological abnormality in patients with Disorders of Gut-Brain Interaction and in experienced hands, well-chosen motility testing helps the diagnosis and management. Besides input from motility testing, management of patients with Disorders of Gut-Brain Interaction remains firmly built on the strength of clinical skills and attitudes such as history taking, observation of behaviors and reactions, communication skills, grasping of co-existing psychosocial issues, and partnering with the patient in a longer-term therapeutic approach.

In this book, eminent clinical experts in pediatric functional and motility disorders provide an in-depth review of the state of knowledge on disorders of gastrointestinal motility and sensitivity in children. The normal physiology and development, pathophysiological mechanisms, disease entities, and how to diagnose and manage them were written by international leading physicians, physiologists, psychologists, and other therapists.

This third edition of the "Pediatric Neurogastroenterology Textbook" is an indispensable companion for healthcare providers who are involved in the care for children with chronic disorders of Neurogastroenterology and motility and scientists with an interest in this field. I applaud the authors for an outstanding and comprehensive book, which I hope you will find an enjoyable and enriching reading experience, with direct benefit to the care of pediatric neurogastroenterology patients.

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Preface

Ten years on…

In 2012, we launched the first edition of the pediatric neurogastroenterology and motility textbook, recognizing the lack of a definitive up-to-date and comprehensive resource for the field. Year 2017 saw the release of the second edition following a realization that the world of pediatric motility disorders was evolving at an unprecedented rate and a state-of-the-art revision of the book was needed. Now, 10 years after the initial edition, it is clear that pediatric neurogastroenterology and motility is not only progressing even more rapidly but with increasing relevance across a range of pediatric specialties. Thus, the need for a further update.

As such, we are delighted to present the third edition of our textbook. It has not only been updated by experts in their respective fields but has also been enriched by new chapters on chronic pain, allergy and neurogastroenterology, gastrointestinal disturbances in autism spectrum disorders, and surgery in neurogastroenterology. Other key chapters, such as that on functional disorders (now called Disorders of gut brain interaction) have been updated according to the most recent concepts and experts' vision.

The technical aspects of investigations are still carefully and practically described and have been updated along with an emphasis on clinical application. New techniques and technologies available in pediatric neurogastroenterology (e.g., functional luminal impedance planimetry—FLIP) have been introduced. These chapters provide a uniform overview of techniques and their practical use.

The plethora of experts that we are able to garner has of course made our task easier, and we are hugely grateful to all those who have kindly agreed to devote their valuable time to have their substantial brain power harnessed and crammed into this third edition.

We hope the book remains practical and clinically applicable yet provide the reader with an up-to-date insight into the basic science that underlies the spectrum of motility disorders.

We are immensely pleased that this book has become the reference textbook for pediatric neurogastroenterology and motility and trust that both specialists and generalists will continue to find it invaluable. We finally hope that the book will stimulate and encourage young colleagues to join the family of the pediatric neurogastroenterologists!

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The original version of the book was revised: Copyright, Dedication, and Foreword pages text has been updated. The erratum to the book is available at https://doi.org/10.1007/978-3-031-15229-0_52

Preface to the First Edition

In the past 20 years, major advances have been achieved in the care of children with pediatric gastrointestinal motility and sensitivity disorders. This is a reflection of the progress that has been made understanding such conditions at the developmental and molecular levels as well as the development of novel tools to investigate and treat them. These progresses have led to the birth of a new "science," namely, *neurogastroenterology*, which is devoted to "study the interface of all aspects of the digestive system with the different branches of the nervous system" and which has now established itself as a major area of clinical practice and research. In the past two decades, there has been an almost exponential increase in publications of scientific papers in the field, a plethora of international fora for the discussion of such conditions, and creation of dedicated journals with respectable citation indices. Pediatric neurogastroenterology and motility has not lagged behind and arguably is fast becoming a major and popular subspecialty in its own right.

With this book, we aim to draw upon an extensive international expertise to provide a contemporary state-of-the-art reference textbook for pediatric neurogastroenterology and motility that both specialists and generalists alike will find helpful.

Overview of the Book

The first chapters are dedicated to some of the success stories of the field. Utilizing a range of animal models and studies in the human itself, we now have a remarkable understanding of the mechanisms involved in the formation of a functional enteric neuromusculature. It is clear that development is a complex spatiotemporal process involving the coordinated interplay of a number of genes regulating cellular properties and organogenesis. This complexity is reflected in one of the most commonly recognized gut motility disorders, Hirschsprung's disease, a condition caused by a failure of development of the enteric nervous system. The ontogeny of motility patterns within the GI tract is now understood in great detail. Utilizing new technologies, animal models, and some studies in humans, researchers have been able to show that GI motility is regulated by a number of mechanisms that vary in relation to the stage of development, maturity, and region within the GI tract. It is very likely that the coming years will see an increasing recognition of the developmental and related functional pathogenic mechanisms underlying a range of disorders involving enteric nerves, muscles, and interstitial cells of Cajal. The rich sensory innervation that not only underlies the normal functioning of the GI tract but has also increasingly been implicated in a range of functional GI disorders is thoroughly described. This sensory innervation and its processing appear to be plastic and influenced by a number of disease mechanisms and clinical states, including infection, inflammation, and psychological stress. How visceral sensation is modulated by the interplay among the CNS, neurogastrointestinal system, inflammation, and gut microbial ecosystem, especially in relation to irritable bowel syndrome, is addressed in a subsequent chapter. This theme is further developed with the discussion of the biopsychosocial influences on enteric neuromuscular function and how the social and cultural settings of patients act to modify physiologic responses.

The belly of the book summarizes the practical investigations that are available in the pediatric neurogastroenterologist's armamentarium. In many respects, this is where much of the recent strides of the field have taken place, moving it into the realms of a high-tech futuristic specialty. Major highlights have been the advent of impedance and high-resolution manometry technologies, which did not exist when the first textbook on pediatric gastrointestinal motility was published but are now well-accepted and standardized diagnostic techniques. The role of sensitivity tests, namely, barostat and satiety drinking tests, in recognizing altered gut sensation as a key pathophysiologic component of functional gastrointestinal disorders is discussed. The application to clinical investigation of radionucleotide scintigraphy tests, which have seen in recent years a wider application given their improved tolerability, cost, and safety profile, is described in detail. Older and newer technologies ranging from electrogastrography and transit studies to 3D ultrasonography and wireless motility capsule are presented. Finally, there is a discussion of autonomic function testing as an indirect measure of gastrointestinal function. The subsequent chapters deal with the practical approach to and description of the pathology of disorders of enteric neuromusculature and the genetic underpinning of motility disorders.

The next section of the book focuses on a journey through the GI tract, detailing motility disorders that occur in each region. Feeding and swallowing disorders in a range of GI and systemic diseases are discussed. Pediatric esophageal and gastric motor disorders are summarized, and intestinal pseudo-obstruction syndrome and Hirschsprung's diseases, the most severe forms of GI dysmotility, are discussed in great detail. The book then focuses on secondary (malformative) and postsurgical motor disorders.

The book then transitions from more classic motility disorders to Disorders of gut brain interaction, arguably one of the most common and challenging group of conditions encountered by primary care providers and subspecialists. The role of the Rome criteria in developing the field of pediatric Disorders of gut brain interaction is highlighted. Infant regurgitation and gastroesophageal reflux disease, infantile colic, functional dyspepsia, irritable bowel syndrome, cyclic vomiting syndrome, aerophagia, adolescent rumination syndrome, and functional constipation are discussed.

The final section of the book is dedicated to therapy, including pharmacotherapy, cognitive behavioral therapy, gastric electrical stimulation, intestinal transplantation, and potential use of stem cells.

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To our wives (Sophie, Daniela, and Catherine), children (Alexandre, Timothé, Clémentine, Gaspar, Mario, Cristina, Francesca, Valentina, Sachin, Nayan, and Kira) and grandchildren (Léandre, Malo, and Olympe) for all their love, support, and patience throughout the preparation of this book.

Montreal, QC, Canada — Christophe Faure
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Contents

Part I

Physiology and Development of Enteric Neuromuscular System and Gastrointestinal Motility

Introduction to Gut Motility and Sensitivity

1

Christophe Faure, Nikhil Thapar, and Carlo Di Lorenzo

Evolution, the Gastrointestinal Tract, and the "First Brain"

Whether or not one believes in the theory of evolution [1], it is apparent that some of the first multicellular organisms to have inhabited the earth, including the presumptive earliest ancestors of humans, were elongated structures with a core gut tube [2, 3]. In the absence of an obvious heart, brain, or liver, this core system helped sustain life by performing fundamental processes including respiration, the assimilation of nutrition, and metabolism. On this basis it is perhaps not surprising that the gastrointestinal (GI) tract has evolved to become one of the most complex and diverse organs of the human body, with an incredible repertoire of activities from digestion, absorption, and excretion to homeostatic, endocrine, and immune functions. Many of these processes are dependent on highly coordinated sensory and effector mechanisms, which monitor the GI lumen and wall, respond to specific cues, and interact with a diversity of cell types within the GI tract. In conjunction with a drive to maintain homeostasis within the body and control gut inflammation, the effector mechanisms regulate blood flow, adjust the balance between absorption and secretion, and coordinate mixing and propulsion of luminal contents along the length of the bowel. This latter "motility" activity is executed by region-specific peristaltic contractions and emptying mechanisms, which are dependent on highly coordinated interactions among the components of the gut neuromusculature. These components comprise the intrinsic nervous system (including neurons and glial cells) of the gut (enteric nervous system—ENS), the smooth muscle coats, and the interstitial cells of Cajal (ICC) (Fig. 1.1).

It is the mere presence and complex characteristics of the ENS that also lends itself to the notion of the gastrointestinal tract as a pioneer organ, with the potential emergence of the ENS prior to that of a recognizable brain. Therefore, arguably, the ENS should be referred to as the "first brain," given evidence that the central nervous system (CNS) evolved subsequently, as organisms acquired locomotion and more complex interactions with the environment [2]. Either way, perhaps reflective of a common development, the ENS shares many similarities with the CNS, including an overall inherent complexity in structure, organization, and function. It contains as many neurons as the spinal cord and a diversity of neuronal subtypes and properties of enteric glial cells akin to that seen in the CNS [4, 5]. Perhaps even more importantly, the brain and ENS appear to be functionally hard-wired reflected in an almost complete interrelation between stress or psychological factors and gut function. Many of the functional gastrointestinal disorders discussed within this book appear to have a clear basis in complex interactions between biological, psychological, and social factors. Not surprisingly and very adeptly, such functional disorders have been recently renamed "disorders of gut-brain interaction" (DGBI) [6]. Equally, nonfunctional or organic conditions have significant impacts on psychosocial well-being. This interplay has made neurogastroenterology and motility one of the most interesting but challenging fields requiring a multidisciplinary approach.

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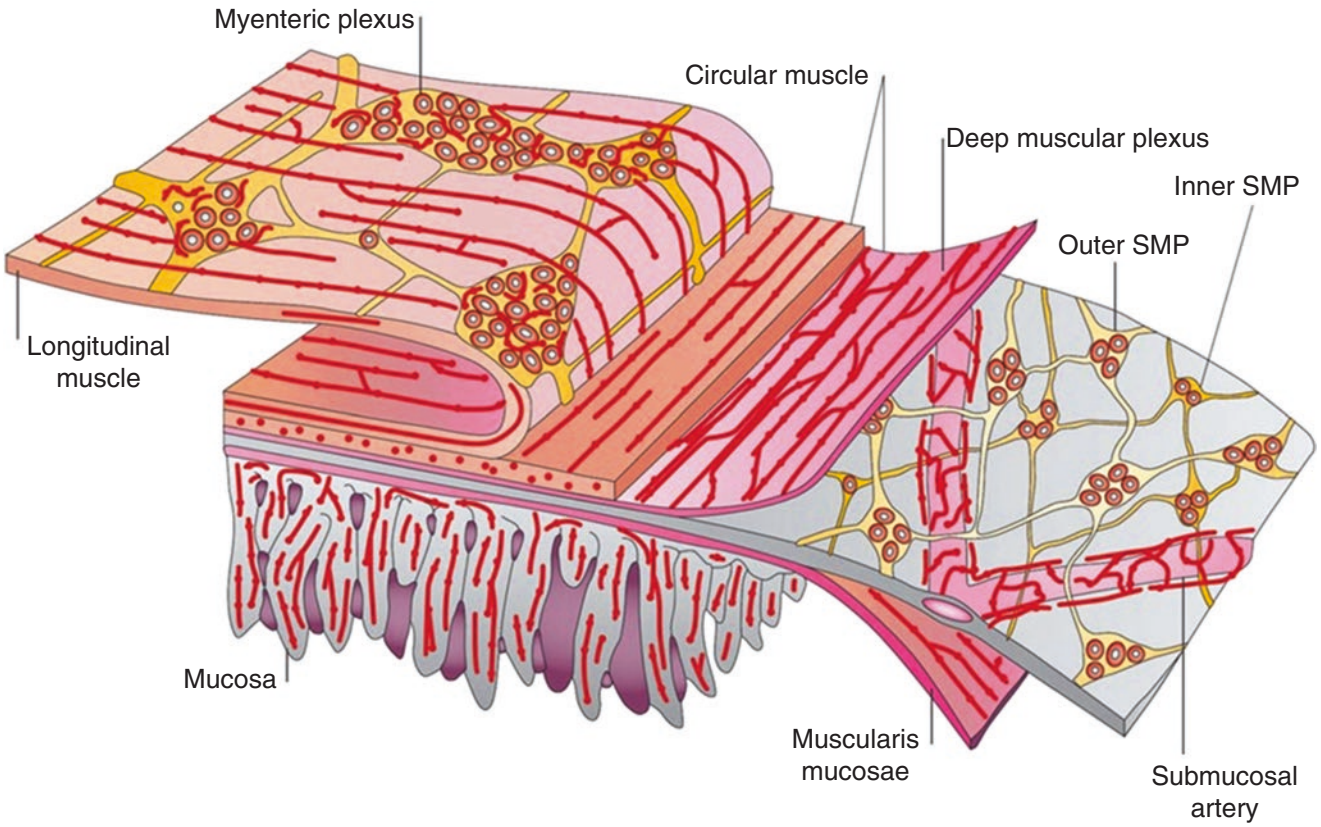

Fig. 1.1 The organization of the ENS of human and medium–large mammals. The ENS has ganglionated plexuses, the myenteric plexus between the longitudinal and circular layers of the external musculature, and the SMP that has outer and inner components. Nerve fiber bundles connect the ganglia and also form plexuses that innervate the longitudinal muscle, circular muscle, muscularis mucosae, intrinsic arteries, and the mucosa. Innervation of gastroenteropancreatic endocrine cells and gut-associated lymphoid tissue is also present, which is not illustrated here. *Abbreviations*: *ENS* enteric nervous system, *SMP* submucosal plexus (From Furness JB. The enteric nervous system and neurogastroenterology. *Nat Rev Gastroenterol Hepatol*. 2012;9(5):286–94. Reprinted with permission from Nature Publishing Group)

The Enteric Nervous System

The ENS represents the intrinsic nervous system of the GI tract, comprises enteric neurons and enteric glial cells, and is present along its entire length. The ENS is one of the largest and more complex components of the peripheral nervous system and organized as plexuses of interconnected ganglia that enmesh the GI tract. In the small and large intestines, these plexuses are present in two distinct layers, the outer myenteric plexus that sits between the inner circular and outer longitudinal muscle layers and the inner submucosal plexus present between the mucosa and the inner circular muscle layer. The ganglia are interconnected by bundles of nerve fibers that run along the individual plexuses as well as those that run between them. The real complexity of the ENS is revealed at the ultrastructural level where an intricate circuitry is evident (Fig. 1.2). A variety of neuronal subtypes partakes in this and can be classed in terms of functional and structural characteristics. Subclasses include sensory and motor, excitatory, and inhibitory. There are neuronal subtypes and neurotransmitters present within the ENS (Table 1.1) akin to and aligned with those present in the CNS befitting the title conferred upon the ENS as the "second brain" [7]. Recent studies using single cell RNA sequencing have revealed a novel taxonomy of myenteric neuron classes of the mouse small intestine defined by their unique communication features [8].

Enteric glial cells are more than a support of enteric neurons. They play key roles in the control of inflammation and response to infection [9], in the maintenance of intestinal epithelial integrity [10], and in regeneration [11]. They also specifically regulate intestinal motility [12, 13].

The development of the ENS is similarly complex (Chap. 2). The neurons and glia of the ENS all arise from precursor cells derived from the vagal, sacral, and rostral trunk neural crest [14, 15]. These cells migrate into the oral and anal ends of the embryo and enter the foregut and hindgut, colonizing the entire GI tract. ENS maturity results from an adequate number of correctly differentiated neurons with sufficient axon outgrowth and branching. Recent human

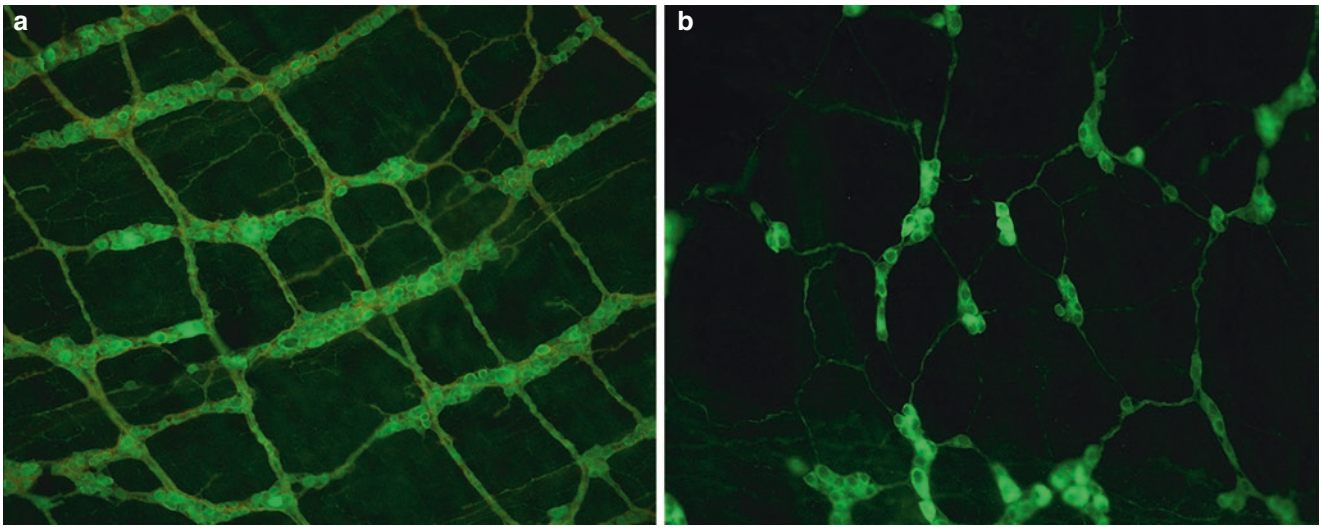

Fig. 1.2 Whole mount preparation of rat myenteric (**a**) and submucosal (**b**) plexuses (immunofluorescent staining with an antibody to the neuronal marker PGP9.5). Neuronal cells are grouped together in ganglia that interconnect both within and between the myenteric and submucosal plexuses. The neuronal cells of the plexuses comprise the enteric nervous system, and, along with the glial cells, smooth muscle cells and interstitial cells of Cajal are the intrinsic components of the enteric neuromusculature

Table 1.1 Multiple transmitters of neurons that control digestive function

Type of neuron	Primary transmitter	Secondary transmitters, modulators	Other neurochemical markers
Enteric excitatory muscle motor neuron	ACh	Tachykinin, enkephalin (presynaptic inhibition)	Calretinin, γ-aminobutyric acid
Enteric inhibitory muscle motor neuron	Nitric oxide	VIP, ATP, or ATP-like compound, carbon monoxide	PACAP, opioids
Ascending interneuron	ACh	Tachykinin, ATP	Calretinin, enkephalin
ChAT, NOS descending interneuron	ATP, ACh	ND	Nitric oxide, VIP
ChAT, 5-HT descending interneuron	ACh	5-HT, ATP	ND
ChAT, somatostatin descending interneuron	ACh	ND	Somatostatin
Intrinsic sensory neuron	ACh, CGRP, tachykinin	ND	Calbindin, calretinin, IB4 binding
Interneurons supplying secretomotor neuron	ACh	ATP, 5-HT	ND
Noncholinergic secretomotor neuron	VIP	PACAP	NPY (in most species)
Cholinergic secretomotor neuron	ACh	ND	Calretinin
Motor neuron to gastrin cells	GRP, ACh	ND	NPY
Motor neurons to parietal cells	ACh	Potentially VIP	ND
Sympathetic neurons, motility inhibiting	Noradrenaline	ND	NPY (in some species)
Sympathetic neurons, secretion inhibiting	Noradrenaline	Somatostatin (in Guinea pig)	ND
Sympathetic neurons, vasoconstrictor	Noradrenaline, ATP	Potentially NPY	NPY
Intestinofugal neurons to sympathetic ganglia	ACh	VIP	Opioid peptides, CCK, GRP

5-HT 5-hydroxytryptamine, *ACh* acetylcholine, *ATP* adenosine triphosphate, *CCK* cholecystokinin, *ChAT* choline acetyltransferase, *CGRP* calcitonin gene-related peptide, *GRP* gastrin-releasing peptide, *IB4* Isolectin B4, *ND* not determined, *NOS* nitric oxide synthase, *NPY* neuropeptide Y, *PACAP* pituitary adenylate cyclase-activating polypeptide, *VIP* vasoactive intestinal peptide

Adapted from Furness JB. The enteric nervous system and Neurogastroenterology. *Nat Rev Gastroenterol Hepatol*. 2012;9(5):286–94. Reprinted with permission from Nature Publishing Group

data suggest that complete colonization and formation of a structurally mature ENS (embryonic weeks 7–11) is followed by the development of several key enteric neuronal subtypes (embryonic weeks 12–14) and of coordinated electrical activity at embryonic week 16 [16]. This 4-week developmental time period may be critical for the "correct"

assembly of a functional ENS. Another recent work reveals transcriptional programs of generic cell states of the developing ENS [8].

Several lines of evidence show that enteric neuronal development is not completed at birth. Indeed, in the murine gut, changes in morphology of the plexuses [17] and in the total number of neurons have been reported during the first 4 weeks of life [18]. Submucosal plexuses appear later than myenteric plexuses, and the number of submucosal neurons also increases during the same time period [19]. ENS neurochemical maturation reaches an adult pattern only at 1 month of postnatal life. In infants, data on functional maturation of the ENS are lacking but it has been reported that the number of cell bodies present within ganglia appears to change according to the age of the individual between 1 day of age and 15 years [20]. A number of human studies have reported the persistence of ENS progenitors through adult life given the ability to harvest bipotent cells capable of generating enteric neurons and glia [21]. Postnatal neurogenesis remains debatable, although it is possible it may occur with limited capacity, from glia, in response to significant insults [22, 23]. This has allowed the intriguing possibility to develop a potential therapy to generate new neurons in aganglionic colonic segment in Hirschsprung's disease [24].

Enteric Muscle Coats

The smooth muscle of the gastrointestinal tract, although present within the mucosa and the blood vessels of the submucosa, is primarily organized into three discrete muscle layers. The innermost, muscularis mucosa, sitting between the mucosa and submucosa, is the least developed of these layers, being only a few cells in thickness. The other two, grouped within the muscularis propria, are much thicker and comprise the inner circular muscle layer, with its cells arranged concentrically, placed between the submucosa and the myenteric plexus of the ENS, and the outer longitudinal muscle layer, with its cells running along the long axis of the gut, placed between the myenteric plexus and the outermost serosal layer. In the small intestine, the circular muscle appears well developed in sequential segments along its length giving the appearance of concentric rings. In the large intestine, bands of smooth muscle and connective tissue (taenia coli) run on its outside along its length. Their functional role is not completely clear. The enteric smooth muscle is organized in syncytia of cells that are electrically coupled to elicit upon activation contractile activity of the muscle layers. The circular and longitudinal muscles work in concert by contracting to result in segmentation and shortening to execute peristalsis and aboral propulsion of gastrointestinal luminal contents. Contraction of smooth muscle cells derives from two basic patterns of electrical activity across the membranes of smooth muscle cells: slow waves and spike potentials. The membrane potential of smooth muscle cells fluctuates spontaneously. These fluctuations spread to adjacent cells, resulting in "slow waves," which are waves of partial depolarization. The frequency of slow waves varies according to the localization in the GI tract: in the stomach, they occur at a frequency of 3 per min, in the duodenum jejunum 12–15 per min, and in the ileum 8 per min. Slow-wave activity is an intrinsic property of smooth muscle cells independent of intrinsic innervation. "Spike potentials," which result from exposition to excitatory transmitters, occur at the crest of the slow waves and provoke muscle contractions at a maximal rhythm dependent upon slow-wave frequency. Although the development of enteric smooth muscle remains unclear, there has been progress in the generation of enteric smooth muscle for regenerative medicine approaches [25].

Interstitial Cells of Cajal (ICC)

In 1893, a Spanish physician and professor of pathology provided the first description of a distinct group of cells that appeared to reside in the "interstitium" between enteric nerves and smooth muscles. These cells, now termed interstitial cells of Cajal (ICC), are now established as critical components of the enteric neuromusculature regulating gastrointestinal motility, playing roles as pacemakers and as mediators of enteric motor neurotransmission. They are present in a number of subtypes and morphologies throughout the layers of the GI tract, each of which may relate to distinct physiological functions. One of the key ICC subtypes, myenteric ICC (ICC-MY), is present in highly branching networks within the myenteric plexus of the small intestine and appears to initiate slow waves that are spread passively to the adjacent electrically coupled smooth muscle cells. Depolarization of neighboring smooth muscle cells leads to activation of the contractile apparatus. There has been considerable recent interest in the potential role of ICC disorders in the pathogenesis of human gut motility disorders [26], and loss of/reduced ICC numbers have been implicated in Hirschsprung's disease, slow transit constipation, chronic intestinal pseudo-obstruction, and esophageal achalasia. Some debate exists over whether there is true loss of ICCs, dedifferentiation, or loss of the cell surface receptor that defines ICCs' c-kit. ICCs appear capable of transdifferentiation to smooth muscle cells, a cell type with which they share the same mesenchymal progenitor. Regeneration of ICCs also appears possible. Further studies are required to understand the role of ICCs in disease [26].

Control of the Enteric Neuromusculature and the Gut-Brain-Microbiota Axis

Although it has been recognized that the neuromusculature of the gut is capable of independent function, this largely relates to fairly rudimentary observations of the retention of basic functions such as contractility, which depend on the integrity of intrinsic reflex circuits that integrate sensory inputs and effector outputs, both excitatory and inhibitory. Thus, in the experimental setting, segments of isolated gut dissected out of the body and placed in a water bath in vitro are capable of efficiently propagating a bead introduced at its rostral end. However, as discussed above, it has long been recognized that the gastrointestinal tract is a portal for, and dependent on, a whole multitude of interactions that facilitate its many and varied functions.

In addition to the complex interactions with the CNS, it is clear that the autonomic nervous system (ANS) exerts critical control of gastrointestinal function. Like the ENS, the ANS is also part of the peripheral nervous system and traditionally further subdivided into the parasympathetic and sympathetic nervous systems with craniosacral and thoracolumbar outflows, respectively. Much of the parasympathetic innervation to the GI tract travels via the vagus nerve and sacral nerves and the sympathetic along mesenteric blood vessels from the prevertebral ganglia. These tracts carry both sensory and motor innervations. Akin to their other functions, these two subdivisions schematically function in opposition to each other with the parasympathetic primarily excitatory to gut function by promoting secretion and peristalsis and mainly mediating physiological (nature and composition of the intestinal content and motility and contractile tension of the smooth muscle) rather than harmful sensations and the sympathetic inhibitory by decreasing peristalsis and reducing perfusion of the GI tract and transmitting information on potentially noxious stimuli. As a consequence, disorders of the autonomic nervous system are related to disturbances in GI motility and sensing.

Beyond control by the CNS and ANS, the extrinsic modulation of the ENS is much more complex. This is reflected in the multiplicity of factors involved in its development from connective tissue to functional interaction with other organ systems such as the immune and endocrine systems. In children, this process is further complicated by ongoing growth, development, and maturation of the gut and its immune system as well as their interaction and adaptation to postnatal life including psychosocial influences, environmental and dietary factors, as well as establishment and changes in the microbiome. This concept of integrated activity across biological and psychosocial systems is one of the most fundamental concepts that has arisen in the field of neurogastroenterology and reflected in the recognition and study of what is now referred to as the gut-brain-microbiota axis [27], which also incorporates the neuro-immune interactions that occur within the gut itself (Chaps. 4 and 5). Using the example of childhood functional abdominal pain disorders, Fig. 1.3 illustrates the putative role of the bio-psychosocial model and gut-brain-microbiota axis in the pathogenesis of disease.

Not only does disruption of these factors and their interactions contribute to symptoms, but also its integrated working appears susceptible to being "programmed" especially at an early age to give rise to pathology later on in life. Of these, disorders of brain-gut interaction (DBGI) previously known as functional gastrointestinal disorders (Chaps. 36 through 38) appear to provide a key paradigm for such "programming" (Fig. 1.3). It follows, therefore, that there are an enormous range of potential etiopathogenic factors acting over a considerable time period of development that could result in gut motility disorders. This functionality is of course affected by noxious and genetic influences occurring during development that determine the structural and functional viability of its components.

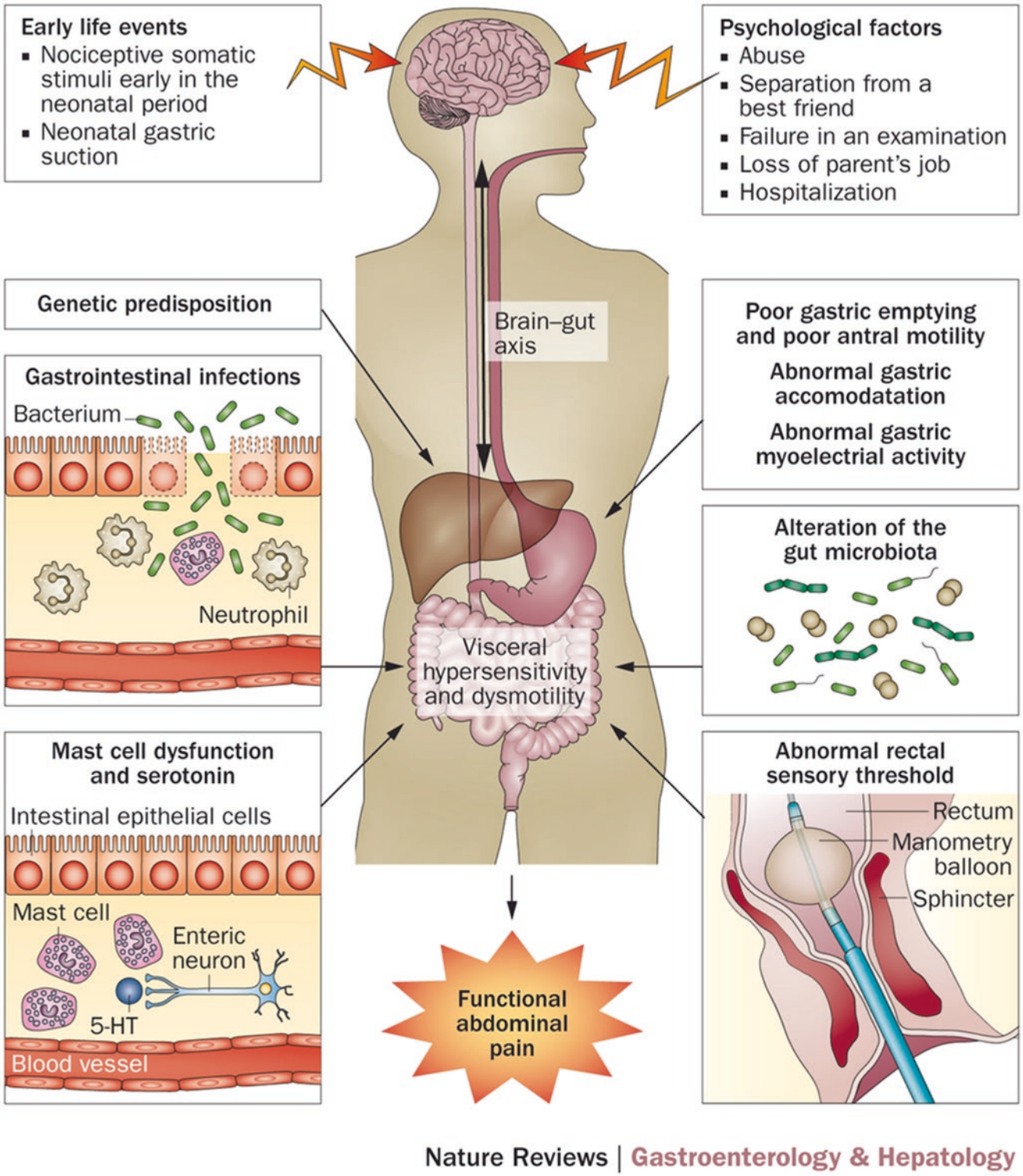

Fig. 1.3 Pathogenesis of childhood functional abdominal pain. Several risk factors are associated with changes in visceral hypersensitivity and motility and contribute to the development of functional abdominal pain. *Abbreviations*: *5-HT* 5-hydroxytryptamine, *FGID* functional gastrointestinal disorder (From Korterink J, Devanarayana NM, Rajindrajith S, et al. Childhood functional abdominal pain: mechanisms and management. *Nat Rev Gastroenterol Hepatol,* **12**, 159–171, 2015. Reprinted by permission from Macmillan Publishers Ltd.)

Sensory Function and the Gastrointestinal Tract

Gut motility disorders are often seen as synonymous with dysfunction of motor activity of the GI tract. Certainly, the most severe disorders are predominated by disturbances or failure in propagation of luminal contents. It is clear, however, that sensory functions of the GI tract are similarly important and their dysfunction often carries significant bearing on the ultimate impact of disease. Although particularly evident in DGBI, sensory symptoms are present throughout the spectrum of GI motility disorders (Chap. 4).

Normally, most of the information originating from the GI tract does not reach the level of conscious perception and is processed in the brainstem. Other sensations such as hunger, fullness, satiety, bloating, and need to defecate that involve adapted behaviors do reach the cortex. As previously stated, extrinsic innervation of the GI tract is composed of vagal, spinal visceral (sympathetic), and sacral nerves. These nerves contain afferent (or sensory) fibers that transmit information from the viscera to the CNS and efferent fibers that transmit information from the CNS to the gut. At the level of the gastrointestinal tract, sensory neurons and enteroendocrine cells serve as transducers. The central processing of visceral sensitivity is complex and involves the somatosensory cortex that provides information about intensity and localization of the stimulus, the anterior cingulate cortex that mainly processes pain characteristics and cognitive aspects of the pain experience, the insula that integrates internal state of the organism, and the prefrontal cortex that is believed to play a key role in the integration of sensory information and in the affective aspect of the sensation. Therefore, it appears that, similar to motor disorders, visceral sensory disorders may result from multiple factors and are prone to be influenced by complex interactions with cognitive and behavioral components.

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Development of the Enteric Neuromuscular System

2

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Gut Embryogenesis

The development of the gastrointestinal (GI) tract begins around the third week post-fertilization in humans. At this stage a primitive tract arises from the endoderm of the trilaminar disc. This tract extends from the oropharyngeal to the cloacal membrane, and later in development will contain contributions from all three germ layers. Of these layers, the endoderm gives rise to the glands and epithelial lining of the gut, and of its associated organs including the liver and pancreas. This layer also lines the yolk sac. The lateral mesoderm gives rise to the splanchnic mesoderm, which yields the connective tissue, smooth muscle, and blood vessels of the GI tract. The ectoderm gives rise to the distal portion of the anal canal, known as the proctodeum, and also generates the cells of the neural crest. As the developing gut continues to elongate, in the fourth week it can be differentiated into three distinct regions known as the foregut, midgut, and hindgut. The foregut develops into the oral cavity, pharynx, esophagus, stomach, and proximal duodenum (to the bile duct opening) and also contributes to the liver, biliary and hepatic ducts, gallbladder, and the pancreas. The midgut contributes to the small intestine below the bile duct opening, the cecum, appendix, and ascending and proximal halves of the transverse colon. The hindgut develops into the distal half of the transverse colon, the descending and sigmoid colons, the rectum, and the superior part of the anal canal. The blood supply to the foregut, midgut, and hindgut is through the celiac artery, superior mesenteric artery, and inferior mesenteric artery, respectively.

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Gut Embryogenesis Abnormalities

Abnormalities in gut embryogenesis lead to a number of well-described congenital disorders. During the sixth week of development in humans, the rapid growth of the gut reduces available space in the abdominal cavity, forcing intestinal loops out of the intra-abdominal space. Normally, the intestinal loops return inside around the tenth week. Two of the most common abdominal wall defects are omphalocele and gastroschisis, in which the intestine remains protruding outside the body [1]. An omphalocele occurs when malrotation prevents the intestine from returning to the abdominal cavity, leaving it in the umbilical cord and covered by a membrane. In gastroschisis, the protruding intestines are not membrane-enclosed. Co-occurrence of other birth defects, including gastrointestinal, cardiovascular, and urogenital defects, is well recognized with both conditions, but is consistently reported to be more common in cases of omphalocele compared to gastroschisis [1].

Smooth Muscle Development

The smooth muscle layers of the gut include the outermost layer of longitudinal muscle, the circular muscle, and the inner muscularis mucosa. These levels of smooth muscle are all derived from recruitment of the splanchnic layer of the lateral plate mesoderm to the primitive gut tube by endoderm-derived signals with subsequent proliferation and gut-specific mesoderm differentiation (reviewed in Roberts [2000] [2]). One of the key signaling molecules in early endoderm-mesoderm interactions is sonic hedgehog (Shh), a member of the hedgehog (Hh) family of cell signaling molecules, all known to be involved in critical developmental processes. *Shh* is expressed in the endoderm of the gut and the *Hh* receptor, *Patched-1*, is highly expressed in the adjacent mesoderm [3]. Animal models that lack *Shh* have significant gut defects, including a reduction in smooth muscle [4]. Transcription factors that mediate the *Hh* pathway, such as

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the Gli family (*Gli1*, *Gli2*, *Gli3*), have also been shown to be involved in gut development. Overall, *Hh*-related signaling pathways are essential in early GI tract organogenesis, with defects involved in a number of human gut malformations including intestinal transformation of the stomach, duodenal stenosis, reduced smooth muscle, abnormal innervation of the gut, and imperforate anus [4].

Smooth muscle precursors within the embryonic gut are initially small and round in shape, but, as differentiation proceeds, cells become elongated and parallel to each other in a circumferential arrangement to form the circular muscle layer [5]. Cells from the outer portion of the circular layer then stretch radially outward, toward the presumptive longitudinal layer. These cells form bundles and bend perpendicularly to form an L shape, thus establishing the orientation of the longitudinal muscle layer [5]. The muscularis mucosa is formed by inward radial patterning, along a rostral-caudal gradient of maturation in early fetal development [5]. In the human gut, the longitudinal, circular, and muscularis mucosae layers of smooth muscle are evident by 14 weeks of gestation [6]. The massive (1000-fold) increase in smooth muscle that forms from embryogenesis to adulthood is accomplished by a combination of three- to fivefold increase in cell size and a 200- to 300-fold increase in cell number through mitotic division of existing muscle cells [7].

Peristalsis in the GI tract requires the development of the contractile apparatus of the smooth muscle cells, enabling the cells to tense and relax, thus generating contractile motion. The contractile apparatus is composed of bundles of actin and myosin filaments (myofilaments), attached to the cell membrane via actin-rich dense bodies; this apparatus is functionally similar to the Z lines in skeletal muscle. As a response to stimulus, signaling activation leads the myosin (thick filaments) to slide over the actin (thin filaments) to produce cellular contractions [8]. Myofilaments are oriented in parallel arrays and cause shortening along the long axis of the smooth muscle cells.

Although smooth muscle can undergo spontaneous contractions, overall coordination of contractions and movement of contents along the GI tract is regulated by integration with the enteric nervous system (ENS) and interstitial cells of Cajal (ICC). One of the differences between smooth muscle and skeletal muscle cells is that smooth muscle cells are uninuclear, in contrast to the multinuclear skeletal muscle cells, and thus communicate via gap junctions to enable passage of electrical impulses between cells and to allow generation of the coordinated progressive wave contractions that are characteristic of gut motility [7]. These gap junctions are observed perinatally in intestinal smooth muscle, consistent with the timeline of initiation of feeding at birth [9, 10].

Smooth Muscle Development Defects in Motility Disorders

Defects in smooth muscle development are increasingly recognized as contributing to the etiologies of the myopathic classification of pediatric intestinal pseudo-obstruction (PIPO). Advances in genetics have identified defects in the ACTG2 gene, which encodes smooth muscle actin filaments, in the pathogenesis of familial forms of hollow visceral myopathy; [11] this discovery has been opening the door to improved management approaches and family screening. While Hirschsprung's disease (HSCR) is predominantly characterized by the absence of enteric neurons and glia from segments of gut, there have been studies suggesting that abnormalities in smooth muscle development can also occur. Defects in ACTG2 have also been identified to coincide with HSCR [12], with a supernumerary coat of smooth muscle described in patients with Mowat-Wilson syndrome both with and without HSCR [13]. Dysregulation of the NRG1/ERBB pathway, furthermore, has been associated with aganglionosis, hypoganglionosis, and abnormalities in intestinal smooth muscle [14].

Interstitial Cells of Cajal

Interstitial cells of Cajal (ICC) are small mesenchyme-derived cells involved in the pacemaking of the GI tract, first described by Spanish neuroanatomist Ramon Santiago y Cajal in 1889 [15]. ICC can be found in close apposition to both enteric neurons and smooth muscle cells throughout the GI tract [16] and can also be found within gut sphincters [17]. There are several different types of ICC, which vary depending on their location in the GI tract, including the myenteric ICC (ICC-MY) that forms networks around and between the myenteric plexus and the intramuscular ICC (ICC-IM) that is intercalated between intramural neurons and smooth muscle cells [16]. ICC morphology has also suggested a pacemaker role, as gap junctions are present between adjacent ICC and smooth muscle cells. Gap junctions play an important role in slow wave propagation, as they allow ICC inter-network communication and slow wave transmission to the target smooth muscle cells.

Platelet-derived growth factor receptor α (PDGFRα$^+$) cells are another type of interstitial cell that are commonly found around ICC and follow a similar distribution. PDGFRα$^+$ cells also appear to be in close association with enteric motor neurons; however, they share fundamental structural differences that distinguish them from ICC. PDGFRα$^+$ cells have been found to play a role in enteric motor neurotransmission [18].

ICC Development

Similar to smooth muscle cells, ICCs originate from the mesoderm [19–21]. ICCs have been detected as early as week 9 in the human [6] and embryonic day (E) 14.5 in the mouse, [10] both following the differentiation of smooth muscle. The development of ICC has been shown to be dependent on intracellular signaling via the receptor tyrosine kinase Kit, with the blockade of Kit in late gestation leading to the loss of ICC networks and pacemaker activity [22]. ICCs mature rapidly, with Kit immunoreactive cells seen around myenteric ganglia in humans by week 11. Similar timing of ICC development following that of enteric neurons has also been described in mice and zebrafish [23–25].

Clinical Implications of ICC

The involvement of ICC in GI pathologies has been implicated in a range of GI conditions, including achalasia, infantile hypertrophic pylori stenosis, PIPO, HSCR, inflammatory bowel disease, and slow transit constipation [26, 27]. While associated abnormalities may involve loss of ICC or disruption of ICC networks, in many cases it can be challenging to determine whether the ICC abnormalities are either the primary cause of the GI pathology or secondary to the pathologies themselves. For example, in HSCR, some human and animal studies have reported disruptions in ICC numbers and networks in regions of aganglionosis [28, 29] while in other studies, ICC networks are normal even with the lack of enteric neurons [30, 31].

The Enteric Nervous System

The ENS is the center of integrative neuronal activity of the GI tract and is composed of two ganglionated plexuses: the myenteric plexus between the longitudinal and circular muscle layers, and the submucosal plexus between the circular muscle and muscularis mucosae. The complexity of the ENS is underscored by the presence of microcircuits composed of intrinsic primary afferent neurons, interneurons, and motor neurons, as well as by communication with extrinsic nerves and with non-neuronal cells within the gut wall [32].

ENS Precursors and Migration

The ENS derives from the neural crest [33]. Precursor cells delaminate from the neural crest at various axial levels, each level corresponding to the origin of a different neuronal class. The enteric neural crest-derived cells (ENCCs) that migrate to the gut come from the vagal, truncal, and sacral levels of the neural crest (Fig. 2.1). The majority of the ENCCs come from the vagal crest and colonize the entire bowel [34]. A smaller set migrates from the sacral crest and only colonizes the postumbilical gut [34–37]. The truncal crest contributes to the colonization of the esophagus [38]. New insights have further identified a population of Schwann cells, which enter the caudal midgut with extrinsic nerves and give rise to about one-fifth of neurons in the colonic ENS, with ongoing postnatal neurogenesis [39] (Fig. 2.1). The ENCCs that migrate to the bowel constitute a heterogeneous population that changes progressively as a function of developmental age, both while precursor cells are migrating and after they have reached the gut [40–44]. Crest-derived precursors are sorted into lineages, which can be identified by a combination of the signaling molecules, transcription factors, and growth factors on which they depend. This sorting, furthermore, is mediated, in part, by the interactions of ENCCs within the enteric microenvironment. The fates of enteric neuronal and glial cell precursors are thus determined by both intrinsic and extrinsic factors.

The migration of ENCCs as they move into and along the developing GI tract has been tracked using fluorescent-labeling techniques of either selective labeling of ENCC or use of transgenic mice. ENCCs have been found to advance through the gut as multicellular strands, with isolated cells preceding the migratory wavefront [45–47]. The pattern of advance pauses at the cecum and the cells separate and adopt a solitary meandering behavior. After several hours, the cells then leave the cecum and continue to progress through the hindgut as a network of interconnected cells and ultimately to complete gut colonization. The ability to label individual ENCCs in living tissues has further revealed that a balance of non-directional and directional movements of individual cells regulates the "directional dispersion" of ENCC, in which there is a balance of ENCC that populates each region of the gut with ENCC that moves with an overall caudal bias [47, 48]. Immature neurons can be found coexisting with migrating ENCCs and also to exhibit rostral-to-caudal migration, but with slower movement than precursor cells [49].

Among the various signaling molecules and transcription factors that influence the survival and migration of ENS progenitors (reviewed in Nagy and Goldstein [50]), are three regulators that are considered as the most central: transcription factor SRY-box transcription factor 10 (SOX10), the homeodomain transcription factor paired-like homeobox 2B (PHOX2B), and rearranged during transfection proto-oncogene (RET) (Fig. 2.1). All crest-derived progenitors express SOX10 as they delaminate from the neural tube and begin their migration in the gut. SOX10 is required for the survival of ENCC, and if missing, the result is aganglionosis in both

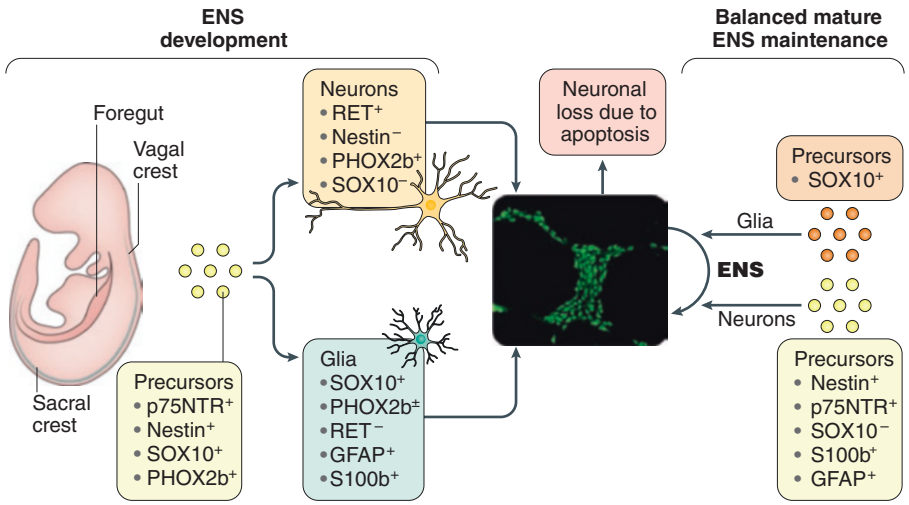

Fig. 2.1 The dynamic life history of enteric neurons and glia. A new report from Kulkarni et al. [7] has challenged the prevailing view of the permanence of the enteric nervous system (ENS). This schematic summarizes the dynamic life history of enteric neurons and glia. During ENS development, precursors emigrate to the gut from the vagal and sacral neural crest. The population as a whole, if not each cell, is pluripotent and diverges to give rise to enteric neurons and glia. Uniquely, there seems to be little cell death within the bowel and neurons are generated in the appropriate numbers. Markers that ENS precursors, neurons and glia express are indicated. A colonic myenteric ganglion, immunostained to demonstrate the neuronal cell body marker, ANNA-1, is shown (centre). After development, maintenance of the mature ENS is a balanced phenomenon, in which the process of apoptotic cell death causes extensive neuronal loss that is complemented by an equally active process of neurogenesis. Gliogenesis also occurs. In contrast to the developmental period, neuronal precursor cells of the mature bowel do not express SOX10, although they continue to express nestin and p75NTR [51]

humans and animal models [52–54]. The expression of SOX10 is also required to maintain ENCC in an undifferentiated and proliferative state, [55, 56] with continued expression by enteric glial cells but turned off when ENCC differentiates into neurons. PHOX2B is expressed by ENCCs as they enter the gut mesenchyme [57] and promotes ENCC proliferation and survival [58]. Similar to SOX10, deletion of PHOX2B leads to intestinal aganglionosis [54, 58].

The expression of both SOX10 [59] and PHOX2B [58] is required for the expression of RET. RET is a receptor tyrosine kinase that is activated by the glial cell line-derived neurotrophic factor (GDNF) family of ligands, a group of transforming growth factor proteins that activate RET in a complex with one of its family of corresponding co-receptors, GDNF family receptor α1–4 (GFRα1–4) [60, 61]. These ligands bind initially to the GFRα1–4 co-receptors, but signal transduction is mediated by activated RET. To survive, develop, or both, vagal and sacral crest-derived precursors must express RET and its ligand-preferring GFR-α co-receptor. RET is stimulated on formation of a complex with the GDNF family receptor GFR-α1 and GDNF [40, 60, 62]. In transgenic mice that lack RET, [63] GFR-α1, [64, 65] or GDNF, [66, 67] there are no enteric neurons below the esophagus and the proximal stomach (domain of the truncal crest-derived cells). While the survival and development of the truncal precursors is not totally GDNF/GFR-α1/RET dependent, the number of esophageal neurons is severely reduced in mice that lack RET [68]. The RET pathway also plays a prominent role in ENCC migration. GDNF, expressed within the gut mesenchyme, is a factor not only for survival, but also for chemoattraction of ENCC [69].

Proliferation in the ENS

The colonization of the gut takes place over many days, from week 4 to 7 in humans and from E9 to E15 in mice [6] (Fig. 2.2). During this period, the gut is growing considerably in length with ongoing growth during the fetal and postnatal periods. In order to continue colonization in the caudal direction and to keep pace with the expanding length, the ENCCs must continue to proliferate while undergoing migration. Even with the ability to proliferate after reaching the gut, the starting pool of progenitor cells is still critical to ensure complete colonization of the GI tract. In experimental models, if the initial pool of ENCCs is reduced, there is a

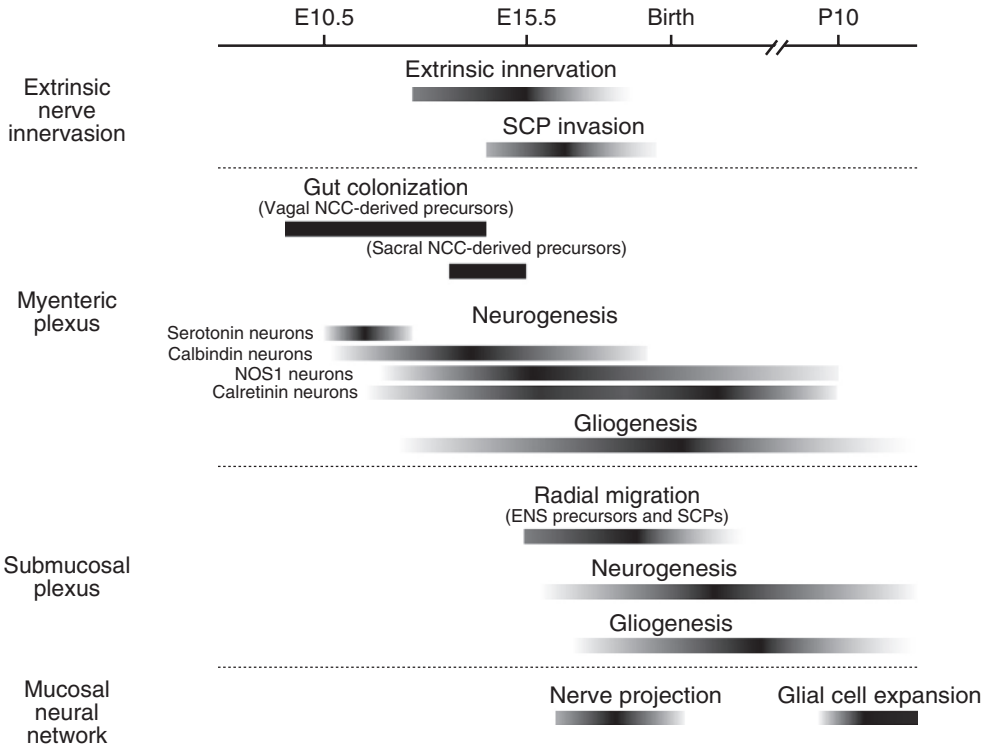

Fig. 2.2 Timing of developmental events during ENS development in the mouse. There is considerable overlap in the timing and duration of developmental processes. The timing of neurogenesis for different neuron sub-types refers to their time of exit from the cell cycle [70]

failure of ENCC to colonize the distal gut [71–73] or to appropriately populate the entire GI tract with neurons [74]. Insights from mathematical modeling have suggested that ENCC proliferation is a key driver for colonization; these insights have been further substantiated by experimental data [75–77].

In addition to survival and migration, signaling through the RET pathway also participates in ENCC proliferation. GDNF has been shown to increase the rate of proliferation and number of ENCC in vitro and in vivo [74, 78, 79]. RET/GDNF signaling can further be modified by other factors, including from the endothelin receptor-B (EDNRB) pathway. Activation of EDNRB on ENCC enhances the proliferative effects of RET signaling, [80] and the EDNRB ligand, endothelin-3 (ET-3), modulates the action of GDNF by inhibiting neuronal differentiation [79]. Retinoic acid has also been shown to be involved in ENCC proliferation, with retinoic acid itself being able to enhance proliferation of subsets of ENS precursors and increase neuronal differentiation, [81] and the retinaldehyde dehydrogenases that produce retinoic acid, being involved in ENS development and function [82]. Further research is revealing that the impact of retinoic acid signaling is dependent on developmental stage; signaling blocked at early premigratory or migratory stages causes aganglionosis, but if retinoic acid signaling is blocked at later stages, then phenotypes include hypoganglionosis and abnormalities in neuronal differentiation [83].

Differentiation in the ENS

The mature ENS is composed of an extensive variety of neuronal cells type and glial cells, which have been increasingly distinguished based on morphology, immunohistochemical profiles, and electrophysiological properties [84–88]. Differentiation of ENCC begins as early as during migration and is ongoing into the postnatal period [89] with evidence of ongoing plasticity in the adolescent [90] and adult periods [91] (Fig. 2.2). To generate the distinct classes of ENS neurons and glial cells, there is progression during ENCC development from bipotential ENS progenitor cells, capable of giving rise to both neurons and glial cells, to separate neural and glial progenitor cells, with further subdivision into specific neuronal and glial types (Fig. 2.1).

Enteric Neuronal Differentiation

Advancements of neuronal precursors through stages of progressive lineage restriction have classically been delineated through culture techniques and transgenic mice. These methods have identified transcription factors such as Mash1, which generates a subset of serotonergic neurons, [92] and Hand2, which is involved in the development of vasoactive intestinal polypeptide (VIP) neurons [93] and in signaling processes of terminal differentiation [94]. More recently,

cerebral dopamine neurotrophic factor (CDNF) has been identified as promoting the development of dopaminergic neurons [95]. The application of single-cell RNA sequencing to the understanding of enteric neuronal diversification is identifying a new framework in which enteric neurons can be classified according to their expression patterns of transcription factors, neurochemical markers, adhesion markers, and other signaling molecules [96–98]. While these exciting approaches are generating hypotheses for ongoing future studies, they also build on previous key concepts such as the correlation of neuronal birth date with cell identity [97, 99] and of the central role of GDNF in ENS development and regulation [98].

Enteric Glial Cell Differentiation

Enteric glia cells are small, astrocyte-like cells that closely associate and communicate with enteric neurons and nerve fibers [100]. Enteric glia and astrocytes share similarities on a molecular level such as expression of typical identification proteins, including intermediate filament glial fibrillary acidic protein (GFAP) and calcium binding protein S100β [100]. Transcriptional profiling of enteric glial cells has further led to the discovery that almost all enteric glia express proteolipid protein 1 (PLP1) and express more genes in common with myelinating glia than with astrocytes [101]. Overall, emerging evidence is highlighting that enteric glia constitute a heterogenous population with recent single-cell sequencing experiments indicating the presence of distinct glial subsets that vary according to location in the GI tract, in both humans and animal models [100].

Enteric glial cells are derived from ENCC bipotential progenitor cells in which expression levels of SOX10 are maintained and PHOX2B and RET are downregulated [102] (Fig. 2.1). Once gliogenesis is complete, the enteric glia form a heterogenous population that are adaptive to their different microenvironments. The current working model defines enteric glia based on their morphology and anatomic location throughout the GI tract [100]. Glia associated with myenteric and submucosal plexuses are further characterized as intraganglionic, interganglionic, and extraganglionic based on their association with the neuronal cell bodies, or with nerve fibers between or outside ganglia. The intramuscular glia associate with nerve fibers in the longitudinal and circular muscle layers and the mucosal glia are located in the lamina propria. There are limited data to date regarding the factors that contribute to the specification of enteric glia. Myenteric glia have been observed as early as E12.5 in mice and to subsequently give rise to submucosal glia [103]. The mucosal glia are also born in the myenteric plexus but do not colonize the lamina propria until the early postnatal period; this migration has been found to be interrupted if the normal gut microbiota are missing [104].

Ganglia Formation and Connectivity in the Developing ENS

Ganglia are the functional units of the ENS. Each ganglion contains a variety of neuronal cell types and enteric glia, forming specific interactions with ICC, PDGFRα^{+} cells, and with extrinsic nerves, and integrating information from the gut mucosa, smooth muscle layers, and blood vessels [18, 102]. Earlier work has characterized the role of cell adhesion molecules, such as the neural cell adhesion molecule (NCAM), in ganglia formation [105]. Neurons and non-neuronal cells have been found to express a differential in expression of NCAM, with the level of NCAM on the surface of cells correlating with the ability to form aggregates in vitro [106]. The number and size of ganglia have also been found to impact GI function. For example, the increased number of neurons in hyperganglionosis has been associated with the ganglioneuromas characteristic of multiple endocrine neoplasia type 2B (MEN2B), a disorder related to a missense mutation in the RET gene [54]. Increased density of neurons in an animal model has been linked to increased severity of inflammation [107]. On the other hand, the decreased number of neurons in hypoganglionosis has been associated with GI dysmotility in humans and animal models, often on a spectrum including aganglionosis [14, 83, 108].

Disorders of ENS Development

Hirschsprung's disease is marked by varying lengths of aganglionic bowel; both long- and short-segment forms of HSCR have been defined. The disease occurs in 1:5000 live births and is the most visible birth defect of the enteric nervous system [109]. Because the aganglionosis of HSCR is so obvious and its clinical consequences so severe, most developmental studies of the bowel have focused on identifying genes, which, when mutated, cause the crest-derived precursors of enteric neurons to fail to colonize either the whole bowel or its terminal segment. This research has been both interesting and valuable in that it has allowed many genes that regulate the development of crest-derived cells to be discovered. Thus far, at least 13 genes have been associated with the development of aganglionosis in humans and/or mice [54, 110, 111]. Of these, the most important in humans is RET, which is mutated in 3–35% of cases, and EDNRB, which is mutated in 5–15% of cases.

Unfortunately, the GI tract is prone to far more developmental defects of the enteric innervation than just HSCR. The

pathophysiological basis of these is largely unknown. They include severe diseases like PIPO, as well as infantile hypertrophic pyloric stenosis, achalasia, and MEN2B [112]. Other conditions may arise because of defects in the intestinal innervation, but remain controversial, including necrotizing enterocolitis (arising in premature infants who lack the nerve-mediated housekeeping activity of the bowel) and the irritable bowel syndrome (especially its pediatric variants). The hypothesis has been proposed that congenital defects of the ENS, which are more subtle than HSCR, or the establishment of the extrinsic innervation, may underlie these non-HSCR dysmotility syndromes [109]. The genes that give rise to HSCR and aganglionosis affect early stages of the development of ENCC. Subtle defects arise when late genes or genes that affect the enteric innervation are mutated.

Development of Enteric Neuromuscular Interactions

In this chapter, we have outlined fundamental events in the development of the smooth muscle layers of the GI tract, ICC, enteric neurons, and glia. The smooth muscle layers and ICC originate from the mesoderm-derived mesenchyme and the enteric neurons and glia are derived from the neural crest. Even though the lineages are distinct, studies in humans and animal models suggest that normal neuromuscular development requires interactions between smooth muscle and neural crest progenitor cells during key time periods, such as the requirement for GDNF expression in the outer gut mesenchyme during the migration and proliferation of ENCC, and the proposed dependence on enteric neuronal precursors for the formation of functional networks of ICC. Looking forward, it is anticipated that a combination of newer techniques such as single-cell RNA sequencing combined with physiological studies will continue to unravel the complex relationships of the multiple neuromuscular cell types required to form and maintain GI homeostasis.

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Development of Gut Motility

3

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Introduction

Coordinated movements of the gastrointestinal (GI) tract are crucial for the primary functions of this organ: digestion of food, absorption of nutrients, and removal of waste products and pathogens. Several complex motor patterns involving coordinated contractions and relaxations of the external muscle layers of the gut have distinct roles in gut motility (see below). These motility patterns have been intensively studied and characterized in adults, but much less is known about gut motility during development. Here, we review the motor patterns present in the gut of developing laboratory animals and humans. We also discuss the mechanisms that regulate intestinal movements during development.

Motility Patterns and their Control Mechanisms in the Mature Gut

Coordinated movements of the gastrointestinal tract include mixing, propagating motor activities, and receptive relaxation. These are regulated by multiple control systems including extrinsic neurons, intrinsic neurons, and glia (the enteric nervous system [ENS]); epithelial cells; interstitial cells of Cajal (ICC); platelet-derived growth factor receptor α (PDGFRα)-expressing cells; and myogenic mechanisms, which can all interact and operate simultaneously [1–6]. The relative contribution of each control system to any specific behavior varies between gastrointestinal regions [7]. Indeed, animal studies show that the relative contributions of different control systems to intestinal contractile activity vary with developmental age [8]. Thus, the control of gut motility is very complex [2, 9].

The esophagus is a conduit between the pharynx and the stomach, and its only physiological motor pattern is peristalsis. During the pharyngeal phase of swallowing, the upper esophageal sphincter (UES) relaxes, and there are then sequential contractions of esophageal muscle from the proximal to the distal end, followed by lower esophageal sphincter (LES) relaxation to allow a bolus to enter the stomach. This integrated sequence of reflexes induced by swallowing constitutes *primary peristalsis*. Peristalsis is also initiated by esophageal distension, termed *secondary peristalsis*. In humans, the upper third of the esophagus, which is striated muscle, is controlled entirely by neurons in the brainstem via the vagus nerves. The lower, smooth muscle regions of the esophagus are controlled by the vagus nerve, intrinsic neurons, and myogenic mechanisms [7].

Differing motor patterns occur in the proximal and distal stomach [7]. The proximal stomach exhibits receptive relaxation and accommodation, which are each mediated by neurons in the brainstem via vago-vagal reflexes. The distal stomach exhibits different motor patterns in the fed and fasted states. In the fed state, the distal stomach grinds and mixes. Extrinsic neurons are not essential for this contractile activity, but it can be modulated by vagal pathways. In the fasted state, the antrum plays a key role in the migrating motor complex (MMC; see below).

Multiple motor patterns occur in the small and large intestines. In the small intestine, the dominant motor pattern in the fasted state manifests at any one point as a period of quiescence (phase I), then a build-up of irregular contractile activity (phase II), followed by a period of synchronized strong contractions (phase III). Phase III contractions sweep slowly along the gastrointestinal tract leading to the whole

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pattern being termed the migrating motor complex (MMC), which clears indigestible food, mucus, and epithelial debris in the fasted state. In humans, MMCs occur around once every 2–4 h; most originate in the distal stomach, where they are the primary fasted motor pattern (some start in the proximal duodenum) and propagate along the majority of the small intestine [7]. Initiation of MMCs is modulated by vagal input and motilin released from the duodenum, while both initiation and propagation depend on enteric neurons. In humans, MMCs occur only in the fasted state and only in the small intestine [7]. But in some other species, MMCs occur in both fed and fasted states and also in the colon.

The fed state of the small intestine is dominated by two motor patterns: (1) segmentation, alternating stationary waves of contraction and relaxation, which mixes intestinal contents with digestive enzymes and exposes nutrients to the absorptive epithelium (small intestine) or facilitates water extraction (colon); and (2) peristalsis, contraction waves that migrate in an anal direction, which moves intestinal contents to new gut regions and is essential for elimination of undigested material. In the large intestine of some species including humans, haustration—the mixing of feces to absorb water—occurs in sac-like structures called haustrations.

Studies in animal models have shown that the ENS is essential for segmentation in the small intestine [10], but ICCs clearly also have a major role [11]. Peristalsis in the small and large intestines is controlled by an interplay between the ENS, ICC, and myogenic mechanisms [2]. The ENS, however, is essential for intestinal peristalsis as shown by the bowel obstruction caused by the aganglionic region of infants with Hirschsprung disease [12]. Enteric neural circuits also underlie contractile complexes that propagate anterogradely or retrogradely across the ileo-colonic junction spanning the small and large intestines of mice [13]. Studies in the rabbit colon have shown that haustral formation and propagation is neurally mediated [14, 15]. Furthermore, water and electrolyte secretion is regulated by the ENS, as is the integration between motility and secretion [16].

Development of Motility Patterns and their Control Mechanisms: Studies of Laboratory Animals

Unlike humans, the mechanisms controlling motility patterns during development can be examined in intact segments of gut of laboratory animals in vitro or in vivo. The most useful studies involve video recordings of the behavior of these segments followed by construction of high-resolution spatiotemporal maps of contractile activity at each point in the segment [8, 17–19]. Most studies of mammals have been performed using segments of fetal or postnatal mouse intestine in vitro. In vivo studies have focused on larval zebrafish that are transparent allowing propagating contractile activity and transit studies using fluorescent food or beads [20–25], including studies to model and understand the pathogenesis of an inherited form of chronic intestinal pseudo-obstruction [26]. In this section, we focus by necessity on the small and large intestines as there are relatively few studies on the development of motility patterns and their control mechanisms in the esophagus and stomach of laboratory animals.

Motility Patterns Present in the Developing Gut

Although fetal mammals receive nutrition solely via the placenta, contractile activity in the gut begins well before birth. The esophagus of preterm piglets (delivered by caesarean section at 91% of full gestation) exhibits esophageal contractions in response to oral feeding, but compared to term piglets, the frequency of contractions is lower and the contractions propagate at a lower velocity [27]. In fetal mice, shallow contractions that propagate both orally and anally are first observed in preparations of small intestine in vitro at embryonic day (E) 13.5 (the gestation period for a mouse is around 19 days) [8]. Spontaneously propagating circular smooth muscle contraction waves are present in the chicken intestine by E6 [17, 18]. Moreover, propagating constrictions are observed in zebrafish larvae before the yolk sac is fully absorbed [21–24]. The physiological role of prenatal (or pre-yolk sac absorption) gastrointestinal contractile activity is unclear. Fetal mammals swallow amniotic fluid, which advances along the gut [28–30], and this meconium progresses toward the distal regions of bowel during late fetal stages [31]. Although it is highly likely that the propagating contractile activity that occurs prior to birth contributes to the propulsion of meconium anally prior to birth [8], this is yet to be conclusively demonstrated. The complex systems of enteric neurons, enteric glia, extrinsic nerves, epithelial cells, ICC, PDGRF+ fibroblast-like cells, and smooth muscle that mediate motility differentiate and become functional at different times during development. Motility patterns become increasingly intricate as these components mature and interact with one another with the adult outcome depending on all of them. The next sections will discuss what is known about the development of each component and their roles in motility.

Development of Enteric Neurons and their Role in Motility during Development

Neural control specifically requires ordered neural circuits involving sensory neurons, interneurons, and both excitatory and inhibitory motor neurons that innervate the smooth mus-

cle, and all are present in the enteric nervous system. Thus, differentiation of the different neural subtypes, their correct wiring (axon outgrowth and synaptogenesis), and formation of functional connections to the smooth muscle are key components of development of normal gastrointestinal motility. It is, however, clear that even prior to the formation of neural circuits exerting control of motor functions, neural activity has a role in specifying or regulating neuronal differentiation and hence axon guidance and synaptogenesis.

The ENS arises from neural-crest-derived cells that emigrate primarily from the caudal hindbrain [32, 33], although sacral level neural crest cells also give rise to some enteric neurons, mainly in the colon and rectum [34–36]. Moreover, neural-crest-derived Schwann cell precursors give rise to a substantial proportion of submucosal neurons (~20%) in the colon [37, 38] and elsewhere. Some evidence suggests that a subset of duodenal neurons derive from pancreatic stem cells (endoderm) rather than the neural crest [39], but this remains to be confirmed. Vagal neural-crest-derived cells that colonize the colon travel significant distances as the gut is growing as they migrate [40–42]. Neuronal differentiation commences early as pan-neuronal markers are expressed by a subpopulation of neural-crest-derived cells as they are migrating along the gut in fetal mice and rats [43, 44]. Post-migratory neural-crest-derived progenitors give rise to ENS clonal units that are organized spatially and functionally within the gut wall [45]. Further, action potential firing can be detected in newly differentiated enteric neurons very shortly after they begin to express neuron-specific markers [46, 47].

In the mature ENS, there are many different (more than 20 in mouse colon) subtypes of enteric neurons that can be defined by their neurochemistry or transcriptome, which correlates with their putative functions [48–53]. Prior to neuronal differentiation, precursors exit the cell cycle. Studies in mice have shown that different neuron subtypes exit the cell cycle at different developmental ages: in the mouse small intestine, serotonin interneurons exit the cell cycle first, at mid-embryonic ages, while some excitatory motor neurons appear to be the last to exit the cell cycle, around birth [54–56]. The timing of exit from the cell cycle probably differs between regions as early differentiating neurons in the small intestine appear before precursors have reached the distal colon in embryonic mice. Furthermore, it is now clear that there are significant differences in the neurochemical identities of neurons between small and large intestines in mice [50, 52, 57] indicating that distinct developmental profiles may apply. Cells expressing markers for some enteric neuron subtypes are present shortly after the first expression of pan-neuronal proteins [58], but other enteric neuron subtypes first appear at different ages [47]. The interval between cell cycle exit and the first detectable expression of enteric neuron subtype markers varies from under 2 days to about a week [54]. There is evidence that some enteric neurons change their phenotype during pre- and/or postnatal development [54, 59, 60]. Research is constantly advancing our understanding of mechanisms that drive enteric neuronal subtype differentiation. Several soluble factors produced by the gut mesenchyme and transcription factors that mediate enteric neuron differentiation have been identified [52, 61–63].

Myenteric neurons can be broadly divided into those expressing neuronal nitric oxide synthase (nNOS—the synthetic enzyme for nitric oxide), and those expressing choline acetyltransferase (ChAT, the synthetic enzyme for acetylcholine), although each of these has several subtypes [48, 50–53]. Neurons that lack both enzymes are uncommon. For these reasons the development of nitrergic and cholinergic enteric neurons, or their subtypes, is the most extensively studied. nNOS neurons in the mature ENS include interneurons and inhibitory motor neurons to the external muscle layers [64, 65]. ChAT neurons include intrinsic sensory neurons, excitatory interneurons, and excitatory motor neurons to the external muscle layers [65, 66]. In both zebrafish and mice, nNOS neurons are among the first enteric neuron subtypes to appear during development [22, 58, 67, 68]. In zebrafish, the proportion of enteric neurons expressing nNOS does not change between 72 and 120 hpf (hours post-fertilization) [68], while in mouse colon, the adult proportion of such neurons is reached within 2 weeks after birth and remains stable thereafter [69]. In guinea-pigs, however, the percentage of myenteric neurons expressing nNOS declines during postnatal development [70], which contrasts with the rat, in which the proportion of myenteric neurons expressing NOS increases postnatally [71]. Cholinergic neurons also appear early in mouse ENS development shown by uptake of ^{3}[H]-choline [72] and the presence of neurons expressing ChAT [61, 73]. In rats, the percentage of ChAT-immunoreactive myenteric neurons increases during postnatal development [71]. Changes in the proportions of some subtypes of enteric neurons have also been reported between weaning and adulthood in rodents, suggesting that the ENS is not fully mature at weaning [50, 69, 74–76].

Dynamic changes in the architecture of both enteric plexuses occur as ganglia are stretched further apart due to the anatomical expansion of the diameter and length of the gastrointestinal tract during development [61, 69]. Indeed, the architecture of the ganglia depends on the contractile activity of the smooth muscle as well as the overall expansion [77, 78].

The formation of functional connections between enteric neurons remains poorly understood. Prior to birth nearly all differentiated myenteric neurons have axon-like neurites that project anally along the intestine [79], but in the adult many neurons have either oral projections or project circumferentially [80, 81]. What produces this change and what determines the targets of individual neuron subtypes

are yet to be determined. However, mice lacking components of the planar cell polarity (PCP) signaling pathway have defects in the axonal projections of some neurons and hence connectivity defects [81]. The PCP mutant mice are particularly interesting as they have severe motility defects including distension of the small intestine and colon, defects in the frequency of colonic motor complexes (CMCs), and defects in pellet production, but there are no changes in the density of myenteric neurons, or in the density of the major neuronal subtypes [81].

On the postsynaptic side, changes in dendritic morphology and axon projection lengths of murine enteric neurons continue well beyond the early postnatal period [80]. The somata of enteric neurons receive significantly more close contacts from varicosities containing synaptic vesicles after weaning than before, which strongly suggests that significant synaptogenesis occurs in the postnatal gut [69]. Indeed, it has been reported that dynamic neurogenesis and apoptosis in the gut persists well into adulthood [82], which implies that there must be ongoing synaptogenesis and axon outgrowth and retraction.

Communication between neuronal and non-neuronal enteric neural crest cells in the form of spontaneous intercellular calcium waves mediated by P2 purinoceptors is seen at E11.5 in embryonic mice [83]. But the earliest direct evidence for synaptic transmission between enteric neurons is at E12.5 when blocking nicotinic acetylcholine receptors was found to depress neural calcium responses to electrical activation of the plexus [84]. Acetylcholine is the primary excitatory transmitter in the ENS [85]. Functional nicotinic acetylcholine receptors are expressed in the mouse gut shortly after ChAT neurons develop, but the contribution of different nicotinic acetylcholine receptor subunits to synaptic transmission changes during pre- and postnatal development [84]. Thus, while cholinergic transmission between neurons appears early, it matures and changes character over a prolonged period. An ultrastructural study reported synapse-like structures in the stomach of E12.5 mice, and mature-looking synapses were present along the entire gut by E16.5 [86]. Intracellular electrophysiological recording not only revealed synaptic activity in many enteric neurons in newborn mice, but also showed that maturation of enteric neural properties continues for some time after birth [80]. Little is known about the molecular mechanisms regulating the formation of synapses and connectivity in the developing ENS. Some cases of intestinal pseudo-obstruction or functional bowel disorders in infants and children may be due to defects in the development of ENS circuitry, and such defects cannot be detected by standard pathological testing.

Many ion channels involved in regulation of neuronal excitability are expressed during early ENS development [87] and the ENS is one of the first parts of the nervous system to show mature forms of electrical activity [46, 61]. Nevertheless, studies in mice, chicken, and zebrafish using pharmacological inhibitors of neural activity or mutants lacking enteric neurons show that the first motility patterns are not neurally mediated [8, 18, 21, 88]. There is a significant delay between the first appearance of enteric neurons and of synapses between them and when neurally mediated motility patterns are observed. This may reflect slower formation of neuromuscular transmission than the initial synaptogenesis in the developing enteric circuits.

In mice, neurally mediated motility patterns are not observed until shortly before birth in the duodenum [8], and a week after birth in the colon [19]. A similar rostral-caudal polarity for the maturity of motility patterns occurs in the chicken gut; neurally mediated motility occurs first in the duodenum a few days before birth at E16 [88]. Inhibitory neuromuscular transmission and excitatory transmission to the same smooth muscle operate according to different developmental timetables in different species and regions. This probably reflects the growth of motor axons into the muscle and differential development of intramuscular interstitial cells of Cajal and PDGRFα+ fibroblast-like cells, which act as transducers of neuromuscular transmission (see below). In longitudinal colonic muscle strips from rats, electrical field stimulation-induced contractions are reduced by a muscarinic acetylcholine receptor blockade starting at postnatal day (P) 14, whereas the inhibition produced by nitrergic neurons is only detectible from P36 [71]. Thus, cholinergic neuromuscular transmission to the longitudinal muscle in the rat colon does not develop until postnatal stages and precedes the development of nitric oxide-mediated transmission. In contrast, cholinergic neuromuscular transmission in the guinea-pig taenia caeci, chicken, and frog intestine appears after inhibitory or nitric oxide-mediated transmission [88–90]. In the mouse small intestine, cholinergic neuromuscular transmission commences at late fetal stages [91]. In the longitudinal muscle of human and guinea-pig intestine, nitric oxide-mediated transmission is relatively more prominent at postnatal stages than in adults [70, 92].

Enteric neurons may regulate other processes important for the proper development of gut motility since they are active prior to the commencement of neurally mediated gut motility. Neurotransmitters and neurotransmitter-related substances released or expressed by enteric neurons that differentiate early appear to influence the later development of the ENS [40, 93, 94]. For example, mice lacking tryptophan hydroxylase 2 (TPH2), the enzyme required for the synthesis of serotonin by neurons, have decreased myenteric neuron density; as serotonin neurons are generated early during ENS development (see above), it appears that release of serotonin by some of the first neurons to differentiate promotes the differentiation of ENS precursors [93]. Further, an RNA-sequencing study has shown that enteric neuron clusters form through two trajectories derived from two subsets of enteric neurons that were generated as dividing progenitors undergoing neurogenesis [51].

In summary, although enteric neurons develop early, the first gastrointestinal motility patterns are not neurally mediated. However, neurally mediated contractile activity is prominent in the upper small intestine of the mouse by birth and is essential for propulsive activity in the colon of newborn humans as shown by the bowel obstruction that occurs proximal to the aganglionic region immediately after birth in infants with Hirschsprung disease. One of the first subtypes of enteric neuron to develop are the nNOS neurons and, although there are some exceptions, nitric oxide-mediated transmission develops earlier and/or is more prominent during pre- and postnatal development than in adults. As the relative importance of different neurotransmitters to gastrointestinal contractile activity changes significantly during development, drugs that successfully treat motility disorders in adults will not necessarily have similar effects in infants and children.

Development of Enteric Glia and their Role in Motility during Development

Enteric glia are the other important cellular constituents of the ENS. They are a heterogeneous cell population that are connected to many other cells within the layers of the gut wall [48, 52, 95, 96]. It is increasingly apparent that these cells do not just play a supportive role to the neurons, but have multifaceted roles in gut physiology [97]. Indeed, enteric glia play important roles in modulating gastrointestinal motility. In mice, myenteric neurons activate glia during colonic motor activity [98]. Selective activation of enteric glia can drive neurogenic contractions in the ileum and colon and increase colonic motility in vivo [99]. Ca^{2+} responses in the glial network were demonstrated to affect whole gut and colonic transit in vivo [100]. Further, gliotransmitter release via connexin 43 hemichannels and Ca^{2+}-dependent exocytosis can differentially modulate gut motility [101]. During development, enteric glia differentiate after neurons, with the mature markers S100β present around E14.5 [102] and glial fibrillary acidic protein at E16.5 [103] in mice. Maturation of certain glial subtypes continues after birth [96]. It is not yet known when enteric glia are first electrically active and when neuron and glia communication commences in the gut.

Development of Enteroendocrine Cells and their Role in Motility during Development

Initiation and progression of motility along the GI tract after birth relies on chemo- and mechanosensitive elements that detect the nutrients and stretch that luminal contents exert on the gut wall.

Intestinal contents influence gut motility [10, 104, 105]. Specialized epithelial cells known as enteroendocrine cells sense chemicals and nutrients in the gut lumen via expression of several "taste" receptors, channels, and transporters, such as G-protein-coupled receptors, free fatty acid receptors, and transporters for all kinds of nutrients [106]. Once activated, enteroendocrine cells then release various hormones that can act on neighboring cells, including terminals of enteric neurons, or via local paracrine effects to initiate an appropriate response [106, 107]. Activation of the gut mucosa with microbial metabolites (e.g., short-chain fatty acids) and 5-hydroxytryptamine (5-HT) in mature animals stimulates enteric neurons [108]. Enteric neurons begin to project neurites into the lamina propria by E13.5 in mice. These respond to electrical stimulation of the mucosa by E15.5 and exposure to 5-HT by birth [109]. Little is known about the maturation of enteroendocrine cells in the gut mucosa. Enteroendocrine and other epithelial cells are derived from stem cells at the base of mucosal crypts. These stem cells are rare at birth in mice but their numbers are established by P7–P14 through to weaning [110].

Subtypes of enteric neurons and enteroendocrine cells of the mucosa are mechanosensitive [1, 111]. Enterochromaffin cells are the largest subset of enteroendocrine cells. They produce 95% of the body's 5-HT, which is an important regulator of gut motility [112]. Enterochromaffin cells express Piezo2 mechanosensitive ion channels [1]. The time course of appearance of the different mechanosensitive elements is still under investigation, but the work of Chevalier and colleagues shows that mechanosensitivity is a key regulator of embryonic development [77, 78, 113].

Development of Fibroblast-like Interstitial Cells (Including Kit+ Interstitial Cells of Cajal [ICC] and PDGFRα+ Cells) and their Role in Motility during Development

Diverse populations of fibroblast-like interstitial cells are present in the adult gut. Loss or dysfunction of these cells has been linked to a wide variety of gastrointestinal disorders including achalasia [114, 115], gastroparesis [116–119], infantile hypertrophic pyloric stenosis [120], idiopathic chronic intestinal pseudo-obstruction [121], and slow transit constipation [122, 123]. This broad group of cells comprises various subpopulations of Kit-positive interstitial cells of Cajal (ICC) and fibroblast-like cells that express platelet-derived growth factor receptor alpha (PDGFRα) and are sometimes termed telocytes [124].

ICC myenteric (ICC-MY) located at the level of the myenteric plexus mediates slow waves, the electrical events that time the occurrence of phasic contractions [125–128]. In dog and mouse colon, ICCs located at the level of the submucosal plexus (ICC-SMP) also generate slow waves [129,

130]. The ICC intramuscular (ICC-IM) and ICC associated with the deep muscular plexus (ICC-DMP) and PDGFRα+ cells located within and surrounding gastrointestinal muscle bundles serve as intermediaries in both excitatory and inhibitory neuromuscular transmissions [131–135]. The smooth muscle cells (S), ICC-IM (I), and PDGRFα+ cells (P) form a functionally coupled unit known as the SIP syncytium.

Unlike enteric neurons and glia, ICCs do not arise from the neural crest during embryological development as ICCs develop in explants of avian and mammalian embryonic gut that have been removed prior to the arrival of neural crest cells in that region [136, 137]. Furthermore, ICCs are distributed normally and slow wave activity is generated in the bowel of mutant mice lacking enteric neurons [138, 139]. Hence, ICC development and maintenance are independent of neural-crest-derived cells in mice. In an infant with intestinal aganglionosis extending into the jejunum, abundant ICCs were present in the myenteric region, but degenerating ICCs were observed in the circular muscle of the aganglionic region [140]. Thus, in humans, ICCs also arise independently of neurons, but some subpopulations of ICC may directly or indirectly require neurons for their long-term survival.

Developmental studies in mice suggest that smooth muscle cells and ICC have a common mesenchymal precursor following a process of epithelial-mesenchymal transition (EMT) [141–143]. Both ICC and the CD34+ fibroblast-like cells that form a resident ICC producing stem cell population derive from the coelomic epithelium, most likely from a progenitor expressing the chloride channel anoctamin-1 and smooth muscle actin alpha [141]. Differentiation to the ICC-MY phenotype during embryogenesis depends on cellular signaling via the tyrosine kinase receptor, Kit [91, 143–145]. The natural ligand for the Kit receptor is stem cell factor (SCF or *steel*), which is expressed in both enteric neurons and smooth muscle cells [138, 139, 146]. Mutations leading to deficiency of Kit in W/W^{v} mice or membrane-bound SCF in Sl/Sl^{d} mice result in disruptions of particular ICC populations, notably ICC-MY, and aberrant gastrointestinal motility [126–128]. Both migrating motor complexes and higher-frequency phasic contractions can be recorded from the small intestine of W/W^{v} mice, which lack intestinal ICC-MY [147], but the phasic contractions are characteristically abrupt and uncoordinated [148]. Treatment of embryonic jejunal explants with Kit-neutralizing antibodies prior to the emergence of cells with the ultrastructural characteristics of ICC prevents the development of ICC-MY and slow wave activity in the small intestine [91]. The postnatal maintenance of ICC-MY also appears dependent upon Kit-signaling as injection of Kit-neutralizing antibodies resulted in loss of these ICCs and lethal paralytic ileus in neonatal mice [145]. Loss of ICC due to Kit blockade is accompanied by a loss of electrical slow wave activity in the small intestine and reduced neural responses in the small bowel and colon [149]. In the absence of Kit-signaling, ICC-MY takes on a smooth muscle phenotype, but retains, at least in the short term, the ability to regenerate the ICC phenotype if Kit-signaling is restored [144]. In contrast, the ICCs associated with the deep muscular plexus of enteric nerve terminals in the circular smooth muscle (ICC-DMP) develop in the absence of Kit-signaling according to a distinct rostro-caudal timetable [150].

During embryogenesis there is a rostral-to-caudal development of ICC-MY along the gastrointestinal tract. In embryonic mice and chickens, the circular muscle layer differentiates prior to the longitudinal muscle layer [88, 143]. In mice, nearly all the mesenchymal cells between the serosa and the newly formed circular muscle layer, consisting of precursors of both longitudinal muscle and ICC, initially express Kit [91, 149]. As embryonic development progresses, a subpopulation of these mesenchymal precursors stops expressing Kit and differentiates into longitudinal smooth muscle [143]. The Kit-positive cells on the circular muscle side of this newly formed longitudinal muscle layer develop into the anastomosing network of ICC-MY. The time course of differentiation of the alternative pacemakers in the colon (ICC-SMP) and their embryological source remain open questions.

Motility patterns of the stomach during development have not been extensively researched in laboratory animals. In mouse, 2 days prior to birth, ICC-MY and slow wave activity are present in the gastric antrum while spindle-shaped ICC-IMs are evident and neurally mediated responses can be recorded from the gastric fundus [151].

It is now well established that the tripartite SIP syncytium plays a key role in both nitrergic and cholinergic neuromuscular transmissions, and ICC-IM and ICC-DMP are closely associated with the varicose terminals of both excitatory and inhibitory motor nerves (for review see, [124, 134]). Despite this close anatomical arrangement between nerves and ICC-IM, the outgrowth of motor nerve processes does not appear to depend on ICC as the distribution of both excitatory and inhibitory nerve processes is normal in W/W^{v} fundus muscles devoid of ICC-IM [135, 152].

Electrical rhythmicity can be recorded from segments of mouse small intestine 3 days prior to birth [91, 144] and continues to develop and mature until well after birth [153]. But the first propagating contractions in mouse intestine are evident earlier, in the mid stages of embryonic development (E13.5), before the appearance of a Kit-positive ICC network or slow wave activity at E18.5 [8]. The frequency of these initial contractions is similar in wild-type mice and in mutant (W/W^{v}) mice lacking ICC-MY, providing further evidence that these contractile patterns are myogenic[1] rather than ICC mediated. A similar transition from smooth muscle to ICC-driven motility is reported in the chicken embryo [113]. In

[1] In the field of gastrointestinal motility, the term "myogenic" has been used to describe contractile activity generated by ICC as well as muscle cells, but here we use the term myogenic to refer to contractions specifically originating from the muscle cells themselves.

mice, at E18.5, after anastomosing networks of ICC-MY have established, slow waves and phasic contractions occur at a similar frequency suggesting that myogenic contractions become entrained by ICC-MY [8]. Around 5 days after birth, a second layer of Kit-positive cells, termed ICC-DMP, is present in the region of the deep muscular plexus of the rodent small intestine [143, 151, 154–156]. ICC-DMP in the small intestine and ICC in the region of the submucosal plexus in the colon (ICC-SMP) arise from smooth muscle progenitors expressing leucine-rich repeats and immunoglobulin-like domains protein 1 (LRIG1) [157]. Loss of LRIG1 expression results in loss of ICC-DMP and ICC-SMP but preservation of ICC-MY suggesting that LRIG1 plays an essential role in the differentiation of smooth muscle progenitors to subpopulations of Kit-expressing ICC [157]. Interestingly, development of ICC-IM (and possibly ICC-DMP) has been found to be independent of Kit, despite these cells being characterized by Kit-immunoreactivity; rather they appear to require the third element of the SIP syncytium, the PDGRFα+ cells and PDGRFα signaling [150]. Development of neuromuscular responses to stimulation depends on both the development of ICC-DMP and of the motor nerve terminals (see above) [156] suggesting their role as mediators of neurotransmission in the intestine. It has also been suggested that Ca^{2+} signaling within ICC-DMP underlies the motor pattern of segmentation within the small intestine [11]. Interestingly, intestinal transit is delayed and the abdomen becomes distended in LRIG1-null mice lacking ICC-DMP suggesting these cells serve a functionally significant role in intestinal physiology [157].

Kit-negative fibroblast-like interstitial cells within the gastrointestinal tract have been described for many years [158–161]. The discovery that PDGFRα is a reliable biomarker of these cells accelerated investigations into their distribution and functional role within the GI tract [124, 162], leading to the identification and characterization of the SIP syncytium. This has been described in various regions within the rodent, primate, and human gastrointestinal tract including within the plane between the muscularis mucosae and the circular muscle layer and within circular muscle bundles—where it is contacted by excitatory and inhibitory nerve terminals [133, 163–165]. PDGFRα+ cells apparently mediate inhibitory inputs from purinergic nerves as, in addition to being closely apposed to motor nerve terminals, they are enriched in components required for the detection and transduction of purinergic signals [166] and exhibit calcium transients and large-amplitude apamin-sensitive K+ currents in response to exogenously applied purines [133, 167]. The developmental progenitors of PDGFRα+ cells and the timing of their differentiation within the gastrointestinal tract are still unclear. But it is likely that they share common progenitors with the circular muscle and much of this development appears to occur postnatally with a rostro-caudal gradient at least in the mouse [150, 168]).

Role of Myogenic Mechanisms in Intestinal Motility during Development

Studies in embryonic mice, chickens, and zebrafish have shown that the first intestinal motility patterns to appear during development—spontaneous contractions that propagate anally and orally—are not mediated by neurons or ICC [8, 18, 21]. Hence the contractions must be myogenic, that is, generated by the smooth muscle cells themselves. In the chicken gut, the first detectable spontaneous contractions are from the circular smooth muscle cells at E6, followed by those mediated by longitudinal smooth muscle cells at E14 [88]. This early motility pattern is generated by intracellularly generated waves of calcium propagating via gap junctions between circular smooth muscle cells [17]. In the duodenum and colon of fetal mice, the myogenic contractions require the entry of extracellular calcium [8], but it is unknown how they are initiated or propagated. Interestingly, mechanical stress in the gut wall mediated by early spontaneous circular smooth muscle contractions induces a longitudinal strain on the developing ENS thereby influencing the architecture of enteric plexuses [77]. Motility patterns that are not mediated by either neurons or ICC are present in the intestine of mature animals, but under normal conditions are not very prominent [169, 170]. However, propagating contractions in other organs of mature animals, including the upper urinary tract, vas deferens, and uterus, are entirely myogenic in origin [171].

Environmental Influences on Motility Patterns during Development

In the adult gut, specific nutrients can change the function and phenotype of the ENS [172]. The composition of gut contents changes dramatically immediately after birth and then at weaning, and it is likely that these changes induce changes in motility patterns. Daily butyrate enemas performed on seven-day-old rats for 10 days did not affect body weight, histological appearance of the colon, or the number of myenteric neurons/ganglion, but induced increases in the proportion of neurons expressing markers of cholinergic neurons and nNOS neurons and increases in distal colonic transit time [173]. Further, introduction of solid food at weaning induces changes in some of the properties of MMCs in piglets [174]. Diet is also known to affect both motility and gene expression in the ENS of mature rats; in particular, long-term exposure to a resistant starch diet enhanced colonic propulsive motility and increased the number of ChAT-immunoreactive myenteric neurons [175]. Furthermore, malnutrition during early postnatal life results in grossly abnormal stomachs and gastrointestinal dysmotility in a sex-dependent manner [176].

The gut is colonized by vast number of microbes, known as the gut microbiota, primarily after birth. Maturation and establishment of gut microbiota occurs over a protracted period postnatally [177, 178]. Studies using animals lacking a microbiome have shown that, in addition to aiding food processing, the microbiota influence the nervous system including the brain [179–181]. Indeed, marked differences in the neurochemical phenotypes of myenteric neurons in ileum and colon of mouse have been shown to depend on the composition of the luminal microbiota [57]. The microbiota also play important roles in the development of the ENS. Mice lacking a microbiome have fewer mucosal glial cells [96] and fewer myenteric neurons, but a higher proportion of nNOS neurons [182]. Antibiotic exposure during the neonatal and post-weaning period significantly impacts the microbiota, ENS, and colonic motility in mice [178, 183]. Research within the last few years has revealed various mechanisms by which microbiota interact with the ENS [177]. For example, within the colon of developing mice, it appears that lipopolysaccharide (LPS)-mediated activation of toll-like receptors during gestational development is required to maintain normal populations of nitrergic inhibitory nerves [184]. Microbiota [184] can affect the developing ENS by impacting enterochromaffin cells and 5-HT biosynthesis during early postnatal stages [183]. Moreover, piglets treated with a probiotic show increases in the expression of some neurotransmitters in submucosal, but not myenteric, neurons [185].

Motility in Human Neonates and Children

In human infants, gastrointestinal motility is very complex, and, as in laboratory animals, is almost certainly influenced by maturational changes in the central nervous system (CNS) and ENS, gut muscle and ICC, as well as diet and changing anatomical postures during infancy. Furthermore, in the vulnerable high-risk infant in intensive care units, hypoxia, inflammation, sepsis, and other comorbidity conditions can complicate the feeding process and gastrointestinal transit.

Enteric neural crest cells enter the human foregut at embryonic week (EW) 4, then migrate in an oral-anal fashion to fully colonize the gastrointestinal tract by EW7 [186]. Immunohistochemical studies of human fetuses have shown that neurons, muscle and ICC differentiate from proximal-to-distal and that the longitudinal and circular muscle layers and myenteric and submucosal plexuses have a mature appearance by EW14 [186, 187]. Significant morphological and functional maturation of the ENS appears to occur in the period between late first trimester and early second trimester [188, 189]. By EW12, TuJ1+ enteric neurons and S100+ glia are found in the myenteric plexus of human colons [189]. As in laboratory mammals, many sub-types of enteric neurons develop prior to birth [47]. Markers for subtypes of cholinergic enteric neurons including vesicular acetylcholine transporter (VAChT) and substance P are present in the colonic myenteric plexus by EW12, while expression of nNOS was found later at EW14. By EW16, electrical stimulation of whole-mount colonic preparations can induce calcium transients in enteric neurons that are mediated by voltage-gated sodium channels [189]. Kit-expressing ICC-MY first appear around weeks 7–9 [186, 187]. In the stomach, ICC-MY, ICC-IM (intramuscular) and ICC-SEP (ICC located within connective tissue septa separating muscle bundles) are all present by the end of the fourth month of development [190].

The simple physiological functions of the neonatal foregut, midgut, and hindgut, respectively, are to facilitate: (1) safe feeding by steering ingested material away from the airway, (2) gastrointestinal transit and mixing of luminal contents to permit absorption and propulsion, and (3) evacuation of excreta to modify the intestinal milieu. In this section on human neonates, we will review the developmental aspects of (1) pharyngo-esophageal motility, (2) gastric motility, (3) small intestinal motility, and (4) colonic motility. In particular, we will also review recent advances and discoveries.

The importance of reciprocal interactions between aerodigestive systems, enteric nervous system, and central nervous system across the age spectrum is increasingly evident; developmental and maturational aspects of these entities are highlighted here. Specifically, advances in the field of developmental aerodigestive reflexes and gastrointestinal motility are briefly discussed in the following sections and fully referenced.

Developmental Pharyngo-Esophageal Motility in Human Neonates

Swallowing Prior to Birth

Numerous studies have shown that the human fetus swallows amniotic fluid [28, 191]. By 11 weeks of gestation, the ability to swallow has developed and by 18–20 weeks sucking movements appear. There is an increase in the volume swallowed with gestational age, and by near term, the human fetus swallows around 500 mL of amniotic fluid per day [191]. Studies in sheep have shown that, as in adults, swallowing in near-term fetuses involves central cholinergic mechanisms [192].

Upper and Lower Esophageal Sphincter Functions and Esophageal Peristalsis in Human Neonates

Upper esophageal sphincter (UES), esophageal body, and lower esophageal sphincter (LES) functions have been characterized in neonates using micromanometry [193–195]. The resting UES tone increases with maturation from around 18 mm Hg in 33-week preterm infants to 26 mmHg in full-term-born neonates compared to 53 mmHg in adults. In contrast, the motor events associated with LES relaxation in

healthy preterm infants 33 weeks and older have similar characteristics to adults [196].

In 33-week preterm infants, primary esophageal peristalsis occurs, but considerable maturation occurs pre- and postnatally [194, 195]. For example, evaluation of consecutive spontaneous solitary swallows in preterm infants at 33 weeks, preterm infants at 36 weeks, full-term infants, and adults showed significant age-dependent changes in the amplitude and velocity of the peristaltic contractions [193].

During anterograde movement of a bolus following swallowing or during retrograde movement of a bolus during gastroesophageal reflux events, the bolus comes in close proximity to the airway. Peristalsis is the single most important function that ensures clearance of luminal contents away from the airway. During primary esophageal peristalsis, there is a respiratory pause called deglutition apnea that occurs during the pharyngeal phase of swallow (Fig. 3.1). This brief inhibition in respiration is due to a break in the respiratory cycle (inspiratory or expiratory) and is a normal reflex. On the other hand, during esophageal provocation events (for example, infusion via a manometry catheter, or gastroesophageal reflux), proximal esophageal contraction and distal esophageal relaxation result in secondary peristalsis, which occurs independent of central swallowing mechanisms (Fig. 3.2) [197–199]. These reflexes prevent the ascending spread of the bolus and promote descending propulsion to ensure esophageal clearance.

Secondary esophageal and UES contractile reflexes have been compared in 33 weeks and 36 weeks mean postmenstrual age premature infants [200]. The occurrence of secondary peristalsis was volume dependent, and the characteristics matured with age. Furthermore, as the premature infant grew older, the occurrence of secondary peristalsis increased significantly with increments in dose volumes of air or liquids. Thus, it appears that vago-vagal protective reflex mechanisms that facilitate esophageal clearance are present in healthy premature neonates, but these mechanisms mature with age.

Esophageal provocation can also result in an increase in UES pressure [198, 199]. This reflex is the *esophago-UES-*

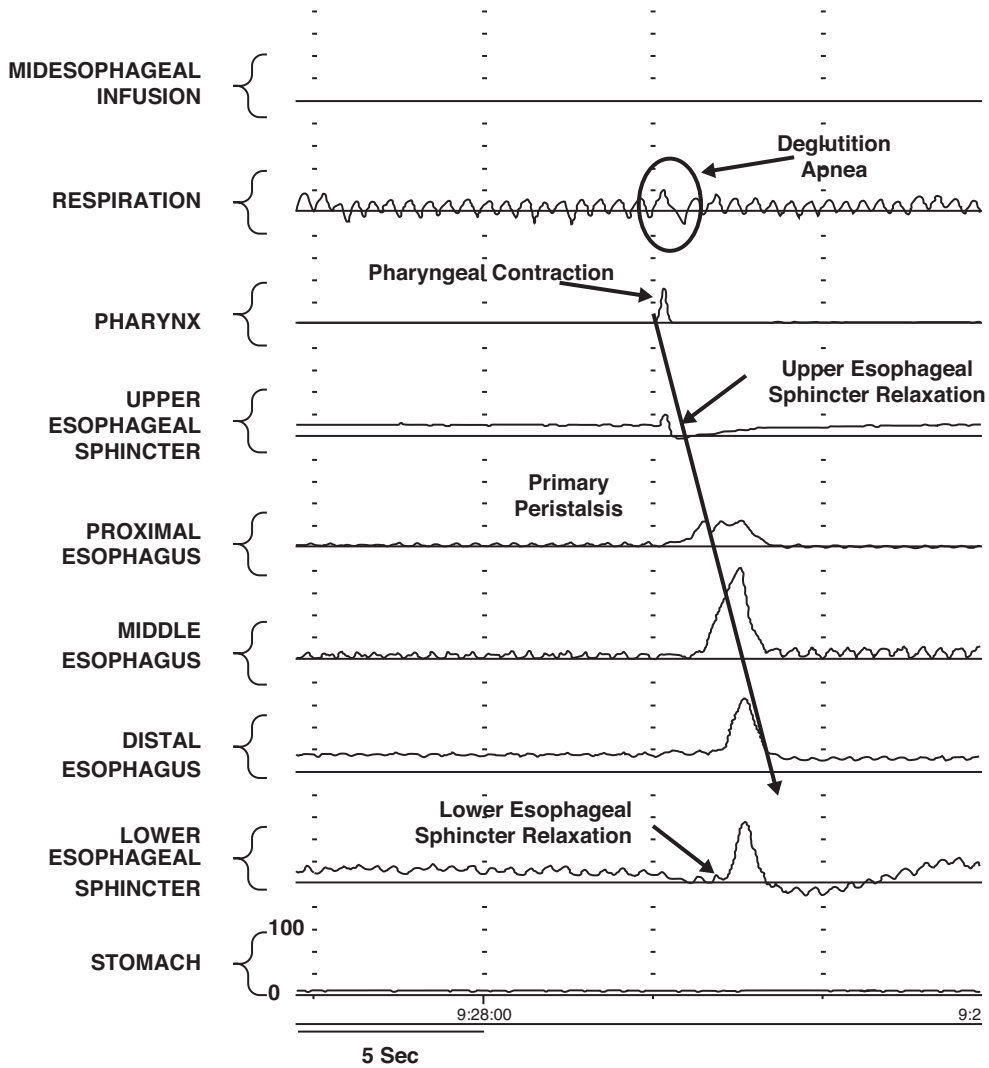

Fig. 3.1 An example of spontaneous primary esophageal peristalsis in a premature infant evoked upon pharyngeal contraction. Such sequences facilitate swallowing and esophageal clearance. Note the brief respiratory modification and deglutition apnea during pharyngeal waveform suggesting cross-communications between the pharynx and airway

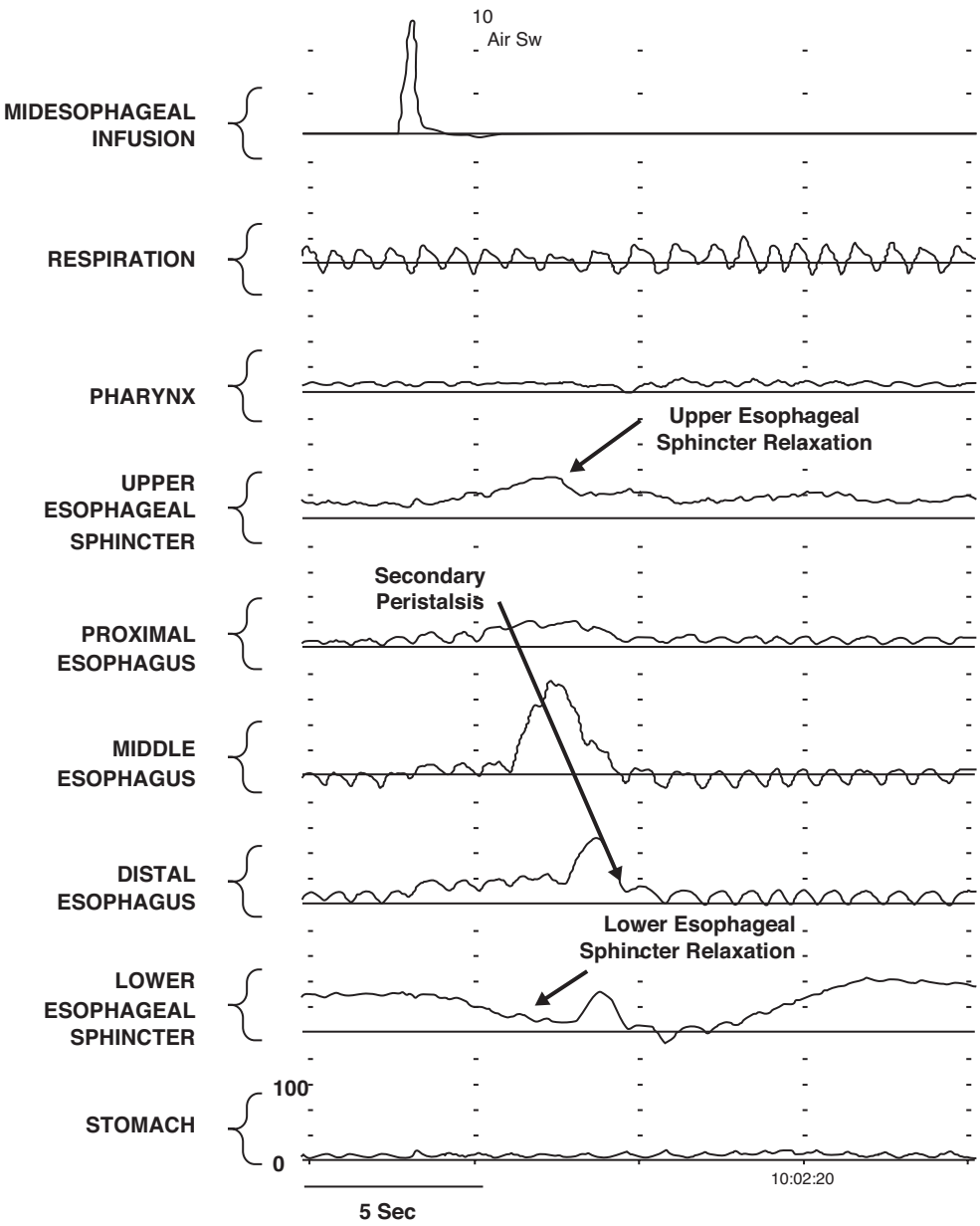

Fig. 3.2 Swallow-independent secondary esophageal peristalsis in a premature infant in response to a mid-esophageal infusion. Such sequences are evoked during esophageal provocations and contribute to esophageal and airway protection by facilitating clearance

contractile reflex, which is mediated by the vagus. The UES contractile reflex has been studied in premature infants and, like secondary peristalsis, is volume dependent and matures during prenatal stages. This reflex may protect the airways by limiting the proximal extent of the refluxate during spontaneous gastroesophageal reflux events. The summary of aerodigestive reflex characteristics in health and disease is shown in Table 3.1.

Aerodigestive Motility Reflexes, Threatening Events, and Sleep States

Neonates and infants sleep for more time than they are awake and this ratio decreases in favor of more wakeful periods during maturation. Sleep is a physiological state wherein there is excessive inhibition or suppression of the effects of somatic and visceral stimuli from reaching central neural pathways, regulated by the reticular activating system and may be related to elevated sensory thresholds. However, the organism is vulnerable to internal and external threats, and must respond to maintain homeostasis. Aerodigestive provocation and risk for aspiration are frequent threats in infants; such risks are more common in situations of immaturity, neuropathology, chronic lung disease, gastroesophageal reflux disease, and/or during sleep. Newborn infants may sleep up to 80% of the time and arousals from sleep have been considered to be important central awareness and protective responses in infants [201]. Premature infants can perceive visceral sensitivity during anterograde esophageal

Table 3.1 Infant esophageal motility characteristics in health and disease

Organs	Controls	Preterm	Neurological disorders	HIE in full term
Upper esophageal sphincter (UES)	• Intact airway protective contractile and relaxation • Contraction, most common response to esophageal stimulation • Relaxation, most common response to pharyngeal stimulation	• Intact contractile and relaxation kinetics	• Increased UES resting pressure • Increased maximum contractile pressure • Increased contraction magnitude • Most rapid response sensitivity resulting in contractile reflex	• Increased magnitude of UES contraction
Peristaltic reflexes	• Recruited upon stimulation of the mid-esophagus • Secondary peristalsis is primary mechanism • Pharyngeal reflexive swallowing during pharyngeal stimulation	• Primary peristalsis is recruited more frequently withesophageal bolus • Secondary peristalsis increases with maturation	• Prolonged reflex response latency to liquids • Secondary peristalsis is the primary clearance mechanism upon esophageal stimulation	• Secondary peristalsis is the primary clearance mechanism upon esophageal stimulation
Esophageal body	• Exhibit anterograde muscle contractile activity in response to a bolus	• Decreased peristaltic velocity • mplitude and esophageal contraction duration are similar with controls	• Increased amplitude and prolonged duration of esophageal contraction	• Prolonged peristaltic duration • Increased polymorphic waveforms
Lower esophageal sphincter (LES)	• Relaxes during either basal or adaptive swallowing	• Relaxation reflexes intact • As infant matures, relaxation magnitude increases and duration decreases	• *Decreased* duration of LES relaxation • *Increased* nadir duration	• Lower (−) nadir pressure and prolonged duration of relaxation

transit as in swallowing and this is associated with activation of cortical and subcortical arousal mechanisms [202]. Perceived threat is greater with GER events extending proximally and retrograde transit resulting in heightened excitation and prolonged activation of cortical pathways [202].

Lack of arousals does not, however, mean inadequate aerodigestive protection. Other aspects of regional and local reflexes contribute to redirect a stimulus away from the introitus and prevent its ascending spread while maintaining sleep. Sensory effects of esophageal mechanosensitivity, osmosensitivity, and chemosensitivity are progressively advanced in sleep during maturation as evidenced by increased frequency recruitment of motor responses [203]. With growth and development, premature infants handle provoking stimuli more effectively and avoid sleep disturbances as they age, which may also be attributed to somatic changes in esophageal length reducing proximal migration of the stimulus. Sleep modulates the frequency recruitment and type of aerodigestive reflexes [203].

The incidence of apparent life-threatening events varies from 0.5 to 6% and accounts for about 1% of emergency visits [198, 204, 205]. In such infants, prolonged spontaneous respiratory disturbing events as evident by apneic events >2 s or at least two missed breaths, or changes in cardiac and respiratory rhythms have been associated with ineffective esophageal motility, which suggests dysfunctional regulation of swallow-respiratory junction interactions, activation of exaggerated pharyngo-glottal closure reflexes, or esophago-glottal closure reflexes. During feeding or during gastroesophageal reflux events, the bolus stimulates the activation of pharyngo-esophageal reflexes primarily, and can also secondarily activate cardiorespiratory and airway reflexes. Thus, a stimulus can provoke reflex responses within the organ (pharynx or esophagus) and also in airway or cardiac rhythms, particularly when the bolus material is in the vicinity of proximal aerodigestive tract [204]. Such responses are attributed to vigilance, arousals, and cross-systems interactions.

In summary, the frequency of GER events as well as physical and sensory symptoms is lower during sleep [206]. Sleep is associated with inhibition of the reticular activating system, resulting in elevated sensory threshold. The frequency of physical and sensory symptoms is lower during sleep. Cardiorespiratory symptoms during sleep are likely to be related to non-GERD causes. Mechanisms of symptom generation and adaptation are different during sleep and wake states, underscoring the differential ability of infants to perceive esophageal sensitivity during sleep [206].

Mid-esophageal stimuli provoke arousals associated with altered esophageal responses more than 50% of the time; these are increased respiratory arousals and frequent sleep state changes [202]. However, the latency, response duration of peristaltic reflexes, and UES contractile reflexes are prolonged and more frequently associated with cortical hyper-

vigilance [202]. With maturation, an ability to handle provoking stimuli and avoid sleep disturbances occurs and may be attributed to brainstem maturation or an increase in esophageal length that prevents more proximal migration of provocative stimuli [203]. Though the sensitivity to stimuli is well developed in premature infants, the frequency of defense mechanisms is better with maturation [203].

Effects of Maturation on Foregut-Airway Interactions

Pharyngeal stimulation occurs primarily during oral bolus propulsion or during proximal ascent of the gastroesophageal refluxate, and pharyngo-esophageal reflexes are activated. Pharyngeal reflexive swallow is the most frequent response, often associated with a pharyngo-lower esophageal sphincter-relaxation reflex. The sensory-motor properties of pharyngeal reflexive swallowing are similar during longitudinal maturation but LES relaxation properties accelerate and become robust with age implying the maturation of inhibitory pathways at the LES [207]. Furthermore, the infant esophagus can distinguish gas vs. liquid stimuli, in that the liquids result in increased recruitment and magnitude of LES relaxations, as well as decreasing their durations [207]. Thus, with age, liquids are cleared more efficiently and peristaltic reflexes are more robust in function, and may be related to better coordination of excitatory and inhibitory pathway functions.

Comparing the development and maturation of the upper esophageal sphincter and esophageal body across the age spectrum, we found that the preterm infants at a young age had a decreased frequency of solitary propagated swallows/minute compared to full-term infants [208]. In addition, when compared with adults, infants showed decreased resting UES tone that was evident among all groups of infants, decreased magnitude of UES relaxation, increased duration of UES relaxation, increased UES relaxation nadir, and increased UES residual nadir pressure [193]. Infants also generally had lower esophageal contractile amplitudes compared with adults, but these were similar among the infant groups. Peristaltic velocity from proximal to distal esophagus was slower for preterm infants across longitudinal maturation, and remained slower when compared at later age with full-term-born infants [193]. Thus, all these neuromotor activities suggest that sensory-motor neuromotor and muscular functions continue to develop and adaptational responses mature through infancy and childhood.

When esophageal-stimulation-induced reflexes were studied in preterm-born infants at term-equivalent postmenstrual age, it was found that former very-preterm infants have characteristics approaching those of infants born closer to term with regard to UES contractile reflex latency and duration. Response latency of the UES contractile reflex decreases with increasing gestation; thus, with increased prematurity comes increased risk for aspiration [208]. Active LES relaxation reflex duration is prolonged, i.e., increased duration to achieve full LES relaxation was noted with liquid stimuli (vs. air) in former very-preterm infants but not for later-born preterm infants. With increasing birth gestation comes decreasing LES relaxation response latency in response to liquid stimuli and prolonged duration of active LES relaxation. Collectively, these discoveries reveal that the potential modulators to the underlying mechanisms may include myelination or consequences and comorbidities of prolonged neonatal intensive care unit (NICU) stress [208].

Effects of Perinatal Asphyxia on Foregut Motility Mechanisms

Perinatal asphyxia has effects on central and enteric nervous systems, as well as on regulation of aerodigestive biorhythms. Infants with birth asphyxia are at increased risk for oromotor dysphagia, pharyngo-esophageal dysmotility, and gastrointestinal dysmotility, so that chronic tube feeding strategies due to inadequate peristaltic coordination. Surviving infants are at increased risk for gastroesophageal reflux and emesis, as well as for anterograde or retrograde aspiration. The mechanisms for such maladaptation are now increasingly clear. For example, infants with perinatal asphyxia differ from healthy controls in demonstrating increased resting UES tone, decreased LES nadir pressure, increased LES nadir duration, increased peristaltic duration, more frequent polymorphic waveforms, more frequent occurrence of secondary peristalsis, and increased magnitude of UES contractile reflex [209]. Potential mechanisms of dysfunction include ischemia-reperfusion injury to brain stem mediated adaptational responses, or inappropriate alteration of neurotransmitter release and or activity.

Effects of Perinatal Asphyxia on Adaptive Swallowing Reflexes

Infants with perinatal asphyxia have dysphagia and frequent aerodigestive problems, the mechanisms of the symptoms remain difficult to clarify. Therefore, the available diagnostic work up or modifications in therapies are questionable. To understand the mechanisms of feeding dysfunctions, we studied infants with perinatal asphyxia [210]. Notably, infants with hypoxic ischemic encephalopathy (HIE) compared with healthy controls had increased UES resting tone and increased occurrence of Pharyngo-UES contractile reflexes in lieu of pharyngeal reflexive swallow which is the most frequent reflex in health [210]. In addition, these infants, displayed increased recruitment of pharyngeal peaks per stimulus, delayed restoration of aerodigestive quiescence, increased presence and duration of polymorphic waveform activity, decreased proximal esophageal contractile amplitude and increased contractile duration, increased mid-esophageal contractile duration, decreased LES resting tone, decreased

frequency of Pharyngo-LES relaxation reflex, and increased LES nadir duration [210]. Potential mechanisms include summation of contraction in a phenomenon similar to tetanic contraction, or hypoxic exposure blocking the release of acetylcholine at the neuromuscular junction [210].

Gastric Motility in Human Neonates

Scant information is available about receptive relaxation in the fundus in human neonates. Ultrasound studies of the fetal stomach detected gastric emptying as early as 13 weeks of gestation [211], and the length of gastric emptying cycles in fetuses increases just prior to birth [212]. The rate of gastric emptying is not influenced by non-nutritive sucking, but is influenced by calorific value and stress: calorically denser formula accelerates gastric emptying and extreme stress, like systemic illness, delays gastric emptying [213].

Evaluation of Gastroesophageal Reflux

Gastroesophageal reflux (GER) is the physiological passage of gastric contents into the esophagus affecting 10.3% of infants in freestanding children's hospitals in the USA [214]. Under or over diagnoses of GER has been noted to be associated with an increased length of stay and hospital costs [214]. To aid the evaluation of troublesome symptoms consistent with GER disease (GERD), esophageal pH-Impedance studies along with symptom correlation are the current gold standard. Esophageal manometry may aid in characterization of potential mechanisms that lead to symptom occurrence utilizing a pH-impedance probe that is passed trans-nasally through the esophagus providing the ability to identify detailed physico-chemical and spatio-temporal characteristics of refluxate. Each ascending refluxate that is observed during the 24 h pH-impedance tracings is distinct. The content can be acidic (pH < 4) or weakly acidic (pH > 4). It could also be liquid reflux, a gaseous reflux, or a combination of the two. The proximal extent and the duration of refluxate are other varying parameters and may be related to esophageal peristaltic motility reflexes, bolus clearance mechanisms and acid-neutralization mechanisms.

When the relationship between height and duration of specifically acid reflux was studied, it was found that acid reflux was predominantly reaching the distal esophagus, more frequently than ascending proximally [215]. However, the occurrence and frequency of symptoms and the height and clearance time of the acid are directly related [215]. Similarly, it has been shown that symptoms in GERD not only depend on the proximal extent and duration of dwell of refluxate but also on the physical and chemical composition of reflux events [216]. Additionally, feeding plays a crucial role in the occurrence and frequency of GER [217]. Prolonged feeding durations and slower flow rates are associated with a decreased frequency of GER. While observing feeding methods, orally fed infants had more GER than gavage fed infants [217].

Although the relationship between symptoms and reflux is still unclear in preterm neonates, many attempts have been made to better the diagnostic techniques for the proper diagnoses of GER—hoping to ease the burden of troublesome symptoms.

Small Intestinal Motility in Human Neonates

In 28–37 weeks of gestation preterm infants, the majority of the contractile activity in the small intestine consists of clusters of low-amplitude contractions that propagate for a short distance or not at all [218]. Propagating, cyclical MMCs with clearly defined phases develop between 37 weeks and term [219].

In adults, motilin, which is released from mucosal cells in the duodenum, is an important regulator of MMCs, and initiation of phase III of the MMC (intense rhythmic contractions) in the antrum is correlated with an increase in plasma concentrations of motilin [7]. In human neonates, fasting plasma concentrations of motilin are similar to those in adults, but there are no detectable increases in motilin levels coincident with the initiation of MMCs [220]. Erythromycin triggers initiation of the MMC in preterm infants whose gestational ages exceed 32 weeks [221]. Administration of erythromycin fails to trigger MMCs in infants younger than 32 weeks, suggesting immaturity of the neuronal circuitry mediating MMCs or that the motilin receptor cannot be activated by erythromycin at these ages.

Gastroduodenal Motility in Human Neonates

Migrating motor complexes (MMCs) during fasting assist in luminal content propagation throughout the gastroduodenal tract and are induced by both motilin receptors and non-motilin receptors, and are likely hormonal or neurally regulated [221–224]. In infants, during phase III, motilin receptor-mediated MMCs occur by 32 weeks of gestation, while non-motilin-mediated responses are not observed until term [221]. In infants with immature foregut motility, these MMCs are often rare and/or non-propagating, but improve with maturation [218–220, 225, 226]. Erythromycin, a motilin receptor agonist, has been shown to increase MMC frequency and amplitude of the burst, and thus accelerate gastric emptying [227–229]. Although erythromycin has been proven to improve gastroduodenal motility in healthy preterm infants [221, 230, 231], it does not improve gastrointestinal function in feeding intolerant preterm infants [232].

Developmental Colonic Motility in Human Neonates

There is a marked lack of data on colonic motility in neonatal humans owing to technical limitations and ethical concerns.

Mechanisms Controlling Motility in Human Infants and Children

As in laboratory animals, enteric neurons and ICC appear to be essential for normal motility in human infants and children. An essential role for enteric neurons in gut motility after birth is best demonstrated by Hirschsprung's disease, where the segment lacking enteric neurons is unable to propel gut contents. Genetic alterations of Kit, and reduced ICC density, have recently been directly linked to a severe case of idiopathic constipation and megacolon in a 14 year old child [233], demonstrating the critical relationship between Kit function, ICC development and functional gastrointestinal motility patterns in the human intestine. Other studies have reported alterations in ICC networks in Hirschsprung's disease, chronic idiopathic intestinal pseudoobstruction and pediatric constipation [234–240], but these defects may be an indirect consequence, rather than the cause, of the gut dysfunction. However, it is important to remember that motility disorders in children are not necessarily due to defects in neurons or ICC. For example, X-linked intestinal pseudo-obstruction has been shown to be a myopathy, and is caused by mutations in FLNA, which encodes filamin-A [241]. Studies in mice have also shown that defects in the gut muscle can also result in motility defects [242].

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Visceral Sensitivity

4

Adrian Miranda

The central nervous system (CNS) continuously receives information from the gastrointestinal (GI) tract related to the state of the organs and to the content of the gut. CNS must integrate this information with input from other organs or from the environment in order to initiate suitable responses. The amount of information is so high that normally most of this information originating from the GI tract do not reach the level of conscious perception and is processed in the brainstem, below cortical level. Sensations such as hunger, fullness, satiety, bloating, focal gut distension, and need to defecate (as well as their physiological correlates, i.e., gastric and rectal distension) that implicate an adapted behavior do reach the cortex.

Gastrointestinal pain is reported as dull, vague, and diffusely localized. Stimuli for visceral pain include distension or traction on the mesentery as well as ischemia and inflammation that stimulate afferent nerve terminals. Cutting and crushing (e.g., mucosal biopsy sampling) of the GI tract are not perceived when applied to conscious subjects.

Visceral pain alerts us of potential or actual tissue damage, but, in many cases, there is no obvious underlying cause for the pain. Chronic visceral pain can negatively impact quality of life and lead to significant disability. Heightened visceral sensitivity or hypersensitivity is considered a primary characteristic of functional gastrointestinal disorders (FGIDs) [1]. This chapter covers the physiology of visceral sensitivity and reviews the pathophysiology and potential mechanisms of visceral hypersensitivity.

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Neuroanatomy and Processing of Gastrointestinal Tract Sensitivity

Visceral Innervation

Similar to somatic sensitivity, gut afferent signals reach conscious perception through a three-neuron chain (Fig. 4.1). Extrinsic innervation of the GI tract is composed of vagal afferents and spinal sensory afferents that include the lumbar splanchnic and sacral pelvic nerves. The cell bodies of the splanchnic and pelvic afferents are located within the thoracolumbar (T10-L1) and lumbosacral (L6-S1) dorsal root ganglia (DRG), respectively [3]. These nerves contain efferent fibers that transmit information from the CNS to the gut and afferent (or sensory) fibers that transmit information from the viscera to the CNS. Visceral afferent fibers are composed of sensory neurons that, arising from the cell body, project two neurites, one as peripheral fiber and one as central fiber. Visceral afferents participate in the transmission of sensory signals from the periphery to the CNS, allowing communication from the gut to the brain via the "brain-gut axis."

Vagal Innervation

The vagus nerve (cranial nerve X) is the longest cranial nerve and travels from the brainstem to the colon, innervating major visceral organs such as the heart, the lungs, and the gastrointestinal (GI) tract, including the esophagus, stomach, small intestine, cecum, and proximal colon. It is also a major component of the parasympathetic nervous system that, along with the sympathetic nervous system, makes up the autonomic nervous system (ANS). Sensory afferent neurons predominate numerically in the vagus nerve with 80% of the vagus nerve fibers being afferent fibers while only 20% are efferent [4]. Vagal afferent fibers can sense a variety of interoceptive stimuli including pressure, chemical, osmotic, and inflammation.

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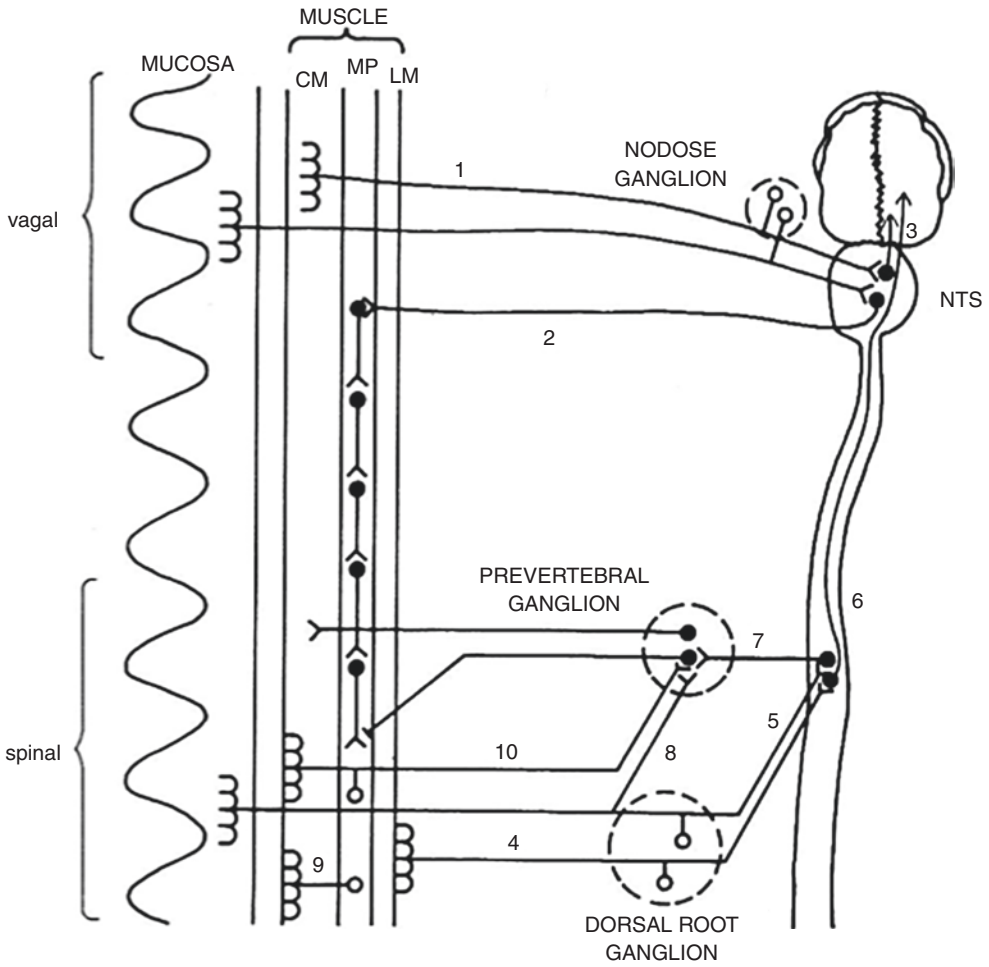

Fig. 4.1 Spinal and vagal innervation of the gastrointestinal tract. *Upper portion*: sensory information from vagal receptors is carried by vagal afferent nerves (1) with nerve cell bodies in the nodose ganglion to the sensory nucleus tractus solitarius (NTS). Second-order neurons transmit the information either to higher centers in the central nervous system (CNS) (2) or via efferent vagal fibers (3) in the form of vago-vagal reflexes back to the enteric nervous system (ENS). *Lower portion*: sensory information from spinal receptors located in the mucosa, muscle, or serosa is carried by spinal afferent fibers (4) with nerve cell bodies in the dorsal root ganglion to second-order neurons in the spinal cord. Second-order neurons transmit the information either to the CNS (5) or via sympathetic nerves (6) to prevertebral ganglia, to the ENS, and to the gastrointestinal muscle (spinal reflex). Collaterals of spinal afferents also form short reflex loops with postganglionic sympathetic nerves in the prevertebral ganglion (7). In addition to spinal afferents, sensory structures with nerve cell bodies are also located within the intestinal wall (8, 9). *CM* circular muscle layer, *LM* longitudinal muscle layer, *MP* myenteric plexus [2] (Modified from Mayer EA, Raybould HE. Role of visceral afferent mechanisms in functional bowel disorders. *Gastroenterology*. 1990;99(6):1688–704, with permission)

Luminal nutrients trigger vago-vagal reflex to initiate digestion through efferent fibers that are involved in the control of motility and secretion in the gastrointestinal lumen [5]. Preganglionic neurons of vagal efferents originate in the dorsal motor nucleus of the vagus (DMNV), below the nucleus tractus solitarius (NTS) where vagal afferents project to. The NTS acts as a "relay station" that communicates with higher centers such as the locus coeruleus (LC), thalamus, amygdala, and the hypothalamus. The DMNV, along with the NTS and area postrema, forms the dorsal vagal complex of the brainstem, a major reflex center of the ANS.

Spinal Innervation

Visceral afferents running in the spinal cord are referred to as "spinal afferents" while the term "sympathetic innervation" is restricted to spinal efferent innervation [3]. Spinal innervation is provided by the greater splanchnic nerve that forms three main ganglia from which they distribute to the viscera: the celiac ganglion distributes nerves to the esophagus, stomach, and duodenum; the superior mesenteric ganglion distributes nerves to the intestines down to the ascending colon; and the inferior mesenteric ganglion distributes nerves to the colon from the hepatic flexure to the rectum. Sensory affer-

ent neurons account for 10–20% of fibers in spinal afferents, and cell bodies are located in dorsal root ganglia (DRG) at the cervical, thoracic, and upper lumbar spine [3]. Their central processes terminate in the dorsal horn of the spinal cord. Spinal afferents transmit information on potentially noxious mechanical or chemical stimuli and are involved in sensation of visceral pain [6]. However, it should be kept in mind that in the CNS, vagal inputs likely integrate with the inputs from the spinal pathways, and therefore perception of pain is the result of modulation of vagal and spinal inputs [7]. Vagal and spinal afferents are predominantly unmyelinated C-fibers or thinly myelinated A-delta fibers with low conduction velocity. The distal third of the colon is innervated by pelvic nerves and pudendal nerves. This area of the GI tract receives dual spinal innervation from splanchnic and pelvic afferents [7]. Pelvic spinal afferents connect to the periphery through parasympathetic nerves innervating the pelvic organs, and their cell bodies are located in the DRG.

Sensory Terminals

At the level of the gastrointestinal tract, sensory neurons and enteroendocrine cells (EEs) can transduce internal or external signals to a format that the nervous system can interpret [8]. Gut sensory terminals and receptors include mechanoreceptors, chemoreceptors, thermoreceptors, and nociceptors [9]. Recently, most evidence points toward polymodality of the visceral receptors.

Vagal Terminals

The transmission of signals from the vagus nerve begins at the afferent nerve terminals involving chemosensitive and mechanosensitive neurons. Three different vagal nerve terminals have been described and exhibit discrete structural characteristics and distribution properties. These include intraganglionic laminar endings (IGLEs), intramuscular arrays (IMAs), and mucosal afferent endings [8]. IGLEs are situated at the surface of myenteric ganglia and are activated by tension of the gut wall. They are believed to transmit signals that are perceived as non-painful such as the sensation of fullness. IMAs are concentrated in the upper gastrointestinal tract and located within the circular or longitudinal muscle layers. They appear to be stretch receptors and are in close contact with the interstitial cells of Cajal. Mucosal projections extend into the lamina propria and can respond to light mucosal stroking as well as nutrient influx [10]. Interestingly, Miranda et al. have demonstrated that gastric injury, through fundus ligation, can lead to aberrant remodeling of IMAs and change the mechanotransduction properties of these vagal afferents [11].

Spinal Terminals

Spinal terminals are less well characterized and are anatomically not clearly identifiable. Studies have shown that mechanonociceptors mediating transduction of pain evoked after high-amplitude distension are spinal afferents [8]. Fine "varicose branching axons" that appear as specialized endings can be demonstrated in the serosa and mesentery, around blood vessels [10, 12]. The peripheral projections of spinal afferents innervate all layers of the colon and rectal wall with multiple, distinct endings identified to date. In humans, these include mucosal afferents, muscular afferents, muscular/mucosal afferents, vascular endings, and mechanically insensitive afferents (MIAs) [13]. Interestingly, MIAs, under normal physiological conditions, do not encode noxious mechanical stimuli, but can be sensitized after brief exposure to inflammatory mediators [14].

Enteroendocrine Cells (EEs)

Endoderm-derived enteroendocrine cells are distributed in the crypts and villi of the gastrointestinal mucosa and account for approximately 1% of the total gut epithelium cell population. These specialized cells sense luminal content, producing and releasing hormones and signaling molecules that modulate a variety of physiological GI functions. They resemble sensory cells in the lingual epithelium taste buds. They have an apical tuft of microvilli exposed to the luminal content and release bioactive molecules, including serotonin (5HT), and hormones such as cholecystokinin (CCK), leptin, orexin, and ghrelin. Enteroendocrine cells are involved in chemosensitivity and respond to nutrients, playing a key role in the glucose homeostasis [15]. It has also been shown that the gut is able to "taste" odorants, spices, and bitter taste via enteroendocrine cells [16]. EEs contain 5HT that is known to be released in response to endogenous chemical stimuli [17], exogenous dietary amines, tastants, or microbiota-derived metabolites (e.g., short-chain fatty acids) [18]. They play a key role in intestinal mechanosensitivity in response to mucosal deformation. By acting on $5HT_3$ receptors, 5HT release is involved in the peristaltic reflex through activation of intrinsic neurons (IPAN) and in visceral sensations by activating mucosal endings of sensory afferents. EEs, thus, represent the first level of integration of information from the lumen and when stimulated, they release signaling molecules that activate afferent terminals, particularly from the vagus nerve. Vagal afferents then transmit stimuli to the NTS in the brainstem, which represents a component of the bidirectional communication known as the brain-gut axis. Alterations in this bidirectional communication can negatively impact gut function, including motility, luminal secretion, blood flow, and neuronal sensitization. Such alterations may also impact gut homeostasis, leading to chronic visceral hypersensitivity.

Receptors on Visceral Afferents Involved in Visceral Pain

A large number of bioactive substances and chemical mediators have been implicated in the sensory signal transduction of visceral pain. These substances produce their effects by three distinct processes: (1) direct activation of a receptor, which generally involves the opening of ion channels; (2) sensitization, which results in afferent hyperexcitability; and (3) through genetic change that alters the phenotype of the afferent nerve (alterations in the expression or activity of channels and receptors). Figure 4.2 depicts the complexity of receptors and bioactive substances involved in visceral sensitivity in terminal afferents.

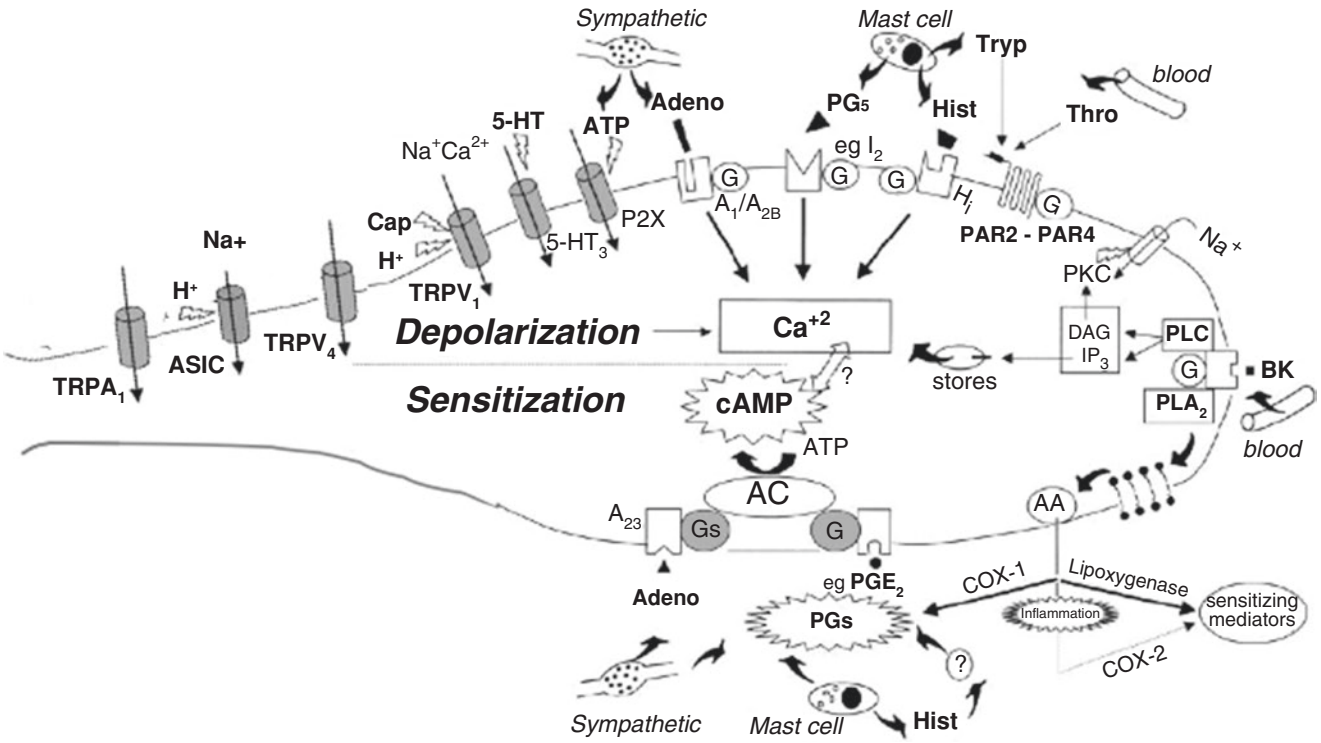

Fig. 4.2 Some of the potential receptor mechanisms underlying activation (depolarization) and sensitization at the terminal of a gastrointestinal sensory afferent [19, 20]. Separate mechanisms underlie activation and sensitization. Some mediators such as serotonin (5HT) cause activation via 5HT3 receptors, whereas others like prostaglandin E2 (PGE2) acting at Prostaglandin E2 receptors (EP2) sensitize visceral afferent responses to other stimuli. Still others, for example, adenosine (Adeno), cause both stimulation and sensitization, possibly through distinct receptor mechanisms. Bradykinin (BK) has a self-sensitizing action, stimulating discharge through activation of phospholipase C (PLC) and enhancing excitability via prostaglandins (PGs) after activation of phospholipase A2 (PLA2). Inflammatory mediators can be released from different cell types (e.g., sympathetic varicosities, mast cells, lymphocytes, and blood vessels) present in or around the afferent nerve terminal. 5HT, adenosin triphosphate (ATP), H+, and capsaicin (Cap) can directly activate cation channels such as TRPA1 [21], TRPV1 [21–23], _ENREF_9 P2X [24], TRPV4 [22, 23], and ASIC [25, 26]. Adenosine, histamine, prostaglandins (not PGE2), and proteases such as mast cell tryptase (Tryp) and thrombin (Thro) act on G-protein-coupled receptors (PAR-2 [27] and PAR-4 [28]) leading to a calcium-dependent modulation of ion channel activity. TRPV4 is co-localized with PAR-2 and mainly in colonic sensory neurons with an important interaction in visceral hypersensitivity. Cannabinoids produce peripheral analgesic effect by activation of TRPA1 and indirect activation of TRPV1 [29]. Sensitization, however, may be mediated by increased intracellular cyclic adenosin monophosphate (cAMP). Adenosine and PGE2 can generate cAMP directly through G-protein-coupled stimulation of adenylate cyclase (AC). In contrast, histamine (Hist) may act indirectly through the generation of prostaglandins. The actions of cAMP downstream are currently unknown but may involve modulation of ion channels, interaction with other second messengers (e.g., calcium), or even changes in receptor expression. *AA* arachidonic acid, *ASIC* acid-sensing ion channels, *COX-1* and *COX-2* cyclooxygenase-1 and cyclooxygenase-2, *DAG* diacylglycerol, *IP3* inositol 1,4,5-trisphosphate, *PARs* protease-activated receptors, *TRPA1* transient receptor potential cation channel A1, *TRPV1* and *TRPV4* transient receptor potential cation channel subfamily V member 1 and 4 [20] (Modified from Kirkup AJ, Brunsden AM, Grundy D. Receptors and transmission in the brain-gut axis: potential for novel therapies. I. Receptors on visceral afferents. *Am J Physiol Gastrointest Liver Physiol*. 2001;280(5):G787–94, with permission)

Central Pathways of Visceral Sensitivity

Vagal Central Pathway

Vagal afferents project to the NTS in the brainstem, which displays a viscerotopic organization [30]. The NTS acts as a relay for the enormous amount of information arriving from abdominal viscera and, in turn, sends out a network to the motor nucleus (nucleus ambiguus (NA) and dorsal motor nucleus (DMN), providing the circuits for basic reflexes of the GI tract. The NTS also projects fibers to higher centers: (1) information is relayed to parabrachial nuclei (PBN), which in turn are connected to higher brain centers (amygdala system), and (2) long projections terminate in the thalamus, hypothalamus, and anterior cingulate cortex (ACC) and insular cortical regions regulating arousal, emotional, autonomic, and behavioral responses (see below) [3, 7]. The DMN of the vagus nerve lies medial to the NTS and integrates input from the area postrema (AP), hypothalamus, amygdala, raphe nuclei, olfactory system, and reticular formation to transmit vago-vagal feedback to the GI tract. More than 80% neurons in the DMN project to GI organs and most are modulated by glutamatergic, cholinergic, and GABAergic inputs from the NTS [31].

Spinal Central Pathway

After entering the spinal cord, first-order neurons synapse in the dorsal horn and second-order neurons project to the brain through a number of different tracts: spinoreticular, spinomesencephalic, spinohypothalamic (which activate unconscious reflex autonomic responses), and spinothalamic [32]. The spinothalamic tract, the most important pathway involved in conscious sensations, is classically subdivided into lateral spinothalamic tract that mediates the sensory-discriminative aspects of pain (localization, intensity) and medial spinothalamic tract mediating the motivational-affective aspects of pain (suffering, unpleasantness). Lateral spinothalamic tract projects to the ventral posterior lateral nucleus of the sensory thalamus, from which information is relayed to the somatosensory cortex (SI and SII) and the insula cortex. The medial spinothalamic tract projects to medial dorsal and ventral medial posterior nuclei of the thalamus and mainly projects, with spinoreticular, spinomesencephalic, and spinohypothalamic tracts, onto brainstem and midbrain structures such as reticular formation, NTS, periaqueductal gray (PAG), PBN, and hypothalamus. From these structures, third-order neurons project to areas involved in emotional functioning, like the anterior cingulated cortex (ACC) and the orbitomedial prefrontal cortex (PFC). Animal studies have shown that the spinal dorsal column (dorsal funiculus) seems to also play an important role in viscerosensory transmission, especially in nociceptive transmission, but evidence in humans is limited and discussed on the basis of the effectiveness of midline myelotomy in visceral pain due to cancer [33].

Central Processing of Visceral Input

The main function of the somatosensory cortex (SI and SII) is to provide information about intensity and localization of the stimulus (sensory discriminative). The ACC mainly processes pain affect (unpleasantness, pain-related anxiety) and cognitive aspect of the pain experience (attention, anticipation). However, important interactions between these two systems are certainly present. The insula integrates internal state of the organism and encodes sensory and emotional information related to pain. The prefrontal cortex is believed to play a key role in the integration of sensory information and in the affective aspect of sensation. Furthermore, this region is also involved in the generation of and choice between autonomic and behavioral response patterns and has been shown to be a putative biological substrate of cognitive influences (including placebo effect) on emotions and the affective dimension of pain [32]. These brain regions are actually organized and function in complex networks. Schematically, three of them, the salience network, the emotional arousal network, and the sensorimotor network, are involved in chronic visceral pain (for a review, see [34]).

Though a number of analytic techniques and experimental paradigms have been used, quantitative meta-analysis techniques have permitted to pool the results of 18 studies conducted between 2000 and 2010 using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) in adult controls and adult irritable bowel syndrome (IBS) subjects undergoing supraliminal rectal distension (painful or not). Data from the healthy control subjects confirm that regions activated in response to supraliminal rectal distension include zones associated with visceral sensation (bilateral anterior insula, bilateral midcingulate cortex, and right thalamus), emotional arousal (right perigenual ACC), and regions associated with attention and modulation of arousal (left inferior parietal, left lateral, and right medial prefrontal cortex) [35]. There is evidence that the cerebellum is also involved in nociceptive processing and that symptoms of anxiety and depression modulate cerebellar activity during visceral stimulation [36]. Figure 4.3 summarizes the ascending pathway involved in visceral sensation after colonic stimulation.

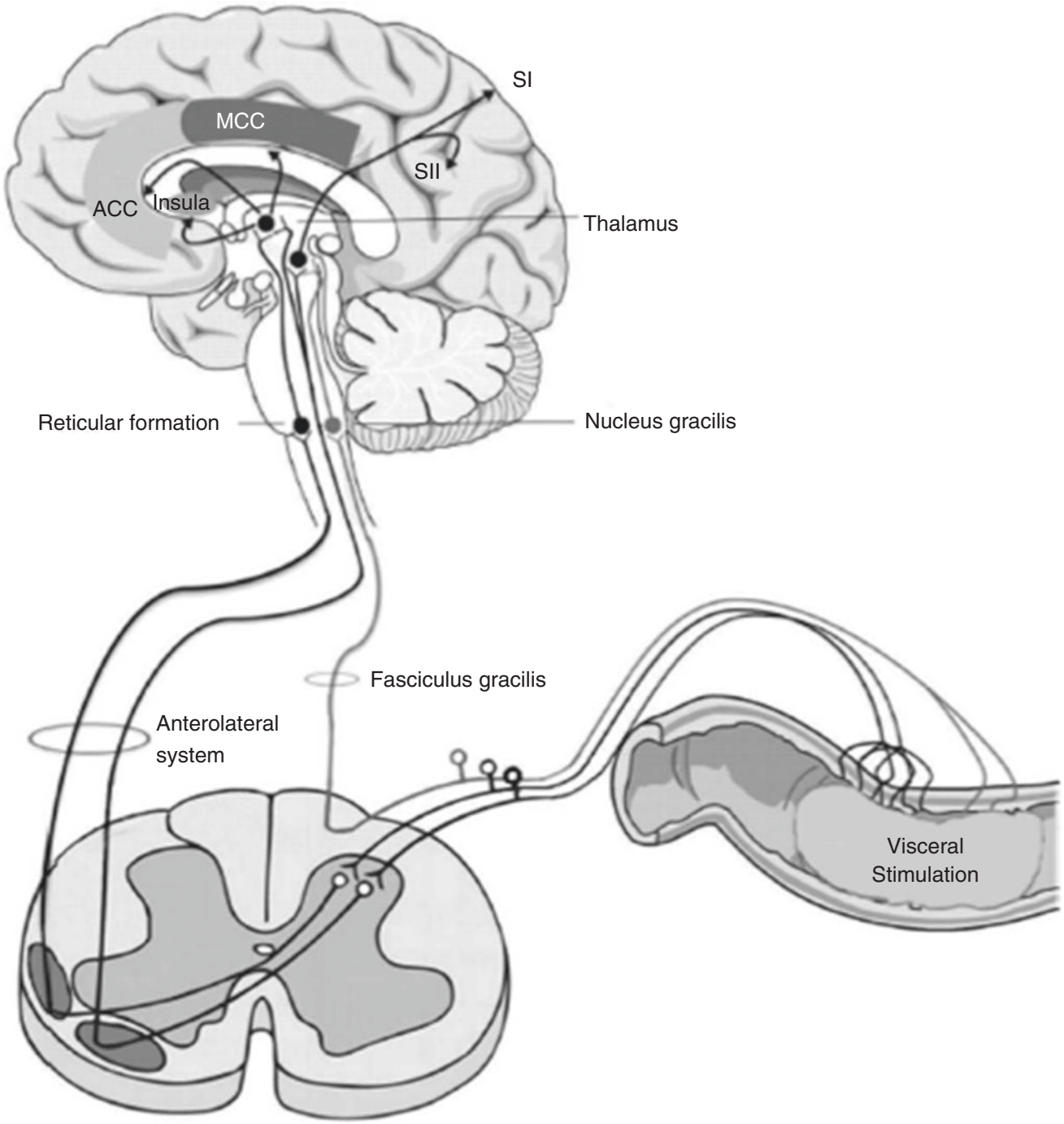

Fig. 4.3 Ascending pathway involved in nociceptive visceral sensation. Colonic stimulation activates afferent spinal terminals whose cell bodies are situated in the dorsal root ganglia. These first-order neurons project to the dorsal horn, and second-order neurons project to the brain through spinoreticular, spinomesencephalic, spinohypothalamic, and spinothalamic tracts. The first three tracts are involved in unconscious reflex behavior, whereas spinothalamic tract drives conscious visceral sensations. Third-order neurons project information to the somatosensory cortex (S1 and S2); to areas involved in emotional functioning, like anterior cingulated cortex (ACC) and the prefrontal cortex (PFC); and to the insula cortex. The spinal dorsal column (dorsal funiculus) seems to play also an important role in viscerosensory transmission, especially in nociceptive transmission

Descending Modulatory Pathways

Electrophysiological studies in animals have demonstrated descending influences on spinal nociceptive processing. Pain afferent stimuli reaching brain structures induce projections able to modulate ongoing transmission of those inputs at the level of the dorsal horn, thus achieving a descending modulatory control. Descending modulation can be inhibitory,

facilitatory, or both [3, 32]. At the cortical level, the ACC is the key region involved in this control through projections toward the amygdala and the PAG. Thus, cognitive and affective factors may exert influence on pain transmission through the ACC. The amygdala and the PAG project in turn to the locus coeruleus, the raphe nuclei, and the rostrolateral ventral medulla, which send projections to the dorsal horn and modulate the synaptic transmission of sensory information at this level. In humans, conditioned pain modulation (CPM) is believed to represent the human behavioral correlate of this descending pain modulation. While there are no published normative data for CPM, the test usually consists of an assessment of a painful stimulus on a subject followed by a second assessment at the same time as a distant, "conditioning" painful stimulus that is believed to activate the descending pathway [37]. Although pain inhibition is not universal, most subjects will experience reduced pain during or immediately after exposure to the conditioning painful stimulus. A recent study demonstrated that CPM is significantly diminished in patients with IBS compared to healthy controls, suggesting that abnormal descending pathways may play an important role in the pathophysiology of IBS [38].

Visceral Sensation

Hypersensitivity is defined as an increased sensation of stimuli (appraised by measurement of threshold volumes or pressure for first sensation or pain). *Hyperalgesia* is an increased pain sensation to a known painful stimulus and *allodynia* is a stimulus normally not perceived as being painful that becomes painful. Visceral hypersensitivity is defined as an exaggerated perceptual response (hyperalgesia and allodynia) reported to physiologic stimuli. Theoretically, visceral hypersensitivity could be the result of changes in visceral afferent signaling (reflecting increased visceral afferent input to higher brain centers) or be the consequence of alterations in central pain pathways (e.g., central sensitization or changes in brain connectivity) or a variable combinations of several pathways.

Several independent groups have reported that 75–100% of children affected by IBS have a low rectal sensory threshold for pain (i.e., visceral hypersensitivity) as compared to healthy controls [39–43]. In adults, the prevalence of visceral hypersensitivity varies from 20% [44] to 94% [45] across studies, suggesting that visceral hypersensitivity is a more reliable diagnostic marker in children than in adults.

In adults and in children, visceral hypersensitivity has been suggested to be "organ specific" with a low rectal sensitivity threshold in IBS patients [45–52], a low gastric sensitivity threshold in functional dyspepsia (FD) [53–56], and "diffuse" hypersensitivity in mixed IBS + FD patients [57].

Data from studies on visceral hypersensitivity in FGIDs, and IBS in particular, favor the heterogeneity of causes and mechanisms in a population of patients. Preclinical animal models have permitted investigations into cellular and molecular abnormalities in the gastrointestinal tract as well as in the CNS (spinal cord and brain) [58, 59]. In humans, studies have found several alterations in the rectal and colonic mucosa (inflammation, mast cell infiltration, serotonin pathway anomalies) in IBS patients. Functional brain imaging studies in adults and adolescents have demonstrated an important role for CNS dysregulation in the pathophysiology of IBS.

Peripheral Mechanisms of Hypersensitivity

Inflammation and Epithelial Permeability

While the mechanism has not been completely identified, it has been shown that FGIDs may be triggered by any type of inflammatory process including inflammatory bowel disease, celiac disease, or eosinophilic esophagitis [60–64]. Enteric bacterial infections could also have consequences on local inflammatory mediators, ECs, and mast cells [65, 66]. Low-grade inflammation has been reported in the enteric ganglia [67] and in the mucosa [67, 68] of patients with IBS. A slight increase in fecal calprotectin has also been reported in children with IBS [69]. Proinflammatory cytokine (interleukin [IL]-1, IL-6, and tumor necrosis factor alpha [TNF-α]) production by peripheral blood mononuclear cells is upregulated in patients with IBS [70]. This suggests that inflammation drives local modifications promoting sensitization, even when the inflammation has resolved. Stress via the hypothalamic-pituitary-adrenal (HPA) axis modulates the inflammation and the cytokine production. Increased intestinal permeability, either jejunal or colonic [69, 71], with alterations of the junction protein expression [72, 73] has also been linked to patients with IBS.

Mast Cells

Mast cells are abundant in the gastrointestinal tract and function as gatekeepers at the interface between the intestinal lumen and the environment around the intestinal epithelium. As an effector cell in the intestines, mast cells likely play an important role in the development of visceral hypersensitivity. When activated, mast cells communicate with epithelial, neuronal, and other immune cells and can influence visceral sensitivity by interacting with nearby intrinsic and extrinsic neurons in the GI tract. Abnormal mast cell numbers (increase [74–76] or decrease [77]) and close proximity to mucosal enteric neurites have been reported in stressed rats [74, 75] and in the colon of adult [76, 77] as well as in children [78, 79] with IBS (for a review, see [80]). Stress-related activation of the HPA axis increases mast cell number and triggers mast cell degranulation through corticotropin-releasing factor (CRF). CRF, released by the paraventricular nucleus of the

hypothalamus, activates the CRF1 receptor either in the brain or in the colonic mucosa, and modulates water and ion secretion, colonic motility, and intestinal permeability via nerve–mast cell interaction, as well as directly on intestinal epithelium (for a review, see [81]). Triggers of mast cell degranulation also include Immunoglobulin E (IgE), histamine, substance P (SP), calcitonin-related gene peptide, nerve growth factor (NGF), and lipopolysaccharide. Current evidence suggests that activity and enhanced degranulation of mast cells rather than an increased number is predominant in the pathophysiology of visceral hypersensitivity.

NGF [79, 82, 83], tryptase [27, 84], and histamine are mediators released by mast cells that activate afferent nerves and might therefore mediate the development of visceral hypersensitivity [84]. NGF evokes nerve fiber growth and pain transmission by interacting with the tyrosine kinase receptor A (TrkA). Dothel et al. have shown that patients with IBS have a higher density of mucosal nerve fibers and increased nerve outgrowth in the colonic mucosa. These findings were associated with increased expression of NGF and TrkA, both expressed on the surface of mast cells [85]. Willot et al. also reported a higher NGF content in colonic biopsies from children with diarrhea-predominant IBS [79].

Enteric Glial Cells

Enteric glial cells (EGCs) are a major component of the enteric nervous system with an extensive network throughout the intestinal mucosa that help control gut reflexes in health and also are involved in neuroinflammation. Enteric glial cells are found within the enteric nervous system and have bidirectional interactions with neurons in the gut [86–91]. They play an important role in the control of intestinal motility and are involved in intestinal epithelial barrier function to maintain intestinal homeostasis and in the repair mechanism after mechanical or inflammatory injury. EGCs can be activated by inflammation, stress, gut microbiota, or neuronal factors to release neuromodulators that act on primary afferent neurons. EGC-derived factors such as *S*-nitrosoglutathione, glial cell derived neurotrophic factor (GDNF), and Transforming growth factor beta (TGF-β) are important mediators by reducing epithelial permeability [91–94]. A recent study demonstrated the association of EGC activation and stress-induced colonic hypercontractility in an IBS-mouse model [95]. The gut microbiome has also emerged as a major component of the brain-gut axis and is now believed to contribute to the development and maintenance of visceral hypersensitivity and FGIDs [96]. It has been suggested that the microbiome could exert an effect on enteric glial function since the mucosal enteric glial cell network co-develops with the gut microbiome in early life [97, 98]. In fact, it has been shown, in animals, that colonization and homeostasis of glial cells in the intestinal mucosa are regulated by gut microbiota [99]. The gut microbiome can also influence enteric glial cells through gliomodulators, such as proteases that have also been implicated in the development of visceral hypersensitivity [100, 101]. However, more work is needed to better explain the relationship between the microbiome and EGCs and its role in FGIDs.

Serotonin Pathway

Serotonin (5HT) is secreted by enterochromaffin cells (EC) cells and plays a critical role in the regulation of GI motility, secretion, and sensation through specific receptors [102–106]. The subtypes $5HT_3$, $5HT_4$, and $5HT_{2B}$ are believed to be the main receptors involved in visceral sensitivity [107]. 5HT synthesis and bioavailability are also under dependence of the microbiota [108, 109]. More specifically, a study found that gut microbiota, derived from human and mouse, promote 5HT production through the effect of short-chain fatty acids on EC cells [108]. The 5HT transporter (SERT) terminates the actions of 5HT by removing it from the interstitial space [110–112]. Genetic polymorphism of SERT could influence visceral sensitivity: the short allele of the gene 5HTTLPR is associated with reduced 5HT transporter (SLC6A4) function and higher rating of rectal pain sensation and altered brain activation [113]. Coates et al. have reported that mucosal 5HT, tryptophan hydroxylase-1 (TpH1, the rate-limiting enzyme in the biosynthesis of 5HT) messenger ribonucleic acid (mRNA), and SERT mRNA were all significantly reduced in colonic mucosa of adult patients with IBS [114]. In children, 5HT content was found to be significantly higher in the rectal mucosa of subjects with IBS as compared to controls, and SERT mRNA was significantly lower in patients than in controls [115]. Park et al. have shown a correlation between EC cells and rectal hypersensitivity in adults, suggesting that these cells play a role in visceral sensitivity [116].

PAR-2 and PAR-4

Protease-activated receptors (PAR) are G-protein-coupled receptors that are activated after cleavage by proteases of their *N*-terminal domain, which releases a tethered ligand that binds and activates the receptor. PARs can be activated by mast cell tryptase, pancreatic trypsin, and exogenous proteinases [117]. PAR-1, PAR-2, and PAR-4 are distributed throughout the GI tract. PAR-1 and PAR-2 are involved in modulation of intestinal inflammation [118, 119], and PAR-2 [120] and PAR-4 are key players in visceral pain and hypersensitivity. Activation of PAR-2 is pronociceptive [27, 121], while PAR-4 appears to be antinociceptive [28, 122]. It is conceivable that visceral hypersensitivity may result from disequilibrium between the pronociceptive effects of PAR-2 activation (or overexpression) incorrectly counterbalanced by the antinociceptive effect of PAR-4 activation (or low expression).

TRPV1, TRPV4, and TRPA1

Members of the transient receptor potential (TRP) family of ion channels are important sensors of environmental stimuli [123, 124]. TRP vanilloid 1 (TRPV1) ion channel is expressed in primary afferent neurons. A role of TRPV1 in visceral hypersensitivity is supported by several studies in rodents showing that TRPV1 mediates visceral nociception behavior [25, 26, 125]. Miranda et al. demonstrated an increase in TRPV1 immunoreactivity in the thoracolumbar and lumbosacral DRG following 2,4,6-Trinitrobenzenesulfonic acid (TNBS) colitis in rats. In that study, a novel TRPV1 antagonist improved microscopic colitis and significantly decreased the response to colorectal distension compared to vehicle controls [126]. In human adults, a potential role of TRPV1 is supported by a higher density of TRPV1 fibers in the colonic mucosa of patients with IBS as compared to controls [126] but not confirmed by others [127]. Rectal application of the TRPV1-agonist capsaicin results in increased pain response in IBS patients [127]. Sugiuar et al. have shown that TRPV1 function is enhanced by 5HT in colonic sensory neurons [128]. Such mechanism involving histamine H1 receptors was recently demonstrated in humans [129]. Therefore, sensitization rather than overexpression of TRPV1 is hypothesized to explain hypersensitivity. Also, recent studies have emphasized the role of TRPV4 expression and function in visceral nociception [22, 23, 130]. TRPV4 is expressed in visceral afferent neurons [131] and epithelial colonic cells [22]. TRPV4 is responsible for 5HT and histamine-induced visceral hypersensitivity [132] and is thought to be the mediator of PAR-2-induced colonic sensitization [22, 130].

TRPA1 is present not only in colonic myenteric neurons, but also in numerous non-neuronal tissues, including the colon [133]. Not only cold and mechanical stimuli but also products formed during oxidative stress can activate TRPA1. Activation of TRPA1 results in mechanical hypersensitivity. Cenac et al. have evaluated levels of metabolites that activate calcium channels TRPV1, TRPV4, and TRPA1 in IBS patients. The level of the TRPV4 agonist was elevated, but not the levels of the other agonists [134]. Figure 4.4 summa-

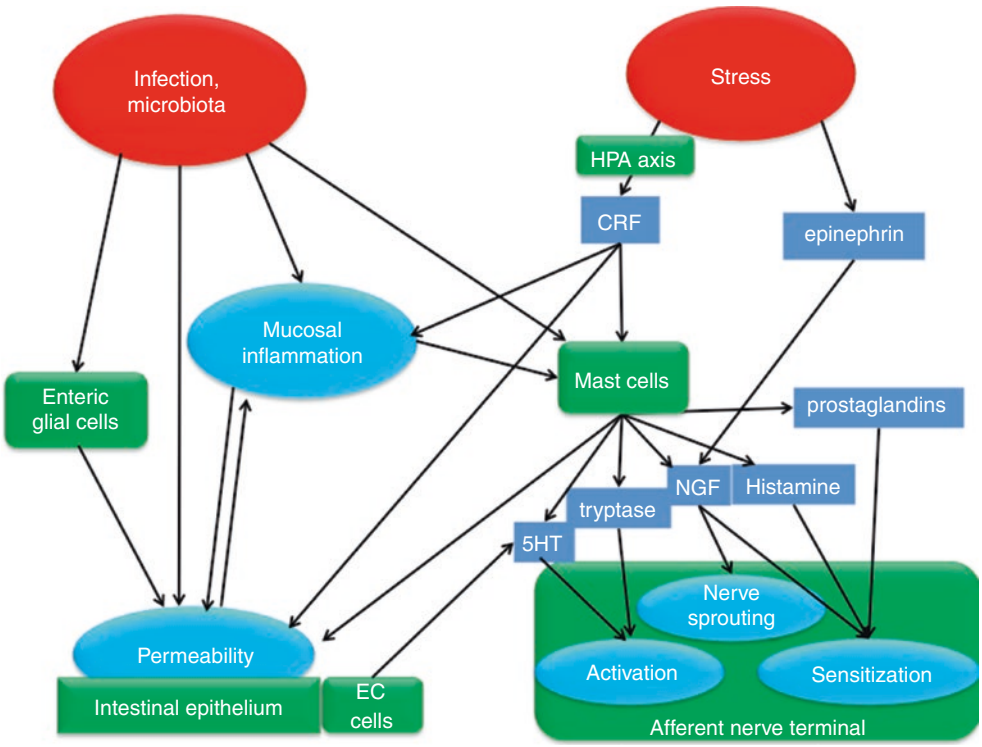

Fig. 4.4 Pathophysiology of visceral hypersensitivity: peripheral mechanisms. Enteric infection, dysbiosis, or stressful events activate intestinal epithelium, enterochromaffin cells (EC) cells, enteric glial cells, mast cells, and afferent nerve terminals. Physiological events such as mucosal inflammation and increased intestinal permeability as well as CRF and epinephrine secretion elicit mast cell degranulation and EC cell stimulation, which in turn secrete neurotransmitters (5HT, histamine), neurotrophins (NGF), proteases, and prostaglandins. These bioactive substances activate receptors present at the terminal end of the afferent nerves and elicit pain, sensitization, and neurite outgrowth leading to chronic changes and maintenance of chronic pain. *Red*: trigger events eliciting visceral hypersensitivity; *green*: tissues involved in visceral hypersensitivity; *light blue*: pathophysiological mechanisms responsible for visceral hypersensitivity; *dark blue*: some of the bioactive substances activating receptors at the terminal end of afferent spinal neuron. Note that some of these components may stimulate mast cell degranulation therefore creating a loop with amplification of the nerve activation. *5HT* serotonin, *CRF* corticotropin-releasing factor, *EC cells* enterochromaffin cells, *NGF* nerve growth factor

rizes the complex interactions among the different factors responsible for visceral hypersensitivity involved at the peripheral level.

Central Mechanisms

When measured by using rectal distensions in humans, the perceptual response expressed by the subject and measured as the rectal sensory threshold can be separated into two components according to the signal detection theory [135–137]: the *perceptual sensitivity* (the physiological capacity of the neurosensory apparatus of the rectum to detect intraluminal distension, i.e., the ability to detect intraluminal distension) and the *response bias* (how the sensation is reported). The *perceptual sensitivity* reflects the ability of the organ to detect and transduce the stimulus to the central nervous system. The *response bias* is the reporting behavior (intensity, painfulness) that represents a cognitive process influenced by past experience and psychological state. Increased response bias (i.e., a tendency to report as painful visceral sensations) with a similar perceptual sensitivity than controls (i.e., same ability as controls to discriminate rectal distensions) has been reported in patients with IBS by one group [138] but was not confirmed by others [139].

Though perceptual sensitivity can be related to peripheral mechanisms, response bias is most likely the result of central processing of the visceral stimuli.

Central Sensitization and Altered Brain-Gut Communication

Central sensitization is a phenomenon that has been described in chronic somatic pain [140, 141]: a peripheral injury triggers a long-lasting increase in the excitability of spinal cord neurons inducing an increase in the afferent activity secondary to profound changes in the gain of the somatosensory system. This central facilitation results in allodynia, hyperalgesia, and a receptive field expansion that enables input from non-injured tissue to produce pain (secondary hyperalgesia). For example, Miranda et al. demonstrated that nociceptive somatic stimulation in neonatal rats resulted in chronic visceral and somatic hyperalgesia during adulthood [142]. Further, the investigators found chronic sensitization of spinal dorsal horn neurons in those with hyperalgesia. Spinal microglia activation has been shown to contribute to the development of visceral hyperalgesia in an animal model of chronic stress [143]. Similarly, it has been suggested that increased colonic NGF synthesis in response to epinephrine contributes to the development of central sensitization [144]. A recent study used electromyographic recordings of the somatic nociceptive flexion (RIII) reflex as a measure of nociceptive processing in the spinal cord in patients with IBS and found evidence for hyperexcitability of spinal processing [145]. Stabell et al. investigated pain thresholds in 961 adolescents with IBS and found that they had lower somatic pain thresholds with widespread hyperalgesia. The coexistence of visceral and somatic hyperalgesia has also been reported in a subset of adult patients with IBS [50, 146, 147]. Alterations in the central pain inhibition processes or CPM (as previously discussed) have also been demonstrated in both adults and children with IBS [147–149]. These findings support an alteration in central pain processing as a possible mechanism responsible for the maintenance of visceral hypersensitivity.

Dysregulation of Pain Processing

Functional brain imaging techniques have led to significant progress in the understanding of cortical and subcortical processing of pain in IBS. Visceral pain processing is a complex process and results from interactions of brain areas operating in networks (the salience network, the emotional arousal network, and the sensorimotor network). Structural and functional alterations in those brain regions as well as prefrontal regions are the most consistently reported findings in adult IBS as compared to controls [34]. A recent study in adolescents with IBS demonstrated a greater activation to rectal distension in a number of key areas of the salience network, especially the cingulate and insular cortices compared to controls. These areas are involved in visceral afferent and emotional arousal processing [150]. Functional magnetic resonance imaging (fMRI) studies in subjects with IBS have also demonstrated alterations in corticolimbic regions, particularly hyperactivity of the amygdala during visceral stimulation [35, 151]. The amygdala plays an important role in emotional regulation, fear, modulation of sensory information, and processing of visceral input in relation to emotional stimuli. A recent study showed that patients with IBS have disturbed amygdala resting-state functional connectivity with the corticolimbic regions [152].

Other Potential Mechanisms

Other neuromediators involved in visceral sensation that have been studied as potential peripheral or central mecha-

nisms of visceral hypersensitivity are listed below. Some of them are (or have been) actively studied as possible targets for the treatment of FGIDs.

- Glucocorticoid receptor [153].
- Neurokinins, which include the substance P (SP), neurokinin A, and neurokinin B, and their respective neurokinin receptors NK1R, NK2R, and NK3R [154].
- Cannabinoids [155] and cannabinoid receptor-1, which regulate intestinal barrier [156].
- Opioids [157].
- Gamma aminobutyric acid (GABA) [158].
- Glutamate (and ionotropic and metabotropic receptors) [159].
- Voltage-gated sodium channels [160].
- Carbon monoxide and hydrogen sulfide [161].
- NaV 1.9 [162].

Visceral Hypersensitivity: A Pediatric Perspective

Although visceral hypersensitivity has been demonstrated in children and adolescents with abdominal pain related to FGIDs, most studies have been conducted in adults for whom the duration of symptoms is significantly longer, precluding the possibility of uncovering the initial pathophysiological mechanisms. Besides the previously discussed peripheral and central mechanisms associated with visceral hypersensitivity, numerous other factors specific to a child with functional abdominal pain, such as age of the child, genetic background, neuroplasticity, temperament, psychological traits, adverse early life events, parental beliefs, as well as parental interaction, may lessen or exacerbate the severity and duration of symptoms.

It is well known that maturation of pain pathways and the development of the brain-gut axis is a dynamic process that occurs throughout development, starting during fetal life (before the microbiome is established) and continuing throughout adolescence [163]. Although the development and maturation of the enteric nervous system is well described, the precise interactions between the enteric nervous system (ENS), the central nervous system, and microbiome throughout development that form the brain-gut axis are largely unknown. Studies done in rodents indicate that the neonatal period is characterized by a very high susceptibility to stress leading to visceral hypersensitivity in adulthood. Neonatal colonic [164] or gastric [165] irritation, and maternal deprivation [166] have been shown to induce visceral hypersensitivity in animal models. Miranda et al. have demonstrated that gastric injury, through fundus ligation, can lead to aberrant remodeling of vagal fibers and change the mechanotransduction properties of vagal afferents [167].

In humans, studies on somatic pain have shown that early traumatic and painful experiences can induce long-term alterations in sensory and pain processing in children [168, 169]. Some studies have also shown that surgical procedures in infants may lead to chronic abdominal pain [170], and, though different from neonatal stress, childhood trauma and abuse are strongly associated with the development of IBS in adults [171].

Because processing of visceral signals is highly complex with involvement of peripheral and central nervous systems influenced by cognitive and psychological processes, not all infants who experience early trauma will develop functional pain. Individual differences among babies as well as parental attitude, and parental psychological traits and beliefs may amplify or dampen their response to these events and influence pain reactivity later in childhood [171, 172]. In keeping with this idea, it has been shown that response to pain in school-aged children with a previous experience in a neonatal intensive care unit (NICU) is highly influenced by the mother's behavior [173]. Epigenetic changes should also be considered important in the development of visceral hypersensitivity since emerging evidence exists for changes in deoxyribonucleic acid (DNA) methylation in animal models of IBS and patients with IBS [174, 175].

Figure 4.5 depicts a schematic overview of the complex interactions between a child, his/her parents, and the environment leading to visceral hypersensitivity and chronic visceral pain.

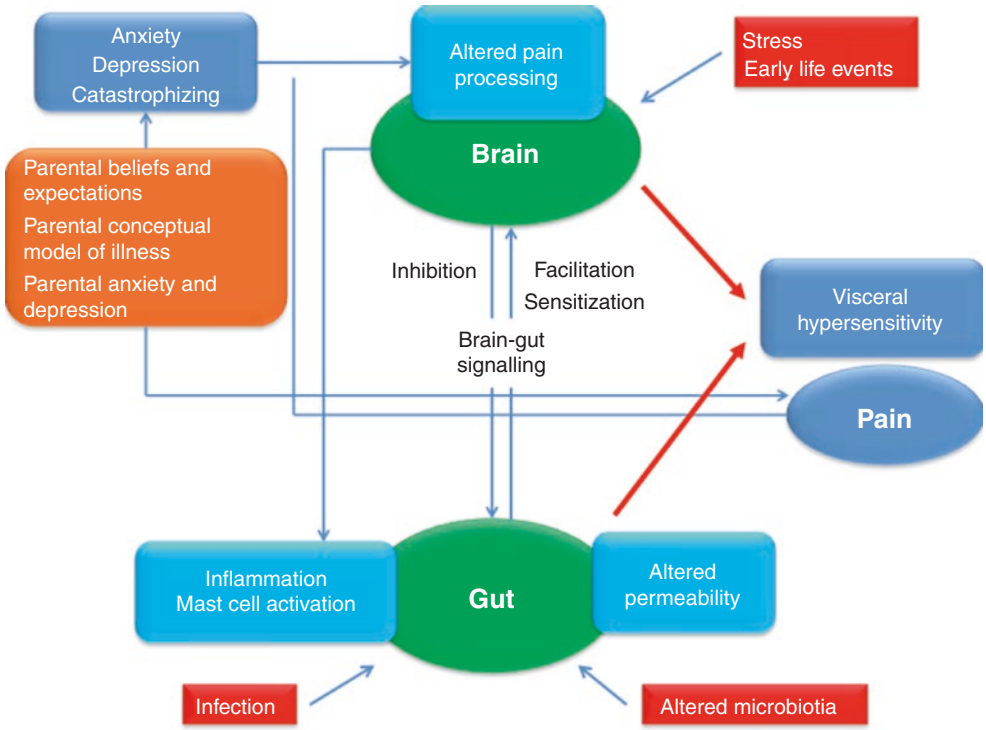

Fig. 4.5 Conceptual framework of visceral hypersensitivity in children. Enteric infection or dysbiosis activates intestinal epithelium and promotes inflammation, mast cell activation, and increased intestinal permeability leading to sensitization of afferent nerves and visceral hypersensitivity. Activation of the gut-brain axis with possible central sensitization and abnormal descending inhibition or increased facilitation can alter the central pain processing and generate visceral hypersensitivity. Stressful events, either in the neonatal period or later in life, induce an activation of the hypothalamic-pituitary-adrenal axis, which promotes peripheral mast cell activation and inflammation favoring peripheral visceral hypersensitivity. Stress may also alter the central pain processing and brain-gut axis leading also to abnormal visceral sensitivity. Pain, especially in the context of parental catastrophizing or misunderstanding of the situation, can trigger anxiety and depression in the child, which in turn will increase stress and alteration of pain processing leading to a vicious circle with an amplification loop conducting to a chronic pain. *Red*: trigger events eliciting visceral hypersensitivity; *dark blue*: child-related specific characteristics; *green*: organs involved in visceral hypersensitivity; *light blue*: pathophysiological mechanisms responsible for visceral hypersensitivity; *orange*: factors associated to the child's parents

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Chronic Pain in Neurogastroenterology

5

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Chronic pain of the gastrointestinal tract may occur in patients with underlying health conditions (e.g., inflammatory bowel disease or motility disorders) or more commonly as a primary pain disorder defined as disorders of gut-brain interaction (DGBI) [1–3]. DGBI, previously known as functional gastrointestinal disorders, are a group of disorders presenting with variable combinations of chronic or recurring gastrointestinal symptoms that result from abnormal functioning (sensation/motility) of the gastrointestinal tract in the absence of measurable structural or biochemical abnormalities. DGBI are categorized into clinically distinct groups based on symptoms according to the Rome IV criteria [2, 3]. More specifically, pediatric pain-predominant DGBI (p-DGBI) include irritable bowel syndrome (IBS), functional dyspepsia, abdominal migraine, and functional abdominal pain not otherwise specified [2].

Abdominal pain and dysmotility often coexist in p-DGBI and may be difficult to separate, with symptoms and treatment often interrelated. Conceptually, this relationship is challenging, yet important for successful treatment. It is important to understand that treating any underlying dysmotility may reduce, but not guarantee resolution of pain. For example, constipation-predominant IBS incorporates treatment for constipation (dysmotility), while emphasizing treatment of the primary pain disorder (hypersensitivity). In this example, without addressing the underlying pain disorder, treatment of constipation will not guarantee resolution of pain.

DGBI are complex and thought to result from the disruption of the function and/or structural integrity of one or more elements of the microbiota-gut-brain axis (see Chap. 6). The microbiota-gut-brain axis is a bidirectional communication system between the enteric and central nervous systems, linking the brain with peripheral intestinal functions by means of microbial, neural, endocrine, immune, and humoral mechanisms. A disruption in this axis may lead to *visceral* hypersensitivity and *central* hypervigilance resulting in an abnormally heightened sensitivity to and amplification of pain, experienced by patients as chronic pain (Fig. 5.1) [4–7].

Disruption and dysfunction of the microbiota-gut-brain axis can result from genetic, psychological, biological, and environmental factors or events, causing physiologic and biologic changes that predispose an individual to develop chronic pain [4, 6, 7]. Infections, surgery, injury, foods, and social stressors can be inciting events leading to a manifestation of DGBI when superimposed on a background of sensitizing medical and psychosocial risk factors (Fig. 5.1) [3].

Given the complexity and challenges of chronic pain, we will review factors that influence the development of chronic abdominal pain, the assessment of chronic pain, and the framework for its successful treatment in this chapter.

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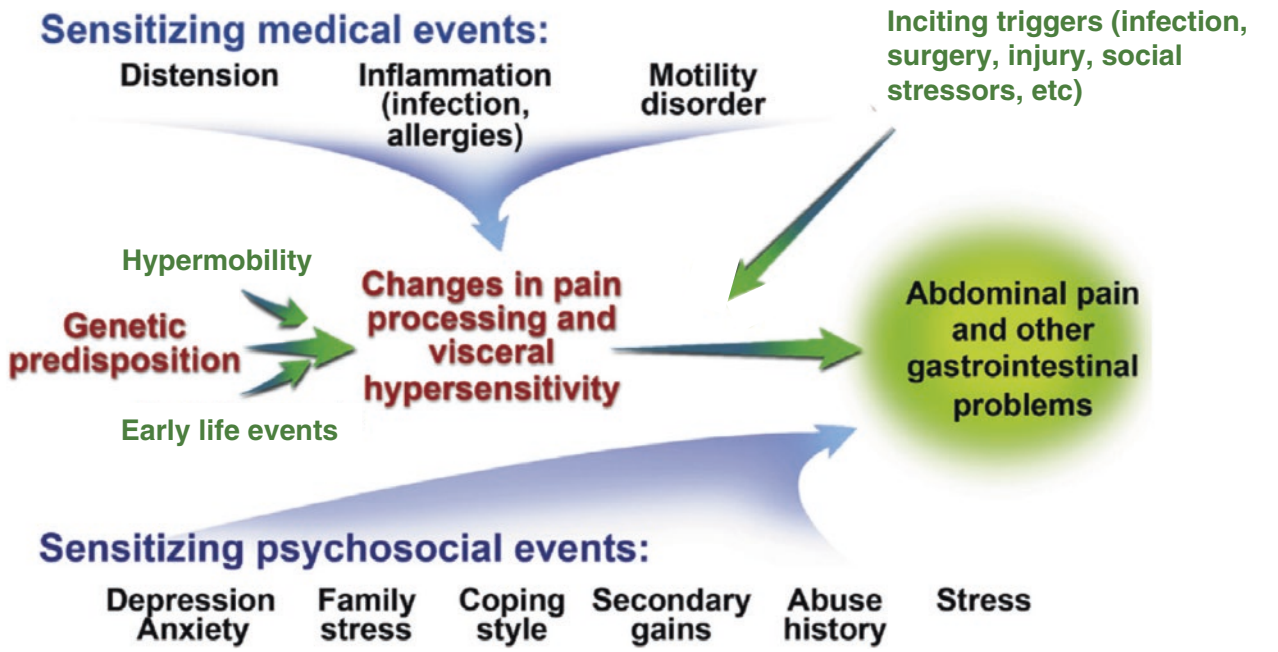

Fig. 5.1 Pathophysiology of DGBI. Summary of likely contributing genetic predisposition, sensitizing psychosocial and medical events leading to the disruption of the structure and/or function of the microbiota-gut-brain axis and development of the core disturbances of DGBI including visceral hypersensitivity and central hypervigilance. Adapted from [2]

Development of Nociception and Pain Pathways

Normal Development

Understanding the neurodevelopment of nociception and factors which influence how pain is experienced by an individual is necessary in order to adequately assess and treat chronic pain. Knowledge of pain perception and the development of the nociceptive pathway in infants and children has grown substantially over the last three decades [8]. Maturation of the nervous system starts at 6 weeks gestational age (GA) and continues well past 42 weeks GA. Sensory neurons synapse into the dorsal horn of the spinal cord by 8 weeks GA, allowing for cutaneous innervation. Afferent synapses to the spinal cord occur by 10 weeks, lamination in the spinal cord by 15 weeks, and by 20 weeks GA there is development of ascending nociceptive pathways, allowing reflexive motor withdrawal a noxious stimulus. By 24 weeks GA, thalamocortical projections are present and somatosensory evoked potentials following cutaneous stimulation will occur at 29 weeks GA. At this time, the peripheral nervous system is developmentally functional, and the impact of a noxious stimulus is identifiable in the brain. By birth, infants and even preterm infants have nociceptive systems present [9, 10].

By activating subcortical mechanisms during the development of the nociceptive pathway, painful stimuli can adversely influence the maturation of thalamocortical pathways [11]. Descending inhibitory control is another key element in modulating the pain experience; however, the descending inhibitory pathway is still immature at birth and finally matures at 6–8 months postnatal age. Therefore, the neonatal cortex has little control over pain processing, so not only are preterm and term infants capable of cortical level pain processing, but they may experience painful stimuli differently and possibly more intensely due to lack of descending inhibition [12]. Both preterm and term infant's response to noxious stimuli is apparent when observing their immediate response with facial grimacing, extremity movements and physiologic changes, which produce cortisol and stress hormones in response to pain [13].

With regard to the development of the microbiota-gut-brain axis (see Chap. 6), there are crucial key processes of development and maturation of all of its elements that underpin its functionality on multiple levels [14]. These include maturation of neuronal subtypes, the organization and integration of interconnected ganglia of the enteric nervous system to form functional circuits, the development of salience networks within the central nervous system, and the establishment of a functionally mature immune system and microbial population within the gastrointestinal tract [4].

Early Life Events

Any interruption of the normal development of pain pathways or their integration into a functional gut-brain axis can predispose individuals to p-DGBI, through a phenomenon termed as "early life programing" [4, 15]. Early life adverse events represent painful experiences, physical or emotional trauma, infections or inflammation, all of which can disrupt neural fibers and thereby alter neuronal circuitry [16–18]. The timing of an insult in childhood plays a critical role with regard to presenting a risk for the development of p-DGBI later in life, likely due to the disruption during a particularly vulnerable time when there is ongoing development and maturation of the gut-brain axis and pain pathways [4]. Often there is an observed delay between the insult and onset of symptoms, although the reason for a delayed presentation is not completely understood [4]. Stress-induced cortisol response to early life adverse events and the subsequent impact on the hypothalamic-pituitary-adrenal axis is one proposed mechanism for how early life events pose a risk [19].

Early painful experiences are represented in multiple examples: neonates experience a heightened behavioral response for days following repeat heel-stick blood draws [20, 21]; boys circumcised without anesthesia have more painful responses to subsequent immunizations [22]; lower pain thresholds are reported in infants that require a neonatal intensive care unit stay [23]; and pyloric stenosis repair or umbilical hernia repair represents an increased risk for chronic abdominal pain [24, 25]. Emotional and physical trauma are also associated with the development of IBS, specifically, children who suffer from parental deprivation, sexual or physical abuse, or those subjected to war [15, 20, 21, 26–29].

Infantile urinary tract infections (UTIs) are another example with a 1.5-fold higher incident density of developing IBS compared to controls, along with further increased risk of recurrent UTIs or presence of vesicoureteral reflux [30]. Cross-organ sensitization between the gastrointestinal tract and other organs may explain how extra-intestinal infections trigger gastrointestinal symptoms [31]. Non-infectious inflammatory conditions such as allergic colitis and Henoch-Schoenlein Purpura are also described as risk factors [32, 33].

However, not everyone who experiences early life adversity will go on to develop chronic pain. Genetic factors, parental stressors and distress, caregiver responsiveness, and other psychosocial features may protect, rather than jeopardize a child [34–37].

Pain Assessment

Assessment of a child's pain experience is essential when developing a comprehensive treatment plan. Pain assessment involves the use of developmentally appropriate tools to determine pain intensity, along with descriptive characteristics of pain; duration, distribution, frequency, and quality. Self-reporting pain, utilizing validated pain assessment scales, to determine the intensity of pain is the gold standard and very helpful when quantifying pain. Generally, a numeric rating scale is used for older children and adults [13]. For children aged between 3 and 8 years, the numeric scale may be modified to a cartoon faces scale that depicts varying levels of pain; alternatively, a composite measure such as the face, legs, activity, cry, consolability scale (FLACC) can be substituted [13, 38]. These scales are typically used for assessing acute pain.

Chronic pain, however, requires an alternative approach. The American Pain Society defines chronic pain in children as a dynamic integration of a biologic process, psychological and sociocultural factors within a developmental trajectory. Assessment of chronic pain is, therefore, best accomplished through an integration of these factors and utilizes a biopsychosocial assessment. Adequate assessment of chronic pain requires clinicians to gather relevant information regarding the pain history and its functional impact on the patient and family [39, 40]. In order to quantify chronic pain in children, the multiple dimensions that influence the pain experience, such as cognitive, developmental, behavioral and cultural factors, temporal and seasonal variations, and need to be assessed and incorporated. Details should include the description of pain experience, associated symptoms, impact on activities of daily living, pain relieving efforts, and interventions used [41–43].

Chronic pain in children has a significant impact on daily function. This impact is evident through evaluation of school attendance and corresponding work quality, sports, social relationships, sleep, and mood [44–46]. Because of the significant impact chronic pain has on function a functional assessment is integral as part of the ongoing assessment of pain management. Several validated measures exist to assess the various domains of function. Some of the more common assessment tools include: The Functional Disability Inventory FDI [44, 47, 48], Pediatric Pain Disability Index PPDI [49], and the Child Activity Limitations Interview [45, 50]. These instruments assess illness and relative activity limitation in children and adolescents with chronic medical conditions.

The Peds Quality and Life Inventory (PedsQL) is a well-validated tool for assessing physical, emotional, social and school function in children aged between 5 and 18 years [40, 41, 46, 51]. This assessment tool also has a parent proxy instrument for younger children, allowing accurate assessment in children as young as 2 years old [52, 53].

For older children (age 8–17), the Patient Reported Outcome Measure Information System (PROMIS) is a self-report questionnaire, which assesses general health domains,

including depressive symptoms, anxiety, mobility, pain, interference, fatigue, peer relationships, and pain intensity [54, 55].

Information gathered through self-report and behavioral pain assessment tools appropriate for children are helpful in formulating a treatment plan [40].

In addition to information gathered from the child or parent's report and from child observation, information gathered from the child's environment may be helpful. Many children with chronic pain conditions suffer from significant school and sleep impairment. These impairments may present as high absentee rates and delayed academic progress [56, 57].

Psychosocial evaluation is also an essential part of the ongoing assessment of a child with chronic pain, since psychological, social, and family functioning can contribute to pain or pain related disability, independent of underlying causes of pain.

Chronic Pain Treatment

Categorization of pain often influences prognosis, evaluation, and treatment. Primary pain disorders (formerly "functional pain syndromes") is a term originally described in 2014 that offers a categorization of ongoing pain that cannot be appropriately explained by medical assessment using conventionally defined medical disease, but is associated with a significant disruption in daily function and living [58]. Providing a primary pain disorder diagnosis (p-DGBI) for patients with chronic abdominal pain and/or chronic gastrointestinal symptoms according to the Rome criteria is very important and increases acceptance, which in turn facilitates treatment [2].

Biopsychosocial Model

Through a biopsychosocial model, primary pain disorders present physical symptoms as the result of a dynamic interaction between biological, psychological, and social factors including genetic, psychosocial, and physiologic subsystems, such as early life events, stress, personality traits, altered mucosal immune function, and disturbed gut microbial environment (Figs. 5.1 and 5.2).

The biopsychosocial model accounts for the complex relationship of biological, psychological, individual, social, and environmental factors that impact the ongoing pain experience and any associated functional disability [59–61]. Therefore, due to its multifactorial nature, the treatment of chronic pain such as those seen in p-DGBI requires a multidisciplinary rehabilitative approach [5, 57, 59–61]. Effective treatment often requires input from providers who span various disciplines including medicine, psychology, psychiatry, physical therapy, occupational therapy, nutrition, social work, and nursing, especially in the more functionally disabled patients. Additionally, treatment plans often incorporate alternative medicine practitioners and fields, such as acupuncture and massage therapy.

Education

The most important aspect in the management of chronic pain is the education of patients and parents, emphasizing that unlike acute nociceptive pain, chronic pain is without protective value and not producing ongoing harm. The goal is to educate, reassure and encourage incorporation treatment through multiple areas of management: *pharmacotherapy, psychological therapy, and physical therapy*, with a focus on promoting improved daily function [58, 62]. Generally all treatments aim to reduce pain by providing supportive care to reduce symptoms, identify, and reduce triggers of pain and to reduce pain signaling (both peripherally and centrally). For example, a patient with IBS may have anxiety or specific foods triggers their symptoms. By identifying and avoiding specific foods and/or treating anxiety, gastrointestinal pain may be reduced.

As mentioned, dimensions of daily function are categorized as sports, social, sleep, and school. Improvement in daily function can be measured through school attendance, participation in social and age-appropriate activities, and sleep hygiene [61, 63, 64]. Improvement in one or more functions often precedes a reduction in pain intensity and strong evidence supports the positive impact of a multidisciplinary approach for the treatment of children diagnosed with chronic pain [57, 59, 61, 65].

Supporting a child with chronic pain, while facilitating physical functioning and reducing pain behaviors, is often challenging for parents. Guidance from the treating medical provider is very important. The initial encounter, education, and anticipatory guidance will set the tone for the subsequent relationship with the child and family. As such, acknowledging that the pain is "real", even if it cannot be tested for directly, is critical so they do not feel dismissed [61, 65]. A thorough explanation of the current understanding of chronic pain as seen in p-DGBI is very important. Comparing p-DGBI to "software" as opposed to "hardware" problems can be helpful to explain that symptoms are real, even if testing results normal: analogous to a computer that has a software malfunction and freezes, but when opened up all the hardware is intact. Specific education

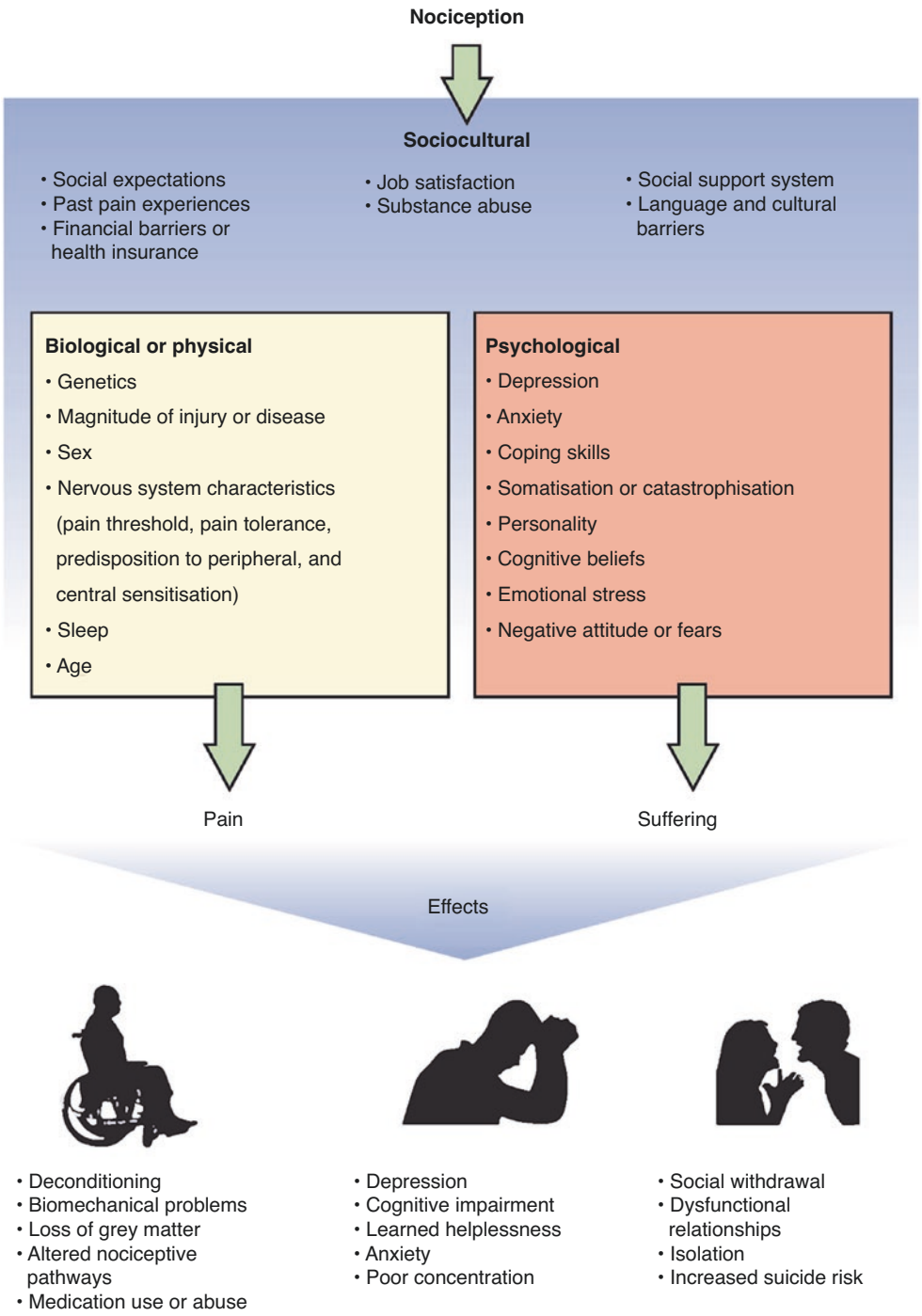

Fig. 5.2 The biopsychosocial model of pain showing the complex interaction between chronic pain and biological, psychological, and social factors [58]

should be provided about the chronic pain being "hurtful, but not harmful" and the importance of returning to normal daily functioning, specifically with respect to school attendance and sleep hygiene. The Comfort Ability Program (CAP) is a psychological intervention for adolescents with chronic pain and their parents designed to address several identified knowledge-to-practice gaps in the field of pediatric pain [39].

Pharmacologic Treatment

Medications are often used as one modality in the comprehensive treatment of chronic pain in children and adolescents, aimed at reducing symptoms and reducing triggers that may exacerbate pain (e.g., Gastroesophageal reflux disease (GERD)). Medications come in a variety of forms (oral, injectable, and topical) and their intended use can be divided

into medications that target the nervous system as a whole and medications that target specific triggers or sources of pain. Neuromodulating agents target the nervous system as a whole, irrespective of triggers, and include antidepressants such as amitriptyline and anticonvulsants such as gabapentin, though their use for pediatric chronic pain is off-label [66, 67]. Neuromodulating medications should be initiated below the anticipated therapeutic dose and titrated slowly to a therapeutic dose to minimize side effects. Because of the lack of high-quality, placebo-controlled trials of pharmacologic treatment for pediatric DGBIs, there is no evidence to support routine use of any pharmacologic therapy. In one systematic review of 6 studies with 275 children (aged 4.5–18 years) evaluating antispasmodic, antidepressant, antireflux, antihistaminic, and laxative agents, compared with placebo, amitriptyline showed 15% improvement in overall quality of life scores ($P = 0.007$) [68, 69].

Use of analgesics will depend on the underlying disease process and specific triggers of pain. Analgesic agents, such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), are rarely helpful in p-DGBI and are associated with certain risks when used for chronic pain management, such as analgesic rebound headaches, gastritis and gastrointestinal ulcers, or worsened abdominal pain [70]. Opioid use for chronic pain from non-life limiting illnesses in children and adolescents is not supported. In fact, data suggest that the use of opioids for chronic pain conditions is often associated with worse overall clinical outcomes [71, 72].

Additional pharmacologic treatment focusing on the gastrointestinal symptoms includes drugs to treat postprandial distress and nausea. H2 blockers or proton pump inhibitors can bring relief in functional dyspepsia. Anti-histamines (cyproheptadine), along with dietary interventions, such as low fructose and fiber based diets, probiotics and prebiotics, have a therapeutic role for the treatment of p-DGBI [73, 74]. Prokinetics can be helfpul for patients who describe bloating, dietary interventions with low fermentable carbohydrates and polyols and high fiber (FODMAP) and/or antibiotic treatment of small intestinal bacterial overgrowth (SIBO) may help [75–81]. Although gluten or wheat free diets have been tried for DGBIs, in the absence of Celiac Disease, this intervention does not appear to be helpful [82]. Prokinetics, such as erythromycin, can be helpful if there is evidence of delayed gastric emptying that may be contributing to symptoms. Botulinum toxin injection into the pylorus has been explored as a treatment for chronic nausea and vomiting as well and has been shown beneficial especially in patients with vomiting [83]. Certain herbal medicines for diarrhea, IBS, and functional abdominal pain may have a positive impact on symptoms [84]. Peppermint oil enteric coated capsules are safe and may be beneficial for irritable bowel syndrome (IBS) [85, 86]. In the case of IBS with constipation, it is important to address the constipation adequately with laxatives, while avoiding overtreatment as the main focus should be on treating the visceral hypersensitivity associated with IBS. Osmotic or stimulant laxatives can be used but may exacerbate symptoms. Alternatively, prescription laxatives such as lubiprostone or prucalopride can be used. Linaclotide specifically has been shown to also positively affect visceral hypersensitivity [87–90]. None of these drugs are approved in the pediatric population to date, but have been shown to have a good safety profile in the use of children and adolescents [88, 90].

Anterior cutaneous nerve entrapment syndrome (ACNES) can be overlooked as a trigger of chronic abdominal wall pain and may improve with pharmacologic intervention. A diagnosis of ACNES should be considered in cases of severe, localized abdominal pain, often worsened with physical activity. Through a combination of these typical findings in history and a positive Carnett test on physical examination, the diagnosis of childhood ACNES can be made. Once ACNES is identified as a source or trigger of ongoing abdominal pain, the transversus abdominus plane (TAP) with rectus sheath block should be considered [91–93].

Physical Therapy

Physical therapy can be valuable for many types of chronic pain [94–97]. Physical therapy for the treatment of chronic pain emphasizes active participation in exercises with an incorporated home exercise program for long-term improvement in function and reconditioning. There is less emphasis on passive strategies, such as massage [52, 60, 98–100].

Physical therapy is premised on offering guided, graded re-entry into exercise. Reconditioning modalities, such as, desensitization, core stabilization, non-invasive pelvic floor work, and learned joint protective strategies, may allow for a return to normal function among certain patient populations with chronic pain [95, 97, 101].

Psychological Treatment

Cognitive behavioral interventions allow for learned, self-regulation techniques, and cognitive strategies to perceive pain as less debilitating [4, 61, 65]. Evidence supports psychological interventions as an effective treatment of chronic pain in children, both for coping and pain modulation. Other strategies targeted to calm the overall state of arousal of the nervous system associated with chronic pain have been shown effective for the reduction of chronic pain, including: meditation, hypnosis, and mindfulness [102–105]. As it relates to DGBIs, systematic review of psychotherapeutic

interventions shows decreased symptoms, which occur immediately after treatment continuing through 12 months after treatment, as compared to the control group [106, 107].

School participation is identified as the largest stressor for children with chronic pain [56, 108]. Reports also indicate that children with chronic pain experience problems with social and peer relationships within a school setting [109]. In order to be successful, reintegration of children and adolescents into these settings in a paced fashion with a graded plan for increasing school and social functioning requires commitment and time from parents and schools along with support from clinicians.

Children and adolescents with chronic pain also struggle with sleep hygiene. Some of the most common sleep difficulties include falling asleep, frequent awakening, and excessive daytime fatigue [46, 110–113]. Sleep interventions may be included as part of cognitive behavioral therapy for chronic pain, but can also be an independent treatment [60, 114].

Intensive Rehabilitation Therapy

While often successfully accomplished through an outpatient care model, the biopsychosocial approach to managing chronic pain may require more intensive rehabilitation, especially in patients experiencing significant disability related to their symptoms. An interdisciplinary rehabilitative inpatient or partial hospitalization program can be considered when a patient continues to suffer from pain and impaired daily function despite outpatient therapy. A systematic review evaluating the efficacy of intense rehabilitation programs supports this approach [65, 115].

Conclusion

Chronic pain results from a complex interplay of biological and psychosocial factors and interactions, with early life adverse events presenting a particular risk due to their disruptive effect on the normal maturation and development of pain circuits and the microbiota-gut-brain axis, resulting in a vulnerability to chronic pain later in life.

Chronic pain in neurogastroenterology may occur in patients with underlying gastrointestinal health conditions, or as a primary pain disorder defined as p-DGBI. Chronic pain as seen in p-DGBI, although hurtful, is not harmful. The abnormal pain signaling itself is the disease, rather than an underlying illness that needs to be uncovered. While p-DGBI all present with pain, disturbances in the gastrointestinal motility can also be present and it is essential to address both pain and dysmotility for successful treatment.

Treatment of chronic pain requires a multimodal and often multi-disciplinary approach including both pharmacologic and non-pharmacologic treatments to address all the complex biological and psychosocial factors that play a role in the emergence and maintenance of chronic pain, as summarized in the biopsychosocial model.

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The Microbiome in Neurogastroenterology

6

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Introduction

The human gastrointestinal (GI) tract harbors a rich and diverse community of organisms referred to as the microbiota. The microbiota contain an even more complex sum of genetic material. This microbiome (trillions of gut microbes and their gene repertoires) contributes to a wide variety of functions critical for intestinal and host health including nutrient assimilation and metabolism, pathogen resistance, immunoregulation, and modulation of intestinal secretion and motility [1–4]. Gut microbes only recently have been acknowledged as integral components within the biopsychosocial model of functional GI disorders, now known as disorders of gut-brain interaction (DGBI) [5]. Microbes are required for normal development and regulation of the enteric nervous system (ENS) and central nervous system (CNS) and, by circulating messages through host cellular mediators, microbes are essential to the bidirectional communication along the gut-brain axis.

This bidirectional communication occurs through the complex interactions of host gene expression, environmental stimuli, and microbial metabolite production orchestrating a myriad of processes including gut motility, sensation, intestinal barrier function (permeability), immunity, mucosal inflammation, hunger, stress, and emotion. Underlying each of these processes, microbial-derived signals pass between epithelial, enteroendocrine, immune, muscle, and nerve cells via receptor-mediated signaling pathways. In turn, the richness and diversity inherent to intestinal microbial ecosystems may be altered by stress, environmental stimuli, introduction of new species (probiotics), substrate availability (diet or prebiotics), antibiotic compounds, or gut-resident bacteriophages.

This chapter outlines the role intestinal bacteria play in regulating the sensorimotor functions of the GI tract and reviews the current evidence for microbiome-based therapies that seek to improve human health in DGBI. These interventions include probiotics—live microorganisms that when consumed in adequate amounts confer a specific health benefit to the host [6]; prebiotics—substrates that are selectively utilized by host microorganisms conferring a health benefit [7]; and targeted antibiotics. The means by which gut microbes affect intestinal barrier function, ion secretion, and immunity are beyond the scope of this chapter and recently have been reviewed elsewhere [4, 8, 9].

A Historical Perspective: The Early Years of the Microbiome and Neurogastroenterology

Gut bacteria became inextricably linked to the field of neurogastroenterology in the mid-twentieth century following the development of the first germfree animal facility at the University of Notre Dame. Early observations revealed costly and surprisingly prevalent morbidity among germfree livestock—intestinal volvulus due to massive cecal enlargement. In 1959, Wostmann and Bruckner-Kardoss challenged the prevailing theory that a nutritional deficiency in the sterilized diet caused the cecum to enlarge. Rather, they suggested, "The absence of certain stimuli, normally arising

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from the presence of the microbial flora and/or its metabolic activity, in these animals appears to be the prime etiological factor." [10] This hypothesis was confirmed by studies showing amelioration of cecal enlargement with the introduction of microbes [11], and by reproduction of cecal enlargement in conventionally-raised mice following antibiotic treatment [12]. Immunohistochemistry revealed an architecturally abnormal myenteric plexus containing enlarged and metabolically inactive neurons [13], and ex vivo organ cultures revealed decreased spontaneous contractile activity and blunted neurotransmitter-induced excitability in the germfree cecum [14].

In 1966 Abrams and Bishop sought to explain their observation that the infectious burden of *Salmonella typhimurium* was several orders of magnitude higher in germfree compared to conventionally raised mice [15]. Hypothesizing that delayed GI transit in germfree animals provided pathogens with additional replication time, the authors revealed markedly delayed transit in germfree mice [15, 16]. Mathias et al. used another infection model in 1976, cholera injection into the rabbit ileal loop, to record for the first time an organized migrating motor complex (MMC) using surgically implanted electrodes. This system prompted the discovery that cholera toxin alters not only small intestinal secretory but also motor patterns [17]. Shortly thereafter, interdigestive MMCs were discovered in humans [18]. Disruption of these "housekeeping" MMCs was associated with small bowel bacterial overgrowth measured by $^{14}CO_2$ bile acid breath test [18], and overgrowth was reproduced in rat models by disrupting the MMCs either medically [19] or surgically [20, 21]. Germfree animals exhibited delayed MMC periodicity, which was corrected by reintroducing microbes to the system [22, 23].

The work by these pioneers led to deeper investigations using the technologies of today. Global transcriptome profiling studies have begun to lend insight into molecular mechanisms underlying the physiologic changes observed in germfree intestines, implicating altered expression of host genes contributing to smooth muscle protein and neurotransmitter function [24]. However, not all bacteria influence contractile patterns and motility equally [25], and the development of culture-independent next-generation sequencing technologies that ushered in the 2007 launch of the international Human Microbiome Project [26, 27] provided new opportunities to define previously undetectable species and to measure entire microbial populations simultaneously. High-throughput sequencing of the bacterial 16S rDNA gene now permits rapid, low-cost microbial population surveys, while newer technologies including full 16S rDNA gene sequencing (rather than selective 16S rDNA variable regions) [28] and whole metagenomic sequencing of all microbial genes [29] and metabolomics, the measurement of microbial- and host-derived small molecule metabolites by mass spectrometry-based approaches, with other emerging 'omics methods, have begun to lend insight into the functional contributions of gut microbes to the field of neurogastroenterology.

The Intestinal Microbiome: Development and Anatomy

The intestinal microbiome matures with age and concomitant dietary exposures, gaining richness (number of different bacteria) and diversity (types of different bacteria) over time. Infants are not born with a complex, adult-like microbial community; rather, bacteria colonize healthy newborns in a predictable sequence known as succession [30]. The notion that healthy infant guts are first seeded by microbes during passage through the birth canal and early breast feeding recently has been challenged by the suggestion that normal microbial colonization may begin in utero [31, 32], although this remains a topic of debate [33, 34]. During the neonatal period, the structure and function of intestinal microbial communities are heavily influenced by components of breast milk and glycan constituents of intestinal mucus [35]. General patterns of succession are predictable, although variations exist based on multiple factors including mode of delivery, antibiotic use, maternal contact and early nutrition, [36, 37] sex, [38] and diet or geographic region [39–41]. The microbiota of most healthy children converge upon a more complex, adult-like community that is thought to be stable [42, 43] and thus more resilient to disturbances that threaten host health. Initially, the maturation process was thought to be completed between the introduction of solid foods and 3 years of life [37, 40, 44];; however, recent studies show that gut microbiota mature at different rates with differences remaining between adults and children up to age 4–5 years [45, 46], pre-adolescents age 7–12 years [47], and 11- to 18-year-old young adults [48].

The microbiome forms environmental niches within each individual, assembling in a nonrandom topography that ultimately benefits both host and microbe [49]. Microbial communities differ not only based on their longitudinal position from the proximal to distal GI tract [38, 50, 51], but also according to their position along the cross-sectional axis, from lumen to the mucosa. One study evaluating patients newly diagnosed with inflammatory bowel disease and healthy controls found that site of sample origin (mucosal biopsy vs feces) was more important as a determinant of microbiota composition than whether a subject was healthy or had active disease [52]. This distinction between mucosal and fecal microbiota is especially important for neurogastroenterology. Given that the ENS with its thousands of ganglia and 400 million neurons embedded within the GI mucosal wall is in closest proximity to the mucosal—not luminal—microbiota, mucosal organisms are thought to influence ENS function, and other biologically relevant aspects such as

mucosal immunity, more profoundly than fecal microbiota that transiently pass through the intestine. The majority of published human studies describe the fecal microbiota exclusively, and these results must be interpreted with caution. However, it also should be noted that surgical or endoscopic mucosal samples are difficult to obtain, especially from healthy controls. Furthermore, the microbial composition of these samples is heavily influenced by standard pre-procedure bowel preparation [53].

Mechanisms of Microbial Influence on the Gut-Brain Axis: Enteric Nervous System Developmental Considerations

Despite the discovery decades ago that gut bacteria influence intestinal sensorimotor function, the majority of mechanisms by which the microbiota communicate with the host nervous systems remain largely uncharacterized. Most studies in this area have sought to elucidate how intestinal bacteria modulate established sensorimotor pathways in adults. Surprisingly little is known regarding how microbes affect the establishment of these neural circuits in early development.

Microbes play important roles in ENS and intestinal epithelial cell lining development. Since Dupont's early observation that rats born in the germfree state develop a hypoplastic and hypofunctioning myenteric plexus [13], further evidence indicates that microbes are essential for normal development of the ENS and motor circuits. Germfree rats have altered crypt-villus and mucosal architecture, with abnormal distributions of enteroendocrine cells secreting the motility-regulating hormones gastrin, serotonin, and motilin [54]. Germfree mice exhibit ENS abnormalities including decreased density of neurons and altered nitrergic expression as early as day-of-life three; these findings correlate with decreased amplitude and frequency of intestinal smooth muscle contractions [55]. Similarly, mice with disrupted gut microbiota early in life, including those subjected to oral vancomycin [56, 57] or protein-calorie malnutrition [58], exhibit altered ENS function and GI motility. However, normal ENS development does not require a completely intact microbiota given that gnotobiotic mice (i.e., colonized by a defined minimal microbial population) have normal motor function [55]. Some developmental effects may be mediated by specific microbes, not just the presence or absence of all bacteria. For example, in neonatal piglets with normal microbiota, supplementation with the probiotic *Pediococcus acidilactici* alters intestinal architecture [59] as well as enteric neuronal distribution and activity [60]. Further characterization of ENS developmental effects by the microbiota and the mechanisms that govern these changes are avenues of active study.

Mechanisms of Cross-Talk between Microbe and Host that Influence Intestinal Motor Patterns

Microbial Factors

Mechanisms by which microbes influence intestinal motor patterns have been explored using germfree, gnotobiotic, and probiotic-supplemented animals. Evaluation methods include in vivo imaging, tracking the movement of a nonabsorbable liquid marker to measure transit time, assessing expulsion of a bead after rectal insertion to determine rectosigmoid motility, implanting surgical myoelectric recording devices or catheters for site-specific measurements of transit time or luminal content or for pharmacotherapy administration, and creating ex vivo organ bath systems that facilitate myoelectric measurements. In some cases, specific microbial-derived molecules that influence motility have been identified, which likely diffuse through the mucus layer to activate receptors on enterocytes or enteric nerves (Fig. 6.1). At this time, the mechanisms underlying microbial-host signaling remain largely uncharacterized. Here we review the current knowledge of enterotoxins, neurotransmitter analogs, and other microbial-derived molecules that influence motility.

Bacterial toxins mediate a wide range of effects on motility through different cells, receptors, and mechanisms. Early studies with purified cholera toxin [17] and conditioned media from either toxigenic *Escherichia coli* [62] or *Clostridioides difficile* [63] provided direct evidence that bacterial secretion products can enhance intestinal myoelectric activity and accelerate transit. However, not all toxins function similarly. *C. difficile* toxin A inhibits small bowel motility [64] and evokes capsaicin-sensitive afferent neuron and immune cell responses [65]. Cholera toxin excites multiple contractile circuits, affecting propulsive and segmentation reflexes via separate pathways [66].

Bacterial cell wall components, which may be toxic, also may affect motility. In a rat model of endotoxemia-induced dysmotility, intravenous administration of *E. coli*-derived lipopolysaccharide (LPS) increases the activity of nitric oxide synthase, delays gastric emptying, and accelerates small bowel transit [67]. An elegant set of studies evaluated germfree mice, mice with antibiotic-depleted microbiota, and mice lacking components of LPS receptor signaling (toll-like receptor 4 or its adaptor protein Myd88). Each of these three "LPS deficient" animal models exhibited delayed intestinal motility and reduced numbers of nitrergic neurons. LPS also was shown to increase the survival of neuronal cells in what appears to be a nuclear factor-KB (NF-KB)-dependent mechanism [68]. In a separate model, intraperitoneal administration of LPS induced nuclear translocation of NF-KB in mouse intestinal smooth muscle and myenteric

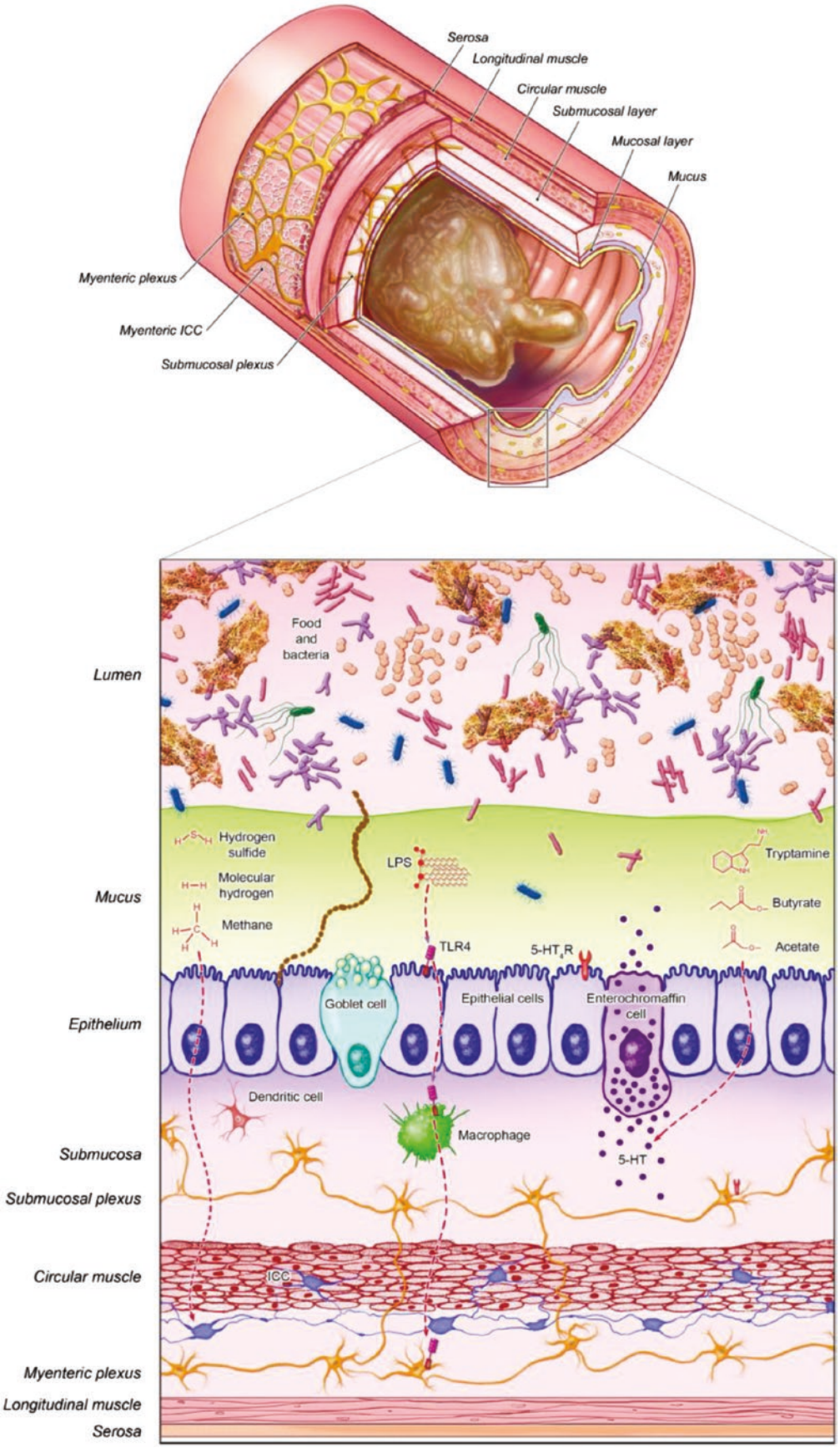

Fig. 6.1 Structural relationship between the luminal and mucosal microbiota and the enteric nervous system. Reproduced with permission from John Wiley and Sons: Neurogastroenterology & Motility [61], copyright 2013. http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1365-2982

plexus cells [69]. Furthermore, recent studies suggest that LPS induces muscularis macrophages to increase their expression of bone morphogenic protein 2, which in turn influences motility via receptors on enteric neurons in a pSMAD-dependent fashion [70].

Microbiota-produced nontoxic compounds also affect host motility. It has been known for decades that some unicellular organisms produce biologically active hormones [71]. For example, *Bacillus subtilis* synthesizes a bioactive somatostatin-like molecule [72], and multiple pathogenic bacteria produce γ-aminobutyric acid (GABA) [73]. Gnotobiotic mice "humanized" by colonization with a simplified human-derived microbiota then given either *Lacticaseibacillus paracasei* or *Lacticaseibacillus rhamnosus* had elevated urine concentrations of the metabolite tryptamine [74]. Tryptamine is an aromatic amino acid compound that enhances intestinal contractility in ex vivo preparations and stimulates the release of other neurotransmitters [75]. *Clostridium sporogenes* was recently discovered to have a tryptophan decarboxylase enzyme capable of synthesizing the neurotransmitter tyramine. Microbial tyramine synthesis is now believed to be present in the intestinal tracts of more than 10% of the human population [76]. Other studies have linked gut bacteria to increased levels of the enteric gaseous neurotransmitters hydrogen sulfide [61] and nitric oxide [77, 78].

Microbes also can receive signals from the host neurobiological environment. Quorum sensing is the microbial regulation of gene expression in response to fluctuations in cell population density [79]. Quorum sensing could provide an evolutionary explanation for the presence of a GABA uptake system in a *Pseudomonas* species [80], if this system evolved to detect the density of other GABA-producing bacteria. However, bacterial functions likely are influenced by differing concentrations of GABA derived from the host as well. In turn, there are multiple examples of human catecholamines that influence a range of bacterial processes including growth, attachment, and virulence [81] (Fig. 6.2).

Short chain fatty acids (SCFAs) are bacterial fermentation products (e.g., butyrate, acetate, propionate) that serve as an energy source for intestinal epithelial cells in a site-specific and dose-dependent manner [82]; they are the most extensively studied class of microbial-derived molecules that influence host motility. Since the discovery that intraluminal infusion of SCFAs stimulates local motility in the human distal intestine [83], key mechanistic insights have been revealed using in vivo and ex vivo models from rats [84–88] and guinea pigs [89]. One potential mechanism by which SCFAs affect motility is by increasing choline acetyltransferase activity in myenteric neurons through a monocarboxylate transporter 2-dependent mechanism. Altered choline acetyltransferase activity was found in rats given either butyrate or a resistant starch diet [90]; the resistant starch

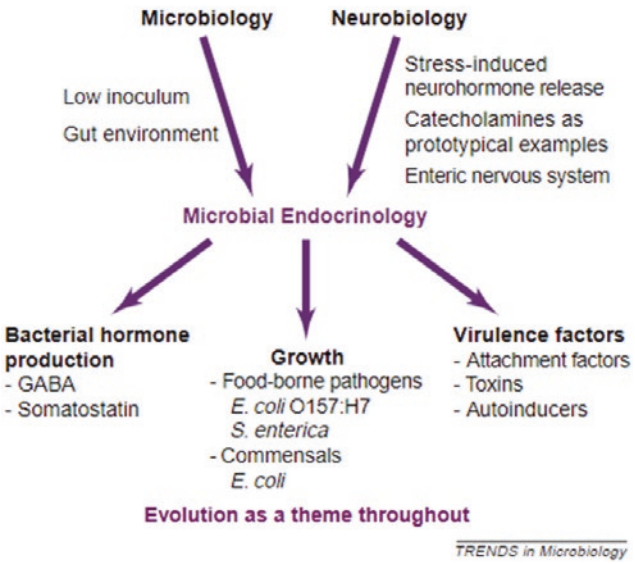

Fig. 6.2 Influence of microbiologic and neurologic factors on microbiota population structure and function. Reproduced with permission from Elsevier Limited: Trends in Microbiology [81], copyright 2004. http://www.cell.com/trends/microbiology/home

may act as a prebiotic to increase the numbers or activity of butyrate-producing microbes in the intestine.

Other bacterial signaling molecules that affect motility are just being discovered or have yet to be fully defined. Early studies revealed that infusion of bile acids into the human distal intestine, most of which are deconjugated by gut bacteria, stimulates local motility [91]. The G-protein-coupled bile acid receptor TGR5 is now thought to be an essential part of this bile acid motor reflex response [92]. Furthermore, a recent longitudinal study of patients with irritable bowel syndrome (IBS) identified specific microbial bile acid transformation products associated with altered colonic fluid secretion in patients with diarrhea-predominant IBS [93]. Similarly, an undefined product of the probiotic *E. coli* Nissle 1917 has myoelectric effects in human colonic strips [94], ,and membrane vesicles from *L. rhamnosus* JB-1 influence peristalsis in mouse colon via interactions with epithelial cells [95]. Further work is needed to define specific bacterial products and their site-specific mechanisms of action in the human intestine.

A fascinating link has emerged between commensal bacteria and intestinal motility via the metabolism of serotonin, one of the key mediators of propulsive transit. Germfree mice have threefold reduced quantities of plasma serotonin compared to conventionally-reared animals [96, 97]. Germfree mice also have reduced colonic expression of tryptophan hydroxylase 1 (*Tph1*), the rate-limiting gene in serotonin synthesis, and increased expression of the serotonin reuptake transporter [97]. Recent studies in germfree and gnotobiotic mice confirmed that gut microbes stimulate

enterochromaffin cells to increase *Tph1* expression, raise intestinal and plasma serotonin levels, and accelerate GI transit [98, 99]. These studies also used culture models of enterochromaffin cells to implicate several microbial-derived molecules, including SCFAs, secondary bile acids, and intermediates of vitamin synthesis, as stimulating serotonin production [98, 99]. Some of these secreted signals may cross the blood-brain barrier, given that germfree mice also have altered hippocampal levels of serotonin metabolites [100]. Butyrate, in particular, increases quantities of serotonin through an inducible zinc finger transcription factor that binds directly to *Tph1*; mice lacking this gene known as ZBP-89 had lower intestinal and plasma levels of serotonin and were more susceptible to infection [101]. Notably, the presence of gut bacteria does not affect a second source of serotonin, *Tph2* in enteric neurons. Studies of *Tph2*-deficient mice reveal this enzyme is the more important isoform in terms of myenteric plexus architecture and constitutive intestinal transit [102]. Whether therapeutic remodeling of the microbiome to influence serotonin metabolism may have roles in DGBI remains uncertain.

Host Factors

Complicating matters further is the fact that gut motility itself influences the microbiome. In animal models, disruption of regular motor patterns produces small bowel bacterial overgrowth [19–21]. In addition, analysis of stool obtained from healthy volunteers with pharmacologically altered GI transit times found a significant positive correlation between the speed of GI transit and total bacterial mass [103]. However, while some bacteria flourish during rapid transit, others prefer a static luminal environment. For example, in mice with congenital colorectal aganglionosis, modeling Hirschsprung disease, there were both increased proportions of Bacteroidetes and decreased Firmicutes [104].

In addition to altering microbiota composition, gut motility also affects microbial function. The controlled environment of an in vitro continuous culture system was used to confirm that flow rate is a key determinant of both the composition and function of human fecal microbial communities [105]. In one example, fecal microbes obtained from adult volunteers with pharmacologically-induced fast GI transit correlated with increased substrate fermentation into SCFAs and decreased pH of the culture medium; the opposite was true for microbes harvested from adults with slow GI transit [106].

Mechanisms governing the associations between intestinal microbial composition and function are even less clear in human disorders of dysmotility, particularly given the coexistence of other host factors intimately linked to GI pathology including physiologic stress. Mouse models reveal that catecholamine release drastically increases certain intestinal microbial populations [107], and may prime the host mucosa to be more permissive to the attachment of enteric pathogens [108]. These and other host-derived factors must be considered in the context of GI diseases associated with altered rates of transit, including but not limited to IBS, inflammatory bowel disease, acute gastroenteritis, and delayed gastric emptying.

In addition to physiologic stress, two recent studies convincingly show that intestinal transit time is inextricably linked to both diet and gut bacteria. The first report analyzed germfree mice, conventionally raised mice, and gnotobiotic mice colonized with a simple humanized microbiota. GI transit in all animals was accelerated either pharmacologically with polyethylene glycol or via the diet with a nonfermentable polysaccharide, cellulose. In contrast, administration of fructooligosaccharide, a fermentable polysaccharide, decreased SCFA production and slowed transit only in mice with microbes. Germfree mice receiving fructooligosaccharide exhibited more rapid transit similar to that following administration of polyethylene glycol. Likewise, decreasing transit with a polysaccharide deficient diet was successful only in mice with intestinal bacteria. These experiments indicate that diet influences motility through both microbiota-dependent and microbiota-independent pathways [109] (Fig. 6.3). In the second study [110], six groups of germfree mice were humanized by fecal microbes from six different environments: a twin pair from the United States discordant for obesity, a lean United States consumer of a protein- and fat-rich primal diet, a Venezuelan living in the rural Amazon, a Bangladeshi living in an urban slum, and a Malawian from a rural village. These groups of mice were in turn fed a succession of different diets with carbohydrate, protein, and fat contents representative of diets consumed by each of the six donors. These experiments found diet-dependent correlations between specific bacterial groups and whole-intestinal transit rate. Fecal metabolomic analyses revealed deconjugated bile acids, which are metabolized from conjugated bile acids by bacterial bile salt hydrolases, to be associated with faster transit. Metatranscriptomic analyses revealed that a component of the Bangladeshi diet, turmeric, influenced transit rates in a manner that was dependent on the amount of bile salt hydrolase activity present in the host [110]. These experiments illustrate not only the complexity of host-microbiome-diet interactions but also the utility of employing top-down, systems-based approaches to complex mechanism discovery.

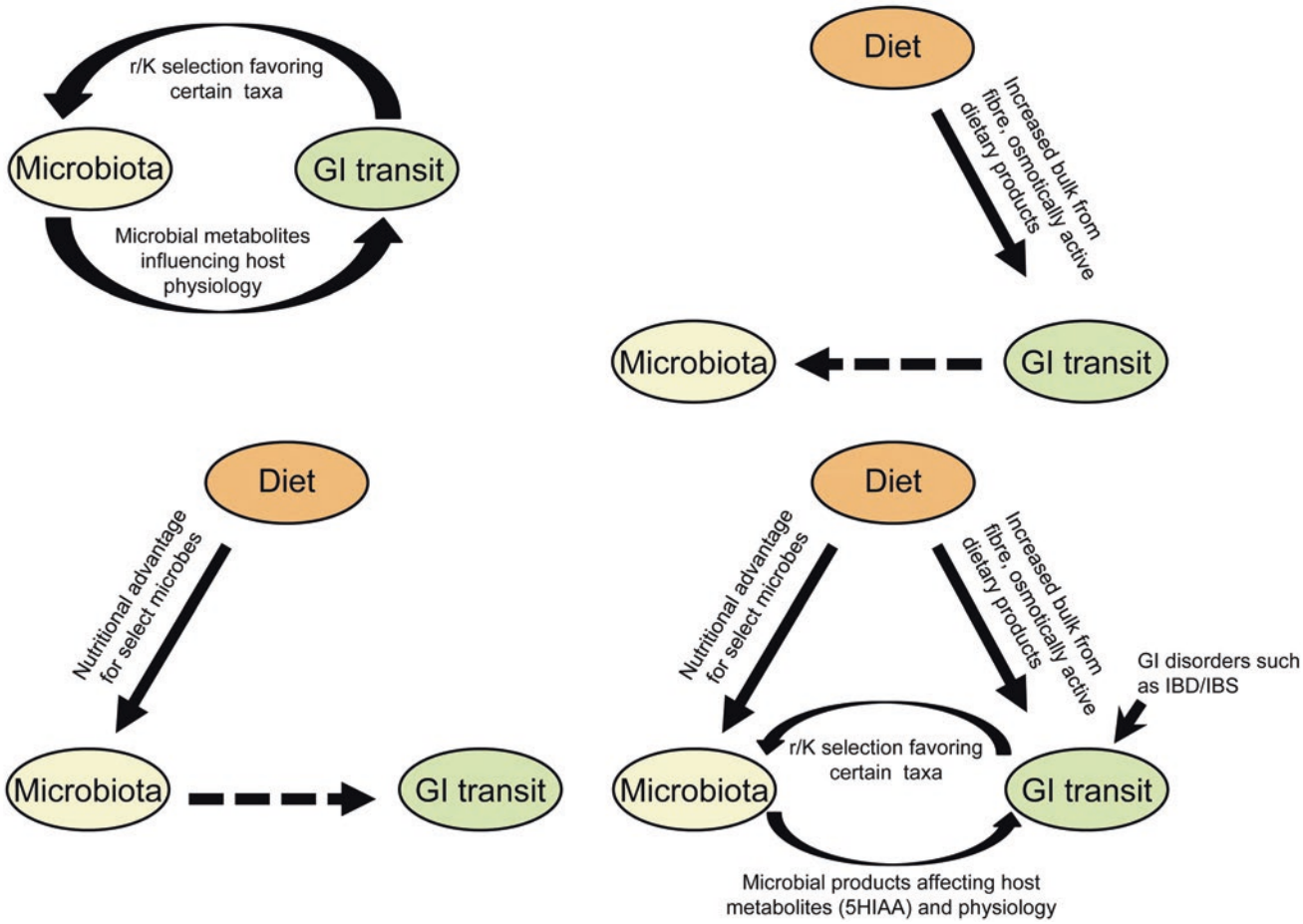

Fig. 6.3 Interactions between diet, intestinal microbiome, and GI transit rates. Reproduced with permission from Elsevier Limited: Gastroenterology [109], copyright 2013. http://www.gastrojournal.org/

Mechanisms of Crosstalk between Microbiota and the Central Nervous System

In comparison to those governing motility, the mechanisms by which gut microbiota communicate with the CNS to influence processes such as pain perception and behavior are less well defined. Much of the current mechanistic knowledge has been obtained using a diverse array of labor-intensive animal model techniques. Neuronal function may be assessed using in situ gene expression or ex vivo patch-clamp action potential recording devices; visceral sensitivity can be assessed by measuring abdominal wall contractions or heart rate during colorectal or gastric distention via intraluminal balloon; and anxiety phenotypes can be replicated by assessing freezing behaviors or other responses to water-avoidant stress, open-field novelty tests, marble-burying, and separation of pups from dams. These and other techniques have uncovered novel mechanisms of brain-gut-microbiota interactions in three main categories: modified signaling pathways in enteric nerves and epithelial cells which affect the CNS, CNS structural or functional changes, and induction of systemic responses that may influence host neurobiology.

Gut bacteria may have effects on sensory neurons including the vagus nerve. Infection of mice with *Campylobacter jejuni* increased the expression of the neuronal activation marker c-Fos both in vagal sensory ganglia and in the nucleus of the solitary tract, a region of the brain where vagal sensory inputs converge [111]. Likewise, *Citrobacter rodentium* enhanced c-Fos expression in vagal sensory ganglia, while eliciting anxiety-like behavior patterns on open-field testing [112]. Sensory function also was altered in a post-infectious hypersensitivity model. Afferent neurons from mice infected with *Trichinella spiralis* demonstrated a biphasic response to ex vivo stimulation, showing hyposensitivity during the acute infection and then

increased basal activity with hypersensitivity several weeks later. This finding appears to be partially mediated by altered serotonin metabolism and has potential relevance to postinfectious IBS [113]. Although most of the signals mediating communication of sensory information between pathogens and enteric nerves are unknown, one study revealed, as measured by increased excitability and expression of proinflammatory markers, that either lysates from *E. coli* cell walls or LPS activate mouse colonic nociceptive dorsal root ganglion neurons [114]. Further work remains to identify the specific bacterial secreted products that influence nociception and the ENS sensory pathways that these products activate.

Early studies with probiotics revealed that *Companilactobacillus farciminis* minimizes the effect of partial-restraint stress on visceral hypersensitivity in mice, perhaps by inhibiting colonic mucosal expression of epithelial cell cytoskeletal contractile element phosphorylated myosin light chain [115]. Similarly, the probiotic *Limosilactobacillus reuteri* decreases dorsal root ganglion nerve firing and blunts the pain response to colorectal distention in rats [116]; this may occur by inhibiting a calcium-dependent potassium channel on neurons of the myenteric plexus thus affecting both sensory and motor reflex pathways [117, 118]. Another mechanism by which probiotics may reduce nociceptive neurotransmission was elegantly illustrated in a classic study by Rousseaux et al. [119] demonstrating *Lactobacillus acidophilus* induced upregulation of μ-opioid and cannabinoid receptor 2, mediators of nociceptive signal transmission. This occurred both in enterocyte cultures and in murine models, leading to increased rat colorectal distention pain thresholds [119]. Decreased enteric neuronal excitability also has been demonstrated in mice treated with the probiotic *Bifidobacterium longum* [120, 121].

It is important to note that neuron-modulating effects may not be restricted to specific pathogens and probiotics. Normal activity by intrinsic primary afferent neurons depends on the presence of intestinal microbes in general. Neurons harvested from germfree mice demonstrated lower resting membrane potentials, decreased excitability [122], and decreased responsiveness to agonist-induced firing [123].

Recent data indicates that CNS structure and function are influenced by the intestinal microbiota. Metabolomic analyses reveal that nearly 20% of mouse cerebral metabolites are altered by the germfree state [124]. In a landmark study, Diaz Heijts and colleagues [125] reported that germfree mice and gnotobiotic mice colonized by microbes as adults exhibit different behavior including both increased locomotor and decreased anxiety-like behavior. That gnotobiotic mice colonized in adulthood behaved like germfree mice suggests a critical early-life window of brain development mediated by a normal microbiota. The authors then used metabolite and gene expression analyses to correlate the altered behavior phenotype with processes influencing the development of neuronal circuits that mediate locomotor and anxiety behaviors [125]. Conventionally-reared mice with antibiotic-depleted microbiota demonstrated similar behavioral changes, correlating with increased hippocampal expression of brain-derived neurotrophic factor, a key mediator of memory, learning, anxiety, and depression [126]. A different study linked behavior changes in germfree mice to altered CNS expression of not only brain-derived neurotrophic factor, but also *N*-methyl-D-aspartate receptor subunit NR2B and serotonin receptor 1A [127]. Other mediators of CNS effects continue to be investigated. For example, *Acinetobacter lwoffii,* an organism that blooms during antibiotic treatment of rats with chemically-induced fulminant hepatic failure, produces an uncharacterized, inactive plasma compound that appears to be converted in the brain to a benzodiazepine receptor ligand that worsens hepatic encephalopathy [128]. Behavioral and gene expression or metabolite changes in the brain also have been reported in conventionally-reared mice infected with *Trichuris muris* [129] or *C. rodentium* [130] or in animals receiving the probiotic *L. rhamnosus* [131] or *Bifidobacterium infantis* [132, 133] by unknown mechanisms. Whether these reported CNS effects in conventional mice are attributed to direct effects of these individual bacteria or to their secondary alterations to the resident microbiome is unclear.

Recent insights have advanced our understanding of microbial mechanisms underlying pathophysiology in other neurological disorders. In a mouse model of Parkinson's disease featuring overexpression of α-synuclein, gut microbiota is required for the development of neuroinflammation and motor abnormalities [134]. Likewise, in a *Caenorhabditis elegans* model of ectopic human α-synuclein expression, metabolites produced by probiotic *B. subtilis* inhibit the formation of and enhance clearance of pre-formed α-synuclein aggregates. These effects occur through multiple pathways including altered host sphingolipid metabolism [135]. Similarly, in the maternal immune activation mouse model of autism, the microbe-derived uremic toxin 4-ethylphenylsulfate is elevated nearly 50-fold in serum of affected animals, is nearly undetectable in germfree mice, and is restored to normal levels by treatment with probiotic *Bacillus fragilis* [136].

Recent data from studies in humans support some of the observations made in these mouse models. Administration of *Lactobacillus helveticus* R0052 and *B. longum* R0175 reduced psychological distress and anxiety among healthy women in a double-blind trial [137]. In another double-blind trial enrolling healthy women, consumption of a fermented drink containing *Bifidobacterium animalis* subsp. *lactis, Streptococcus salivarius* subsp. *thermophilus, Lactobacillus delbrueckii* subsp. *bulgaricus*, and *Lactococcus lactis* subsp. *lactis*, altered brain activity as measured by functional magnetic resonance imaging (fMRI) [138]. In a recent randomized, double-blind, placebo-controlled study enrolling healthy volunteers, 4 weeks of a nine-strain probiotic formulation improved self-reported well-being indices and emotional decision making. These findings, along with altered fMRI parameters, correlated with subtle changes in gut microbial profiles [139]. Further studies are needed to determine whether these probiotic effects may be generalizable to broader groups of patients.

The gut microbiota also is being explored in patients with hepatic encephalopathy, in which specific microbial signatures are associated with the encephalopathy progression [140]. Changes in fMRI were seen in patients with cirrhosis and encephalopathy treated with the antibiotic rifaximin [141]. In a phase I pilot study randomizing 30 cirrhotic adults with minimal hepatic encephalopathy to receive 4 weeks of the probiotic *L. rhamnosus* GG or placebo, the probiotic reduced serum levels of endotoxin and tumor necrosis factor (TNF) but did not improve cognitive indices [142]. Indeed, a recently updated Cochrane review identified 21 randomized trials with 1420 participants and concluded that probiotics may improve recovery, plasma ammonia levels, quality of life, and the risk of developing overt hepatic encephalopathy compared to placebo or no intervention; however, the overall quality of evidence is low, and there is no clear benefit in terms of mortality [143].

Gut microbes have been shown to alter the systemic stress response or inflammatory pathways. Germfree mice have exaggerated adrenocorticotropic hormone and corticosterone responses to partial-restraint stress. This effect is both blunted by mono-colonization with the probiotic *B. infantis* and exacerbated by mono-colonization with enteropathogenic *E. coli*. Similar to the developmental window revealed for the influence of gut microbes on locomotor and anxiety-like behavior, the exaggerated stress response was ameliorated by early but not late colonization of germfree animals [144]. These findings were advanced by a randomized, double-blind, placebo controlled pilot study enrolling adults with IBS and co-morbid anxiety or depression [145]. Six weeks of the probiotic *B. longum* reduced depressive symptoms and improved quality of life. Although probiotic treatment had no effect on anxiety or IBS symptoms, nor on microbial community composition at the taxonomic level, *B. longum* normalized urinary metabolites involved in the noradrenaline/dopamine axis as well as fMRI responses to negative stimuli [145].

Finally, bacteria can alter the body's response to stress through inflammatory pathways. Sun et al. found that exposing mice to 10 days of water-avoidant stress caused several inflammatory related changes including increased corticotropin-releasing hormone, inhibition of the NLRP6 inflammasome, intestinal inflammation, and gut microbial composition alterations [146]. These composition alterations were characterized by decreased Bacteroidetes, increased Firmicutes, and increased γ-Proteobacteria. Intriguingly, healthy mice acquired microbiota composition alterations, increased levels of corticotropin-releasing hormone, and decreased NLRP6 when co-housed with mice naïve to stress. Each of these effects was ameliorated by giving the co-housed mice either broad-spectrum antibiotics or a mixture of three lactic acid-producing probiotics [146]. These data suggest that a portion of the physiologic effects of psychological stress may be driven by various microbial populations.

In summary, gut bacteria exert a myriad of effects on genes, metabolites, and physiologic processes governing multiple neurogastroenterological phenomena. As we continue to develop technology pipelines that enrich our understanding of both known and novel intestinal microbes along with their myriad of secreted products, we will continue to discover new mechanisms of communication between the microbiota and mammalian CNS and new preclinical and

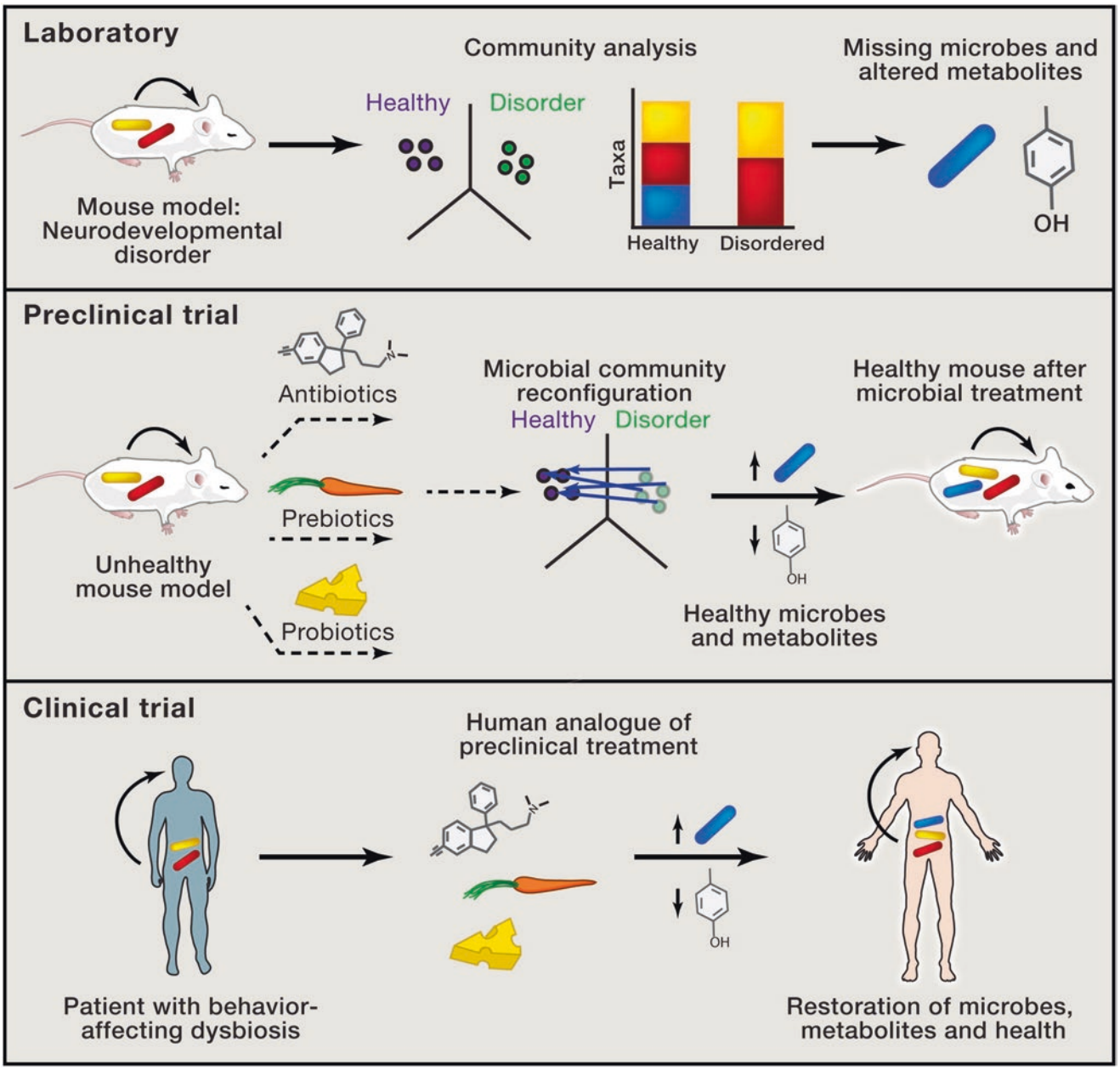

Fig. 6.4 Potential pipeline for the development of therapeutics for disorders of neurogastroenterology. Reproduced with permission from Elsevier Limited: Cell [147], copyright 2013. http://www.cell.com/

clinical tools for maintaining the microbiome in a state of relative health [147] (Fig. 6.4).

Irritable Bowel Syndrome and Related Functional Disorders

Altered gut microbiota populations have been found in individuals with DGBI. Balsari and colleagues were the first to show, using culture-dependent techniques, that fecal microbial populations from adults with IBS were different than those from healthy adults [148]. Compared to controls they found that symptomatic patients had decreased coliforms, lactobacilli, and bifidobacteria [148]. Altered microbial populations in IBS were subsequently reported using more advanced techniques including real-time PCR [149], PCR combined with a phylogenetic microarray [150], PCR with HPLC-based bile acid profiling [151], percent G + C profiling with a 16S rRNA clone library [152], fluorescent in situ hybridization on rectal

biopsy samples [153], high-throughput 16S rRNA gene sequencing [154, 155], and ultimately integrated longitudinal metagenomic, metabolomic, host epigenomic and transcriptomic profiling [93].

Only recently have microbial communities in pediatric IBS been defined. Children with IBS based on Rome III criteria had higher proportions of γ-Proteobacteria, a class containing multiple pathogens such as *Haemophilus parainfluenzae* [156]. In addition, supervised machine-learning algorithms identified specific taxonomic units that distinguished with 98.5% accuracy those children with constipation-predominant from those with unsubtyped IBS [156]. In another study, children with diarrhea-predominant IBS had increased proportions of the genera *Veillonella, Prevotella, Lactobacillus*, and *Parasporobacterium*, and decreased proportions of *Bifidobacterium* and *Verrucomicrobium* [157]. More recently, by leveraging metagenomics and metabolomics together, a classifier with an area under the curve score of 0.93 distinguished children with IBS from healthy children [158]. These investigators reinforced the previous findings of γ-Proteobacteria being enriched in children with IBS, and using whole genome sequencing were able to identify *Flavonifractor plautii* and *Lachnospiraceae bacterium 7_1_58FAA* as being abnormally enriched in children with IBS. Fecal metabolites which were found to be higher in children with IBS included steroid/sterol compounds and secondary bile acids [158]. Although further investigation is needed, these microbiome-related features suggest microbiome-guided diagnostic and therapeutic strategies may prove to be helpful in children with IBS.

Given these associated changes in gut microbiota composition and associated metabolites, manipulation of the microbiome has the potential to address processes that may contribute to IBS pathogenesis including microbial fermentation, nociceptive pathways, inflammatory signaling pathways, and abnormal intestinal motility. Indeed, the number of randomized controlled trials describing the effects of probiotics in IBS is ever expanding (over a hundred) and has given birth to a large number of meta-analyses (over 25). Comparison of the results from the meta-analyses is complicated by differences among studies in the choice of outcomes, the types and quality of studies reviewed, duration of therapy, and the subtype and/or Rome criteria of IBS investigated, among other differences. One could argue there is an inherent problem in examining the effect of probiotics for IBS (or any disorder) given the ways different probiotics may impact immune function, gut barrier function, nociceptive signaling, etc. Most trials use multiple (different) strains of bacteria [159–161]. Rarely are there more than two or three trials using the same strain of bacteria. For example, *Lactobacillus* in eight trials did not show benefit but when only the three trials using *Lactiplantibacillus plantarum* DSM 9843 were considered, a benefit on the persistence of symptoms was found [159]. Yet it was not clear if this probiotic affected global symptoms or abdominal pain scores [159]. Even when a product with the same composition (the eight-strain combination marketed as "VSL#3") is compared in a relatively robust number of trials ($n = 5$), clear benefit was lacking [162]. If there is a benefit from probiotics, it appears to be small overall and whether a particular strain or combination product stands out requires further study based on recent publications [159–161, 163].

To date, three meta-analyses have evaluated probiotics for DGBI exclusively in children [164–166]. One of these included three placebo controlled trials of *L. rhamnosus* GG enrolling 290 children with abdominal pain-related DGBI based on Rome II criteria. This analysis reported a modest but significant benefit for *L. rhamnosus* GG, primarily due to a benefit for children with IBS [165]. Three randomized controlled trials have suggested some benefit of *L. reuteri* DSM 17938 in children with functional abdominal pain [167–169]. A Cochrane review, that also included other studies besides those noted above, concluded that improvement in pain was more likely with probiotics but the evidence was of moderate to low quality depending on the specific pain outcome [170].

Although antibiotic use for non-gastroenterological indications may increase the risk of developing functional bowel symptoms [171, 172], there also is evidence that manipulating the microbiota through antibiotic therapy may be beneficial in IBS. In 2000, Pimentel and colleagues studied a subset (78%) of adults with IBS who had a positive lactulose hydrogen breath test suggestive of small bowel bacterial overgrowth. These subjects were treated with a 10-day course of oral antibiotics after which they returned for repeat breath testing and symptom assessment. Patients with a negative breath test at follow-up reported significant improvements in diarrhea and abdominal pain; furthermore, half of the follow-up breath test-negative patients no longer met criteria for IBS [173]. Subsequent double-blind placebo controlled trials enrolling adults with DGBI based on Rome criteria found statistically significant but modest benefits using the nonabsorbable antibiotic rifaximin [174, 175]. The only meta-analysis that has evaluated the effectiveness of antibiotics for IBS found a small but statistically significant benefit. However, the authors cautioned there is overall insufficient evidence to recommend the routine use of antibiotics in this setting [176]. In children with IBS, a double-blind placebo controlled trial did not find rifaximin to be more beneficial than placebo [177].

Dietary interventions targeting the intestinal microbiota show promise in treating DGBI. Ingestion of a fermentable prebiotic may stimulate the growth or activity of a beneficial group of commensal bacteria [178]. The most commonly studied prebiotics are fructooligosaccharides, a fermentation substrate for multiple genera including *Bifidobacterium* in

the production of SCFAs. Low dose fructooligosaccharides demonstrated beneficial effects in randomized placebo controlled trials of adults with IBS [179] and other DGBI [180]. Likewise, a prebiotic mixture containing galactooligosaccharides increased fecal bifidobacteria counts and improved symptoms in adults with Rome II IBS [181]. However, the paucity of published studies precludes evidence-based recommendations regarding prebiotics for DGBI [182]. In addition, when given at higher doses, fructooligosaccharides may induce symptoms in both adults and children with IBS [183, 184]. Therefore, rather than supplementing the diet with fructooligosaccharides, some have advocated that they be restricted within a low fermentable carbohydrate diet (see below).

Fiber supplementation, which alters colonic microbiome composition and function [185], has been used as a therapy in adults and children with IBS. A meta-analysis [186] that included two fiber supplementation studies in children with functional abdominal pain [187, 188] did not demonstrate efficacy. However, the quality of these studies limits their interpretation. A recent randomized controlled trial including 103 children with IBS identified a benefit for psyllium fiber supplementation vs. placebo (maltodextrin) in children with IBS [189]. Multiple meta-analyses of fiber supplementation in adults with IBS found efficacy and its use (i.e., psyllium) is recommended by the American College of Gastroenterology [190–193]. A clear correlation of dietary fiber supplementation with changes in gut microbiome composition correlating with IBS symptom improvement has not been established.

As an alternative strategy, fermentable carbohydrates, which are associated with affecting gut microbial activity manifested as increased intraluminal gas production and/or increasing osmotic activity [194, 195], may be restricted in the diet. An open label low carbohydrate diet improved symptoms in adults with diarrhea-predominant IBS [196]. Studies have evaluated the role of a low fermentable oligosaccharides disaccharides monosaccharides and polyols (FODMAPs) diet (LFD) in reducing symptoms in adults and children with IBS although few are randomized double-blind trials in which the dietary intervention was provided to participants. The carbohydrates restricted within a LFD include lactose, fructose, fructooligosaccharides, galactooligosaccharides, and sugar alcohols. An Australian study, using a double-blind, randomized crossover design in which all food was provided to participants with IBS showed that a LFD vs a standard diet could improve symptoms within 7–10 days [197]. A study in children using a similar design also showed benefit from a LFD on IBS symptoms within 2 days [198]. A number of studies in which different FODMAPs were administered to adults and children with IBS in a randomized double-blind fashion clearly demonstrate the ability of FODMAPs to exacerbate IBS symptoms in some patients [183, 184, 199]. Interestingly, children with IBS who develop increased pain (vs. those who did not) when given fructans had a different microbiome composition at baseline (decreased diversity and decreased taxa within the Clostridia class) [200]. In addition, children with IBS who were given fructans who developed increasing pain had a different microbiome composition response (increased *Agathobacter* and *Bifidobacterium*). These data lend support to the gut microbiome playing a role in determining diet-related IBS symptoms; however, the mechanisms need to be further elucidated.

In addition to ameliorating GI symptoms in those with IBS, low fermentable substrate diets have been found to alter gut microbiome composition and function (altered fermentation). A low carbohydrate diet decreased gas (hydrogen and methane) production in adults with IBS [194]. Halmos et al. found that when compared to a typical Australian diet, a LFD was associated with higher fecal pH, greater microbial diversity, and reduced total bacterial abundance [201]. The authors also found decreased hydrogen production while on the LFD [201]. Staudacher et al. found that in comparison to a habitual diet, a four-week LFD lowered both concentrations and proportions of bifidobacteria [202]. In children with IBS, Chumpitazi et al. also found decreased hydrogen production while on the LFD [203].

Given that commensal microbes utilize a wide variety of organic substrates for fermentation, a deeper understanding of how the metabolic machinery encoded within the intestinal microbiome affects DGBI pain symptoms may facilitate the discovery of novel prebiotics that have predictable effects on intestinal physiology. In this respect, baseline gut microbiome composition also may play a role in determining whether IBS symptoms are ameliorated during a LFD. Studies in adults and children with IBS suggest that baseline gut microbiome composition and volatile organic compounds in stool can predict whether individuals will respond to the LFD [198, 204, 205]. In the pediatric trial, responders were enriched at baseline in taxa with known greater saccharolytic metabolic capacity (e.g., *Bacteroides*, Ruminococcaceae, *Faecalibacterium prausnitzii*) [198]. Further studies are needed to validate whether one's gut microbiome may predict dietary intervention efficacy.

Prospectus

At present, we have only begun to understand the numerous and complex ways in which intestinal microbes impact human neurogastroenterological function. As high-throughput sequencing and related multi-omic technologies, including statistical methods for drawing meaning from these enormous and complex data sets, continue to evolve at a rapid pace, these new tools will further add to our knowl-

edge base. For example, whole metagenome sequencing ushered in a paradigm shift, allowing us to begin to understand intestinal microbial communities in terms of their function rather than simply their composition. Improved approaches to sequencing the intestinal pool of microbial mRNA, or metatranscriptomics, also will shed light on microbiome function. Another important avenue of research will be to explore the contributions of non-bacterial members of the microbiota, including the virome (both eukaryotic viruses and phages), archaea, and the mycobiome. As metabolomics approaches become more readily available, the measurement of microbial metabolites in multiple body compartments will lend further insight into beneficial or harmful functions conferred by specific microbes and microbial populations. Another key challenge is to understand the structure and function of the mucosal microbiota; these microbial communities are much more difficult to access and study from patients, and particularly, healthy controls, compared to luminal microbes found in feces. It is anticipated that much of the heterogeneity observed in cross-sectional microbiome studies can be overcome with rigorously designed longitudinal study designs [93].

Understanding how microbes influence neurogastroenterological processes will be essential to determining whether altered microbial communities result from disease states (e.g., dysmotility, stress, or inflammation) or whether altered populations actually contribute to the pathophysiology of DGBI. The ultimate goal is to facilitate more rational selection of probiotic strains, combinations of strains, prebiotics, and even development of specific strains for therapeutic trials based on mechanistic principles. Given the multitude of effects conferred by gut microbes on host neurobiology, it is possible that in the future gastroenterologists will be able to identify unhealthy components of the gut microbiome of patients with IBS and other DGBI, and through strategic manipulations may replace pathologic microbial functions with those that promote health.

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7 Integration of Biomedical and Psychosocial Issues in Pediatric Disorders of Gut-Brain Interaction

Miranda A. L. van Tilburg

Introduction

Treating gastrointestinal (GI) symptoms in children is often more difficult than it may seem. Consider the following case.

Johnny is a 6-year-old child who presents with nausea and abdominal pain. Upon history taking, the child appears to experience early satiety and some minor weight loss. You notice pallor and irritability. After thorough diagnostic workup, John is diagnosed with delayed gastric emptying. The family is sent home with a prescription for erythromycin and referral to a dietician. Several months later Johnny returns to you and appears to be doing well. Pallor has disappeared and weight loss has been stopped. Nevertheless, problems continue at home around feeding. Johnny still refuses food and continues to complain of nausea and abdominal pain. You suspect psychological factors may be playing a role. The symptoms started around the time Johnny's parents got a divorce. Mother seems anxious and Johnny is out of school regularly around fear of symptoms.

This scenario is recognizable for many clinicians working with children who suffer from disorder of gut-brain interaction (DGBI). Psychosocial factors often play a role in these disorders and no clinician working with this group of patients will deny their influence. But the interpretation of how psychological symptoms affect the onset and maintenance of these disorders varies considerably among clinicians. Are psychological issues primary causes of some disorders? Can psychological disturbances affect digestive processes? In the case of Johnny: were the continuation of his symptoms after successful treatment of the gastric emptying primarily due to anxiety of his family, who may too easily over-interpret normal symptoms as signaling disease; or was there a behavioral component to his symptoms in the first place, that was not addressed with the medication therapy thereby leading to less effective treatment? Answers to some of these questions can affect the course of suggested treatments for Johnny and other children like him. In this chapter, first the theoretical models explaining the role of psychosocial issues in health and disease will be discussed. These are implicit working models guiding clinical care and scientific research and are important to explore. These implicit working models frequently lead to frustrations in the doctor's office by both patients and clinicians. Then, the current scientific evidence for the role of psychosocial factors on gut functioning will be presented.

Psychological Issues in Health and Disease

Johnny in the example above has continued nausea despite treatment. His clinician may decide to run a few more tests excluding other medical reasons for his symptoms. Finding no apparent medical cause—the physician tells Johnny's parents he is perfectly healthy and refers him to a psychologist for further treatment. Johnny's parents are not satisfied with this answer and demand more testing. After all their son's symptoms are "not all in his head." They may even take Johnny for a second, third, or fourth opinion, always ending up with the same answer which increasingly frustrates all parties involved and leaves Johnny devoid of any meaningful treatment. This is not an uncommon scenario. Despite Johnny's doctors and his parents at increasingly opposite ends, they actually both overwhelmingly agree. They agree that symptoms are either caused by your body or your mind. Johnny's doctors, having excluded any biological causes, know these symptoms are caused by anxiety. His parents, knowing their child could never be this sick without a valid reason and knowing their child isn't crazy or feigning symptoms, keep requesting more tests to find what is biologically

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wrong with their child. This mind versus body dualism is troublesome for the diagnosis and treatment of patients with DGBI yet is the overwhelmingly held model of health and disease.

Biomedical Model: A Symptom Has either a Biological or Psychological Origin

Under guidance of the biomedical model (see Fig. 7.1), medicine has seen great advances over the past centuries. This model has been responsible for some of the most impressive discoveries of modern medicine such as the development of penicillin and vaccines. It is still widely popular today among many clinicians and patients. The biomedical model envisions a direct relation between disease and symptom: Cause A will lead to symptoms B. The more disease-causing A is present, the more symptoms will be observed. If A is eradicated, the symptoms will disappear. This straightforward model of health and disease focuses primarily on biological origins but argues that in lieu of a disease or structural abnormality, psychological factors can cause symptoms. For example, if no biomedical reason can be found for stomachaches (such as lactose intolerance), then these symptoms can be attributed to psychosocial distress, that is, anxiety or school avoidance. The biomedical model is simple and elegant but completely ignores contextual influences on health and disease: symptoms are either caused by biological or psychological causes. If gut symptoms have a biological cause, such as an autoimmune reaction to gluten in celiac disease, the biomedical model allows that psychological factors may change how the patients reacts to the disease. For example, concomitant depression may cause a patient to not adhere to treatment or concomitant anxiety may lead to frequent requests for doctor visits. But in essence a disease is either caused by the body or the mind. This straightforward and appealing approach has led to the notion that if symptoms are not in "the body," it must be "all in the head." It also explains our fascination with drugs as a "quick fix" for *real* symptoms worthy of a clinician's time while behavioral or supportive therapy has become synonym to treating symptoms that are either feigned or a result from being "crazy" and not belonging in a physician's office (see Fig. 7.2). For a more detailed explanation of the biomedical model and its limitations in pediatric gastrointestinal disease, see van Tilburg [1].

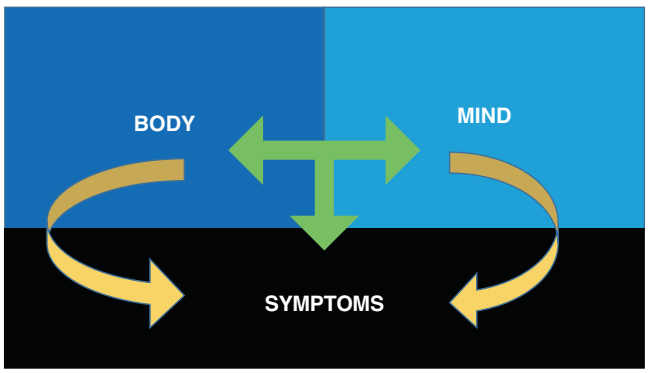

Fig. 7.1 The biomedical and biopsychosocial model of health and disease. Note: Simplified representation of the biomedical and biopsychosocial models, The biomedical model predicts that symptoms are caused either by the body or the mind (dualism; yellow arrows). The biopsychosocial model predicts that an interaction of body-mind (system; green arrows) as well as the social environment (not depicted here) causes symptoms

	No Symptoms	Symptoms
No Biological Cause	*HEALTHY*	*MIND* "Its all in your head" *Annoyance* *Disbelief*
Biological Cause	*SICK* *"Silently suffering"* *Care, Support, Admiration*	*SICK* *Care & Support*

Fig. 7.2 The biomedical interpretation of medically (un)explained symptoms. Note: In the biomedical model, medically unexplained symptoms are seen as originating from someone's mind. For patients, this equates to suggesting the symptoms must be 'all in their head' and they often fight this label. The symptoms and request for more tests and treatment are met with annoyance and frustration by many physicians who feel unable to treat the mind. Whereas people with a disease but no symptoms are simply not believed to be asymptomatic. They are considered stoic and silent sufferers. These patients are met with admiration and respect

Biopsychosocial Model: Brain-Gut Interaction

By the mid-1970s, the well-established biomedical model started to show little cracks. It became clear that there was no perfect association between biomedical processes and symptoms. For example, under the biomedical model, the frequency and amount of gastric acid refluxing into the esophagus should explain the intensity of heartburn complaints. However, there are patients with very severe acid reflux for years, who are minimally or even asymptomatic until developing Barrett's esophagus. On the other hand, there are others with minimal acid reflux whose life is severely affected by their symptoms. The only way to explain these findings with the biomedical model is to see the first person as a "tough" or stoic, silently suffering while continuing with his/her life, while the second is a "wimp" complaining at the tiniest bit of discomfort (see Fig. 7.2). The first elicits admiration and the second contempt. However, imper-

fect associations between biomedical processes and symptoms are so ubiquitous that they seem to be the rule rather than the exemption. The biopsychosocial model (see Fig. 7.1), first proposed by Dr. Engel [2], posits that biochemical alterations do not directly translate into illness. The appearance of symptoms is an interplay between many factors including biomedical, psychological, and social factors; for example, bacteria A leads to more symptoms under stressful circumstances.

The biopsychosocial model has been widely adopted by researchers and clinicians to explain health and disease and is particularly useful for understanding and studying DGBI. There is a robust literature describing the influence of both physiological and psychological factors on the illness presentation of various gut disorders. These studies will be discussed later in this chapter. In fact, the evidence that symptoms are *always* an interplay between the gut and the brain has led to the renaming of henceforth "medically unexplained" gut disorders as disorders of gut-brain interactions (DGBIs). Furthermore, it allowed for studying the involvement of brain and gut factors in diseases that were previously largely perceived as only having biological causes. An example of this is the widely described phenomenon that inflammatory bowel diseases and irritable bowel syndrome share many overlapping features and symptoms, challenging that one exists solely in the body and the other in the brain [3].

Although the biopsychosocial model was presented by Dr. Engel as a system theory, it is nowadays often presented in a reductionist way. Some authors reduce mental and social phenomena to basic biological phenomena, such as activation of the autonomous or central nervous system (CNS) and hypothalamic-pituitary-adrenal (HPA) axis [4]. Johnny from our case at the beginning of the chapter may be anxious which leads to CNS and HPA axis activation, interacting through the brain-gut axis with the enteric nervous system culminating in gastrointestinal symptoms. Systems theory acknowledges that psychosocial processes undoubtedly have biological correlates. However, it argues that the different systems—biological, psychological, and social—interact with each other but cannot be reduced to the lowest—molecular—level. The reasoning behind this is simple: we cannot understand the meaning of psychosocial processes by purely studying its biological correlates; subjective phenomena are equally important.

The biopsychosocial model is also sometimes reduced to a hierarchy of unidirectional cause and effects relationships which includes causes, precipitants, modulators, or sustaining forces [5]. In Johnny's case, anxiety and delayed gastric emptying can be thought to independently cause or sustain his symptoms and it is up to the physician to decide which one is most important and thus should be treated first. The answer to this is often clouded in the question whether psychological issues are a cause or consequence of symptoms. Some authors have found increased anxiety before a diagnosis of DGBI [6], while others have argued that increased psychosocial distress may be a consequence of having to deal with a chronic, unpredictable condition [7]. A large community-based study found that both positions may be right: Psychosocial comorbidity was as likely to be present *before* as *after* seeking care for abdominal pain [8]. If we conceive of our body as a system in which psychosocial and biomedical factors interact continually, then the question of what came first is not relevant. Both factors will interact to cause symptoms and understanding the disorder is exploring this interaction. Johnny's delayed gastric emptying caused pain and fullness, which made him anxious around food. His fears of having pain after a meal in turn may have led to hypervigilance and increased the sensitivity of his nerves to normal digestive processes thereby worsening his symptoms. Thus, anxiety is both cause and effect in this circular loop. Both factors need to be addressed to ensure successful resolution of symptoms. Thus, rather than trying to solve the "chicken-and-egg" dilemma, we should focus on understanding how the different components of the system interact to create these symptoms. Systems theory is an attempt to understand the complex feedback loops over time hypothesized in the biopsychosocial model. Unfortunately, such integrated models of proximal causes and effects over time are difficult to study. The need for complex study designs and sophisticated statistical methods has seriously hampered the testing of systems theory in gut disorders. However, this does not take away the fact that we should interpret any findings in a wider systems framework.

Nowadays the role of psychosocial variables in gut disorders is widely recognized and the biopsychosocial approach is commonly endorsed. The biopsychosocial model postulates that psychosocial factors can interact with the gut through the brain-gut axis: the bidirectional communication between the enteric nervous system in the gut and the brain. This means that emotions and thoughts have the capability to affect gastrointestinal sensation, motility, and inflammation. Reciprocally, gastrointestinal processes are able to affect perception, mood, and behavior. Before we delve into the evidence for the biopsychosocial model in gut diseases, we first need to define psychological factors relevant to gut diseases.

Beyond Stress: A Model of Psychosocial Factors in Pediatric DGBI

When patients have "medically unexplained" symptoms ,they are often labeled as anxious and told to reduce stress. Just like our biology is complex, so are psychosocial factors. In addition to anxiety and stress, there are many other psychosocial aspects relevant to DGBI such as self-esteem, cop-

ing, early childhood experiences, and parental reactions to their child's symptoms, to name only a few [9]. To understand the role of psychosocial factors in DGBIs, it is important to understand how these factors are defined and related. Here I will briefly introduce the most important psychological factors in DGBI. For a more thorough discussion of this literature, please see Newton and colleagues [9].

One of the most common psychosocial factors mentioned in the doctor's office is stress. We all know what stress is and what it feels like. However, defining stress is more elusive than it seems. First, there are the events that may be stressful: being stopped by a policeman for speeding, giving a speech in front of several colleagues, taking your child to the Emergency Room. These are called stressors. Second, there are individual reactions to stress: feelings of anger/fear, trouble concentrating, and physical reactions such as accelerated heartbeat, tensed muscles, and increased perspiration. It is important to realize that not all potential stressors lead to stress reactions and that stress can be both positive and negative. What is stressful for one person may be pleasurable to another or have little impact whatsoever to a third person. A parachute jump or deep-sea dive may elicit enormous fear and anxiety in some, while others find it highly pleasurable and for very experienced professionals it may just a simple routine. Therefore, stress is a subjective experience created by the appraisal of an environmental demand as harmful, threatening, or challenging and appraisal of our ability to meet this demand [10]. If a person has adequate resources to deal with a difficult situation, he or she may not experience stress; but if the demand (almost) exceeds one's resources, a person will be under a great deal of stress. When the term "stress" is used, it may refer to: (1) the stressors, which are usually major life events such as trauma, abuse or divorce but can also be the cumulative effect of small daily hassles; (2) the subjective experience of stress which is usually measured by self-reports of perceived stress; and (3) stress reactions which include behavioral (e.g., withdrawal or confrontation), emotional (e.g., anger, fear, anxiety, depression) and physiological reactions (e.g., skin conductivity, blood pressure, cortisol, and catecholamines). Thus, stress in addition to being itself is also causing itself and resulting in itself.

One common reaction to stress is anxiety, also named psychological distress. When anxiety/worry happens in the context of stressful events, it is normal. However, the word anxiety usually refers to excessive worry and avoidance of something that happens **in the future**. Thus, we're not anxious over the pain that is happening now, we worry about future pain or what the current pain may mean for our future selves (e.g., missing work). Anxiety tells us to avoid situations that will elevate our anxiety which gives temporary relief but usually increases our anxiety over the long term. Hence, an anxious teen with DGBI may worry about and fast to avoid bloating before going to a party. This worry as well as the fasting may make her symptoms worse.

Anxiety and life stressors are without doubt the psychological factor most often studied in pain-related DGBIs [9]. Increasingly, there has been recognition that psychological factors cannot be reduced to stress and anxiety alone. Various studies have found that the effects of stress and anxiety on DGBI symptoms and disability is not direct but mediated by catastrophizing and somatization [11–13]. More evidence comes from studies showing psychological treatment efficacy is not driven by reductions in anxiety but by reductions in catastrophizing [14, 15]. Catastrophizing is assuming the worst while feeling unable to do anything about it. If I make a B on my midterm at school, I will fail the class. If I will fail the class, I will have to drop out of college. If I drop out of college I will end up in the streets. That one B in class, escalated quickly to the worst outcome. Somatization is often understood in the Freudian sense that unexpressed emotions slip out as bodily symptoms. However, most authors nowadays define somatization as simply "an excess of multiple bodily symptoms." The reason why someone may report this excess in symptoms is unknown, and explanations vary from increased attention to symptoms [16], to defects in mitochondrial energy metabolism [17]. Thus, given the complexity of the psychological models in DGBIs, it is important to realize which psychological factors are being referred to when reading and interpreting the scientific literature on the brain-gut axis. Stress is not the most important aspect influencing DGBI outcomes, but it is the most often studied concept. Therefore, the next section will focus on that literature.

How the Brain Can Affect the Gut: How the Gut Can Affect the Brain

Stress and Gastrointestinal Motor Functioning: The Role of CFR

Motility disturbances are a hallmark of many DGBI which may result in symptoms such as altered stool consistency, nausea, or bloating. There is evidence to suggest that stress induces changes in motility. For example, under stressful conditions gastric emptying decreases and colonic transit accelerates [18]. Corticotrophin-releasing factor (CRF), especially CRF_1, plays a pivotal role in these stress-induced motility changes. CRF is best known as the principal instigator of the physiological response to stress through the hypothalamic-pituitary-adrenal (HPA) axis and CRF 1 receptors have been found to regulate behavioral reactions to stress [19–23]. Both brain and peripheral CRF-1 stimulation is associated with accelerated colonic transit, defecation and diarrhea, increased visceral sensitivity and transcellular per-

meability, and stimulates similar brain areas as anxiety and depression [23, 24]. Blocking CFR-1 reduces stress induced gastric motility, pain, and anxiety symptoms [23]. In addition to motility, CRF receptors have also been implicated in visceral hypersensitivity and immune functioning. For example, CFR-1 antagonists have been shown to block the development of stress-induced visceral hypersensitivity in animal models and both stress as well as CFR injections activate colonic mast cells involved in the development of visceral hypersensitivity [23, 25, 26]. For a more in-depth overview of CFR in stress induced motility, and hypersensitivity, see Tache et al. [23, 24].

Stress and Visceral Hypersensitivity

One of the most consistent findings in functional abdominal pain disorders (FAPD; a subcategory of DGBI) is visceral hypersensitivity. Hypersensitivity to gut distension—the reporting of first sensation of pain at lower levels of colonic or rectal pressure than normal—has been found in more than half of adult patients who suffer from irritable bowel syndrome (IBS) and functional dyspepsia [27]. Although these studies are hard to do in children, visceral hypersensitivity has also been described in children with FAPD [28–32]. In addition, visceral *hypo*sensitivity in the rectum has been reported in children with constipation [33, 34]. Reduced sensation in the rectum corroborates the fact that these children do not easily feel an urge to defecate.

The role of stress on visceral sensitivity has only been examined in FAPD. Animal models have shown that acute, chronic, and early-life stress are associated with colonic hypersensitivity [26]. In fact, early life stress induced visceral hypersensitivity which was transferrable to the next generation in mice, possibly due to changes in maternal care [35]. One study reported that stress in adult mice leads to increased visceral hypersensitivity only if combined with an infection [36], which mimics the findings of post-infectious IBS in humans. In humans, acute stress, induced by cold water hand immersion (physical stressor) or dichotomous listening (mental stressor), seems to reduce pain thresholds as well [37, 38]. But other types of stressor have yielded mixed effects. Past stressful experiences (e.g., abuse history) and psychological distress (e.g., anxiety or depression) have been associated with decreased pain thresholds in some studies [29, 39–43] and increased in others, [44] while some have reported no effects of stress at all [29, 41, 45–47]. Thus, most studies report increased sensitivity with stress, but some did not find any effects and one study actually found decreased sensitivity [48]. The reason for the inconclusive evidence may be related to the way visceral sensitivity is measured and what psychological factors are measured, emphasizing the need for a more sophisticated understanding of psychological factors in these studies.

If we assume that under certain circumstances stress can affect visceral sensitivity, an important question becomes at what level in the neural system these effects are most dominant. Sensations from the gastrointestinal tract are relayed to spinal dorsal horn. Visceral sensory information is then conveyed to supraspinal sites and finally to cortical areas where they are perceived [49, 50]. Descending emotional pathways via the periaqueductal gray to the dorsal horn can amplify or suppress new afferent signals from the gut. Amplification of these signals can occur at any level in this neural pathway. Evidence is building that the central nervous system is an important site of modulating the pain response. Studies have shown differences between patients with IBS and controls in activation of various brain regions including those involved with emotions, sensorimotor processing, executive control, and control of the autonomic nervous system [51]. This literature is too vast and detailed to summarize here. The reader is referred to the Rome team working report on the role of brain imaging in disorders of brain-gut interaction [51].

Though the brain is the most likely level for psychological input to interface with visceral input, very few studies have investigated the role of psychological factors in modulating the central nervous system response to visceral sensations. Berman and colleagues studied anticipation of visceral pain [52]. They found that negative affect reduces anticipatory brain stem inhibition. Reduced anticipatory brain stem inhibition in turn was associated with increased brain responsiveness to actual distention [52]. Ringel and colleagues observed that during rectal distension, patients with IBS and abuse history show greater posterior/middle dorsal and anterior cingulate cortex activation, as well as reduced activity of the supragenual anterior cingulate (a region implicated in pain inhibition and arousal) [53, 54]. Gupta and colleagues reported increased connectivity in the left putamen, and decreased connectivity in the supplementary motor area, insular, anterior cingulate cortex, parietal and frontal regions in patients with IBS and a history of early adverse life events [55]. This suggests that early life events may potentiate changes in the brain salience network resulting in increased attention/behavior towards gut sensations. In a case report of a patient with severe IBS and post-traumatic stress disorder, resolution of emotional distress was associated with reduction in activation of the midcingulate cortex, prefrontal area 6/44, and the somatosensory cortex, areas associated with pain intensity encoding [56]. Chen and colleagues [57] found catastrophizing to be related to white matter abnormalities in patients with IBS. Some evidence shows changes in brain responses among IBS patients receiving cognitive behavioral therapy [58] lending credence to the idea that brain focused therapies are helpful in DGBI. Thus, there is evidence that

brain reactions to visceral pain include areas related to emotion modulation and attention control. Although this suggests psychological factors may affect GI sensations through central mechanisms, only a few studies have directly tested this hypothesis. Clinical studies are largely lacking in children with DGBI. Given extensive growth and changes of the brain in the first 25 years of life, the role of the brain in DGBI will need to be studied within a developmental framework.

Stress and the Gut-Brain-Microbiota Axis

In the recent years, the role of gut-microbiota in DGBIs has moved to the forefront of new discoveries. Children and adults with DGBI, compared to healthy controls, have different strains and reduced diversity of the gut microbiota, although studies are far from equivocal in their findings of which strains exactly define DGBI [26, 59]. Most studies have pointed to a decrease in Bifidobacterium spp. [60] in patients with IBS, although this is not specific to DGBI and is reported in a host of other GI and non-GI diseases. It is important to emphasize that most evidence is based on cross-sectional studies that cannot establish cause and effect and the science, although exciting, is far from established.

The purported role of the gut microbiota in DGBIs is likely to occur through the effect on the immune system. Gut microbiota after birth help develop the immune system and can affect how we respond to gut pain [61]. Stress at later points in life has been shown to promote gut microbiota dysbiosis and increase in inflammation [26]. Alterations in gut microbiota are thought to change the gut epithelial barrier, making it more permeable and allowing subclinical inflammatory reactions which may cause DGBI symptoms. Furthermore, these changes in gut microbiota can modulate central brain functioning. Evidence comes from clinical studies showing low-grade inflammation within the gut wall, changes in gut permeability, altered immunological function, and alterations in gut flora in patients with DGBI [62–65]. Many innate and adaptive immune parameters have been studied but among the most robust findings are increased levels of mastcells [66, 67] whose functioning seems to be at least partly driven by CFR-1 as described above. Although most studies have been done in adults, increased gut inflammation has also been shown in children who suffer from FAPD [68–71] and may be associated with co-morbid symptoms such as other pain and nausea [23, 72]. Gut inflammation in IBS is modest and sub-clinical as most patients have normal or near-normal fecal calprotectin concentrations [73, 74] [68, 75].

Psychological factors are thought to affect the microbiota as well as the immune system. For example, there is some evidence in animal models that stress may affect the composition of the gut microbiota [76]. Compared to controls, patients with IBS who also suffer from psychological distress show higher abundance of Proteobacteria, Prevotella/Prevotellaceae, Bacteroides, and lower Lachnospiraceae [77]. There is also robust evidence that stress can affect the immune system. For example, stress reduces antigens production following vaccinations [78, 79] and increases susceptibility to colds [80]. In rats and rodents, stress increased low-grade inflammation in the gut [81–83] as well as esophageal and intestinal permeability [84]. Inhibition of cytokines, such as interleukin-6 (IL-6), normalized stress-induced defecation, suggesting that immune and stress interactions are important in predicting stress-induced DGBI symptoms [85]. Studies in humans also suggest that stress is associated with low-grade inflammation in DGBI. Depression and anxiety scores in IBS patients are correlated with increased mast cells [71, 86]. How close these mast cells are to gut nerves was also associated with ratings of stress and depression [87]. Stress has been associated with increased IL-6 levels in IBS patients [88, 89]. Anxiety has been reported to be associated with increases in cytokine levels in IBS but only after exposure to *Escherichia coli* lipopolysaccharides [90]. Early life stress in IBS patients was associated with brain changes related to mood as well as inflammatory genes [91]. Stress also increases intestinal permeability in healthy volunteers [92]. In youth with IBS, inflammatory markers such as eosinophilia were associated with anxiety [93].

Besides stress affecting the gut, there is also data to suggest that the gut influences the brain. Activation of the immune system either by viral infection or by administration of cytokines or lipopolysaccharide (found on the outer membrane of gram-negative bacteria) induces cytokine secretion and triggers depression and anxiety in healthy volunteers [94, 95]. In addition, immune-targeted therapies such as interferon-alpha treatment for hepatitis C or cancer have been known to induce anxiety and depression in a significant percentage of patients [96–98]. Those who develop major depression during treatment have increased pre-treatment IL6 and IL-10 concentrations [99]. Many authors have suggested probiotic treatment can improve mood, but the evidence is limited at best [100–102]. Only a few trials have investigated the effects of psychobiotics on depression and anxiety with varied results. This may partly be due to differences in types and dosages and duration of the psychobiotics. For now, this evidence seems to suggest that the mood changes in DGBI patients may be partly driven by their gut and hence not completely under their voluntary control [103].

There is large evidence of immune-microbiota interactions suggesting the effect of dysbiosis on gastrointestinal symptoms and mood is through the immune system [104]. However, the interaction of stress with gastrointestinal symptoms may also be through the vagus nerve. The vagal nerve

has been implicated both in neurological modulation of the immune system particularly cytokine control [105] **and** in dysregulation of the brain-gut interactions in DGBI [106]. Vagal sensory neurons react to potentially dangerous bacteria in the GI tract independently of an immunological reaction to their presence: It has been reported that the vagal nerve is stimulated hours before bacteria are able to colonize [107, 108]. In fact, mice with dysbiosis show anxiety-like behavior in the absence of circulating pro-inflammatory cytokines and classic sickness behaviors [107] and in IBS patients no association is found between cytokines and vagal tone [109]. In addition, administration of probiotics reduced anxiety-like behavior in mice with colitis, but only if they had an intact vagus nerve [110]. Thus, the vagal nerve can provide signal to the brain on dysbiosis before inflammatory responses reach the brain through the systemic circulation. Goehler argues that the adaptive value of enhanced anxiety during gut infection may lay in threat avoidance [103]. Behavioral responses to an infection, such as psychomotor retardation, may leave an animal vulnerable to predators. Avoidance of dangerous situations such as open spaces is essential and accomplished by early inducement of anxiety to stimulate threat avoidance. This will put the animal in less danger once sickness behaviors are full-blown. Given that even low-grade inflammation can induce alterations in mood, this may be partially responsible for increased anxiety and depression in DGBI.

Conclusion

There is clear evidence that psychosocial factors can alter gut physiology relevant to DGBI such as effects on motility, visceral sensitivity, immune activity, and gut barrier functioning. The vagus nerve, CRF, and microbiota play important mechanistic roles in stress-related changes of gut-functioning. Some evidence is available that gut-brain interactions are bidirectional, meaning that gut dysfunction can also influence mood. The gut affects mood through similar pathways such as the vagus nerve and microbiota.

One caveat to the above line of research is the almost exclusive focus on a single disease entity: IBS. More research is needed in other DGBI to determine if the bi-directional interactions of stress and gut physiology are general to a larger group of patients and disorders. In addition, pediatric studies are largely lacking. Childhood offers a unique psychosocial environment embedded within different stages of psychosocial and physiological development. Studying these factors would add an extra dimension to the current literature. For example, we know very little about the psychosocial influences on our youngest patients: those with infant regurgitation or toddler's diarrhea; and how early colonization of the gut may be affected by stress. More research is needed to guide our understanding of psychosocial factors in childhood DGBI.

In summary, in order to thoroughly understand DGBI, it is important to look beyond the biomedical causes of these disorders and to consider personal and social factors that influence the symptom report of patients. Clearly, psychosocial factors play a role not only in gut physiology but also in symptom perception and illness behaviors. Children with similar symptoms may show very differential outcomes depending on their psychosocial profile [111, 112]. The child with good coping skills and low anxiety will likely improve quickly; while the child who is anxious, has poor coping skills, experiences a multitude of stressful life events, and has feelings of low self-worth, is more likely to continue to suffer from pain and impairment. Johnny—our case from the beginning of this chapter—was not helped by exclusively treating the biological factors that were driving his symptoms. He needed an integrated treatment approach that consisted of improving delayed gastric emptying (physiological factor) as well as helping him overcome his fear of eating (personal factor) and his mother's worry around feeding (social factor). Symptoms in children with DGBI result from an interplay among biomedical causes and many possible psychosocial factors such as anxiety, depression, hypervigilance to symptoms, inadequate coping, the way parents respond to their pain, bullying, unsanitary toilets at school, and many more.

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Part II

Motility and Sensory Testing

Assessment of Oropharyngeal Function

8

Nathalie Rommel

Introduction

Maturation of feeding skills, fine motor coordination of swallow musculature, and adequate sensory development are key components to develop safe, effective, and efficient swallowing with airway protection and full bolus clearance from the oropharyngeal segment [1–3]. In case of oropharyngeal dysphagia, one or more of these contributing systems may be dysfunctional and the patients' swallow may be considered unsafe and/or ineffective. The relationship between clinical presentation and underlying cause of feeding problems is often unclear and relates to the fact that similar signs or symptoms may reflect different etiologies. Because of this lack of a one-to-one correspondence between clinical presentations and underlying causes of dysphagia, careful identification of symptoms, documentation of their pathophysiology and their relation to the mealtimes is crucial in pinpointing the specific cause of feeding disorders. It is nowadays accepted that feeding difficulties in infants and children need to be assessed from multiple perspectives in order to determine the underlying causes. A multidisciplinary approach has been described leading to better identification and treatment of feeding and swallowing disorders [4]. This chapter describes the clinical as well as most commonly used instrumental techniques that are available to diagnose pediatric patients with dysphagia. The clinical value of these diagnostic tests and their sensitivity to predict outcomes remains, however, often unclear. Despite considerable clinical research efforts, conventional diagnostic methods for pediatric oropharyngeal dysphagia have limited proven accuracy in predicting aspiration and respiratory disease [5, 6].

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Assessment of Oro-Pharyngeal Dysphagia

The assessment of oropharyngeal dysphagia should consist of two major components: the first one is direct observation of the child's feeding and swallowing skills through clinical oral assessment. The second part is assessing the not-visually obvious motor function of pharynx and esophagus through instrumental testing.

Clinical Assessment

The main goal of the clinical oral assessment is to define the underlying cause and the severity of the feeding and swallowing difficulties. In this problem-solving process, the evaluation of the oral cavity and its functions by observation plays a major role. During the clinical assessment, the oral anatomy, motor skills, reflex activity, responsivity, and swallowing are examined and the nature of the feeding problem and necessity for further evaluation of pharyngeal swallowing function with instrumental techniques is established. Normal and abnormal oral motor skills have been described extensively in many anatomy text books, as well as in the developmental and rehabilitation literature [7]. A recent overview published by C. Lau [8] describes the evidence-based research of the past two decades on the development of very-low-birth-weight infants' oral feeding skills. The article provides different functional levels that relate to the child's inability to feed by mouth safely and competently [8]. In order to feed successfully, a child must adapt to the tactile characteristics of tools (breast, bottle, spoon or cup) and food so that the correct motor responses are performed [9]. Oral motor and sensory based feeding disorders can be differentiated [10] and a structured sensory examination in and around the oral cavity allows the examiner to uncover difficulties with the tactile components of feedings. However, it is only possible to observe the reactions to sensations, not the sensations in themselves [11, 12]. Therefore, the term responsivity is more appropriate than sensitivity in the context of

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dysphagia. The child's ability to respond adequately to tactile input can be assessed during a feeding observation or by a structured sensory examination by grading the sensory input. A sensory baseline on consistency, taste, temperature, tools, area of stimulation, and amount needs to be established, defined as the level of tactile input that the child can tolerate without any discomfort. A wide range of tactile responses can be observed and these responses form a continuum of function: aversion, hyperresponsivity, normal tactile responses, hyporesponsivity, and absent responses [9]. When tactile responses are severely diminished or absent, a significant sensory impairment should be suspected which can hinder oral feeding. In hyporesponsivity, strong stimulation is required and the responses are slow or partial. A hyperresponse is exaggerated or out of proportion to the strength of the stimulus. While similar to hyperresponses, aversive responses are even stronger and more negative. Both hyperresponses and aversive responses can be part of a general tactile processing problem or be localized to the face and mouth or even more specifically to a certain part of the mouth, most frequently the tongue [13].

To structure the oral feeding and swallowing assessment, a clinical assessment scale or checklist for pediatric dysphagia can be used. Many scales have been provided; however, only few have a sound theoretical merit [12]. A few systematic literature reviews on the available non-instrumental assessment scales for feeding and swallowing in the pediatric population have been published [5, 14]. The authors confirmed that information on the validity and reliability of these pediatric assessment scales is scarce, hence emphasizing that psychometric evidence was inconsistent and inadequate for the evaluative tools. Psychometric analysis of the used clinical assessment scales is needed to avoid incorrect interpretation and inconsistent use [1, 4, 15]. Recently, more validation evidence on dysphagia assessment tools has become available for specific pediatric populations such as neonates [16] and children with cerebral palsy (CP) [17].

During the examination, the clinician will also determine whether the parent's reports and perceptions match the observations by the clinician [18]. Referrals can then be made for further assessment or multidisciplinary management and a targeted treatment plan can be developed.

Instrumental Testing

Instrumental assessment has the potential to assess oropharyngeal function objectively if selected and applied properly. A variety of clinical and instrumental diagnostic techniques are used. Each technology has strengths and limitations and the specifics of each diagnostic method have been extensively described for use in adults [19, 20]. This section will discuss the most commonly used gold-standard and some emerging evaluations for diagnosing pediatric patients with dysphagia within a multidisciplinary context.

When supplemental instrumental assessment of the pharyngeal swallow is required, a variety of pharyngeal and UES dysfunctions can be distinguished. The pharyngeal pathology varies with the pharyngeal region it occurs in. For example, velopharyngeal hypocontractility may lead to nasal regurgitation, and hypopharyngeal weakness may lead to bolus residue proximal to the UES. Upper esophageal sphincter patterns range from a normal to incomplete UES relaxation.

Common assessment techniques available for use in the pediatric population include fiberoptic endoscopic evaluation of swallowing (FEES), videofluoroscopy, and pharyngeal-esophageal manometry. In practice, the use of a particular instrumental technique often depends on the institutional experience, available resources, and its commercial availability rather than being based on the performance characteristics of the test. The main argument of using instrumental techniques in addition to clinical examination is to provide a more precise understanding of the biomechanics of the child's swallow which then will lead to a more targeted therapeutic intervention [21]. The challenging decision is when to refer for instrumental assessment and for what type of testing.

Videofluoroscopy

Videofluoroscopic swallow study or modified barium swallow has been considered the diagnostic study of choice to evaluate oropharyngeal swallowing anatomy and physiology for many years now [4]. Videofluoroscopy is a dynamic continuous radiological examination of the anatomy and function of the oral cavity, pharynx, and UES opening that includes lateral and frontal views while swallowing a high-density barium or non-ionizing contrast bolus of different consistencies. This test examines oral and pharyngeal regions with the child seated in an upright or semi-reclined position [22]. Once the swallow disorder is identified, postural or therapeutic interventions can be suggested to reduce the swallowing problem [4]. The entire examination is recorded for review afterwards.

The main reason for referral for videofluoroscopy is aspiration risk [23]. The most widely used validated scoring system to assess the presence and severity of aspiration and penetration in relation to swallowing is the Penetration–Aspiration Scale [24].

Videofluoroscopy has limitations, such as the need for ionizing radiation and thereby the reluctance to repeat the procedure, the child unfriendly environment of the radiology

suite and the mainly qualitative nature of information obtained. However, with some custom-made software programs, it is feasible to derive numerical measures such as the timing of opening or closing of the velopharyngeal junction, laryngeal entrance, and upper esophageal sphincter, which provides information on airway protection mechanisms and can be used to assess aspiration risk [25, 26].

Quantative fluoroscopy measures such as 'oral transit time' and 'pharyngeal transit time'are not routinely collected in clinical practise, and more so not in pediatrics, because they are time consuming and their clinical impact is not well documented. Patients are not usually referred for fluoroscopy until they have deteriorated clinically with symptoms. In pediatrics fluoroscopy is, as in adults, mainly used as an assessment method for symptomatic patients, with repeated fluoroscopy only performed occasionally because of the radiation exposure and evidence that fluoroscopy is a fairly poor predictor of development of aspiration pneumonia [23, 27]. Videofluoroscopy with manometrical evaluation has become more commonly used and is indicated to rule out the specific cause of deglutitive aspiration, to assess the presence and impact of pharyngeal dysfunction and upper esophageal sphincter function or in case there is no therapeutic progress 2 months after the initial videofluoroscopy. In other words, videomanometry is used to provide biomechanical and quantitative explanations for the radiological findings as well as for patients symptoms of abnormal pharyngeal bolus transport [27].

Fiberoptic Endoscopic Evaluation of Swallowing (FEES)

In fiberoptic endoscopic evaluation of swallowing (FEES), a flexible laryngoscope is used to view pharyngeal and laryngeal structures before, during, and after deglutition [28, 29]. During the test, the endoscope is introduced transnasally and advanced to enable visualization of the mucosal surface and movement of the tongue base, pharynx and larynx, as well as the bolus transit and airway protection. During the normal swallow, a white-out period of ~0.5 s occurs at the time of epiglottic tilting and maximal pharyngeal closure, which prevents viewing of the entire swallow [29]. During the examination, the patient swallows a variety of foods and liquids with a coloring contrast (blue dye or milk) added to maximize visualization of the bolus. FEES provides visual feedback on aspiration and penetration, qualitative information on morphology, presence of secretions and residue, the timing of the swallow onset, and clearance of residue. FEES is a commercially available diagnostic system and, over the past 15 years, has been used to evaluate swallowing in relation to aspiration and penetration [30], head posture [31], and bolus type [32–34]. Recently, a pediatric protocol, the safety and clinical efficacy of FEES in infants and children have been published [35] This latest study confirms former pediatric reports on the use of FEESs, and describes that the FEES procedure is well-tolerated and safe with no respiratory distress or cyanosis during or after the procedure [36–41], is repeatable and, as it is portable, can be performed at the bedside [37]. The limitations of FEES are that it does not allow quantification of the swallow physiology and relies on subjective interpretation of findings such as residue.

Manometry and Impedance

Manometry can be used to assess pharyngo-esophageal motor function such as pharyngeal weakness or impaired UES relaxation [42] and has been used to describe alterations in pressure patterns in relation to age-related changes, neurodegenerative disease, post-surgical dysfunctions, and UES obstruction [43–45]. However, while manometric recordings may identify functional abnormalities that may predispose to aspiration risk, manometry on its own cannot predict circumstances when aspiration is likely. Therefore, impedance measurements have been used as a technique to detect failed bolus transport in relation to swallow motor function. The combined analysis of manometry impedance measurement to assess the adult pharyngeal swallow function has recently been accepted by an international working group as a core methodology [46].

Manometric and impedance technologies have evolved in recent years such that catheters with closely spaced pressure-impedance arrays are more widely available. Over the last 5 years, high-resolution manometry with impedance (HRMI) with automated pressure flow analysis (PFA) has been accepted as a method to diagnostically interpret pharyngeal and UES function in adults [46, 47]. Pressure sensors measure activity of swallow musculature, whilst impedance electrodes provide metrics which indicate bolus flow. PFA derives a range of swallow metrics that indicate contractile vigor, intrabolus pressure, bolus presence before and after the swallow, bolus flow timing, and UES diameter and thereby delivers a non-subjective evaluation of different mechanical components of pharyngeal swallow [48]. A global swallow risk index (SRI) generated from PFA metrics as a means to amplify dysfunction has shown in adults as well as in children to correlate with the presence of aspiration and/or postswallow residue as seen on videofluoroscopy [47, 49]. Figures 8.1, 8.2, and 8.3 illustrate, respectively, a normal pharyngeal swallow, an abnormal pharyngeal swallow, and an abnormal UES function during swallowing of a pediatric patient, both on radiology and on high-resolution impedance manometry plot.

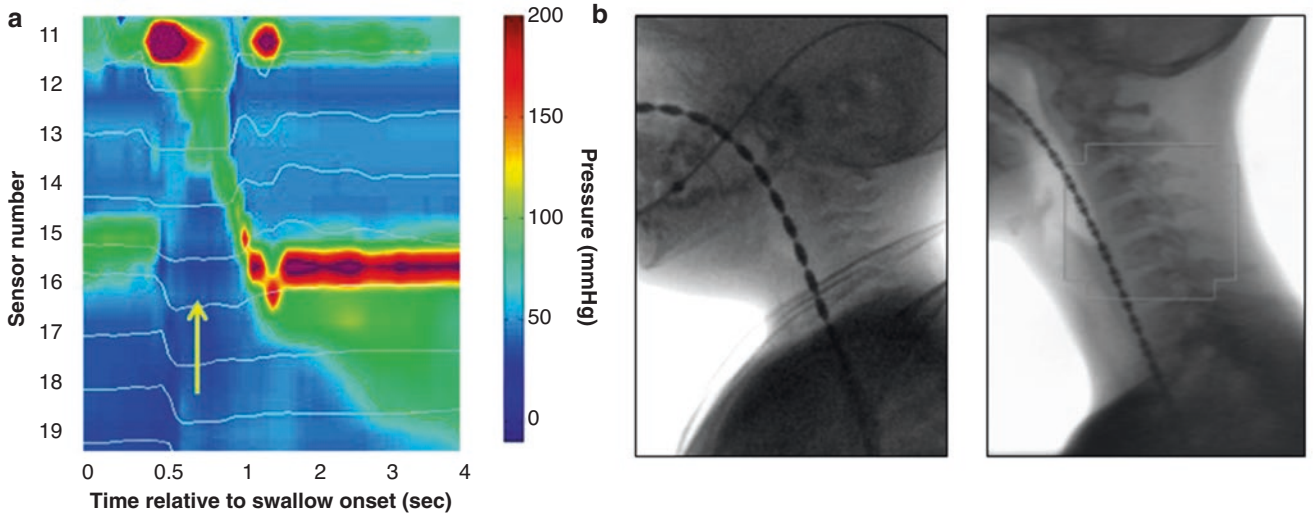

Fig. 8.1 (**a**) HRM color plot of a normal liquid swallow in a 5-year-old child. Pressure is indication according to color code illustrated. (**b**) Lateral radiological view of the pharynx and UES showing the transnasal placement of the HRM solid state catheter in a 5-year and 11-year-old child

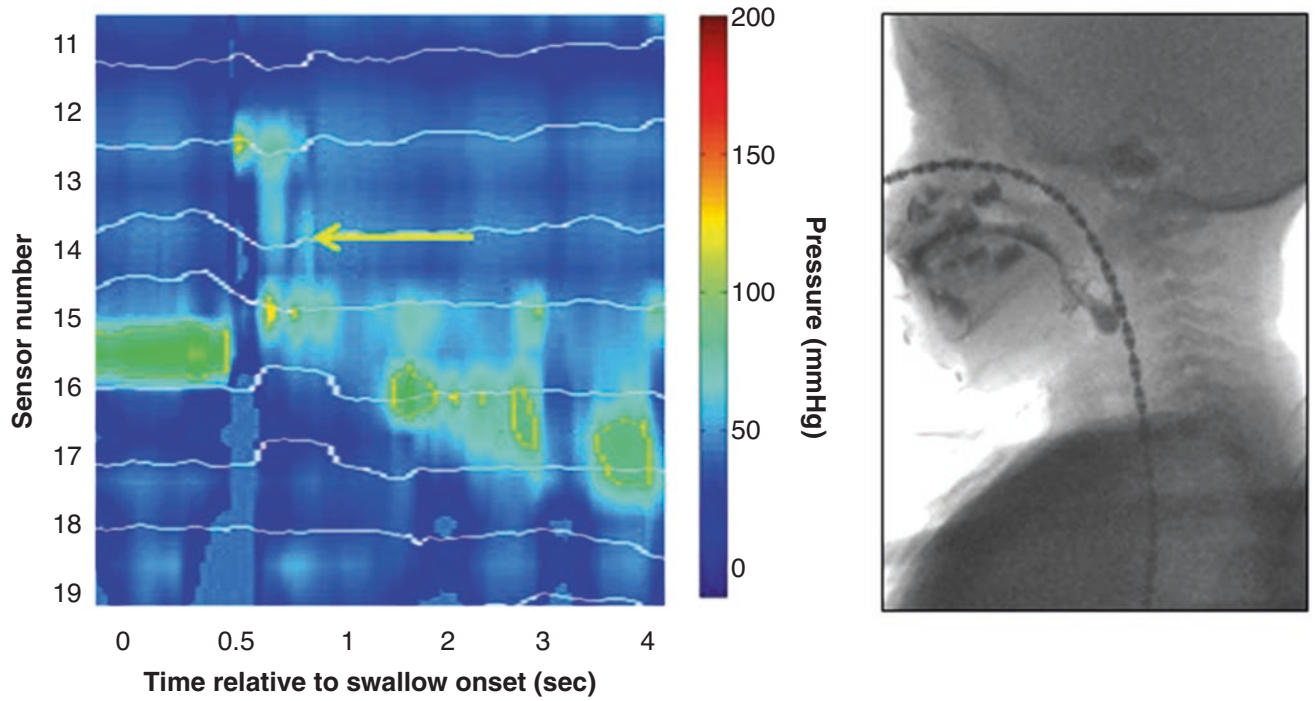

Fig. 8.2 HRM plot illustrating adequate UES relaxation and a hypocontractile pharynx in a 2-year-old patient presenting with dysphagia on liquids. Radiology shows postswallow residue in the piriform sinus and poor UES opening secondary to poor pharyngeal bolus propulsion despite complete UES relaxation

PFA has been validated and is now clinically used in pediatric patients with oropharyngeal dysphagia and showed dominant risk variables predictive of aspiration on videofluoroscopy in children [50–53]. Also, specific pediatric methodological aspects have been described [52]. For example, piecemeal deglutition (defined as swallowing of a single bolus in two or more portions) is a typical normal swallow pattern seen in children. PFA showed reduced bolus volume and altered biomechanics of swallowing in piecemeal deglutition and is therefore a necessary consideration for accurate HRIM analysis of swallow function [52].

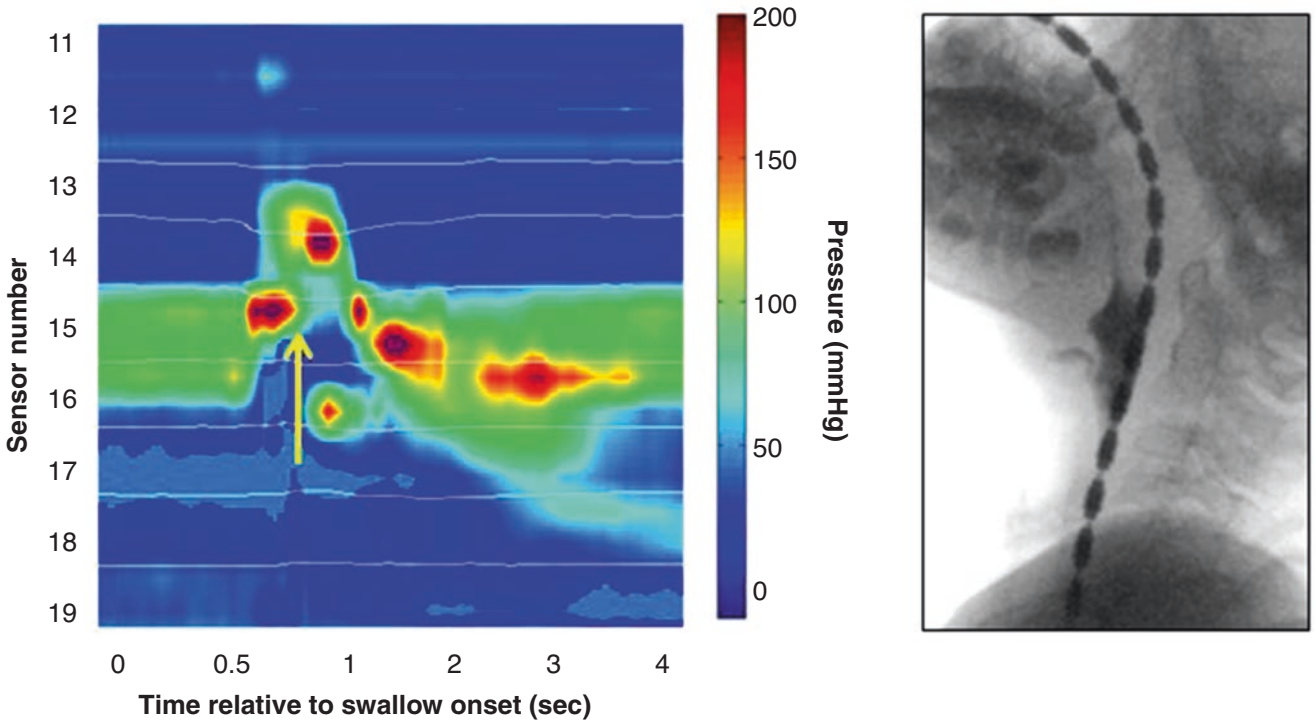

Fig. 8.3 UES dysfunction in a 4-year-old girl with CP presenting with chronic dysphagia and recurrent aspiration pneumonia. Increased pharyngeal intrabolus pressure as a result of resistance to bolus flow across a non-relaxing UES. This example illustrates that intrabolus pressure can only occur when pharyngeal pressures are intact. Naso-oropharyngeal contractions fail in this patient and intrabolus pressure cannot be determined

Summary

Regardless of the primary medical pathology, it is crucial to assess the core biomechanics of swallow physiology with assessment techniques which are as objective as possible. Incorporation of measurable objective assessments into clinical diagnosis is needed and might be key in developing novel therapeutic strategies for infants and children with dysphagia. Recent advances using different instrumental technologies are promising and need ongoing validation in the pediatric population.

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pH Monitoring and Impedance

9

Kornilia Nikaki

Abbreviations

AET	Acid exposure time
CMPA	Cow's milk protein allergy
ERD	Erosive reflux disease
GOR(D)	Gastro-oesophageal reflux (disease)
LOS	Lower oesophageal sphincter
MNBI	Mean nocturnal baseline impedance
NERD	Non-erosive reflux disease
pHMII	pH-IMPEDANCE
PSPW	Post-reflux swallow-induced peristaltic wave
RI	Reflux index
SAP	Symptom association probability analysis
SI	Symptom index

Introduction

Detailed investigations and objective measurements in patients with signs and symptoms suggestive of gastro-oesophageal reflux disease should be performed with the intent of (a) making the appropriate diagnosis and (b) enabling choice of appropriate therapy. This is particularly important in children and especially those who do not respond to standard treatment. The two modalities that are commonly employed in paediatric practice are endoscopy and reflux monitoring. As endoscopy involves a general anaesthetic and its main role is to rule out other pathology [1], reflux monitoring is often the first investigation performed, especially in children under the age of 1 year.

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Reflux Monitoring

pH-Metry

Oesophageal pH-metry can be performed using either a catheter-based or capsule-based wireless system. Despite the invasive nature of catheter-based testing (due to the need for nasal intubation), it is the main type of reflux monitoring applied in paediatrics, as wireless pH-metry can only be applied in children above the age of 4 years and requires an endoscopy under general anaesthesia.

pH-metry allows detection of increased oesophageal acid exposure, and analysis of reflux/symptom association. For the latter, the most commonly used tools are the Symptom Index (SI) and the Symptom Association Probability analysis (SAP). pH-metry is used to assess oesophageal acid exposure. Currently, a reflux index (RI) (i.e. acid exposure time) >7% is considered abnormal, a RI <3% is considered normal and an RI between 3 and 7% is indeterminate [2]. There is a moderate correlation between pH-metry, symptoms evaluation and biopsy results. In a study by Salvatore et al. [3], symptoms recorded by questionnaire (I-GERQ) had poor correlation with pH-metry results. Furthermore, 38% of infants with a pathologic pH-metry had normal endoscopy and biopsy and 53% of infants with histologic oesophagitis had normal pH-metry.

Impedance-pH-Metry

Silny et al. [4] first described impedance monitoring, a novel method of detecting intra-oesophageal bolus movement. The method measured the resistance to alternating current (impedance) of the oesophageal lumen content. The pairs of electrodes on the catheter form a closed circuit when they come into contact with the food bolus, refluxate or oesophageal mucosa. Therefore, the appearance of a liquid swallow, for example, is recognised as a sudden drop in impedance while presence of gas is recognised as a sharp rise in impedance (measured in Ohms).

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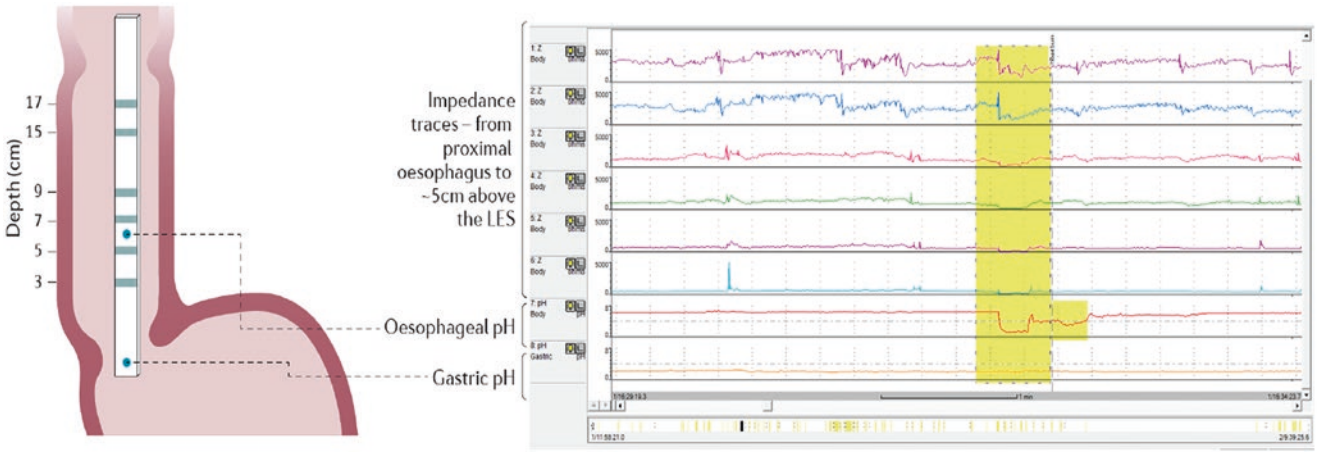

Fig. 9.1 Example of and adult combined multichannel intraluminal impedance and pH catheter. Numbers indicate distance above lower oesophageal sphincter (LOS). The yellow marked area demonstrates an episode of acid reflux – the impedance trace shows an aborally progressing decrease in impedance (liquid reflux). (from Nikaki et al., Nat Rev. Gastroenterol Hepatol 2016)

Oesophageal impedance monitoring allows detection of reflux events regardless of the pH [5] – Fig. 9.1. Impedance and pH monitoring are usually combined allowing a distinction between acid (pH <4), weakly acidic (pH 4–7) and alkaline (pH >7) reflux episodes [6]. Impedance-pH monitoring should be analysed in a quantitative fashion, similar to pH-metry, by detecting increased numbers of reflux episodes (acid and non-acid), prolonged oesophageal acid or volume exposures or increased numbers of proximal reflux events. When analysed in this fashion, the primary goal of the study is to confirm diagnosis of Gastroesophageal reflux disease (GORD) and most investigators prefer to have withheld Proton Pump Inhibitors (PPI) therapy for 7 days before the study.

Catheter Choice, Placement, and Recording Conditions

The pH-impedance catheters for children most commonly have an internal reference electrode, six impedance rings and one antimony pH-measuring electrode in between the two most distal impedance rings (oesophageal pH sensor) with or without a second pH sensor at the most distal end of the catheter (gastric sensor). The catheter length and spacing of the impedance rings are dependent on age (and height/oesophageal length). Usually, for infants (<1 year of age) the impedance rings are spaced 1.5 cm apart and for older children (>1 years) the spacing is 2 cm. Catheters need to be calibrated as per manufacturer instructions and accurate calibration is important to avoid erroneous results and malfunctioning sensors that render the study uninterpretable.

The catheter is passed trans-nasally into the oesophagus and stomach with the aim of sitting the pH sensor at 1.5 cm above the lower oesophageal sphincter (LOS) for infants, 3 cm above the LOS for young children (<10 years) and 5 cm above the LOS for older children (>10 years). The length of the catheter at the nasal flare is estimated based on height either using the Strobel formula [(0.252 x body length in cm) +5] or using the method described by Mutalib et al [7] The position of the catheter is radiologically confirmed so that the pH sensor lies above T8 and/or 2 vertebrae above the diaphragm. If oesophageal manometry is performed, then the pH sensor is similarly distanced above the upper border of the LOS.

The child and family should be advised to continue with their daily routine and eating habits. A bath or shower should be avoided in case the recorder gets wet or the tape holding the catheter in place comes off. Parents should not try to reposition the catheter if the child pulls or vomit it out. Hard candy and chewing gums should be avoided in case they get stuck to the catheter and cause a chocking episode. Fizzy drinks, caffeine, alcohol and acidic fruits/juices should also be avoided (although swallows of acidic foods can be recognised in pH-impedance and excluded from the study analysis). The study duration should be ideally 24 h with a minimum of 18 h for reliable trace analysis. During the study, the parents or older child are asked to record meal times (beginning and end), upright and supine position (periods of sleep) and symptoms. The buttons on the recorder may be re-allocated from what intended from the manufacturer to allow for patient specific reflux symptom correlation and this should be recorded on the patient's diary. With this in mind, it is wise to remember that SI and SAP have been validated in adults for typical reflux symptoms only (i.e. regurgitation, heartburn and chest pain).

Apart from PPIs, antacids, prokinetics, histamine 2 blockers and muscle relaxants that affect the LOS (such as baclofen) should be discontinued prior the study based on their pharmacokinetics and half-life.

The British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN) position statement

[8] and the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) standard protocol [9] offer further detailed guidance on the methodology of pH-impedance monitoring in children.

Interpretation

Once the study is completed and downloaded, an automatic study analysis is performed which needs to be manually assessed and validated before further clinical interpretation and correlation is made. As a first step, the panoramic view of the study should be used to assess for any technical errors (e.g. calibration error of sensors) and an overview of the study results. Then the study should be opened up to a 4–5 min window, so that each individual reflux event can be manually accepted/confirmed and pH drops validated (i.e. exclusion of pH drops related to swallows). During this detailed analysis, the physician should also look at the frequency of air swallows, gastric and supragastric reflux events, extend of proximal events and frequency of symptoms. If the same symptom button has been pressed more than once within a few seconds, then the first event is accepted and the rest deleted in order to avoid a false positive reflux symptom association. Once the manual analysis of the study is completed, then the results of the study should be reviewed and reported. The interpretation of each parameter assessed is discussed below in detail and Table 9.1 offers a compact summary.

Table 9.1 pH-impedance parameters used in the interpretation of paediatric and adult reflux monitoring studies

Parameters	Infants (%)	Children (%)	Adults (%)
Total oesophageal acid exposure (reflux index)	Normal: ≤6 Abnormal: >6	Normal: <3 Indeterminate: 3–7 Abnormal: >7	Normal: <4 Indeterminate: 4–6 Abnormal >6
Total number of reflux events/24 h	Abnormal: >100	Abnormal: >70	Normal: <40 Indeterminate: 40–80 Abnormal:>80
Acid vs non-acid reflux events	In health, acid: 25	GORD, acid: 49	In health, acid: 49 GORD, acid 65
Air vs liquid reflux events	In health, gas or mixed: 7.7	GORD, gas: 4	In health, gas or mixed: 52–64 GORD, liquid: 47–56
Distal vs proximal reflux events	In health, proximal: 85.7–90	In health, proximal: 70	In health, proximal: 30 GORD: 59
Symptom index (SI)	Positive: >50	Positive: >50	Positive: >50
Symptom association probability (SAP)	Positive: 95	Positive: 95	Positive: 95
Novel parameters			
Baseline impedance			Normal: >1350 ohms (Sifrim et al. [10])
PSPW			Abnormal: 15–19 (Sifrim et al. [10])

Oesophageal Acid Exposure Time

The median reflux-related acid exposure (excluding pH-only events) in a study of healthy preterm neonates was 1.66% (range: 0–6.43%), while the median total oesophageal acid exposure time (including pH-only events) was 5.59% (range: 0.04–20.69%) [11]. Due to the ethical considerations of performing an invasive test in asymptomatic children, studies in children are limited to controls subjects and the previous ESPGHAN guidelines suggested that a reflux index (RI) (i.e. acid exposure time) >7% is considered abnormal, a RI <3% is considered normal and an RI between 3 and 7% is indeterminate [2]. These values seem to be in concordance with the adult values that are currently in use. The Lyon Consensus defines as conclusive evidence for GORD an acid exposure time of >6% and borderline or inconclusive an acid exposure time of 4–6% [12]. More recently, in a large cohort of adult healthy volunteers from different ethnic backgrounds, normal values (95th percentile) for oesophageal acid exposure have been assessed and defined as 2.8% for Diversatek and 5% for Laborie studies [10], with no effect of gender or age on these values. In the same study, the nocturnal oesophageal acid exposure time has been defined as 0.9–4% [10].

Total Number of Reflux Events

In regard to the number of reflux events that is considered to be within normal, there are no data derived from healthy children and arbitrarily most centres will use >100 reflux events in 24 h in infants of less than a year of age as the cut-off for a pathological pH-multichannel intraluminal impedance (pHMII) study and >70 reflux events (in 24 h) in children older than 1 year [13, 14]. More recently, an Italian multicentre retrospective study reported on the normal values of reflux events in infants and children who were symptomatic but showed a reflux index below what is accepted as normal for their age group (i.e. RI <6% in infants and <3% for children). They found that there is a positive age correlation for acid reflux events and a negative age correlation for weakly acid

reflux events with the total number of events reported as around 70 for newborns and infants and 50 for older children (>1 year of age) [15]. So far there is no impedance-pH-metry standard parameters that accurately predict the presence of histologic oesophagitis in children [16]. Comparatively, the number of physiological reflux events in adults is set at 40 per 24 h and there is a 'grey' zone for 40–80 reflux events per 24 h [12]. Recently, it has been identified that the 95th centile of total reflux events/24 h in asymptomatic individuals is 55 for Diversatek studies and 78 for Laborie studies [10]. In both paediatric and adult reflux disease, the total number of reflux events increases with the disease severity (NERD, ERD and Barrett's oesophagus) [17–19].

Acid Versus Non-acid Reflux Events

The acidity of reflux events in the absence of GORD has been evaluated in a study of premature neonates and the median number of reflux events was 71/24 h out of which 73% were weakly acidic with the remaining 25% being acidic and 2% alkaline [11]. A positive correlation between age and acid reflux events with a negative correlation of age and weakly acidic events has been reported in paediatric control patients [15]. This signifies that the high proportion of non-acid reflux events in infancy reduces over time and is replaced by dominance of acidic reflux events towards adulthood. The majority of the reflux events in healthy adult volunteers occur in the post-prandial period and are equally distributed between acidic and weakly acidic in nature (49% each) with weakly alkaline constituting only 2% of the events [17]. In paediatric GORD, 15% of symptomatic events are preceded by a pH only event, 42% by a weakly acid event and 43% by an acidic event [20]. A fall in pH <4 in the absence of reflux detected by impedance is described as a pH-only event [21]. In adult GORD, there is a positive correlation between increasing disease severity and the percentage of acidic events (around 65%) [17, 18].

Air Versus Liquid Reflux Events

Only 7.7% of the reflux episodes are gas only (sharp rise of impedance >3000 Ohms) or mixed of gas and liquid events in healthy preterm neonates [11], with the great majority being liquid reflux events (>50% drop in impedance lasting 4 s with a retrograde propagation over the distal two impedance sensors [10]). In children with symptoms of GOR but with normal AET normative values, data on the air-liquid composition of reflux events have not been published till present. Interestingly, there is an intra-observer variability in pH-impedance analysis, with 60% of pH-impedance analysis experts not marking gas reflux events as they were considered as insignificant [22]. In contrast, the majority (52–64%) of reflux events in healthy adults are gas containing [17, 23]. In children with GORD, only 4% of the reflux events are due to gas reflux [20] and the majority are liquid events. In adult GORD, the pattern changes from health to disease state and the proportion of liquid events increases (up to 47–56%) with increasing disease activity [17, 18].

Distal Versus Proximal Reflux Events

The proximal extend of reflux events reaching the proximal oesophagus, in a study of premature neonates with no signs of GORD, is defined as 85.7–90% of reflux events during fasting and feeding periods [11]. Similarly, the majority of reflux events reaches the proximal oesophagus in children as well [24], whereas in healthy adult volunteers, the percentage of reflux events extending to the proximal oesophagus is only 30% [17]. In adult NERD and ERD, the proximal reflux events also increase and make up to 59% of the total [17, 18].

Novel Impedance Parameters

Other impedance parameters (other than the number of reflux episodes or volume exposure) such as gas movement, impedance baseline and the post-reflux swallow-induced peristaltic wave (PSPW) have been recently proposed to increase the yield of diagnosis of reflux disease.

Impedance allows tracking of intra-oesophageal air movement and distinction between gastric belching from supragastric belching [25]. Impedance baseline values correlate well with oesophageal mucosal integrity status [26]. In children with endoscopic oesophagitis, impedance baseline is lower compared to children with NERD [27, 28]. Impedance baseline seems to be age dependent, as a lower baseline impedance is noted in the younger age group (<48 months) [29]. Treatment with PPI increases impedance baseline [30].

Changes in impedance can also be used as a proxy of peristalsis-associated oesophageal clearance [31]. Episodes of gastro-oesophageal reflux are cleared by swallow-induced (primary) or secondary peristalsis. The effect of such peristaltic activity can be assessed by changes in impedance after reflux. The post-reflux swallow-induced peristaltic wave (PSPW) index has been proposed as a measure of the oesophageal clearance ability in adult patients with different GORD phenotypes. The median PSPW value for adult healthy volunteers has been defined as 50%, [10] but it is noted that PSPW cannot be used in isolation for the diagnosis of GORD. The probability of chance association between reflux events and swallowing when calculating PSPW has been

defined to 30% when a 30 s window for PSPW calculation is used [32]. High proximal reflux extend, gas containing reflux events and reflux events occurring in the awake state are more likely to be associated with PSPW in healthy adults, leading to a shorter chemical clearance time [32]. PSPW is correlated to oesophageal hypomotility and is a better indicator for oesophageal reflux clearance to peristaltic contraction reserve [33]. The usefulness of PSPW index is yet to be assessed in the paediatric population.

The value of MNBI (mean nocturnal baseline impedance) and PSPW in adult GORD diagnosis has significantly expanded in recent years. Abnormal MNBI, PSPW and number of reflux events have been shown to improve the diagnostic yield of reflux monitoring in adult GORD [34]. Both of these novel parameters are useful adjunctive metrics in patients with inconclusive GORD based on the Lyon consensus classification [12] and can predict PPI response [35]. Interestingly, abnormal PSPW and MNBI can better predict PPI response, compared to abnormal acid exposure time and symptom association analysis, in patients with reflux related cough as well [36].

Symptom Association Analysis and Reflux Monitoring 'OFF' and 'ON' PPI Treatment

The temporal relationship between reflux episodes and symptoms is expressed by the Symptom Index (SI) and Symptom Association Probability (SAP). The SI is defined as the percentage of reflux-associated symptoms divided by the total number of symptoms. The SI is positive when >50% and is likely to be falsely positive if there is a large number of symptoms with a relatively small number of reflux events. The SAP is a statistical analysis of symptom correlation with the use of Fisher exact test where the study is subdivided in 2 min interval windows, and the presence or absence of reflux events is noted. The SAP is positive when >95% and is likely to be false positive when there is paucity of symptoms recorded and a relatively large number of reflux events. In paediatrics, the clinical interpretation of these markers needs caution as the symptoms are often reported by parents and need to be recorded in a timely fashion to avoid false negative results. Moreover, the physiologically higher number of reflux episodes in infants or a vigilant parent who over-reports symptoms may lead to false positive results, as explained above.

Great debate exists about whether to perform reflux monitoring 'on' or 'off' PPI. Many patients are referred for reflux monitoring after failing empirical PPI treatment. In this scenario, where the pre-test probability of GORD is low, reflux monitoring 'off PPI' can help rule out GORD if both the test and the symptom analysis are negative. Also, children without oesophagitis who are being considered for a surgical or endoscopic anti-reflux procedure should also be tested 'off PPI'. In the case of a patient with a high pre-test probability of GORD (i.e. previous positive endoscopy or reflux monitoring) with refractory typical symptoms while on an adequate dose of PPIs, it is useful to perform pH-impedance monitoring 'on PPI' to identify if residual symptoms are reflux-related.

No studies comparing the usefulness of reflux monitoring performed 'on' and 'off' PPIs are available in paediatrics. Many clinicians believe that since pH-impedance monitoring can detect non-acid reflux, it is acceptable to perform the study 'on' PPI treatment. However, this should not be the case for children without a previously established diagnosis of GORD. The decision of interrupting PPI treatment for the reflux monitoring test has to be balanced against the risk of aspiration in selected patients where PPIs may have a role in reducing gastric volume [37, 38].

Impedance-pH Versus pH-Metry

The added value of impedance pH-metry over pH-metry has been shown in a large study in children with GORD symptoms. Whereas 18% of children only displayed abnormal acid exposure, 37% displayed pathologic pH and impedance measurements and 45% only displayed abnormal impedance measurements [14]. It is estimated that pH-monitoring results change clinical management in 40% of the times, with an added 22% based on the impedance pH-metry results [39].

GORD Phenotyping

The Rome IV subclassification of reflux disease has only recently been adopted in paediatric practice [40, 41]. The Rome IV consensus criteria [42] subdivide adult patients with reflux symptoms into: (1) erosive oesophagitis; (2) non-erosive reflux disease (NERD - symptoms with normal endoscopic appearance and pathological oesophageal acid exposure ± positive symptom-reflux association); (3) hypersensitive oesophagus (symptoms with normal endoscopic appearance, physiological oesophageal acid exposure but positive symptom-reflux association); and (4) functional heartburn (symptoms with normal endoscopic appearance, physiological oesophageal acid exposure and no symptom-reflux association) – Fig. 9.2. All but functional heartburn are deemed to fit within the GORD umbrella – i.e. the symptoms are caused by reflux of gastric contents into the oesophagus.

When the adult classification is applied in paediatrics, the most common phenotype in children is functional heartburn

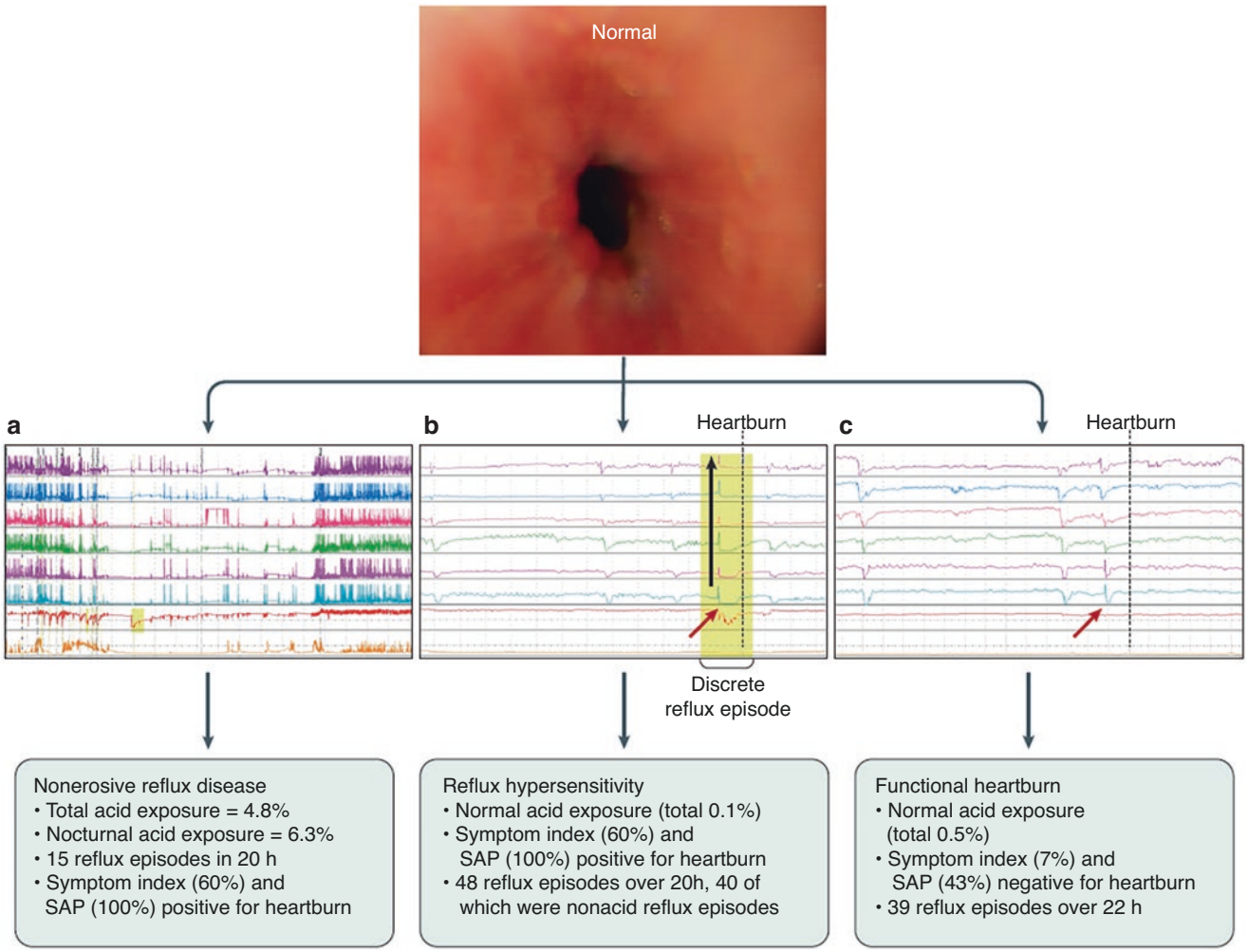

Fig. 9.2 Phenotypes of adult patients with GORD symptoms and normal endoscopy. (**a**) Patient with NERD; increased acid exposure. (**b**) Patient with Hypersensitive Oesophagus; normal acid exposure and positive reflux symptom association (note the symptom marker following a reflux episode). (**c**) Patient with Functional Heartburn; normal acid exposure and negative reflux symptom association (note the symptom marker not preceded by reflux) (from Nikaki et al., Nat Rev. Gastroenterol Hepatol 2016)

(44%), followed by reflux hypersensitivity (29%) and 'true' NERD (27%) [40]. The importance of classifying GORD lies in the implications to choice of treatment (i.e. anti-reflux surgery, PPIs, pain modulators, cognitive behavioural therapy) that have been clearly demonstrated in adult GORD but no so well yet in paediatric GORD [43].

pH-Impedance in Rumination Syndrome

Rumination syndrome is defined by effortless, repeated regurgitation of food into the mouth that is then either chewed and swallowed or expelled, without preceding retching or nausea [44]. Rumination episodes occur when increased intragastric pressure, generated subconsciously by contraction of the abdominal wall muscles, diaphragm and intercostal muscles, overcomes the pressure at the gastro-oesophageal barrier leading to a retrograde movement of gastric contents into the oesophagus and mouth [45]. In clinical practice, patients will present with recurrent regurgitation or vomiting but unless a detailed history is taken with explicit questions targeted to a positive diagnosis of rumination syndrome, the condition is often misdiagnosed or delayed leading on occasions to unnecessary investigations and treatments [46, 47]. In patients where a clinical diagnosis is challenging or not accepted, the current gold standard for the diagnosis of rumination syndrome is oesophageal high-resolution manometry/impedance [48]. More recently though the criteria for the diagnosis of rumination syndrome based on 24 h pH-impedance monitoring have been defined in adults and paediatrics [49, 50] (Fig. 9.3) opening up the opportunity of early diagnosis and improved stratification of patients presenting with PPI-refractory reflux symptoms and reflux hypersensitivity [51].

Fig. 9.3 pH-impedance parameters that distinguish children with rumination syndrome with 75% sensitivity and 80% specificity (from Nikaki et al., JPGN 2020)

Impedance-pH parameters	Cut-off value	Score
Proximal RE per 24 hours	>57.5	1
Postprandial nonacid RE hour	>2	1
SAP for regurgitation/reflux/vomiting	>95%	1

Rumination syndrome diagnosis should be considered when the total score is ≥2. RE = retlux events; SAP = symptom association probability.

Aerophagia, Gastric Belching, and Supragastric Belching

Air swallowing and gastric belching is observed in children with increased oesophageal acid exposure [52]. A median of 29 air swallows per 24 h has been reported in children with total oesophageal acid exposure of <3% and this increases to 72.5 air swallows per 24 h in children with total oesophageal acid exposure of >7% [52]. Air swallowing is increasing the likelihood of gastric belching events and the median number of gastric belches that are related to retrograde bolus flow are significantly higher in children with abnormal oesophageal acid exposure time (15 episodes /24 h) versus children with normal acid exposure (6 episodes/24 h) – $p < 0.001$ [52]. Interestingly, significant supragastric belching is rare in children [52].

CMPA and GORD on pH-Impedance

Feeding difficulties, vomiting and failure to thrive in infants can be attributed to both cow's milk protein allergy (CMPA) and GORD. The causative and pathophysiological relationships between the two entities are not fully established. Recently, it has been demonstrated that there are no diagnostic markers on pH-impedance that can reliably predict CMPA and there are no differences on pH-impedance at baseline between CMPA and GORD [53]. At follow up, pH-impedance shows that in children with CMPA dairy elimination leads to a decrease in oesophageal acid exposure, improved acid clearance time and improved baseline impedance at 5 cm above the LOS, while there is no difference in the number of reflux events, acid and non-acid. The latter is in contrast to previous findings that a cow's milk challenge in infants with CMPA increased the number of weakly acid reflux events, but not the total acid exposure time [54].

Overall, pH-impedance is a valuable tool in the assessment of gastro-oesophageal reflux symptoms when performed accurately and interpreted with attention to detail. The physician reporting the study should keep in mind the limitations of the study in paediatrics and use its results as part of a jigsaw in the clinical diagnosis of GORD and future patient management. Further research in the field is needed in order to determine the parameters of pH-impedance that can predict treatment outcome in infants and children and elucidate the role of the novel pH-impedance parameters in paediatric GORD.

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Esophageal Manometry

10

Michiel van Wijk

Normal Esophageal Motility

The esophagus is a muscular tube that consists of the upper esophageal sphincter (UES), esophageal body, and lower esophageal sphincter (LES). The UES closes the esophagus from above when no food is swallowed and opens when a swallow is initiated. It is composed of the cricopharyngeal muscle, caudal portions of the inferior pharyngeal muscle, and longitudinal and circular fibers of the proximal esophagus and spans approximately 0.5 cm in length at birth and 3 cm in adulthood [4]. The esophageal body consists of multiple layers. The mucosa and submucosa form a barrier between the esophageal lumen and the internal environment and are surrounded by, subsequently, the submucosal plexus, a circular muscle layer, the myenteric plexus, and a longitudinal muscle layer. Neurophysiology and development of esophageal motility are described in detail elsewhere in this book, but in short, peristaltic contractions are primarily generated through activation of the circular muscle layer by the vagal nerve and excitatory neurons of the myenteric plexus [5].

The muscle layers in the proximal esophagus are primarily striated, while smooth muscle predominates in the distal esophagus; a transition zone is present in the upper third of the esophagus. At the distal end, the lower esophageal sphincter spans across the crura of the diaphragm with its distal part being intra-abdominally. Its length is approximately 1 cm at birth—5 cm in adults.

The esophagus has three major motor functions. First, as part of the highly complex process of swallowing, there is a need for the timely relaxation of the upper and lower esophageal sphincter as well as the initiation of a propagated contraction through the esophageal body (primary peristalsis). Second, to prevent gastroesophageal reflux (GER), the LES, together with the crus of the diaphragm and the phrenoesophageal ligament, forms the specialized region of the esophagogastric junction (EGJ). The EGJ is tonically contracted in rest and forms a barrier that overcomes abdominal pressure. It relaxes during swallows and will allow for belching when pressure rises in the cardia of the stomach [6]. Such transient lower esophageal sphincter relaxations (TLESR) are accompanied by inhibition of esophageal body and have been shown to underlie most GER episodes in healthy adult volunteers, healthy infants as well as in adults and pediatric patients with GER disease [7]. Finally, various intra-esophageal stimuli, such as GER or bolus retention after a failed swallow, can trigger secondary peristalsis. This is not only important to clear the esophagus from residual bolus but it also prevents prolonged acid exposure after a GER episode [8].

Esophageal dysfunction is present when normal peristalsis is disturbed or sphincter function fails. High-resolution esophageal manometry is the gold standard to study esophageal function.

Esophageal Manometry

Technical Aspects

Esophageal manometry refers to the measurement of pressures generated within the esophageal body and its sphincters. Conventionally, this was done using catheters with 4–8 pressure sensors. With the introduction of high-resolution manometry (HRM), it became clear that much information was previously missed. Compared to conventional manometry, HRM records pressures throughout the pharynx, esophagus, and stomach with a large number (typically 20–36) closely spaced (1 cm or less) pressure sensors between which pressures can reliably be interpolated. These data can then be shown as a continuum of pressures using pressure topography (iso-contour) plots (Fig. 10.1). Although conventional manometry can still be used if HRM is not available, it will no longer be discussed in this chapter.

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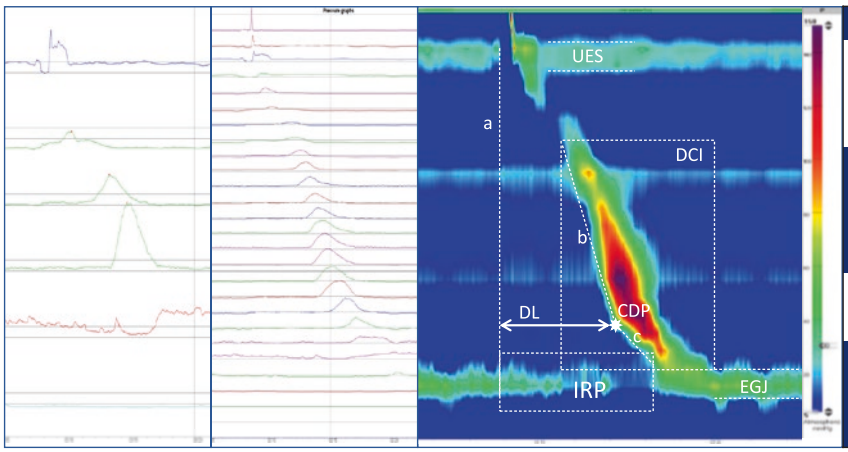

Metric	Definition	Explanation
IRP	mean of the (contiguous or non-contiguous) 4s of maximal deglutitive relaxation pressure (mmHg) starting at UES relaxation (dotted line a)	capability of the EGJ to relax in response to a swallow
CDP (✱)	inflection point between the rapid progression of the esopheal contraction (dotted line b) and the slower contraction more distally (dotted line c)	conversion point between smooth muscle esophageal body contraction and LES after-contraction
DL	time interval (s) between onset of UES relaxation and CDP	identification of premature (spastic) contractions
DCI	amplitude x duration x length (mmHg.s.cm) of contraction exceeding 20 mmHg from transition zone down to the proximal margin of the LES	vigor of distal esophageal contraction

Fig. 10.1 Conventional line plot (**a**), high resolution line plot (**b**) and high resolution pressure topography (**c**) of the same swallow in a 7 year old girl. Landmarks and main metrics of the Chicago classification are shown. UES: upper esophageal sphincter; EGJ: esophagogastric junction; DCI: distal contractile integral; CDP: contractile deceleration point (indicated with*); DL: distal latency; IRP: integrated relaxation pressure; LES: lower esophageal sphincter. See panel (**d**) for details about the metrics. All metrics and definitions adapted from Yadlapati et al. Neurogastroenterology & Motility. 2020; 33: e14058.

Two types of systems are commercially available for HRM. First, water-perfused catheters contain several side holes that are connected to micro-lumina, which are filled with a column of water and then perfused with a constant flow by a pneumohydraulic pump. Each water column transfers the esophageal pressure to an external transducer. Such catheters carry the advantage that they can be custom-made and are relatively cheap. Catheters are generally re-usable after appropriate disinfection, but single-use catheters are now available as well. The procedure to prepare the catheter is labor-intensive and allows for artifacts if not performed correctly. In small infants, due to their limited fluid tolerance, flow rates during (prolonged) measurement may need to be reduced, despite the negative effect on the accuracy of pressures measured. Furthermore, response-time of the system is not suitable to record quick changes in pressure, such as seen in the pharynx.

The other type of system uses solid-state technology. Strain-gauge sensors are mounted on the catheter and the measured pressure is digitalized and transferred to the computer. The catheter connects to the measurement system with a single connector. Solid-state sensors can use unidirectional or circumferential sensors, the latter providing the option to measure asymmetric pressure patterns, as, for example, seen within the esophageal sphincters. Other benefits of solid-state technology include the rapid response time, which allows for adequate pharyngeal recording. No preparation time is needed and cleansing is easy. On the other hand, catheter design cannot be customized, the technique is much more expensive and catheters are more fragile.

Both systems allow for impedance to be included on the catheter, which allows for the recording of esophageal flow and hence a more complete view of esophageal function. In small children and infants, there is no need to measure pressures over a length of 36 cm (as is standard for adult HRM catheters) and thus smaller and thinner (down to 6Fr) catheters are available for children.

Indications

Symptoms of Esophageal Dysfunction

Specific symptoms of esophageal dysfunction include dysphagia, odynophagia, (non-cardiac) chest pain and (recurrent) food impaction. In adults, dysphagia that is limited to solids only suggests structural disease, while symptoms with solids and liquid bolus suggest motility related abnormalities [9]. Such a distinction is harder to make in children. In fact, the symptoms mentioned above are all difficult to express as such in young children and infants. They may present with typical habits during meals (e.g., using lots of water, avoiding certain consistencies, standing up, head, neck, and arm movements) or non-specific feeding problems (crying, fussing, insufficient weight gain). If esophageal dysphagia is suspected, the differential includes structural abnormalities, inflammatory diseases (eosinophilic esophagitis, erosive esophagitis), gastroesophageal reflux disease (GERD), other motility abnormalities (including achalasia), and functional disease. Malignancies, that are an important consideration in adults, are seldomly the cause of pediatric dysphagia. Esophageal manometry has an important role in the workup of these children, but its timing depends on the age, presenting symptoms, and logistics. In children with food impaction that has resolved spontaneously or symptoms that strongly

suggest structural disease, it is preferred to start with an endoscopy and/or barium swallow, as this may alleviate the need for esophageal manometry. However, in children with a history that clearly suggests achalasia, HRM can be performed first.

Follow-Up after Diagnosis

In children with achalasia, follow-up with HRM after treatment may be indicated. In adults, this is standard practice and was shown to predict recurrence and to correlate well with timed barium esophagram [10]. No pediatric data are available. In children with EGJ-outflow obstruction (EGJOO), less therapeutic options are available compared to achalasia. In these patients, repeated HRM may be necessary to show progression to achalasia (Fig. 10.2) [11].

GERD

GERD is a multifactorial disease in which esophageal dysfunction plays an important role. Although esophageal manometry may not have direct clinical consequences in most children with GERD, it may rule out other motility disorders with similar presentation that need different treatment. In addition, it can reveal the presence of a hiatal hernia.

Fundoplication

If GERD is severe and resistant to conservative and pharmacological therapy, a fundoplication can be considered. Each child needs a proper workup before this procedure including an esophageal manometry. The most important reason is to rule out achalasia and EGJOO as a cause of the symptoms that are frequently falsely attributed to GERD [12, 13]. Furthermore, the presence and size of a hiatus hernia can be established with confidence. Finally, based on adult data, there is long-standing debate whether motility abnormalities and especially absent contractility should be considered a contra-indication for fundoplication. Theoretically, fundoplication increases the risk of post-operative new-onset dysphagia or worsening of pre-existent dysphagia [14, 15]. In this light, motility abnormalities should at least be taken into consideration and discussed with parents before surgery. Small studies using combined HRM with impedance in children show some promise in predicting which children may be at more risk of post-operative symptoms [16–19].

Establishing Exact Position of LES Location

In patients that undergo pH(−impedance) testing, catheter positioning is important. Ideally the esophageal pH-sensor should be 3–5 cm (depending on the size of the patient) proximal to the upper border of the lower esophageal sphincter. Several formulas are available, of which Strobel's formula is probably still the most widely used [20]. Confirmation of the catheter's position is, however, needed with all formulas. This can be done with an thoracic X-ray, where the pH-sensor should be located two vertebrae above the diaphragm [21]. However, esophageal manometry provides more accurate information about LES location and a hiatal hernia may be missed on an X-ray (which can lead to a failed pH(−impedance) test) [22]. Despite the extra burden for the patient, this may be a reason to perform esophageal manometry prior to insertion of the pH(−impedance)-catheter.

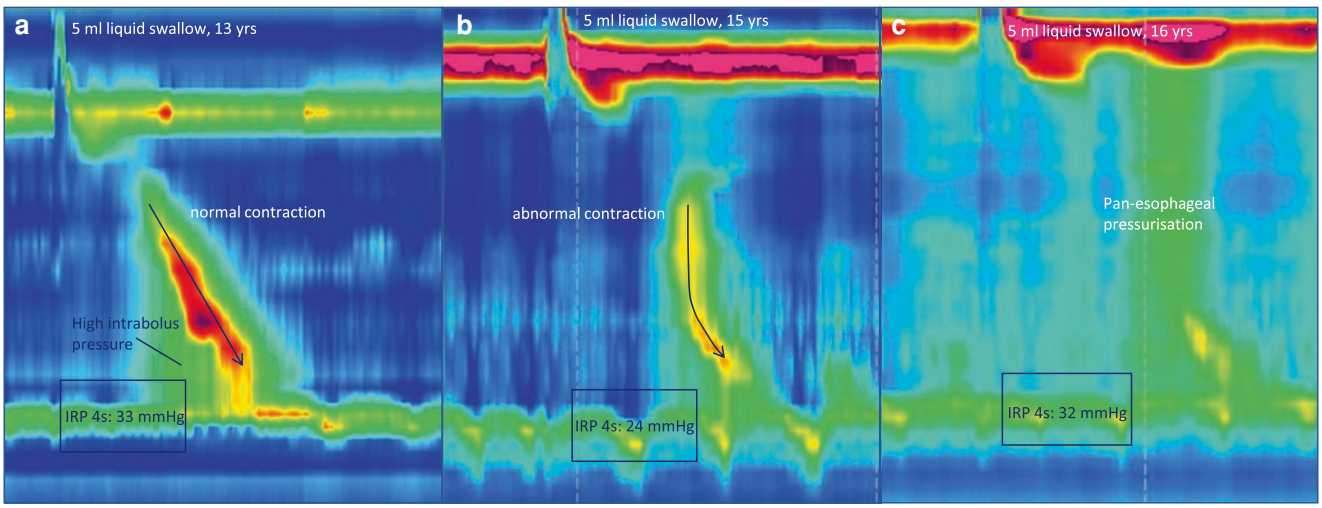

Fig. 10.2 Development of esopgagogastric junction outflow obstruction (EGJ-OO) into achalasia type 2.
Patient presented at age 13 with dysphagia. Panel **a** shows HRM at age 13 with a manometric pattern of EGJ-OO (high integrated relaxation pressure (IRP) with preserved propagated contractions but remarkably high intrabolus pressure, which suggests a high resistance to bolus flow and possible stasis. Panel **b** shows HRM 2 years later at age 15 after two botox injections with limited success. IRP is still elevated and the peristaltic wave has changed, but not disappeared, still EGJ-OO. Panel **c**, shows HRM at age 16. Absent contractility with pan-esophageal pressurisation and elevated IRP, which fits the diagnosis of achalasia type 2. Patient did not react clinically to dilations and is now on waiting list for per-oral endoscopic myotomy (POEM)

Systemic Disease

A special group are the children that have a (suspicion of) a systemic disease. Systemic sclerosis, mixed connective tissue disease, polymyositis, dermatomyositis, Sjögren syndrome, and systemic lupus erythematosus have all been associated with severe esophageal dysfunction [23]. These children may have significant dysphagia as presenting symptom and the manometric pattern (absent contractility) may then give a clue towards the systemic diagnosis. In addition, adults with interstitial lung disease also seem to account for a high percentage of patients with absent contractility [24].

Combined Impedance-Manometry

Rumination Syndrome

In children with a clinical suspicion of rumination syndrome, additional testing is not necessarily indicated. However, in some patients there is doubt about the diagnosis or patient and/or parents do not believe in a functional diagnosis. In these cases, esophageal manometry in combination with impedance may clearly show rumination as a cause of the symptoms. Both, protocols for stationary and ambulatory impedance-manometry, are available [25, 26]. Even if no impedance is available, HRM can reveal rumination syndrome [27].

Inability to Belch Syndrome

Patients with inability to belch experience gurgling noises from the chest which can be associated with pain and other symptoms. In adults, high-resolution impedance-manometry was used to diagnose this novel entity and showed failure of the UES to relax despite a gastric belch and concomitant rise in esophageal pressure [28]. It is likely that this syndrome exists in children as well. Botulin-toxin injections in the UES show promising results in adults [28], but have not been described in children for this indication. Children with these specific symptoms could be studied as per the adult protocol [28].

Aerodigestive Disease

Combining HRM with impedance has been suggested for patients with aerodigestive diseases as it may show esophageal stasis that puts these children at risk for aspiration. Further studies are needed to establish its exact role in this patient group [29].

Practical Protocol

A practical protocol for the use of HRM in children was established and endorsed by NASPGHAN and ANMS [3]. It should be noted that this protocol largely relies on the adult Chicago-classification protocol for the performance and analysis of adult HRM studies, which has been updated since [2].

Preparation of the Patient

If clinically possible, patients should be instructed to stop medication that might influence esophageal motility 48 hours before the test, including prokinetics, narcotics, and anticholinergic drugs, unless the clinical question is related to the efficacy of the drugs. PPI and H2 receptor-antagonists can be continued unless other investigations for GERD are planned. If no sedation is given, patients should be fasted for a few hours to reduce the chance of vomiting during placement of the catheter. In adults 4 h are recommended, but this should be tailored to patient's age [2].

Although HRM is a short procedure that provides clinical diagnoses in most, approximately 75% of performed HRM are imperfect due to patient related imperfections [30]. The procedure induces anxiety in nearly all children. Creation of a child-friendly environment is therefore of the utmost importance and child mental health support can improve the patient's experience *and* the quality of the measurement.

Placement of the Catheter

Xylocaine spray or viscous lidocaine can be used as topical anesthetics that can be administered through the nose. And although there is a long-standing debate and conflicting literature about the effect of midazolam on esophageal motility, the only available pediatric study from 1992 shows little effect on basal LES tone and other motility parameters measured during conventional manometry. More recently, a study in adults showed negligible effects during HRM [31]. Midazolam in a low dose may be an option, but should be reserved for those children where HRM seems unfeasible otherwise. Cardiorespiratory monitoring should be available and personnel must be trained to give adequate resuscitation if necessary.

For the introduction of the catheter, patients are placed in the upright or semi-recumbent position. The HRM catheter is introduced through a nostril and into the stomach. After entering the pharyngeal cavity, it may be helpful to ask the patient to put its chin on the chest and drink sips of water, while passing the UES. Positioning using the UES and LES high-pressure zones that can be on screen results in correct placement in most children, but if in doubt the pressure inversion point (PIP) should be identified to fully assure correct position. The PIP is the location where inspiration-related pressure changes from negative (thorax) to positive (abdomen). Deep breathing can help to clarify the position in difficult cases.

Study Protocol

When patients are fully cooperative, a measurement protocol as suggested for adults in the Chicago-4.0 protocol can be followed, but adaptation may be necessary as patient-related artifacts, such as crying, restlessness, and piecemeal deglutition, may make it impossible to fully comply with such a protocol [2, 30].

For adults, it is suggested to study a patient in both supine and upright position [2]. Performing the protocol in two positions allows for a subtle improvement in the discrimination between EGJ-outflow obstruction and achalasia [2]. This doubles the time a patient is intubated and, moreover, in children, the distinction between achalasia and EGJ-outflow obstruction relies more heavily on clinical and manometric pattern recognition rather than numerical differences in the parameters describing EGJ-function. This is a result of the absence of true normative data and EGJ-characteristics changing with age [32–34]. In most centers, children are therefore studied only in the semi-recumbent position.

After intubation, the patient is allowed to adapt. This may take longer than in adults as children may need to calm down. Other children want to get things done as soon as possible and in those, a short baseline period will suffice to record anatomical landmarks (UES, LES), PIP and basal EGJ pressure. If in doubt about the catheter position, ask the patient to take one or more deep breaths, which will magnify the difference between thoracic and abdominal pressure. During this baseline period, especially in patients with a suspicion of GERD, make sure a stable EGJ pressure is recorded for at least three respiratory cycles to determine the presence of a hiatal hernia [6]. Thereafter, try to collect at least ten good quality liquid swallows, with 30 seconds in between. In some children this is simply too long. In these, make sure the EGJ pressure has returned to its previous baseline before administering the next bolus.

With ten good-quality liquid swallows, a clinically meaningful result can be obtained in most. Depending on the clinical question, the already observed swallows and the child's behavior, additional provocative tests may be added [35, 36]. A rapid drink challenge, where a patient is asked to drink a cup of water (100–200 mL) through a straw in one go, can reveal outflow obstruction that was not seen during the single swallows or may confirm normal peristalsis [35, 37]. In addition, when a patient has dysphagia symptoms, but has normal findings thus far, a solid bolus challenge can be given that may reveal subtle motility abnormalities which are only relevant if the patient has symptoms during the test [38]. Try to record at least five, but preferably 10 solid bolus. Adjust the food-type and size to the age of the patient. Although often used and seemingly helpful from experience, there are no studies available confirming this additional value of a rapid drinking test or solid test bolus in pediatrics.

Analysis

In the HRM isocontour-plot, anatomical landmarks (UES and EGJ) can easily be identified (Fig. 10.1). A hiatal hernia can be recognized as the separation of the high-pressure zones of the LES and the crural diaphragm, where they normally form a single high-pressure zone (EGJ). Within the esophageal body, three distinct pressure segments are present, separated by low-pressure troughs [39]. The low-pressure segment at the transition zone at approximately one-third of the esophagus demarcates the end of the proximal esophageal segment consisting of striated muscle and the beginning of the distal esophagus, consisting of primarily smooth muscle.

For a detailed evaluation of the EGJ and esophageal peristalsis, the Chicago classification (CC) was developed for adult patients with normal anatomy and without previous esophageal surgery [2]. It was first published in 2009 and has been updated three times since. As there is no specific analysis method for pediatric HRM studies, the CC is generally used for children as well and explained in summary below. For more details on the analysis, the latest CC can be consulted [2].

First, it is essential to know the type of catheter used before commencing analysis, as refence values differ per catheter type [40].

The CC is semi-automated in most manometry systems. Landmarks and regions of interest need to be drawn or checked manually, while the software uses this input to calculate the accompanying parameters. These parameters are needed within the hierarchical classification scheme and are further explained in Fig. 10.1. On top of the scheme are ***disorders of EGJ outflow obstruction*** (achalasia and EGJOO, Fig. 10.3) In both conditions, the median EGJ integrated relaxation pressure (IRP) of the 10 liquid swallows is too high, indicating that there is too much resistance to antegrade flow from the esophagus to the stomach during swallows. If this is accompanied with 100% absent peristalsis in combination with either failed peristalsis, pan-esophageal pressurization (>20% of swallows), or premature contractions (>20% of swallows), this is referred to as *achalasia, type I, II, and III,* respectively. If IRP is elevated, but peristalsis is not absent in 100% of swallows, the manometric pattern fits *EGJ-OO*. For a clinical diagnosis of EGJ-OO, timed barium swallow or endoflip needs to be performed and confirm the diagnosis.

If IRP is not elevated, ***disorders of peristalsis*** are hierarchically considered. First, if there is 100% failed peristalsis (with normal IRP*), absent contractility* is diagnosed, which can be part of a systemic disease, consequence of GERD and/or idiopathic. If contractility is not absent and > 20% of swallows show premature contractions (short distal latency [DL]), this leads to the diagnosis of *distal esophageal spasm*. If there are no premature contractions, and >20% of swallows show contraction vigor (distal contractile integral (DCI)) above normal values, this is called a *hypercontractile esophagus*. If swallows are not hypercontractile, but ineffective in >70% or failed in >50%, the pattern fits with *ineffective esophageal motility*. Finally, if this is not the case, the study is normal [2].

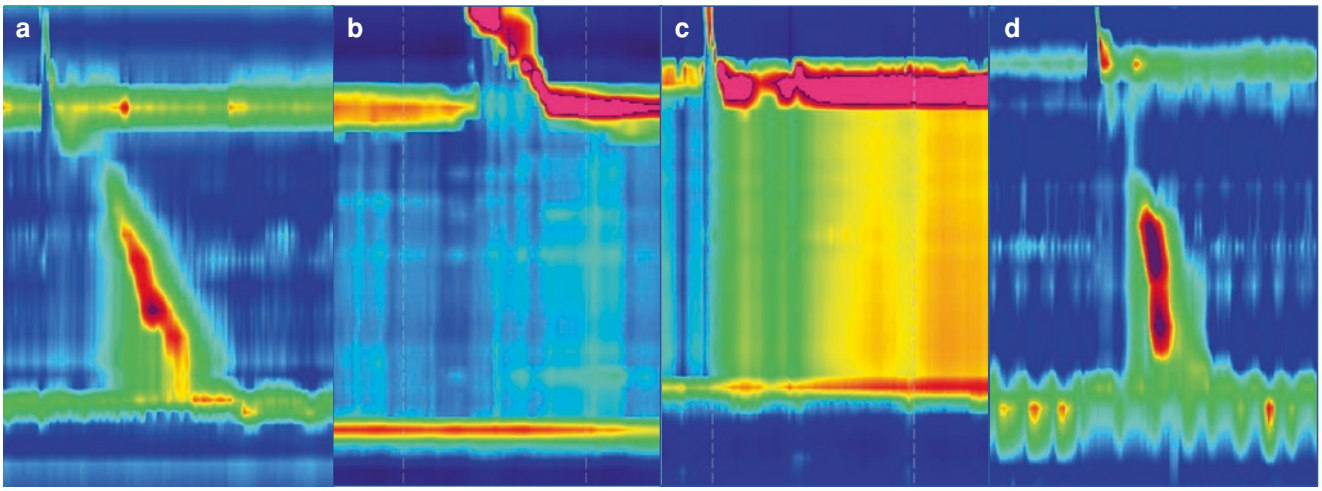

Fig. 10.3 Examples of disorders of EGJ outflow obstruction in children. **Panel a** shows EGJ-OO (failure of EGJ relaxation (elevated IRP) with normally propagated contraction (normal DL & DCI) in a 13 yr old boy ; **Panel b**: type I achalasia (failure of EGJ relaxation with absent contractility) in a 12 yr old girl; **Panel c**: type II achalasia ((failure of EGJ relaxation with absent contractility and pan-esophageal pressurisation) in an 8 yr old boy; **Panel d**: type III achalasia ((failure of EGJ relaxation with premature contraction (short DL and elevated DCI)) in an 8 yr old girl with triple-A syndrome (Achalasia in combination with Addison disease and alacramia)

Note that the evaluation of the UES, presence of hiatal hernia, and patterns that may fit rumination or inability to belch are not part of this scheme. Although criteria for hiatal hernia are available for adults [6] and criteria for rumination syndrome in children have also been proposed [25], these diagnoses are mainly considered based on pattern recognition.

Pediatric Aspects of the CC Analysis

HRM according to the CC-protocol is not possible in infants and very small children. Attempts have been made to describe the development of peristalsis in neonates using HRM, but no standardized clinical approach to its analysis exists for infants and young children [41, 42]. Potential indications in this specific age group include infants with feeding problems that are suspected to have congenital esophageal stenosis, arteria lusoria, eosinophilic esophagitis, or severe GERD (before fundoplication).

The CC was neither created for nor validated in older children and age or size specific normal values for the CC metrics do not exist. Nevertheless, it is clinically used in children as young as 2 years of age [1]. Yet, it was shown that a shorter length of the esophagus and a smaller lumen have an influence on IRP and DL. Using adult cutoff values carries the risk of overdiagnosing motility disorders, especially for EGJOO and distal esophageal spasm [43]. As a consequence, pediatric adaptation of the cutoff values has been proposed, first in older children and later in (premature) infants, but these are not incorporated in software packages as yet [43, 44]. They should nevertheless be taken into account when interpreting HRM results in children.

The issue of the lacking normal values has complicated implementation of HRM and CC in clinical care [43]. In addition, pediatric recordings are often harder to interpret due to a higher likelihood of piecemeal deglutition and patient-related artifacts (e.g., body movement and crying) [30, 45–47].

In some children, piecemeal deglutition cannot be prevented. However, the initiation of a new swallow will inhibit esophageal peristalsis and induce complete relaxation of the LES (deglutitive inhibition). Furthermore, the contraction following the last swallow may be augmented. Future studies need to unravel how such swallows can nevertheless be used to come to an unequivocal diagnosis. In pharyngeal manometry, it was suggested to use impedance concomitantly to select the predominant swallow for manometric analysis [48].

Despite the shortcomings and difficulties of pediatric studies, the inter- and intra-rater reliability of the CC diagnosis of pediatric HRM recordings was shown to be good in general [33]. However, subtyping achalasia appears to be more challenging, even among raters considered to be experts on HRM analysis [34].

It appears that HRM and the CC have limitations that are specific to the diagnosis of achalasia in children. First, the diagnosis of achalasia is driven by the IRP. This is a complex metric, not only depending on the adequacy of lower esophageal sphincter relaxation, crural diaphragm contraction, and EGJ opening, but also on the pattern and timing of distal esophageal contractility. In clinical practice, instances of clinically evident achalasia with IRP that does not meet diagnostic criteria do exist, especially in type I achalasia patients with low intra-esophageal pressures and type II achalasia patients with short periods of pan-esophageal pressurizations [49]. In those cases, pattern recognition is crucial, yet opens

up the possibility for different interpretations amongst different health care professionals.

Because of these problems, additional evidence in support of a CC diagnosis is particularly important in children. Timed barium esophagram may be used for disorders of EGJ outflow obstruction. Alternatively, intraluminal impedance can be measured in conjunction with HRM to provide additional information regarding bolus flow but without the exposure to radiation. In pediatric achalasia, it was shown that bolus flow time through the EGJ may be of additional value in diagnosis and assessment of therapeutic effect [50]. Impedance can, at least in theory, also support the clinical significance or the absence thereof, in disorders of peristalsis as diagnosed per CC-criteria. More detailed information on impedance-manometry can be found in more detail elsewhere in this book.

In conclusion, esophageal HRM has largely replaced conventional manometry. Several sizes and configurations of catheters are available both for water perfused and solid-state systems. HRM is easy to learn and relatively easy to perform. In most children a meaningful result can be obtained, although many studies are imperfect due to patient-related artifacts. Adult protocols and analysis schemes are available, and although these need further refinement for pediatrics, HRM can help identifying esophageal dysfunction in children of all ages and is the reference standard for diagnosing achalasia and other motility disorders in older children.

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Antroduodenal Manometry

11

Anna Rybak, Efstratios Saliakellis, Nikhil Thapar, and Osvaldo Borrelli

Introduction

Antroduodenal manometry (ADM) is a diagnostic tool that provides both a qualitative and quantitative assessment of the foregut motor function by recording intraluminal pressure changes within the gastric antrum and the proximal small intestine. Specifically, such pressure readings provide a measure of coordination and contractile activity of the foregut. Since first manometric recordings, methodological improvements have steadily occurred, progressing ADM manometry from a purely research technique to an investigation commonly performed in adults and children for definitive clinical purposes. A substantial development has been the ability of the recording equipment to digitize online manometric recordings so that the latter can be easily analyzed by computer programs. Although the test is still performed in highly specialized motility centers, ADM has provided an improved understanding of the pathophysiology of neuromuscular disorder of the stomach and small intestine.

Normal Motility

In healthy individuals, the primary function of the small intestine is the absorption of nutrients, and the motor pattern is programmed to promote this function by assuring timely propulsion of luminal contents and avoiding stasis or, conversely, rapid transit of luminal contents. Under physiologic conditions, the motor activity of the antrum and the small intestine is characterized by patterns of organized motor activity in the fasting and postprandial periods [1].

Fasting or interdigestive gastrointestinal motility comprises a sequence of three main components or phases with a combined total average duration of about 100 min (50–180 min), which together constitute the so-called migrating motor complex (MMC) (Fig. 11.1) [2, 3]. Phase III of the MMC, the most distinctive and well-studied pattern of gastrointestinal motor activity, is a characteristic burst of high-amplitude rhythmic contractions of at least 2 min duration occurring at the maximum frequency allowed by the underlying myoelectrical rhythm for a given segment of the gastrointestinal tract [4]. For instance, in the antrum the contractions occur at a rate of 2–3 per minute, whereas in the proximal small bowel this increases to 10–14 per minute. In children, phase III may begin anywhere from the stomach to the ileum, but in about 70% it starts in the gastric antrum, 18% in the proximal duodenum, 10% in the distal duodenum, and 1% in the proximal jejunum [2, 3]. Migration is a basic requisite of phase III activity, which usually propagates aborally over various lengths of the small intestine; however, only 50% of these propagate beyond the middle jejunum, and only 10% reach the distal ileum [5]. The duration of phase III progressively increases in the aboral direction ranging between 2 and 5 min in the duodenum and 10–20 min the distal ileum [2, 6–8]. Conversely, the propagation velocity of phase III decreases from 5–10 cm/min in the proximal small bowel to about 0.5–1 cm/min in the distal ileum [1, 2, 7]. The average amplitude of single contractions is at least 40 mm Hg in the antrum and 20 mm Hg in the small intestine. Finally, the mean interval between episodes of phase III varies with age. It ranges between 25 and 45 min in newborn, approximately 60 min in children less than 2 years, and 85–110 min in adolescent and adults [3, 8–12]. However, significant variation between subjects and within the same individuals may be seen [2, 13, 14]. Phase III activity is usually followed by quiescence or phase I, which is defined as less than three pressure waves every 10 min [15]. Phase I is followed by a period (Phase II) of irregular contractions (more than 3 pressure waves every 10 min), which represent in the small intestine about 70–80% of the whole cycle.

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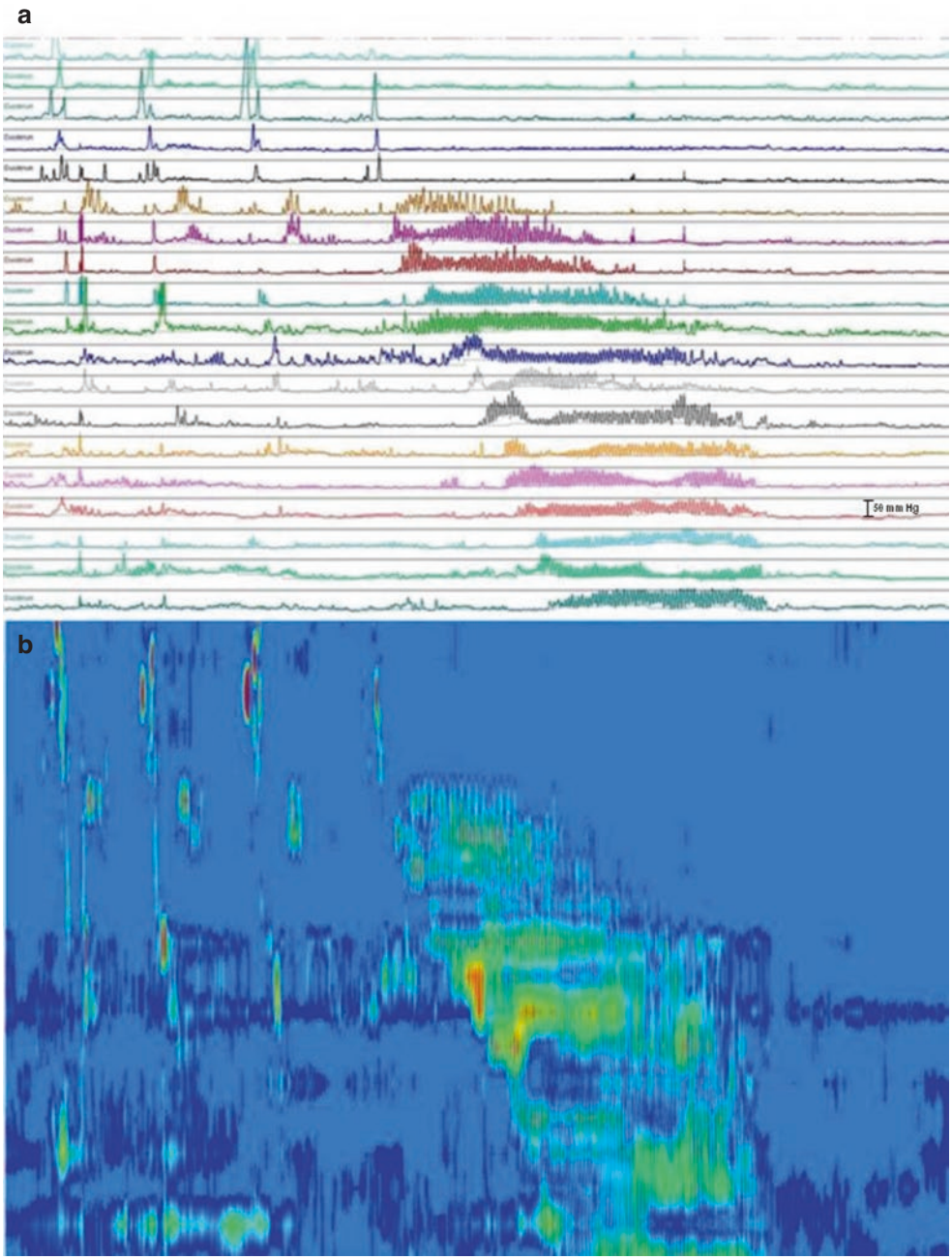

Fig. 11.1 Examples of conventional (**a**) and spatiotemporal plot (**b**) of normal migrating motor complex (MMC) recorded in a child with recurrent vomiting. All three phase (phase I, phase II, and phase III) are well represented. The phase III is seen starting in the duodenum and migrating aborally toward the proximal jejunum. A period of quiescence (phase I) follows phase III; the latter is preceded by intermittent phasic activity (phase II). Phase III is readily recognized by using spatiotemporal plots. The recording has been performed with a 20-channnel manometric catheter (side holes 2.5 cm apart)

Phases I and III of the MMC require an intact enteric nervous system (ENS) with modulation by the central nervous system (CNS) and gastrointestinal regulatory peptides [5, 16, 17]. For instance, endogenous motilin blood concentration peaks during late phase II and phase III of the MMC cycle [18, 19]. However, motilin is not required for initiation or aboral migration of Phase III in the small bowel but seems to be involved in the antral participation of phase III [20, 21]. Conversely, phase II activity seems to rely more on extrinsic modulation of CNS, given it is suppressed during sleep and abolished after vagotomy [5, 16]. The importance of MMC is highlighted by the fact that its absence is associated with bacterial overgrowth [1]. Indeed, the pulsatile flow ahead of phase III is of paramount clinical importance for clearing secretion, debris, and microbes during the interdigestive period, whereas colonization of the foregut with gram-negative bacteria is observed when phase III is impaired or absent [22]. For this reason, phase III has been termed as the "gastrointestinal housekeeper." MMC cycles do not occur in the intestine of premature infants aged less than 34 weeks, which instead show a pattern of clustered phasic contractions lasting between 1 and 20 min and occurring every 4–35 min. As post-conceptional age increases, this activity becomes longer and the frequency of occurrences decreases. By term,

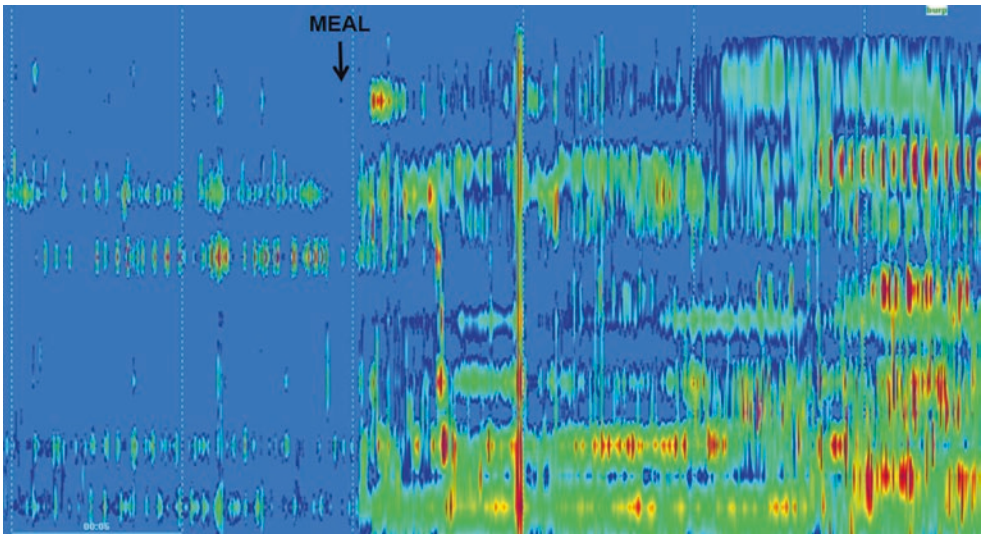

Fig. 11.2 Examples of spatiotemporal plot of normal postprandial activity characterized by irregular but persistent phasic activity. Temporal and pressure resolution easily recognize the increase in motility index. The recording has been performed with a 20-channnel manometric catheter (side holes 2.5 cm apart)

well-defined cyclical fasting motor activity is present with distinct phase I, II, and III activities, with the latter showing less variability in term of length and intervals [11, 23].

Following the ingestion of food, the MMC cycle is interrupted and replaced by a pattern of regular antral contractions associated with apparently uncoordinated contractions of variable amplitude in the small intestine, termed "postprandial" or "fed" pattern (Fig. 11.2) [5, 16, 24]. These phasic contractions also show variable frequency and propagation. Typical postprandial contractions usually propagate over a shorter distance than those of phase III, and almost 80% of them propagate less than 2 cm [24]. This minute movement of postprandial contractions is devoted to mixing and grinding of the nutrient chyme, stirring, spreading, and exposing the intestinal contents to a larger surface, and thus promoting its optimal absorption. Moreover, minute aboral transport is also sufficient in preventing bacterial colonization. Thus, normal postprandial motor activity is a compromise between optimal absorption and adequate clearance. The postprandial period lasts from the time of the evident increase in frequency and/or amplitude of contractions occurring after the introduction of a meal to the onset of the following phase III and is affected by the amount of calories as well as by the composition of the meal [25]. For instance, fats induce a more prolonged fed pattern than protein and carbohydrates. Extrinsic neural control is a prerequisite for a normal postprandial pattern, since persisting MMC activity after meal intake has been reported after vagal cooling [26, 27]. Neural reflexes, endocrine, and paracrine mechanisms also play a key role [17]. In small infants aged less than 32 week's post-conceptional age, who usually receive only small volumes of enteral feeding, the fasting pattern is not disrupted by either the bolus or continuous feeding. Between 31 and 35 week's post-conceptional age, the larger volumes of enteral feeding induce a degree of postprandial activity, but it is only over 35 week's post-conceptional age that a disruption of cyclical activity can be seen with feeds [10].

The presence of other distinct motility patterns has been identified in both healthy individual and patients. *Discrete clustered contractions (DCCs)* or *cluster of contractions (CCs)* are defined as the presence of 3–10 pressure waves of slow frequency, each having a significantly higher amplitude and duration compared to isolated individual contractions [15, 28]. They propagate aborally for less than 30 cm at rate of 1–2 cm sec^{-1} and usually show a rhythmic pattern with regular intervals of quiescence lasting at least 30 sec (Fig. 11.3) [3]. DCC are usually recorded during phase II, although they are occasionally seen during the postprandial period (phase III-like activity) [3, 14, 28, 29]. Postprandially, clusters of contractions seem to occur in association with mechanical obstruction or intestinal pseudo-obstruction, and they are characteristically non-propagated [30]. *Bursts of contractions* are defined as sequences of intense irregular pressure waves, which do not correspond to the definition for phase III or for DCC. They can be clearly distinguished from background pressure wave activity during both phase II and the postprandial period. Short bursts of propagating contractions have been described in healthy individuals, whereas sustained bursts of contractions confined to one limited segment (non-propagated) lasting for a period of >30 min and associated with tonic intermittent baseline pressure elevation are considered an abnormal neuropathic pattern [21, 31, 32]. *Giant migrating contractions* or *prolonged intestinal contractions* are pressure waves of prolonged duration (>20 s) and high amplitude more than 30 mm Hg. In healthy individuals they occur primarily in the distal ileum and propagate uninterruptedly and rapidly with highly propulsive force over long distance in aborad direction in the small intestine and colon [33, 34].

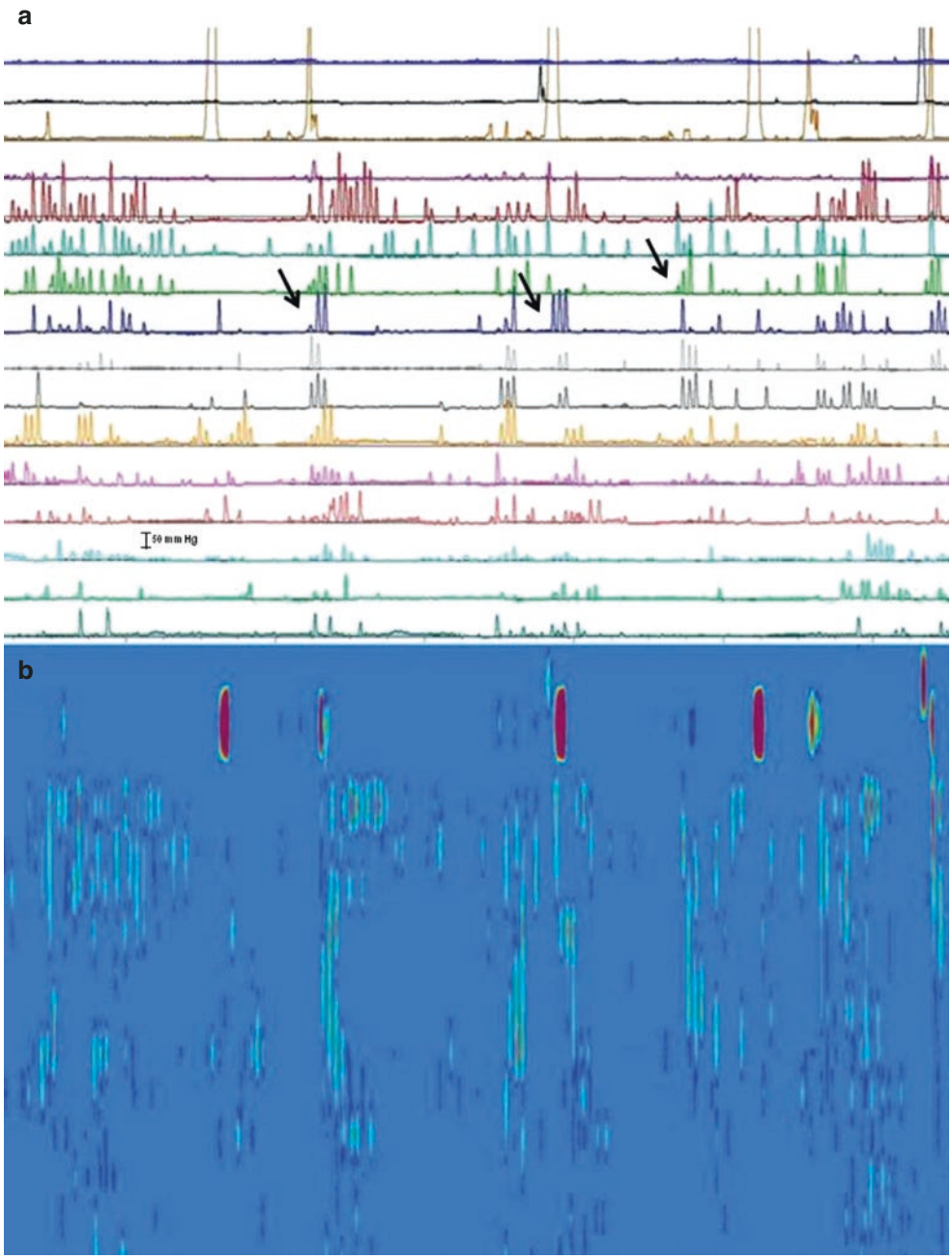

Fig. 11.3 Examples of conventional (**a**) and spatiotemporal plot (**b**) of short burst of contractions (arrow) recorded in the duodenum during phase II lasting more than 2 min. They can be clearly distinguished from background pressure wave activity during phase II. The third channel is localized in the antrum. The recording has been performed with a 20-channnel manometric catheter (side holes 2.5 cm apart)

Technical Aspects

Manometry is by nature a highly technical evaluation. When knowledgeably used, manometric examination provides an accurate description of intestinal neuromuscular function, but only if physical principles and equipment characteristics are respected [35]. In general, manometric data are reliable only if the methodology used to acquire them is accurate.

A manometric apparatus setup consists of a pressure sensor and transducer combination that detects the gastric and small intestine pressure complex and transduces it into an electrical signal, and a recording device to amplify, record, and store that electrical signal. The pressure sensor/transducer components of a manometric assembly function as a matched pair and are available in two general designs: either water perfused catheters connected to a pneumohydraulic perfusion pump and to volume displacement transducers or strain gauge transducers with solid state circuitry [35, 36].

Low Compliance Perfused Manometric System

The water infusion system includes a catheter composed of small capillary tubes, a low compliance hydraulic capillary infusion pump, and external transducers. In adults, the small capillary tubes usually have an internal diameter of approximately 0.4–0.8 mm and an opening or port at a known point along the length of the catheter. In adults, the most used catheters have an overall diameter of 4.5 mm [35]. In children in order to reduce the diameter of the catheter smaller capillary tubes (with internal diameters of 0.35 mm) are utilized; moreover, the study is performed at lower infusion rates [36, 37]. The manometric probes are usually tailored to the child's size, and the distance between the recording ports should be decided based on the purpose of the investigation [35, 36]. Since one antral recording site is insufficient to provide an accurate recording of antral motor activity due to its continuous forward and backward movement, the manometric catheter should have at least five recording ports with the two most proximal side holes spaced 0.5–1.5 cm apart positioned 1 cm proximal to the pylorus to provide measurements of antral activity, while the remaining side holes positioned in the small intestine and spaced 2.5–5 cm apart in infants and toddlers and 5–10 cm apart in children and adolescents [35–37]. Each capillary tube is connected to an external transducer. The infusion pump, a simple and essential device for stationary manometry, perfuses the capillary tubes providing a constant flow rate without increasing the compliance of the manometric system. When a catheter port is occluded (e.g., by a muscular contraction), there is a pressure rise in the water filled tubes that is transmitted to the external transducers. High-fidelity recordings of intraluminal pressure are achieved by infusion rates from 0.1 to 0.4 mL min^{-1}, even if they may provide an unacceptable amount of water to small babies or premature infants. To overcome this problem, perfusion rates as low as 0.02 mL min^{-1} have been successfully used [38]. Furthermore, for prolonged studies, the use of a balanced saline solution should be considered.

A device activating the pressure transducers, storing their signals, and displaying the latter in such a way to allow immediate interpretation and analysis is needed. The personal computer has become the heart of any manometry system. It interfaces with purposed-designed electronic modules that activate and receive signals from pressure transducers, while commercially available software programs are essential for acquiring, displaying, and storing pressure recording data. The technical adequacy of different commercially available device recording systems is quite comparable. Probably the dominant consideration that should determine the choice of a system is the level of technical assistance and the training available locally to support the user.

The required characteristics of the manometric recording apparatus is defined by the magnitude of the pressure to be recorded and the frequency content and waveform of foregut contractile waves. It has been shown that the frequency response of manometric systems required to reproduce foregut pressure waves with 98% accuracy is of 0–4 Hz (maximal recordable dP/dt: 300 mm Hg/s). Most of commercially available manometric systems can provide a pressure rise rate of 300–400 mm Hg/s, which is adequate for faithful recordings in the gastric antrum and small intestine.

Solid-State Manometric System

The main alternative to the water-perfused manometric system is a manometric assembly incorporating strain gauge sensors and solid-state electronic elements [39]. In this system, the manometric probe contains miniature strain gauge pressure transducers built into the catheter at a fixed location along its length, so that pressure changes directly influence the transducers to generate electrical output signals. The probe can be plugged into a small box containing the electronics, which is then connected to the recording device and to a personal computer. In the ambulatory system, the recording devices are blind and need to be connected to a personal computer with the appropriate software to display and analyze the recording. The main advantage of using solid-state catheters is that the pressures are recorded directly from the area and are unrelated to the relative position of the subject; therefore, manometric studies may also be performed with the subjects in the upright position. This, and the fact that it does not require water perfusion, makes solid-state catheters suitable for long-term ambulatory monitoring of the intraluminal pressure [40]. It has been calculated that for a given number of pressure-recording points on a recording assembly, solid-state catheters are 20 times more expensive than a perfused manometric assembly. In the last years, the improvement in miniaturizing transducers has allowed the production of solid-state catheter with up to 36 recording channels with an external diameter comparable to that of the water perfused manometric catheter used in small infants and children. However, there is still a very little experience in pediatric patients.

High-Resolution Manometry

Manometric techniques have improved in a stepwise fashion from few pressure recording channels to the development of high-resolution manometry (HRM), which is a relatively recent technique that enables more detailed definition, both in term of space and time, of pressure profiles along segments of the gut [41]. This has been achieved by a combination of new manometric assemblies allowing intraluminal pressure to be recorded from up to 72 pressure sensors

spaced less than 2 cm. At the same time, advances in computer processing allow pressure data to be presented in real time as a compact, visually intuitive "spatiotemporal plot" of gastric and small intestine pressure activity. HRM recordings may reveal the complex functional anatomy of the foregut, and recent studies suggest that spatiotemporal plots may provide objective measurements of the intraluminal pressure profile in the small intestine and improve the sensitivity and specificity of manometric recording by removing much of the ambiguity usually encountered using line plot analysis [42]. However, further efforts to define the role of HRM in the diagnosis and management of neuromuscular disorders are needed.

Methodological Aspects

Preparation of the Patient

Before starting the ADM manometric recording , it is important to assess patient information regarding medical history, symptoms, medication, and allergies. Any drug with a known effect on gastrointestinal motility should be discontinued at least 72 h before the study.

It is important to emphasize that ADM manometry in children is performed in a different fashion to that in adults due to differences in size, cooperation, and neurological and developmental maturation. Performing manometric studies in children require great patience from the operator. The parents should be present during the testing in order to settle the child and provide the child with a model of cooperative behavior with the physician. The cooperation can also be improved by using age-appropriate relaxation techniques. For example, infants may relax with swaddling and the use of a pacifier. Having a favorite toy can comfort toddlers. School age and older children benefit when equipment is shown and explained prior to the procedure. ADM manometry is best performed without sedation [37]. However, in many children sedation is necessary, and midazolam has been shown to be effective with no or minimal influence on pressure measurement [43]. It is advisable to wait for complete child recovery from any drug effect before starting the motility tests. Finally, before starting the procedure it is important to obtain and verify a signed informed consent and it is also necessary to check that the fasting period has been of adequate duration. In healthy children an overnight fast is enough, whereas in infants at least 4 h are necessary to eliminate nausea, vomiting, and aspiration. In children on parenteral nutrition, it should be stopped 12 h prior to the study, because of the effect of nutrients on hormones, which may affect the intestinal motility [17]. Similarly, blood glucose levels should be carefully assessed since hyperglycemia inhibits gastric emptying and reduce the occurrence of phase III [44, 45].

Study Procedure

The manometric catheter can be placed either nasally or orally, but there is broad consensus that studies are better tolerated when the catheter is introduced through the nose. The catheter can also be placed through an existing gastrostomy, or jejunostomy. The manometric probe should be positioned deep enough in the small intestine in order to prevent its falling back into the stomach as a consequence of postprandial gastric distension or duodenal contraction (Fig. 11.4). The tube placement can be performed either fluoroscopically or endoscopically [37, 46]. Under fluoroscopy, the probe placement usually requires high skill to pass the pyloric region, which may be easier with a firm probe rather than a soft, flexible one. The former, however, is more difficult to advance beyond the duodenal bulb due to its acute angle. Moreover, a hard probe may cause greater discomfort during the recording time especially in young children. The addition of a weighted probe tip may facilitate the placement as it utilizes the advantage of gravity. The probe can be also advanced through the pylorus using an endoscope and biopsy forceps, taking care to use as little air as possible to insufflate the bowel, given that over-inflation may affect gastrointestinal motility and provoke a backward movement of the manometric probe. In some centers the manometric recording is performed the day after the tube placement with additional radiology confirmation to ascertain appropriate catheter position, allowing for correction if necessary.

During the manometric recording using a water-perfused system, the patients usually maintain the same position

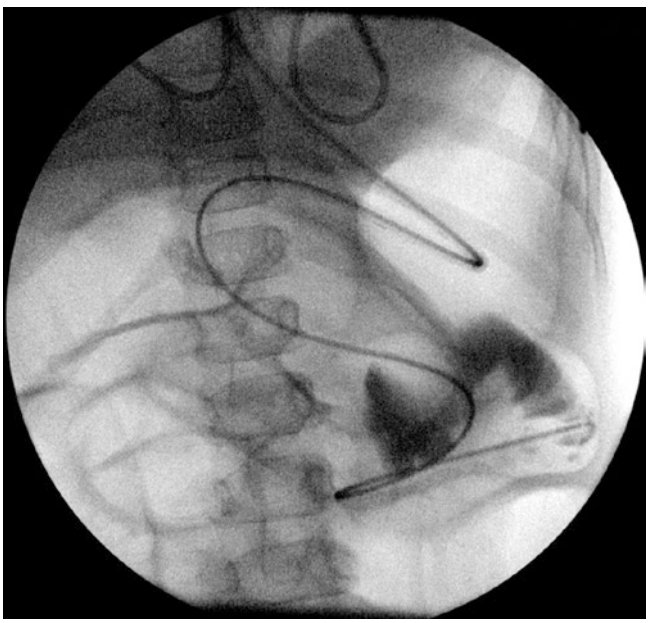

Fig. 11.4 Fluoroscopic placement of ADM catheter. Note the position of the tip is in the distal duodenum at level of the ligament of Treitz

(supine), whereas when using portable solid-state equipment the patients are encouraged to perform daily activities when possible [36, 37]. When using water-perfused system, patients require regular (4–6 hourly) electrolytes monitoring due to potential water toxicity [47].

Ambulatory manometry is usually performed for 24 h, whereas for stationary manometry, recording must be carried out until a phase III and/or clear-cut abnormalities are recorded. However, it is generally advisable to perform a fasting recording for at least 6 h (or two MMCs), and postprandial recording for at least 90 minutes [36, 37]. There is single study in children showing that ADM recording can be affected by the anesthetic drugs on the day of the catheter placement, suggestive of the need to perform extended recording on the following day, in selected patients [48].

The type and the size of meal should be adjusted according to patient's age and preference. In older children the test meal should be of at least 400 kcal, in order to ensure an adequate postprandial response in the small intestine lasting for at least 90–120 min [25, 36, 37]. In younger children the test meal should provide at least 10 kcal kg^{-1}. The meal should be balanced with at least 30% of calories provided as fat content. However, in some cases it is impossible to provide a predetermined volume to a patient, for example, one with severe gastrointestinal dysmotility and inability to tolerate oral or enteral feeding. Finally, if no phase III is recorded during fasting, a drug stimulation test should be performed using iv erythromycin (1 mg kg^{-1} over a period of 30 min), which is able to induce a gastric phase III and allows assessment of its migration in the small intestine [49, 50]. Other agents such as azithromycin, octreotide [51] amoxicillin/clavulanate, ghrelin, and neostigmine were also found to induce phase III activity, increase amplitude and duration of MMC; however, there is still a lack of adequate clinical experience in the use of these agents to allow for a general recommendation [49, 52–56].

Analysis of Manometric Recording

Both qualitative and quantitative analysis of the ADM tracings should be performed. Qualitative analysis includes the recognition of specific motor patterns as well as the overall characteristics of the fasting period (typical cyclical pattern of the MMC, characteristics of phase III activity including the total number of phase III occurrences, migration pattern, mean amplitude, mean peak velocity, and intervals) and fed period (presence of change in motility after test meal). Quantitative analysis includes the calculation of distal antral and duodenal motility indices (MI), expressing the contractile activity as the natural logarithm of the area under the manometric pressure peaks above a threshold pressure. Computerized data evaluation, including wave identification algorithms, artifact removal, and algorithms for detection of propagated activity offer an improved degree of objectivity in the analysis of pressure tracing and can facilitate the quantitative analysis of relevant parameters [57].

Table 11.1 Manometric features associated with gastrointestinal motility disorders

Interdigestive or fasting period
• Absence of phase III
• Short intervals between phase III
• Abnormal phase III
– Stationary
– Retrograde
• Non migrating burst of contraction
• Sustained simultaneous cluster of contractions
• Low amplitude contraction
Postprandial or fed period
• Failure to switch to postprandial period
• Postprandial hypomotility
– Low frequency of contraction
– Low amplitude of contraction
• Non migrating cluster of contraction

A normal motility pattern is defined as the presence of at least one MMC per 24 h of recording (it has been shown that almost 95% of normal children have phase III within 4 h fasting study), conversion to the fed pattern without return of MMC for at least 2 h after a 400-kcal meal, distal postprandial contractility (MI per 2 h >13.67), small intestinal contraction >20 mm Hg, and absence of abnormal findings described in Table 11.1 [58]. Therefore, the presence and characteristics of the MMC and its response to nutrients is used as a marker of enteric neuromuscular function.

Based on the findings of abnormal manometric features, various clinical/pathophysiological categories of abnormalities can be recognized [36, 37, 58]. In patients with *enteric neuropathy,* the motor activity is typically disorganized and/or uncoordinated. The most compelling finding is represented by the absence of a MMC during a sufficient recording time (ideally 24 h); however, this scenario is a rare event in patients with enteric neuropathy. More common findings include the presence of retrograde or uncoordinated phase III activity (Fig. 11.5), increased frequency of phase III (in adults and older children >1 MMC cycle per hour) (Fig. 11.6), presence of non-propagated bursts and sustained uncoordinated phasic activity, antral hypomotility, inability to establish a fed pattern after a test meal, and presence of phase III-like activity in the fed period. In patients with *enteric myopathy* the normal manometric patterns are usually preserved, but the amplitude of contractions in both preprandial and postprandial periods do not exceed 20 mm Hg (Fig. 11.7); however, low amplitude contractions may also represent a consequence of gut dilatation proximal to an obstructive segment. For this reason, the absence of dilated loops is a prerequisite for a diagnosis of enteric myopathy.

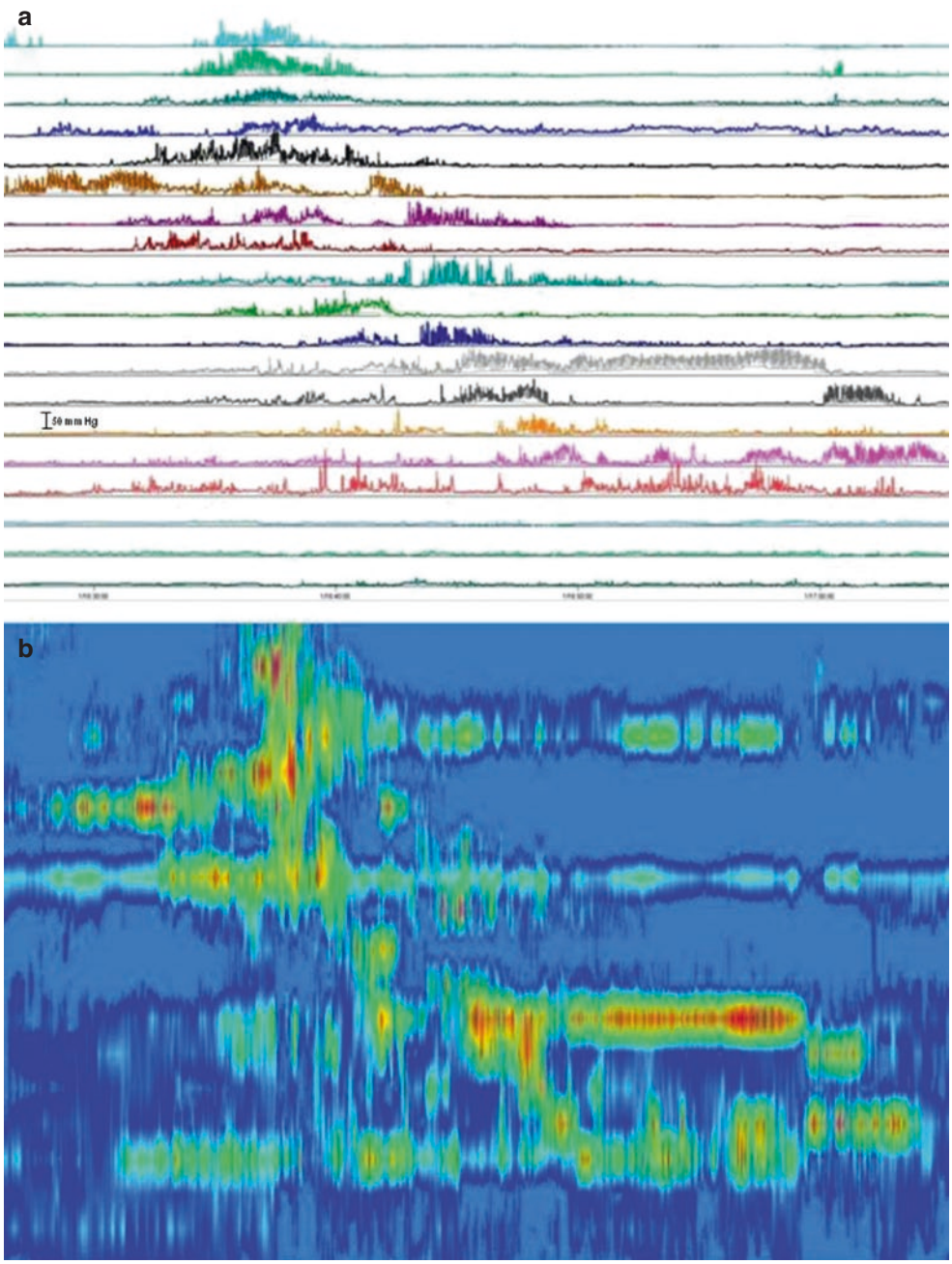

Fig. 11.5 Examples of conventional (**a**) and spatiotemporal plot (**b**) of an abnormal propagation of phase III in a child with neuropathic pediatric chronic intestinal pseudo-obstruction (PIPO). The fifth channel is localized in the antrum. The recording has been performed with a 20-channnel manometric catheter (side holes 2.5 cm apart)

Recently, the protocol for enhanced analysis of ADM contractile patterns, including a scoring system, was published [59]. The scoring system was able to discriminate between PIPO and non-PIPO patients, but also between distinct histopathological pathologies. However, further studies are needed on larger population to validate these results.

In patients with *mechanical obstruction,* multiple simultaneous giant contractions as well as the presence of simultaneous DCCs in the postprandial period are frequently reported. In neonates, the presence of high-amplitude retropropagated contractions should raise the suspicion of mechanical obstruction. In children with *CNS abnormalities,* it has been shown an abnormal frequency and propagation of phase III, increase proportion of nonpropagated DCCs, antral hypomotility, abnormal proportion between periods of phase I and II activity, and altered postprandial pattern duration with the presence of phase III-like activity [60]. Finally, in adult patients with *postvagotomy syndrome,* the most common manometric findings are an increased frequency of MMC, the absence of antral phase III and the presence of antral hypomotility after test meal, and altered postprandial pattern duration with a rapid return of MMC activity. An example of the different parameters that should be included in a manometric report is shown in Table 11.2.

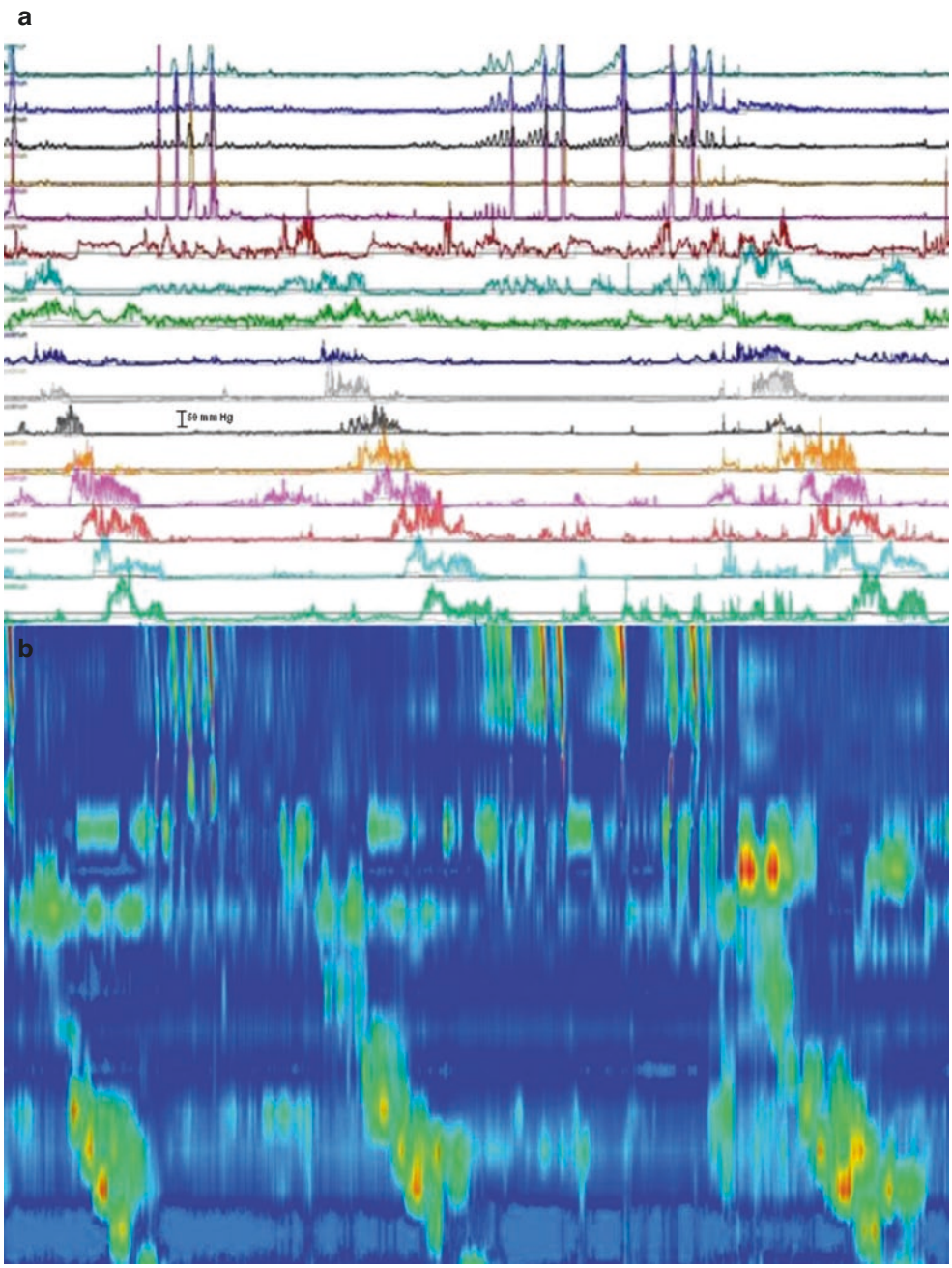

Fig. 11.6 Examples of conventional (**a**) and spatiotemporal plot (**b**) of short intervals of phase III child with chronic intestinal pseudo-obstruction. The phase III occurred separated by interval of 10–15 min. Note also the tonic component within phases III, which are defined as an elevation of the baseline more than 10 mm Hg for longer than 1 min. The recording has been performed with a 20-channnel manometric catheter (side holes 2.5 cm apart)

Reference Values

Prior to interpreting the recorded data and deciding whether abnormalities of gastric and small intestinal motor activity are present, it is of pivotal importance to define the spectrum of normality. Unfortunately, the lack of normal controls is an important limiting factor for the establishment of normal motility patterns, making the interpretation of manometric recording data difficult and subjective and occasionally leading to over-interpretation. However, some normal values have been published (Table 11.3). Although each center performing ADM should have an own set of normal values, it is suggested that "normal" ranges proposed by one group could be used by another if the investigation is performed and interpreted in the same way.

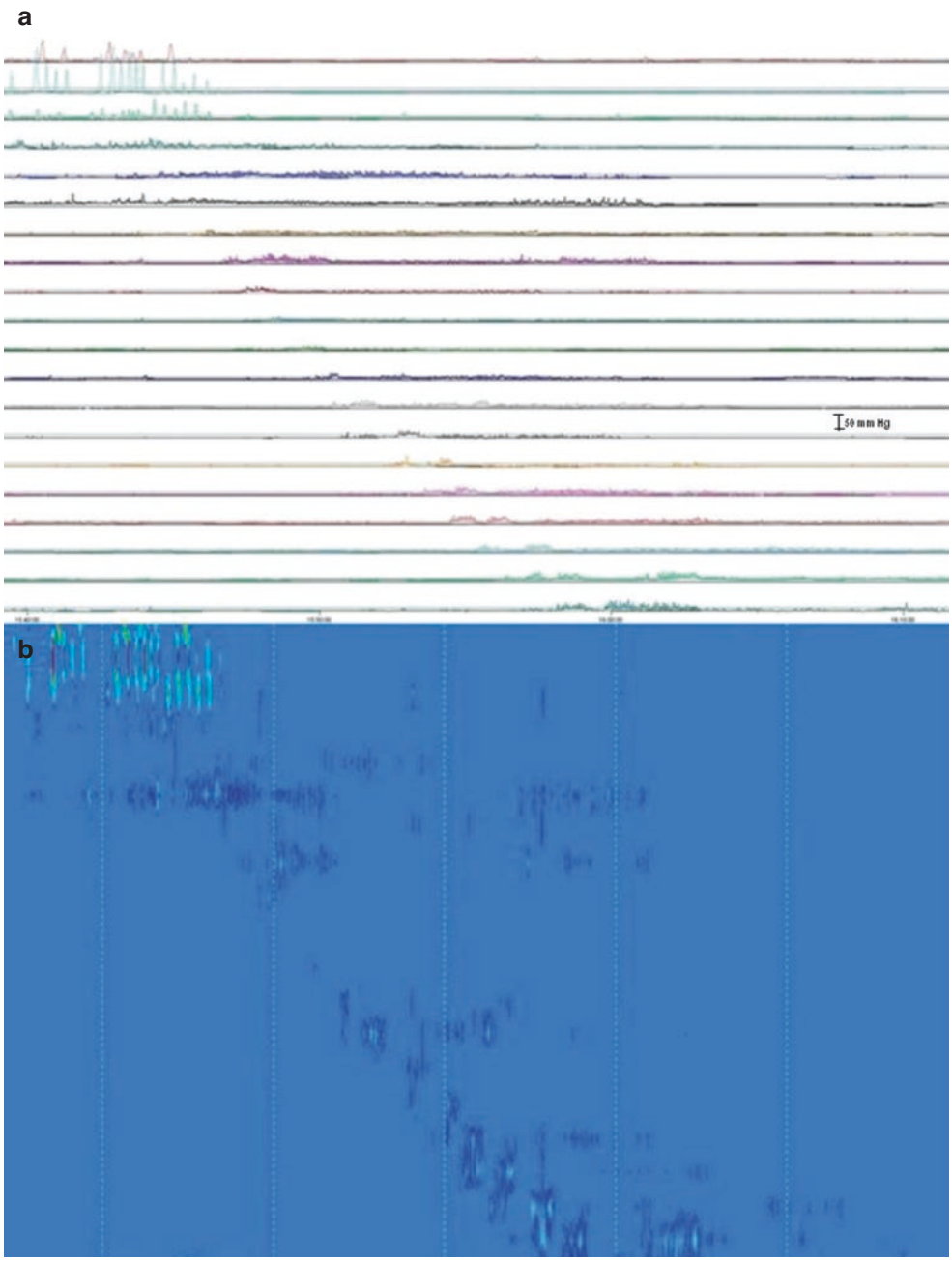

Fig. 11.7 Manometric tracing in a child with myopathy pediatric chronic intestinal pseudo-obstruction (PIPO). Note the low amplitude but normal propagation of the phase III and the paucity of other contractile activity in the small intestine in both conventional (**a**) and spatiotemporal plot (**b**). The recording has been performed with a 20-channnel manometric catheter (side holes 2.5 cm apart)

Table 11.2 Components of the report

General information
1. Patient ID
2. Date and time of the procedure
3. Referring physician
4. Medication used during the test
5. Person performing the study
6. Type of catheter used
7. Indications for the study
8. Study duration
9. Test meal (y/n); route of delivery; calories eaten
10. Catheter placement (nostrils/gastrostomy)
11. Position of the catheter tip (?Beyond DJ flexure)
12. Any significant symptoms reported
Fasting period: Analysis of 3 distinct phases of MMC (presence, propagation and duration):
1. Number and duration of cycles of all 3 phases
2. Phase III
– Highest contraction frequency of duodenum
– Highest contraction frequency of duodenum
– Highest contraction frequency of antral activity (normal 3 cpm)
– Highest amplitude (normal >20 mm hg)
– Presence of phase III
– Duration of phase III (normal 3–4 min)
– Number of phase III during the study
– Propagation of phase III (normal/abnormal)
3. Phase I
– Duration (normal 40–50 min)
4. Phase II
– Frequency
– Presence of discrete clusters of contractions
– Presence of single bursts of contractions (single, propagated, simultaneous)
5. Presence of symptoms
6. Drug stimulation
Postprandial
1. Start and end of the meal should be stated.
2. Presence of postprandial contraction pattern (fed-response)
3. Duration of postprandial phase (normal at least 2 h after meal ingestion)
4. Pre- and postprandial motility index (MI) calculated 30 min before and 30 min after test meal.
5. MI ratio (ratio between postprandial and preprandial motility index)
6. Amplitude ratio (ratio between postprandial and preprandial amplitude)
Interpretation

Table 11.3 Normal values for preprandial motor activity (mean and ranges) [8, 9, 12, 23]

Parameter	Infants	Children	Adolescents
Duration of phase 1—Small intestine (min)		12	
Duration of phase 2—Small intestine (min)		40	
Duration of phase 3 (min)			
• Antrum	3.5 (3–4)		
• Small intestine	3.5 (3–7)	4.4	5.0
Amplitude of phase 3 contractions (mm hg)			
• Antrum		131.8	
• Small intestine	20 (15–30)	55.3	35 (30–40)
Frequency of phase 3 contractions (contr./min)			
• Antrum	3.3 (3–3.5)		3 (2.5–3.5)
• Duodenum	12 (11–12.5)		11.3 (10.8–11.6)
Migration velocity of phase 3 (cm/min)			
• Stomach to duodenum	2 (1–4)		12 (7–30)
• Duodenum/jejunum	2.5 (1–5)		9 (3–15)
Interval of phase 3 (min)		103.9	100 (40–240)

Adapted from Tomomasa T. Antroduodenal manometry p 195–214. In Pediatric Gastrointestinal Motility Disorders. Hyman PE ed. Academy Professional Information Service

Indications

Although ADM is indicated in patients with otherwise undiagnosed gut motility disorders unresponsive to conventional therapies and whose quality of life is substantially impaired (by symptom severity and the diagnostic uncertainty), it is a rather cumbersome procedure to perform, not always easy to interpret, and practically useful in the clinical management of only a minority of patients. For instance, it has been shown in children that there is an excellent interobserver agreement for the number of fasting phase III and their measurement, whereas the interobserver agreement for the detection of other motor abnormalities, such as sustained phasic contraction and postprandial simultaneous clusters, is significantly low [61]. Therefore, given that the small bowel manometry requires expertise and dedicated equipment and personnel, it should be ideally performed in a limited number of referral centers with a specific interest in the field.

Table 11.4 Clinical indications for antroduodenal manometry

1. Clarify the diagnosis in patients with unexplained nausea, vomiting or symptoms suggestive of upper gastrointestinal dysmotility
2. Differentiate between neuropathic vs myopathic gastric or small bowel dysfunction in patients with chronic intestinal pseudo-obstruction.
3. Identify generalized dysmotility in patients with colonic dysmotility (e.g., chronic constipation), particularly prior to subtotal colectomy
4. Confirm diagnosis in suspected chronic intestinal pseudoobstruction syndromes when the diagnosis is unclear on clinical or radiological grounds
5. Assess for possible mechanical obstruction when clinical features suggest, but radiological studies do not reveal, obstruction
6. Determine which organs need to be transplanted (isolated vs multi-visceral transplantation) in patients with chronic intestinal pseudo-obstruction being considered for intestinal transplantation
7. Confirm a diagnosis of rumination syndrome

ADM serves to clarify a clinical diagnosis of abnormal motility or exclude a gastrointestinal (GI) motility disorder. There are only a few indications for the test (Table 11.4). Manometry is indicated in children with suspected chronic intestinal pseudo-obstruction in order to verify the diagnosis, clarify the pathogenesis, and optimize clinical management [62]. For instance, the presence of a myopathic pattern is an indicator of a poor response to enteral feeding, whereas the presence of MMC predicts clinical response to prokinetics therapy and success of enteral feeding [25, 63]. Manometric assessment may allow determination of the extent of disease (localized or diffuse) and the optimal route for nutritional support (gastric, enteric, or parenteral). ADM may be useful in guiding the intestinal transplantation strategy in children with chronic intestinal pseudo-obstruction by identifying the extent of GI dysmotility [25]. Severe gastric or duodenal motor abnormalities seem to compromise the postoperative course of the intestinal graft recipient. In patients with intractable constipation, ADM manometry should be performed if surgery is being considered, given that patients with small bowel dysmotility have generally a poor outcome after the surgery. ADM is also indicated in patients with recurrent subocclusive episodes, in order to differentiate a pseudo-obstructive syndrome from a mechanical obstruction, which may sometimes be overlooked even by an experienced radiologist [64]. Manometry is indicated in the investigation of children with severe unexplained gastrointestinal symptoms, such as vomiting, nausea, abdominal distension, and abdominal pain who fail to respond to an appropriate therapy, and in this context the test helps to differentiate between vomiting and rumination [65, 66]. For instance, in children with suspected rumination syndrome, the ADM is useful in confirming the diagnosis by showing a characteristic motor pattern, characterized by postprandial simultaneous pressure increases at all recording sites [65]. This is covered elsewhere in the book. There is evidence of the utility of ADM in investigating patients with orthostatic intolerance with associated GI symptoms, like nausea, vomiting, and abdominal pain [67, 68]. Finally, an entirely normal study in children clinically suspected of having a severe dysmotility syndrome may help to redirect the diagnostic effort, and may result in the consideration of other diagnoses such as fabricated or induced illness (formerly Munchausen's by proxy syndrome) [69, 70].

In adults, ambulatory ADM is often performed. It is a safe and useful tool and the most common indications for ambulatory ADM are chronic abdominal pain, slow-transit constipation, refractory gastroparesis, chronic diarrhea, recurrent episodes of subocclusion, postsurgical evaluation, suspicion of gut involvement in systemic disease, and unexplained nausea [71].

Conclusion

Antroduodenal manometry provides relevant physiological information on the neuromuscular activity of the foregut and is useful in diagnosing and guiding the management of enteric neuromuscular disorders. Because of the complexity in performing and analyzing ADM, it requires considerable experience and skills that may only be available in referral centers with a specific interest in the field of GI motility. The development of recording equipment and advanced computer analysis that are in progress appear to have the potential to substantially improve our understanding of normal and abnormal foregut neuromuscular function.

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Colonic Manometry

12

Carlo Di Lorenzo, Desale Yacob, and Phil G. Dinning

Introduction

The colon is tasked with what appears to be a mundane and unsophisticated function of stool disposal. This task is, however, very complex and is accomplished by multiple unique and diverse motor activities all working in synchrony. The colon's main functions are achieved through slow net distal propulsion, continuous mixing, exposure of its content to mucosal surfaces, and tonic and phasic intraluminal pressure changes. The organized patterns that make this process efficient have specific characteristics at different regions of the colon. Much is known about the in vitro activity on a cellular level of this process; however, there are still unanswered questions regarding the in vivo activity, in part, due to the lack of a suitable animal model. The introduction of colonic manometry and recent innovations in its technique, the modalities of catheter placement, and its analysis has now made it possible to understand more thoroughly the motor characteristics of the entire colon.

It is estimated that the ileum transfers around 1.5 L of predominantly liquid content into the cecum every day [1]. Over the next 12–30 h, the content moves in an irregular, stepwise fashion towards the rectum. During this time, content is mixed so that bacterial fermentation of carbohydrates occurs, fluid and short chain fatty acid are absorbed, and feces are formed, stored, and eventually evacuated. Controlling the movement of luminal content through the colon is a series of coordinated contractions and relaxations of the circular and longitudinal smooth muscles. These motor patterns are influenced by several physiological stimuli such as meals, exercise, sleep, waking, and a variety of emotions. The motor patterns of the colon also respond to chemical and mechanical stimuli. Researchers have used various stimuli to help define normal colonic motor patterns and to gain insight into the myogenic and neurogenic mechanisms that cause the responses. A diminished response to physiological or chemical stimuli in patients with colonic and/or anorectal disorders provides insights into the cause of their disorders. In this chapter, we will review the techniques used to record colonic manometry, define the different types of motor pattern identified, and detail their potential physiological role in the colon and the mechanisms that underpin them. Finally, we will discuss the clinical findings from colonic manometry studies in children with functional colonic disorders.

Indications for Performing Colonic Manometry

1. Severe constipation.
   (a) To assess patients with severe constipation unresponsive to adequate medical, behavioral, and dietary therapy.
   (b) To guide surgical interventions including placement of diverting stoma, segmental colonic resection, or formation of a conduit for the administration of antegrade enemas.
   (c) To evaluate the function of a disconnected colon before possible closure of a diverting ostomy.
2. Pediatric intestinal pseudo-obstruction.
   (a) To determine if the colon is involved in the disease.
   (b) To help plan which organs to transplant before a small bowel or multi-visceral transplant.
3. Hirschsprung's disease and repaired imperforate anus.
   (a) To clarify the pathophysiology of persistent symptoms after removal of the aganglionic segment or repair of anorectal malformations when there is no anatomical abnormality likely to explain the symptoms.

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How to Perform Colonic Manometry

The contractile function of the colon in children has traditionally been measured using highly flexible, small diameter catheters which are placed within the colonic lumen, with pressure-sensitive ports placed along the catheter length. The catheter types, their placement techniques, and the software for data analysis have all evolved over the past few years, leading to a more sophisticated mapping of the colon's motor function.

Water-perfused catheters have been in use for many years and are still being employed by many centers. It is important to note that most published pediatric studies utilized water-perfused catheters, and hence the basis for most of our understanding of the subject matter emanates from this methodology. The spacing between the recording sites of these catheters is variable but usually ranges between 5 and 15 cm, based upon the age of the child and the length of the colon to be studied. Each port is connected via a separate lumen (recording channel) to individual strain gauge pressure transducers, allowing multichannel studies. Perfusion is at a constant flow rate and is achieved by use of distilled water at constant pressure [2]. Contractions of the colonic wall occlude the manometric opening and impede the flow of water. Resistance to flow is measured as pressure change. The advantages of this system include its simplicity, the relatively inexpensive components, and the ease of sterilization. These catheters are also available in disposable versions. Disadvantages of this system include the need for the patient to be connected to a stationary apparatus, the amount of water infused during prolonged studies which can potentially place small infants at risk for water intoxication, and the large spacing between the pressure sensors, making it hard to detect contractions that propagate for short distances.

More recently, high-resolution catheters are being utilized more often to perform colonic motility testing. These catheters typically incorporate between 36 and 84 pressure recording sites, spaced between 10 and 30 mm. High-resolution catheter types include water perfused, solid-state, or fiber-optic. Direct comparisons among the three catheter types have not been performed; however, solid-state catheters were found to be as reliable at detecting high-amplitude propagating contractions (HAPCs) when compared to the water-perfused ones [3] and every described motor pattern in the literature has been detected by all three systems. The new technology is proving to be superior in providing a more precise topographic mapping of the colon's complex motor function [4], thus remedying the deficiencies of the older system (Fig. 12.1). Disadvantages of both the fiber-optic and solid-state systems include the significantly higher cost and the relative fragility of the equipment, in comparison to water perfused systems.

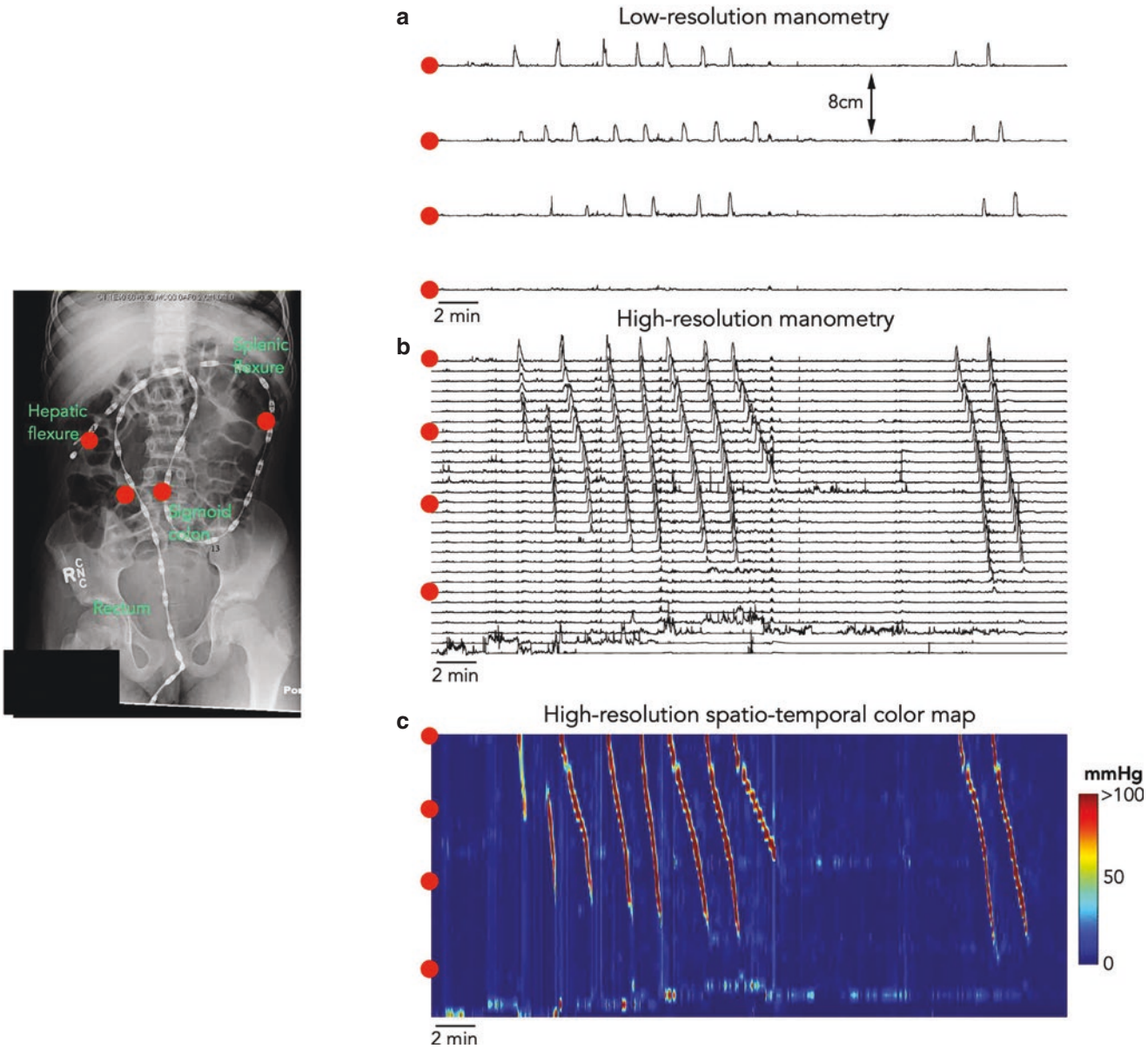

Fig. 12.1 A comparison between low and high-resolution colonic manometry. The X-ray shows the placement of a solid-state high-resolution manometry catheter into the colon of a child with constipation. (**a**) Representation of a low-resolution recording, with pressure data shown from every eighth sensor. (**b**) Show the same data from (**a**) but pressure data is now shown from every sensor. The high amplitude propagating contractions can be clearly seen. (**c**) Shows the trace in (**b**) shown as a spatiotemporal color plot

Colonic Manometry Catheter Placement

Placement of colonic catheters constitutes one of the most challenging portions of the testing in children. In pediatrics, the placement is done transanally, in a retrograde fashion, except in the presence of ostomies which may allow placement of the catheter through the ostomy in an antegrade or retrograde manner depending on the location of the ostomy. Colonoscopic placement requires bowel cleansing which some studies have suggested may affect basal motor activity [5, 6] but may also standardize the procedure. Different endoscopic techniques can be used for the placement. A biopsy forceps can be passed through the biopsy channel, grasping the manometry catheter via a suture loop tied to the catheter tip. The catheter is then advanced along with the colonoscope to the desired location, the forceps is opened, and the scope is then slowly retracted suctioning as much air as possible. Recently, it has been the practice of many to have the catheter clipped to the colonic mucosa, making it less likely for it to be dislodged during testing (Figs. 12.2 and 12.3) [7]. This can be

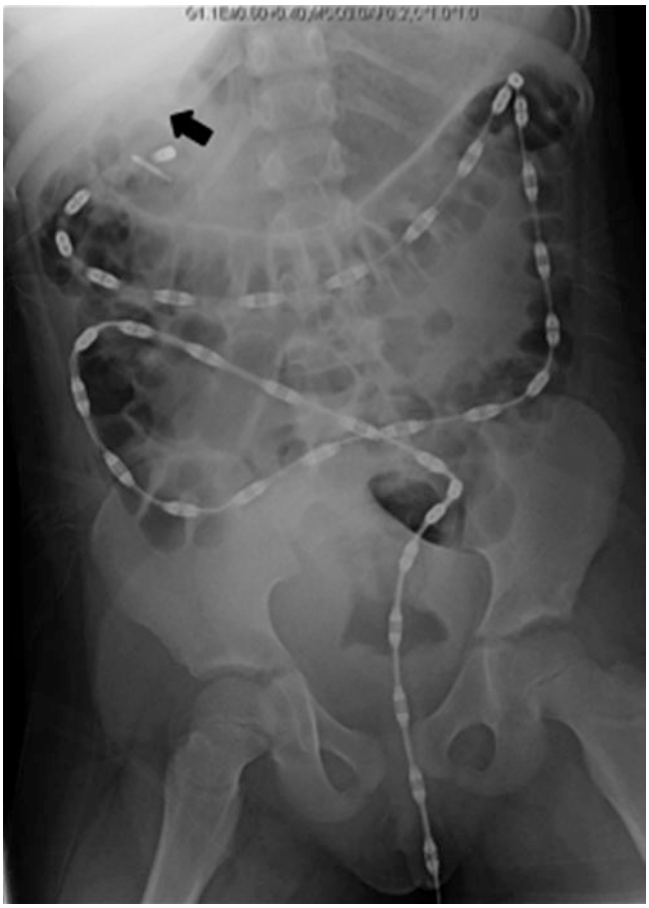

Fig. 12.2 Abdominal radiograph showing a high-resolution solid-state colonic motility catheter placed with its tip at the hepatic flexure. The *arrow* points to the endoclip used to secure the catheter in place

accomplished by grabbing the suture loop with a hemostasis clipping device that is then deployed on a mucosal fold when the desired location has been reached and the catheter is released. Once the test is complete, a gentle pull is all that is needed to remove the catheter. In our center, the suture is tied to both the tip of the catheter and to one of the endoclip prongs that has been passed through the biopsy channel of the scope, which is then closed and pulled back into the channel. Successful placement requires skilled maneuvers and patience given the redundant and dilated distal colon that is common in the patient population needing manometry evaluation. An alternate transrectal placement technique uses a guidewire passed though the biopsy channel and left in place during the removal of the colonoscope. The manometry catheter is then advanced over this guidewire with fluoroscopic assistance. It should be emphasized that in children the endoscopic placement is always done under deep sedation or general anesthesia. The dilated and redundant colons of patients with severe and chronic constipation are not always easy to cleanse with regular cleanout regimens prior to colonoscopy. In the most recalcitrant cases, a 1- or 2-day admission to the hospital for an inpatient cleanout prior to the catheter placement and testing may be necessary. Fluoroscopic placement of the catheter into the proximal colon may also be performed by skilled interventional radiologists, but it is associated with exposure of the patient to radiation [8].

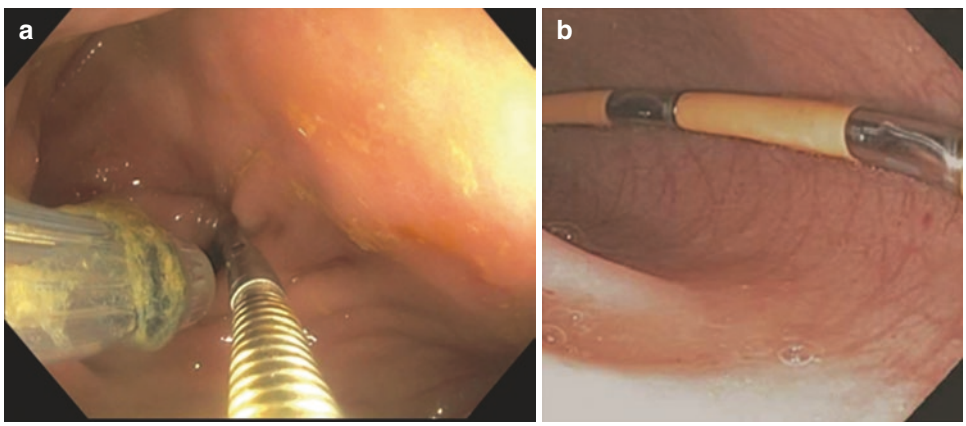

Fig. 12.3 Endoscopic image of colonic motility catheters, (**a**) water-perfused catheter in the process of being clipped to a fold in the cecum and (**b**) a solid-state catheter in the colonic lumen with the pressure sensors in silver

Colonic Manometry Protocols

Colonic manometry protocols are not standardized and therefore there is a lot of variability in the way studies are performed. There are no prospective data indicating superiority of any specific one. Studies of relatively short duration, approximately 4–8 h (Fig. 12.4), are usually adequate to evaluate response to stimuli and form a plan of intervention. However, studies lasting 24 h allow the colon to fill again and can provide more physiologic data. Pediatric studies are initiated after the effect of the sedation or the anesthesia used for placement of the catheter has resolved. Some have suggested that the study can be performed as early as 4 h after recovering from anesthesia [9], but others have reported an important effect of anesthesia on the study interpretation when the study is performed the same day of anesthesia [10], although there are other variables, such as the colon becoming partially filled again, that could contribute to the results being different on the following day. Typical protocols in pediatrics start with a fasting period when baseline colonic motility without stimulation is monitored for 1–2 h. The child is then offered and asked to eat a large, age-appropriate meal (children often have a ravenous appetite during the test after having received a clean-out and a period of fasting!). The postprandial motility assessment starts at the beginning of meal ingestion and continues for at least 1 more hour after the end of meal. Pharmacologic provocation is then usually performed with 0.2 mg/kg of bisacodyl (max 10 mg), which is infused through the motility catheter into the most proximal portion of the colon or via an ostomy opening if present. Symptoms experienced by the child are noted during the entire study. It is particularly informative to observe the child's reaction to the onset of the urge to defecate associated with the administration of bisacodyl. Thus, it is imperative that a nurse or a physician is in the room with the child undergoing the test at all times. The patient is most likely to report abdominal cramping and have a bowel movement as a result of the HAPC. It is not unusual for the child's withhold-

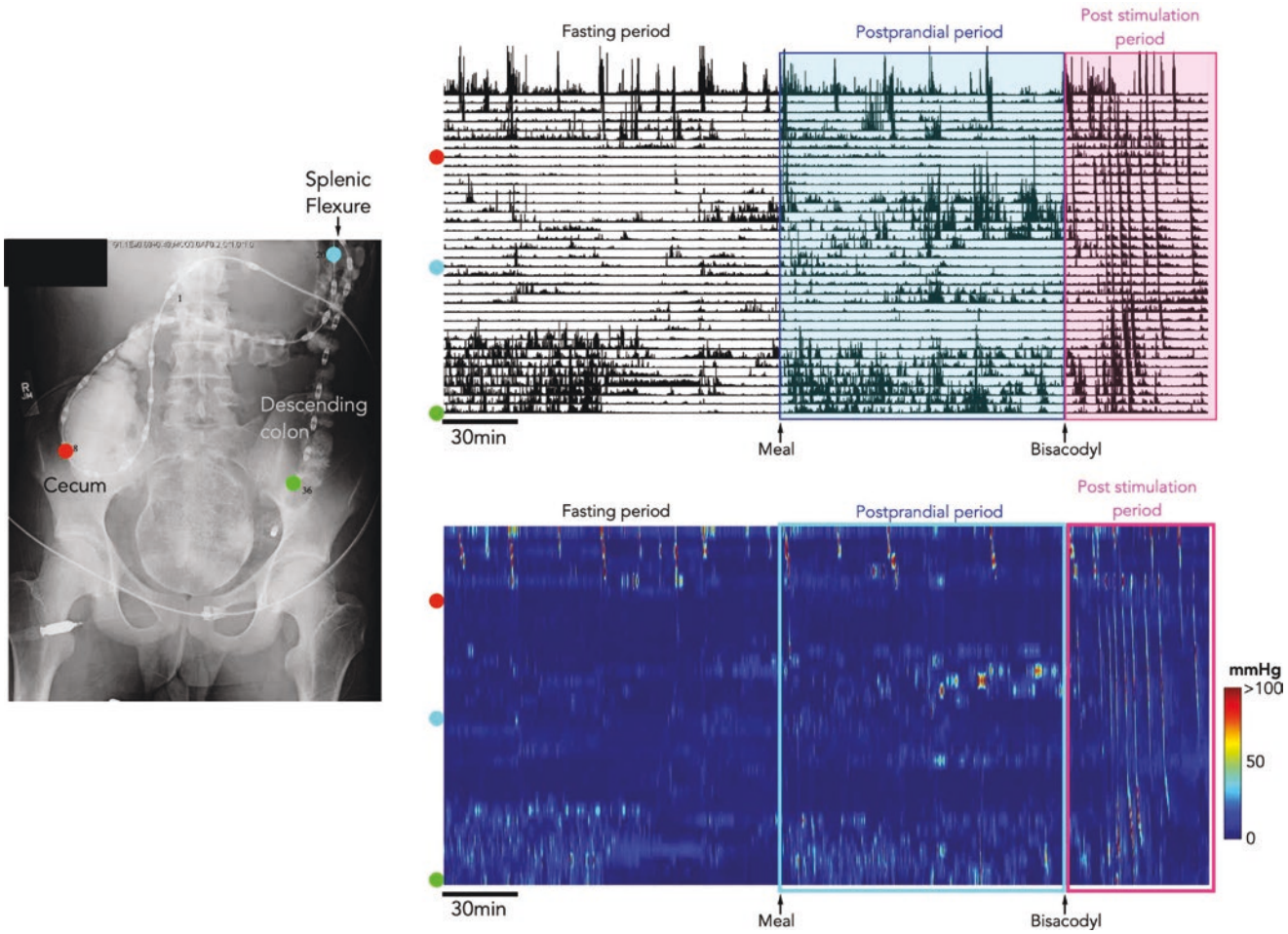

Fig. 12.4 A 5.5-h-long colonic manometry study with fasting, postprandial, and post-stimulant motility tracing. The X-ray shows the catheter placement through a cecostomy, with the tip located in the sigmoid colon. The manometry trace is shown as a line plot (top) and a spatio-temporal color map (bottom)

ing behavior to be finally recognized as such by the parents once it is pointed out by the medical provider observing the study. Some children wrongly identify the cramping that is due to colonic contractions with pain or deny any sensation, although their non-verbal cues suggest otherwise, and elect to lay in bed instead of heading to the commode. The feedback from the medical provider as this is taking place has the potential to be very educational to both the patient and the parents [11].

Normal Colonic Physiology

Ethical constraints limit the use of colonic manometry to children with suspected colonic motility disorders. Thus, the details of normal colonic motor patterns in response to physiological and chemical stimuli have been obtained from studies in healthy adults or children in whom, in retrospect, there were minimal symptoms and no motility disorders. In the next section, we will describe current understanding of the myogenic and neurogenic control of colonic motility, the motor patterns detected by colonic manometry and their association with spontaneous defecation, sleep and morning waking, ingestion of a meal, and in response to bisacodyl.

Myogenic and Neurogenic Control of Colonic Motility

Normal colorectal motility involves the coordinated activity of the enteric muscles, the enteric nervous system (ENS), and the interstitial cells of Cajal (ICC) and is modulated by the sympathetic and parasympathetic components of the autonomic nervous system. The ENS provides the gastrointestinal tract a local nervous mechanism within its walls. However, although the various intestinal functions are regulated locally by the ENS, its control of intestinal motility is modified and enhanced by inputs from the central nervous system and other entities that reside in the gut. The myenteric plexus controls the motor function by directly innervating the circular and the longitudinal muscle layers of the colon. Sensory input affecting motility is accomplished via intrinsic sensory neurons which are activated by stretch and muscle tension. They are also activated by intraluminal chemical stimuli that act on the chemical and mechanical receptors found within the mucosal epithelium [12, 13]. The autonomic nervous system, via the sympathetic nervous systems, directly innervates smooth muscle, but a large amount of its influence is indirectly mediated by influences on the enteric neuronal circuits. The parasympathetic nervous system is influenced primarily by vagal efferents to the proximal colon [14]. There is little or no vagal effect beyond the distal colon where sacral parasympathetic influences come into play. The sacral parasympathetic pathways are identified as being responsible for the process of defecation [15]. These processes combine to form an array of motor patterns responsible for the normal physiological processes of the colon.

Defecation

The process of defecation has four stages: basal phase, pre-expulsive phase, expulsive phase, and the end phase [16]. The *basal phase* describes the period of colonic motility during the non-defecatory stage, when the colon performs all of its normal physiological functions; mixing luminal content, fluid absorption, propulsion of content towards the rectum, and formation of stool. This is accomplished through infrequent HAPC, antegrade and retrograde low-amplitude propagating contraction (LAPC), and the cyclic motor pattern. The *pre-expulsive phase* describes the period in the hour prior to defecation. It occurs in the absence of any urge. During this period, there is a build-up in the number of antegrade LAPC. Over a 1-h period, the LAPCs shift their site of origin to more distal regions of the colon, presumably to move content towards the rectum in preparation for evacuation. The *expulsive phase* describes the lead up to and the actual evacuation of stool. It commences 15 minutes prior to defecation occurring. During this period, there is a gradual increase in the amplitude, extent of propagation, and frequency of antegrade propagating contractions, the majority of which reach an amplitude to be classified as HAPC (Fig. 12.5). These sequential propagating contractions during this phase propagate to the rectum and are associated with an urge to defecate. During the expulsion phase, intra-abdominal pressure increases along with descent of the pelvic floor and straightening of the anorectal angle. The increase in rectal pressure results in an involuntary relaxation of the internal anal sphincter, followed by expulsion of stool when the external anal sphincter relaxes. The final phase, the *end phase* describes the period immediately after defecation has occurred. During this phase, the basal rectoanal pressure gradient is re-established and continence is restored. Specific motor colonic patterns during this phase have not been described.

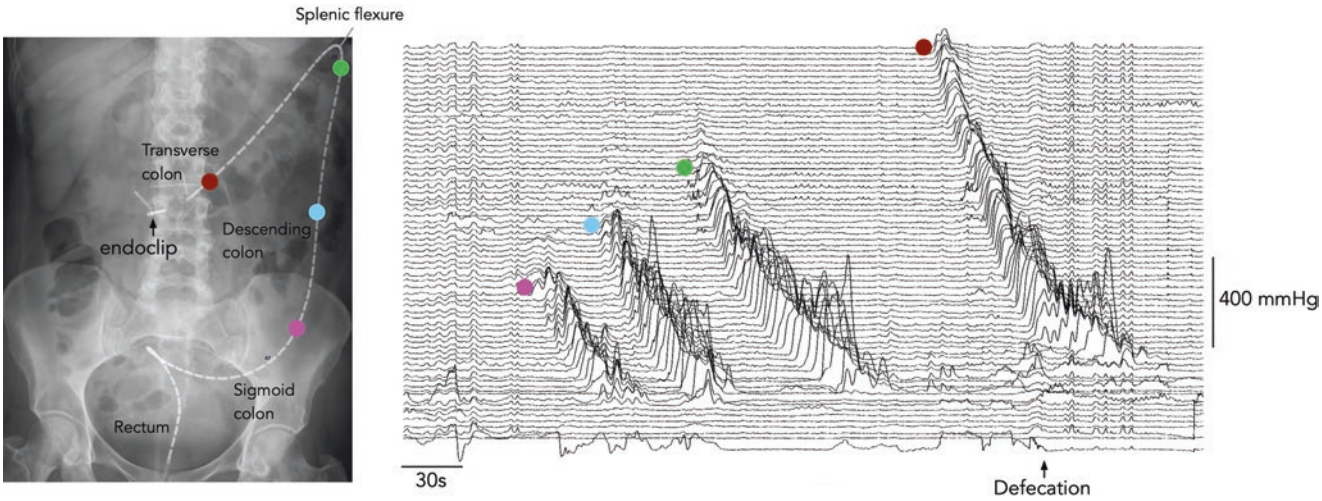

Fig. 12.5 Abdominal radiograph showing a fiber-optic manometric catheter placed in the colon with the tip located in the mid-transverse colon. To the right of the X-ray is a manometric trace showing an array of high amplitude propagating contractions (HAPC) in the build up to defecation. The colored circles on the X-ray image correspond to the location of the start of each of the HAPC. The first HAPC (pink circle) originates at the rectosigmoid junction, the second HAPC (blue circle) originates at the mid-transverse colon, the third HAPC (green circle) originates at the splenic flexure, the final HAPC (brown circle) is associated with defecation and this originates at or proximal to the mid-transverse colon

Colonic Response to Sleep and Morning Waking

From the earliest X-ray observations of the human colon in 1907, it was noted that it was more sluggish at night than during the day [17] In the 1940s using fluid filled balloons motor patterns were shown to be inhibited during sleep [18]. Colonic manometry studies have confirmed the nocturnal suppression of LAPC and HAPC [19], with one demonstrating a strong correlation between depth of sleep and the suppression of activity [20]. In contrast to suppression of LAPC and HAPC, the cyclic motor pattern in the distal colon become more prolific at night [21]. This motor pattern is hypothesized to act as a recto-sigmoid brake, controlling and diminishing nighttime rectal filling, so that no urge to defecate occurs when asleep [22]. Waking promotes an increase in the number of HAPCs [23, 24].

Colonic Response to a Meal

Since the early 1900s, a meal has been shown to be a powerful stimulus for colonic motility, with the term "Gastrocolonic reflex" coined in 1913 [25]. In low-resolution colonic manometry studies, ingestion of a meal was shown to rapidly increase the number of LAPC and HAPC [24, 26]. This increase in HAPC has become one of the hallmarks of a "normal" colonic response to meal. However, it is important to note that the studies that describe the increase in HAPC were usually conducted over a 24-h period. Therefore, if the subject had had a bowel preparation, the colon would have started to fill again. Other prolonged studies placed the colonic catheter through the nose and thus recordings were made in an unprepared colon (filled with feces) [19]. Colonic distension is a potential stimulus for HAPC and the removal of feces may take away this stimulus. High-resolution colonic manometry studies tend to record contractile activity over a short duration (<8 h) in fully prepared (feces removed) colon. As such, these studies now report that many healthy subjects fail to generate HAPCs after a meal [27–29] Studies in healthy adults with a fiber-optic manometry catheter have shown a significant increase in cyclic motor pattern after a meal in most healthy adults. This is particularly prominent in the sigmoid colon and with pressure changes propagating primarily in a retrograde direction [27]. This is likely to represent the previous reporting of an increase in "non-propagating" activity reported in low-resolution manometry studies.

The colonic meal response is related to the calorie content [30] and may be dependent upon the amount of fat in the meal [31]. The increase in the cyclic motor pattern occurs within seconds of starting a meal [27]. The speed of the response and the fact that it can be blocked by pre-treatment with clidinium bromide (an anticholinergic drug) [30] indicates that the early meal response is neurally mediated. After the early response, a second peak in motility can be seen after 50–110 min lasting up to 3 h. It is hypothesized that this delayed response may be caused by circulating hormones released after eating.

In clinical studies, an increased motor activity following a meal may be regarded as an indication of the integrity of the neurohumoral control of colonic motility. However, it is important to note that despite the number of studies performed in healthy adults over many years, there is still no clearly defined colonic response to a meal. Even in healthy adults, a colonic response to meal is not always detected. In studies conducted in a cleansed colon, the presence of postprandial HAPC is a good indicator of intact intrinsic nerves to the colon, but an absence of such motor patterns does not necessarily imply an abnormality, given many healthy adults, who have had a bowel preparation, also lack such motor patterns after a meal.

Colonic Response to Bisacodyl

While many drugs have been used to stimulate or inhibit colonic motor patterns, the most used during colonic manometry testing is bisacodyl. This drug is broken down to its active form desacetyl-bisacodyl in the lumen of the gut where it stimulates sensory nerves in the mucosa. This in turn is likely to stimulate extrinsic vagal nerves, because regardless of the site of application of bisacodyl, it initiates an array of HAPCs which originate in the proximal colon. A recent study in healthy adults showed that a rectal infusion of bisacodyl could stimulate HAPC originating in the ascending colon [29]. Thus, the ability to trigger HAPC with bisacodyl is good evidence of intact extrinsic nerves to the colon. Once HAPCs start, their ability to propagate along the length of the colon suggests intact enteric neural circuits.

Identifiable Motility Patterns

The terminology used for motor patterns in this chapter is based upon those agreed upon in a recent consensus document [32]. The most recognizable colonic motor patterns is the HAPC, defined as contractions with an amplitude of greater than 75 mmHg, a duration of greater than 10 s, and propagation of 30 cm or more. These motor patterns originate predominantly in the proximal colon and commonly propagate in an anal direction to the sigmoid colon [33]. These relatively infrequent motor patterns have been temporally linked with both propulsion of content and defecation. Low-amplitude propagating contractions (LAPCs), as the name suggests, have a lower amplitude that does not meet the criteria for HAPC. These motor patterns can propagate in an anal or oral direction and while associated with luminal transit, they are more likely to be involved in the mixing of colonic content or propulsion of gas. When LAPCs occur at a frequency between 2 and 8 per minute, they are labeled as a *cyclic motor pattern.* This motor pattern occurs throughout the colon, but its primary site of origin is the rectosigmoid junction (Fig. 12.6). It propagates predominantly in a retrograde (oral) direction.

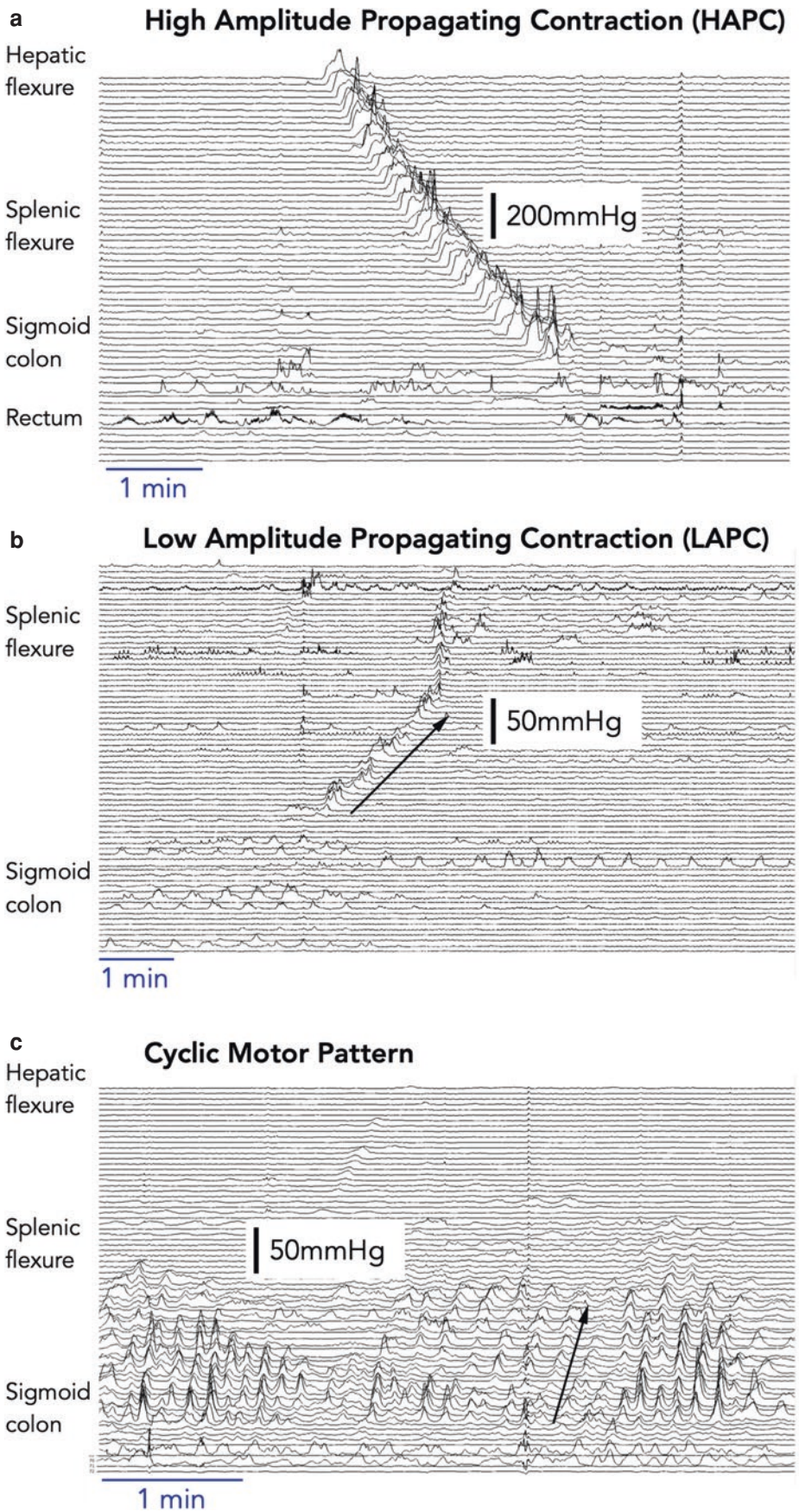

Fig. 12.6 Three of the most commonly recorded motor patterns in the healthy adult colon. (**a**) the high amplitude propagating contraction; (**b**) a retrogradely propagating low amplitude propagating contraction; (**c**) the cyclic motor pattern the majority of which propagates in a retrograde direction. All these motor patterns have also been identified in pediatric manometry studies

Pediatric Colonic Manometry

There are no colonic motor patterns unique to the pediatric colon. HAPCs can occur following meals, upon awakening, and can be induced by bisacodyl and other colonic irritants, such as glycerin. They are, however, more common in younger children [34] and in patients who have had a distal colonic resection, such as in patients after surgery for Hirschsprung's disease, probably due to a loss of an inhibitory recto-colonic reflex [35]. Studies have also shown that propagated contractions of varied amplitude can also be induced by saline infusion and distention of the right colon [36, 37].

An early colonic meal response can be detected in the distal colon and in some children, this may result in an urge to defecate. An increase in colonic motility, particularly during low resolution studies, is often measured as the "motility index" (a parameter which takes into account both frequency and amplitude of contractions). The increase in motility involves both tonic and phasic contractions and may be difficult to quantify especially when the postprandial period is associated with motion artifacts caused by the children moving during and after the meal. High-resolution manometry studies have shown that the cyclic motor pattern is present in the distal colon of constipated children. However, unlike healthy adults, the motor pattern does not increase after a meal [38]. This abnormal response to meal is not dependent on the catheter type (water perfused vs solid state), catheter placement technique, or study protocol used [39]. Evaluation of postprandial changes in colonic tone using the electronic barostat is not commonly done in children [40]. While there is great concordance among different investigators in the recognition of HAPC, the visual interpretation of the gastrocolonic response produces the maximum variability in inter-individual interpretation of the test. The median agreement regarding the overall interpretation of the colonic manometry in children being either normal or abnormal is 87% [41].

Constipation

Most children with constipation have functional constipation, a condition related to a maladaptive response to an uncomfortable defecation. A small proportion of children with constipation have symptoms unresponsive to aggressive medical and behavioral therapy which are severe enough to dramatically affect quality of life. In constipated children, especially in the presence of fecal incontinence, the chronicity of the symptoms can be very frustrating and may lead to distrust of the medical team and loss of self-esteem for the child. Colonic manometry is indicated for the evaluation of such children in order to discriminate normal from abnormal colonic motor function [42–44] which may be associated with an underlying colonic neuromuscular disease. This information can then be used to guide management [45]. Resection of colonic segments found to have abnormal motor function can lead to improvement in symptoms [46, 47]. Interestingly, a study with a fairly small sample size showed no correlation between manometric findings and histopathologic abnormalities, suggesting that our current ability to study the morphology and function of the enteric neuromusculature is limited [48].

The majority of children with constipation display an easily recognizable colonic motor response to administration of bisacodyl. In a recent study, among 165 children undergoing colonic manometry for constipation, 154 responded to a colonic infusion of the stimulant laxative [49]. Therefore, while the bisacodyl infusion helped to isolate the 11 children who failed to respond, the majority could be diagnosed with a "normal" colonic response. However, while patients may respond to bisacodyl, their colon may still fail to respond to the normal chemical and mechanical stimuli produced by their normal colonic content. A study by Villarreal et al. used HAPC as a marker for intact neuromuscular colonic function [50]. The failure to produce either spontaneous or bisacodyl induced HAPC directed the providers to the formation of a diverting ostomy (ileostomy or colostomy). In patients who had evidence of a dilated colon with abnormal motility patterns, repeat manometry testing after a period of decompression (5–30 months) led to an improved motor function. Aspirot et al. evaluated the effect of chronic use of antegrade enemas on colonic motility in children and adolescents with severe constipation [51]. Most of the children with abnormal manometry prior to cecostomy placement showed normalization in colonic motility after using antegrade enemas for at least 1 year. Colonic manometry may also be used to predict clinical response to antegrade enemas. Retrospective studies have indicated that patients with HAPC and an intact gastrocolonic response are more likely to have a satisfactory outcome when receiving antegrade enemas [52, 53]. The propagated contractions seem to be essential to propel colonic contents during antegrade irrigation. However, the motor response is still not a guarantee for success, as even some patients with intact HAPC have had a poor outcome, indicating that motility pattern is important, but there are additional factors, such as compliance with the antegrade enema schedule and anorectal and pelvic floor function, possibly playing a role.

Pediatric Intestinal Pseudo-Obstruction

Pediatric intestinal pseudo-obstruction (PIPO) is a heterogeneous group of disorders that vary in cause, severity, course, and response to treatment [54]. Di Lorenzo et al. studied patients with PIPO and found a subgroup of patients with chronic constipation as part of their PIPO symptomatology

who had abnormal HAPC, absent gastrocolonic response, or complete lack of identifiable colonic motor activity [55]. A thorough manometric evaluation including colonic manometry needs to be performed during the evaluation for possible isolated small bowel or multi-visceral transplantation in children with PIPO, in order to assess which organs need to be transplanted and if a permanent diverting ileostomy will be needed [56].

Hirschsprung's Disease and Anorectal Malformations

After resection of the abnormally innervated bowel in Hirschsprung's disease, a large percentage of patients continue to struggle with abnormal defecatory function [57]. Our approach to these patients, in collaboration with the surgical team, is to first evaluate for anatomical abnormalities, presence of a residual aganglionic zone, absence of dentate lines due to iatrogenic damage, and anal sphincter function. A contrast enema is used to assess the anatomy and rule out obstructive Soave cuff, bowel stricture, or colonic twist. This is followed by an anorectal manometry, an examination of the anorectal area under general anesthesia, and a full thickness biopsy to assess anal sphincter basal pressure, integrity of the anal canal, and presence and morphology of ganglion cells, respectively. If necessary, colonic manometry is then performed for further evaluation. The findings on colonic manometry testing may be classified into four groups, each associated with different physiology [58]. Each category directs different therapy: (1) The first group of patients has spontaneous or bisacodyl-induced HAPC which progress through the neorectum all the way to the anal verge. The amplitude of the HAPC exceeds that of the voluntary contraction of the external anal sphincter. The result is incontinence or rectal pain as the patient attempts to retain the stool; (2) The second group has normal colonic motility with fear of defecation and stool withholding. The negative experience related to attempted defecation before surgical removal of the aganglionic segment or in the postoperative period may result in fecal retention. Identification of normal colonic manometry pattern in these children provides reassurance in the diagnosis and more confidence in the behavioral and medical treatment plan; (3) Abnormal colonic manometry with lack of HAPC, poorly propagating HAPCs, or presence of only simultaneous increases in pressure in the distal colon (Fig. 12.7) may be due to a neuropathic motility disorders proximal to the aganglionic segment, possibly associated with intestinal neuronal dysplasia [59] or with a common cavity phenomenon; (4) Finally, some patients have normal colonic motility and a hypertensive anal sphincter. Successful treatment options for this subset of patients have included myectomy, which in our center we tend to avoid due to the risk of irreversible destruction of the internal anal sphincter,

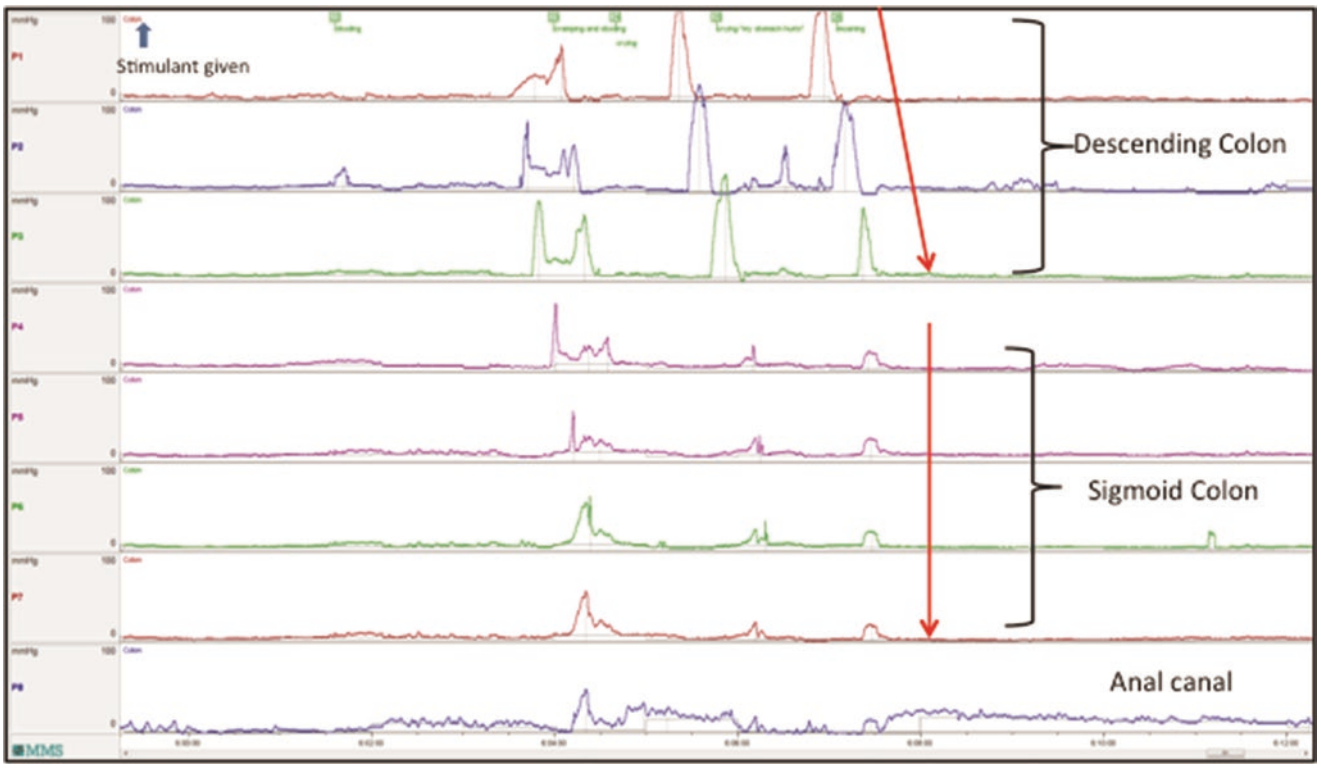

Fig. 12.7 Post-stimulant tracing of normal high-amplitude propagating contractions in the descending colon and abnormal non-propagating low-amplitude pressurization in the sigmoid colon

and botulinum toxin injection into the hypertensive anal sphincter which avoids the risk of permanent sphincter damage but may be associated with the need for repeated injections [60–62]. Similar findings have been described in children with continence disorders after anorectal malformations repair. Heikenen et al. have reported that propagation of excessive numbers of HAPCs into the neorectum as well as internal anal sphincter dysfunction can contribute to fecal incontinence in these children [63].

Additional Types of Studies

Ambulatory 24-Hour Colonic Manometry

A limitation of traditional colonic manometry studies is the duration of the study. There is a well-established circadian variation in colonic motility, which is missed during short studies [64–67]. Twenty-four-hour colonic manometry has been proposed as a more informative test which evaluates a time period felt to be more representative of the normal patient's environment and eating and sleeping patterns. It has been performed in children using water-perfused catheters [68], but it is best done using solid-state catheters, which do not confine the patient to a restricted environment. Solid-state catheters have been placed via colonoscopy with clips adhering to multiple sites of the colonic wall. The patient is then allowed to ambulate, eat, and defecate in a hospital setting for 24 h with continuous manometric measurement. As yet, there are no motor patterns detected by ambulatory studies that have not been identified also in stationary studies and therefore it is unclear how much the additional information collected during a 24-h study changes clinical management compared to a shorter study with meal ingestion and pharmacological stimulation. Ambulatory studies introduce a lot of movement artefact, making the manometry traces difficult to analyze. Given that exercise can potentially impact colonic motility [69] for data to be compared between subjects within- or between groups, the periods of ambulation also need to be tightly controlled, occurring at the same time of day and over the same duration in all subjects. This can limit the "normal" environment of the patient.

Wireless Motility Capsule

This tool has been approved by the US Food and Drug Administration (FDA) for the measurement of gastric emptying and whole gut transit time. Once swallowed, this fairly sizable capsule (diameter and length similar to a video capsule) is capable of measuring intraluminal pH, pressure, and temperature throughout the entire gastrointestinal tract. Data are transmitted to a data receiver and download to a computer for analysis. Gastric emptying is measured by timing the point from ingestion to the point where the pH rises above pH 6, indicating that the capsule has left the acid environment of the stomach and has entered the more neutral pH of the duodenum [70]. Because it has a single pressure measurement, propagation of motor activity cannot be defined. In addition, while it can be determined when the capsule is in the stomach, small bowel or colon, the exact location within those organs cannot be determined. Wireless pH motility capsule has been found to be useful in evaluating colonic transit and has been validated in adults as an alternative to radiopaque markers as a tool to assess colonic transit [71]. A recent publication has validated the use of the capsule in a pediatric population [72]. In 57 children with upper or lower gastrointestinal complaints, the capsules were well tolerated with only 5 unable to swallow the capsule. The transit measures compared favorably with colonic transit measured by a radiopaque marker study.

3D-Transit System

The 3D-transit system also utilizes an ingestible capsule to measure regional and total gut transit time. In this system, the subjects wear a portable detector to track an electromagnetic capsule. As the detectors track the capsule continuously in real-time, the 3D-Transit system can be used to pinpoint the capsule's location at any time. Therefore, it can provide information on the to and fro movements along the length of the colon and the capsule dwell time in each specific colonic region. Its use for transit measures has been validated in both adults [73] and children [74].

Conclusion

Much information has been garnered in the field of colonic motility in the past decade, and pediatric studies have been at the forefront of clinical investigations. Colonic manometry has asserted itself as a standard diagnostic test in pediatrics and represents one of the rare instances of a manometric technique more commonly used in children than in adults. There are now clearly defined indications for its use and meaningful clinical decisions that are determined by its results. Colonic manometry is best performed in specialized centers by investigators with a special expertise in motility and who are comfortable in evaluating children with complex biopsychosocial disturbances. The technological aspects of how the test is performed and our ability to interpret the results continue to evolve. This evolution is accelerated by the introduction of new techniques, such as high-resolution fiber-optic manometry and wireless motility capsule.

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Anorectal Manometry

13

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Anorectal dysfunction encompasses a variety of disease processes ranging from anatomical to functional abnormalities, which may lead to uncomfortable and distressing symptoms. Anorectal manometry (ARM) is used to obtain an objective assessment of symptoms and often aids in identifying disorders of defecation that cannot always be elucidated clinically. In pediatric patients, the test provides comprehensive information regarding anorectal abnormalities by evaluating the rectoanal muscle coordination, integrity and degree of sphincter tonic contractions, baseline reflexes, and perineal and internal rectal sensation. The most commonly evaluated symptoms in pediatrics are constipation and fecal incontinence. Disorders of defecation can be present at birth, or may develop over time. Constipation and defecation abnormalities are common and account for approximately 3% of pediatrician visits [1]. While the incidence of pelvic floor disorders is unknown in the pediatric population, they can affect up to 10–15% of the adult population [2].

As several of the underlying disease processes including Hirschsprung disease, neuromuscular abnormalities, and dyssynergic defecation can have similar presentations but very different treatments, making the correct diagnosis is important. ARM can help differentiate the different etiologies thus helping to guide appropriate therapy. In addition, the ARM can serve as an educational and therapeutic tool by providing information to patients and parents regarding the underlying pathophysiology of their symptoms.

Over the years, there has been progress in the available technology to perform ARM. For decades, the test had been executed using water-perfusion and sleeve catheter systems. More recently, the introduction of both the high-resolution manometry (HRARM) and the three-dimensional high-definition manometry (3DARM or 3DHDM) has enhanced the investigation and appreciation of anorectal dynamics. While our understanding of the role of these newer systems in pediatrics is still evolving, they are being used with increasing regularity for their potential to improve the diagnosis and treatment of patients with defecation disorders. Over the past few years, there has been increasing concern about using 3D manometry due to the rigidity of the catheter.

Normal Physiology

The pelvic floor is a striated muscular sheet that encloses the anorectum and urinary tract and in conjunction with the anorectal sphincters acts to maintain fecal continence and facilitate defecation [3, 4]. The anorectum is comprised of the union of the internal (IAS) and external (EAS) anal sphincters and the levator ani complex, including the puborectalis muscle, which forms a sling posteriorly, angulating the anal canal at rest [5]. The proximal, medial internal sphincter is formed by thickened circular smooth muscle innervated by the enteric nerves and thus under involuntary, reflexive control, while the distal, lateral external sphincter is comprised of skeletal muscle and innervated by sacral nerves, under voluntary control. As the two sphincters are adjoining, they are frequently difficult to differentiate, particularly in younger patients in whom the sphincter size is very small [6, 7].

Continence is maintained at rest by a combination of sphincter pressure with the puborectalis contraction, together greatly exceeding the intrarectal pressure, thus preventing stool passage [8, 9]. The puborectalis muscle (PR), part of the levator ani muscle complex, is made of skeletal muscle. At rest it forms a sling around the anorectum producing an angle between 85 and 105°. By angulating the rectum, it helps to prevent stool passage and thus assists with continence at rest. Normal physiology has been assessed via

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ultrasound and magnetic resonance imaging (MRI), strengthening our understanding of the complex area and the development of the area as a child grows [10].

Defecation requires coordination of multiple muscle systems, involving contraction and relaxation at appropriate times to expel stool. In normal physiology, stool enters the rectum, distending the rectal walls and triggering a reflexive temporary relaxation of the internal sphincter, the rectoanal inhibitory reflex (RAIR) that elicits the urge to defecate. If the subject is not in an appropriate location to pass the stool, voluntary contraction of the external sphincter with persistent contraction of the puborectalis occurs, thus deferring defecation. Once defecation is deemed appropriate by the subject, expulsion of stool can be initiated. In healthy individuals with normal anorectal dynamics, this involves relaxation, contraction, and coordination of muscle systems. Specifically, the abdominal muscles contract to increase intra-abdominal pressure, propelling the stool forward from the rectum through the anal canal. At the same time, there is relaxation of the pelvic floor muscles including the puborectalis muscle, straightening the anal canal, and allowing free passage of stool [11, 12]. Finally, both the external and internal sphincters relax, permitting stool to flow out of the canal and thus completing defecation.

Anorectal Manometry

Technical Aspects

There are two main compartments to an ARM system. These are the catheter or probe with a pressure-sensing apparatus and an inflatable balloon at its tip, the pressure-recording apparatus serving to amplify/record input, display information, and analyze data. Over the past decades, there have been significant advances in technology so that today there are multiple systems available for anorectal assessment, each with its own advantages and disadvantages. For years ARMs have been completed with basic performance systems including sleeve catheters, water-perfusion machines, and air-filled balloon catheters. Their use is now more commonly replaced with high resolution and 3D high definition. For the purpose of this chapter, the most commonly used systems will be reviewed including water perfusion, high resolution, and 3D high definition (Fig. 13.1).

The water-perfusion catheter consists of a flexible thin (diameter between 3.5 and 7.0 mm), plastic tube with four to eight side holes circumferentially or spirally arranged and a central catheter for balloon inflation. The catheter is connected to a perfusion apparatus with a pneumohydraulic pump set to pressures of 10–15 psi with water slowly perfused through the side holes at a rate of 0.1–0.5 mL/min/channel.

In 2007, with advances in technology, a high-resolution, solid-state manometric system was developed that has channels at 0.5–1.0 cm intervals. Each has multiple sensing points which together allow for retrieval of many (usually 36) data points producing a topographical plot of intraluminal pressure. This large amount of data retrieval provides a clearer visualization of the area and prevents loss of potentially important information. The results of the high-resolution catheter correlate well with the water-perfusion studies. Most recently, a 3D high-definition catheter was developed, producing even more accurate and detailed data retrieval. It is 10 cm in length and consists of 256 solid-state microtransducers placed circumferentially 3 mm apart. Due to the placement of these sensors, the results can be interpreted in a multidimensional fashion.

The water-perfusion system has advantages in that it remains a low-cost option with ease of interpretation but can be difficult to calibrate and significant time is needed for maintenance of fluid channels.

The HRARM and 3DHDM are technically easier to use. Once placed in the appropriate position, they do not require significant manipulation and have minimal sensor migration, thus improving accuracy. The newer technology with solid-state catheters also has more sensors at closer intervals, thus providing significantly greater anatomic detail, including a possible differentiation of the internal and external sphincter, which was not achieved previously [13]. In pediatric patients, the 3DARM was used to construct a model of the anal canal pressures noting the longitudinal and radial asymmetry. Thanks to this technology, it is now known that the EAS contributes to distal canal resistance, while PR and IAS contribute to proximal canal [14]. In this way, 3DARMs may help to further understand the anatomy in those with anatomical anorectal disorders or for pre-procedural planning [15].

Limitations of 3DARM and HRARM are their cost, significant time required for cleaning, shorter life span, and temperature sensitivity. Additionally, the larger, more rigid probes 3DARM probes do not conform to the anorectal angle, which may cause discomfort and generate artifact [16].

Overall, 3D- and HRARM's enhanced spatial resolution has led to increase use over the past decade. A 2017 survey of adult gastroenterologists reported greater than 50% were using HRARM [17]. Clinical use, and study publication, in pediatrics is still growing, with one recent systemic analysis reporting use of HR-ARMs in only 3% of studies [18].

As routine use of these new modalities increases, there is growing efforts to standardizes practices, which vary widely among pediatric centers. In 2017, the American Neurogastroenterology and Motility Society (ANMS) and North American Society of Pediatric Gastroenterology, Hepatology and Nutrition Society (NASPGHAN) published the first consensus document on the use of ARM in children

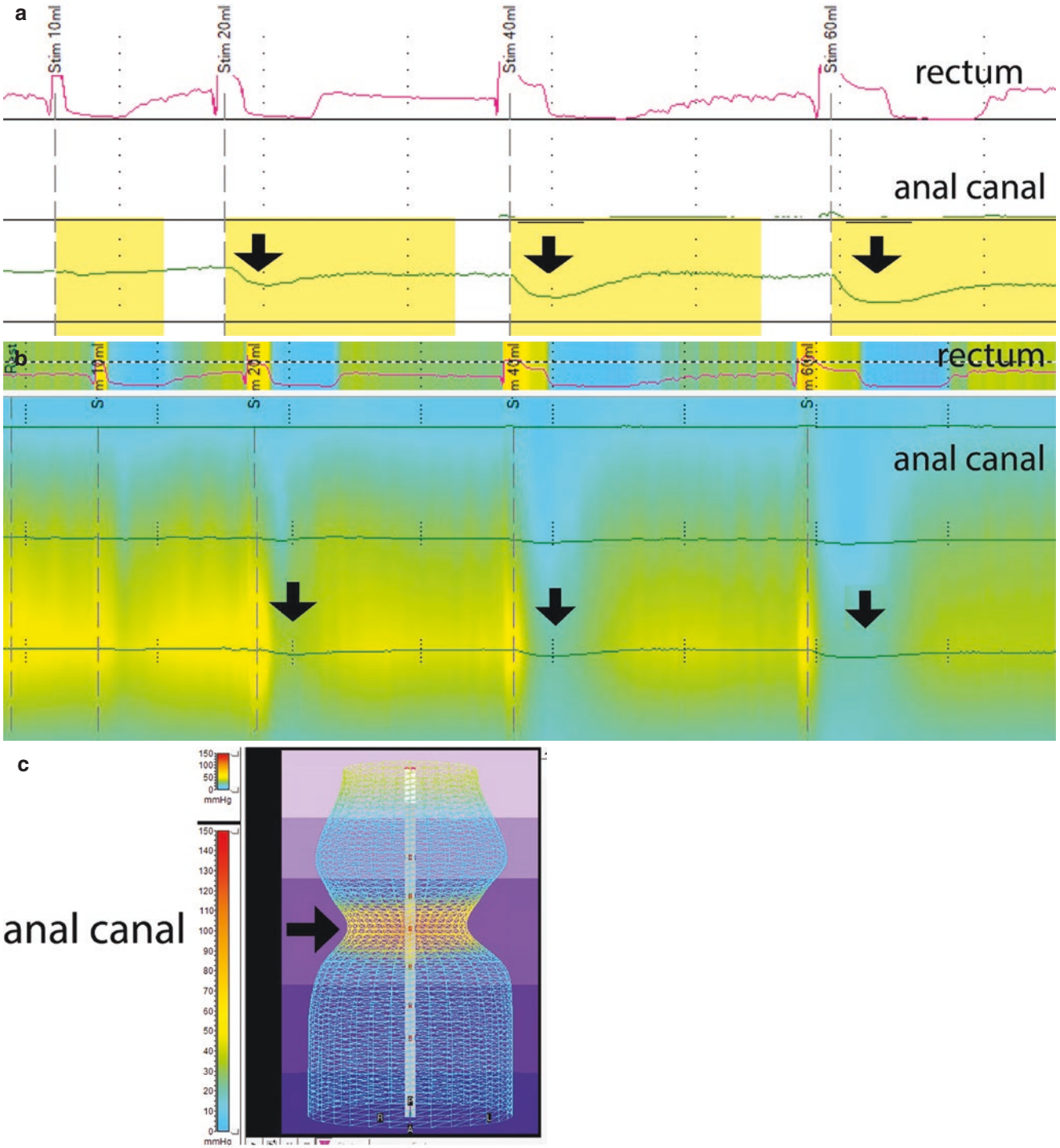

Fig. 13.1 (**a**) Example of a water-perfusion catheter tracing. (**b**) Example of a racing made using a high-resolution catheter. (**c**) Three-dimensional high-resolution catheter anal canal mapping. Arrows point to anal canal relaxation each time balloon inflation distends the rectum (please see Fig. 13.3 as well). (Tracing made using the Diverstek system)

[19]. In adult gastroenterology, the International Anorectal Physiology Working Group (IAPWG) published a protocol for ARMs, and the London Classification for Disorders of Anorectal Function was published based on this protocol in 2020 [20].

Methodological/Practical Aspects

ARM can be done in children of any age; however, only children (usually 5–8 years and older) are typically able to cooperate with the sensory testing (external and internal) and

dynamic components of the test (squeeze and bear-down maneuvers). Thus, for younger patients, the ARM is usually limited to the analysis of anal sphincter resting pressure and RAIR. In preparation for an ARM, patients are encouraged to defecate and empty the rectal vault prior to the study. If there is a suspected large stool burden, oral or rectal bowel therapy is used to prevent stool interference. Typically, as infants have soft stool and enemas may be traumatic at this age, no preparation is necessary [21]. It is suggested that medications that may interfere with function such as opioids or anticholinergics are held during the testing. ARM can be associated with significant anxiety in both patient and their parents, which has been shown to be mitigated with pre-procedural psychological interventions (e.g., psychoeducation video) [22, 23].

To set up for the exam, the patient is placed in the lateral decubitus position, with knees drawn to the chest, thus both hips and knees flexed passed 90°. A digital rectal exam (DRE) should be completed prior to the exam to evaluate the anatomy for abnormalities and gain a baseline assessment of the function of the area. It also provides a sense of the degree of stool burden and the extent of the patient's ability to follow commands which is necessary during the study. Adult studies have shown that the digital rectal exam can produce findings that are comparable to the results from the ARM [24]. Prior to the digital insertion, the perianal area should be examined along with assessment of external perineal sensation and anal wink. A finger is then inserted into the rectal canal to evaluate resting tone, squeeze pressure, and defecation dynamics including the presence of a paradoxical puborectalis contraction on bear down.

After completion of the DRE, a lubricated manometry probe is inserted into the rectum. Once placed and in the appropriate location, it is held there for at least 90 s for the anorectal area to acclimate to the insertion prior to obtaining data. It is important to provide clear and detailed explanations during the study as the clinician's verbal commands and clarifications have been shown to affect accuracy of results [25]. Helping the patient to relax by taking deep breaths or other techniques may be helpful in achieving a better baseline measurement.

Ideally the ARM study is completed in an awake patient without anesthesia or sedation, thus allowing voluntary and sensory testing. However, at times this is not feasible and anxiolytics and/or anesthesia must be given, particularly in the toddler age. As above, one must be aware that this becomes a more limited study as these medications can alter the data. This should be accounted for when interpreting the study. It has been shown that ketamine and midazolam do not affect the sphincter pressure or RAIR response, while propofol decreases the resting sphincter pressure in a dose-dependent manner, although the normal RAIR is maintained [26–28].

Analysis

Baseline, dynamic, and sensory information can be obtained from an ARM study. Typically, a complete study will assess sphincter pressure, bear-down maneuvers, sensation, and reflexes; however, in specific situations, the test can be tailored toward particular questions. The following are the common assessments that are completed during the ARM study.

Resting basal pressure: After the patient is relaxed and comfortable with the probe in place, the basal resting sphincter pressure is obtained. This canal pressure measurement is comprised of mostly IAS tone (80%) with some EAS pressure [29]. A low resting pressure could be indicative of weakness or disruption in the sphincter musculature. With the newer technology, the sphincter pressure can be measured with simple insertion of the catheter and obtaining data from the high-pressure zone. However, with water-perfusion manometry catheters, there are various methods employed. The most common of these is the station pull-through, when sensors are circumferentially arranged on the probe, or continuous withdrawal with spirally arranged sensors.

Squeeze: The squeeze pressure is used to assess sphincter strength/tone. It is produced by the patient voluntarily maximally tightening the anal sphincter and calculated as the highest pressure increase over the baseline resting pressure. This can be calculated as the average of three assessments. It is important to ensure that the intra-abdominal pressure is not increased during this exercise as it would alter the squeeze pressure data. A weak squeeze pressure may indicate myogenic or neurogenic causes (Fig. 13.2b).

Anal canal length: The canal length is the measured distance between the anal verge and the location with ≥5 mmHg pressure increase over the rectal pressure.

RAIR: The rectoanal inhibitory reflex is typically the most important assessment in pediatric ARMs. It is obtained to assess the presence of the local enteric reflex. The absence of a RAIR could indicate the presence of colonic aganglionosis also known as Hirschsprung disease. The reflexive relaxation of the IAS is naturally caused by stool presence but is simulated during an ARM by rapid balloon inflation and deflation. To date, in pediatrics there is no universally agreed criteria for the presence of a RAIR, but it is generally considered to be present with either a drop in pressure by >5 mmHg or >15% of the resting pressure [19]. There is typically a dose-related response with greater relaxation and duration of relaxation with larger balloon volumes (Fig. 13.3a). When conducting the test, the clinician must be aware of possible migration of the catheter out of the sphincter, particularly during balloon insufflation. Catheter migration may falsely indicate a RAIR response when there is none (Fig. 13.3b). This is the most common cause of a false-positive RAIR (an

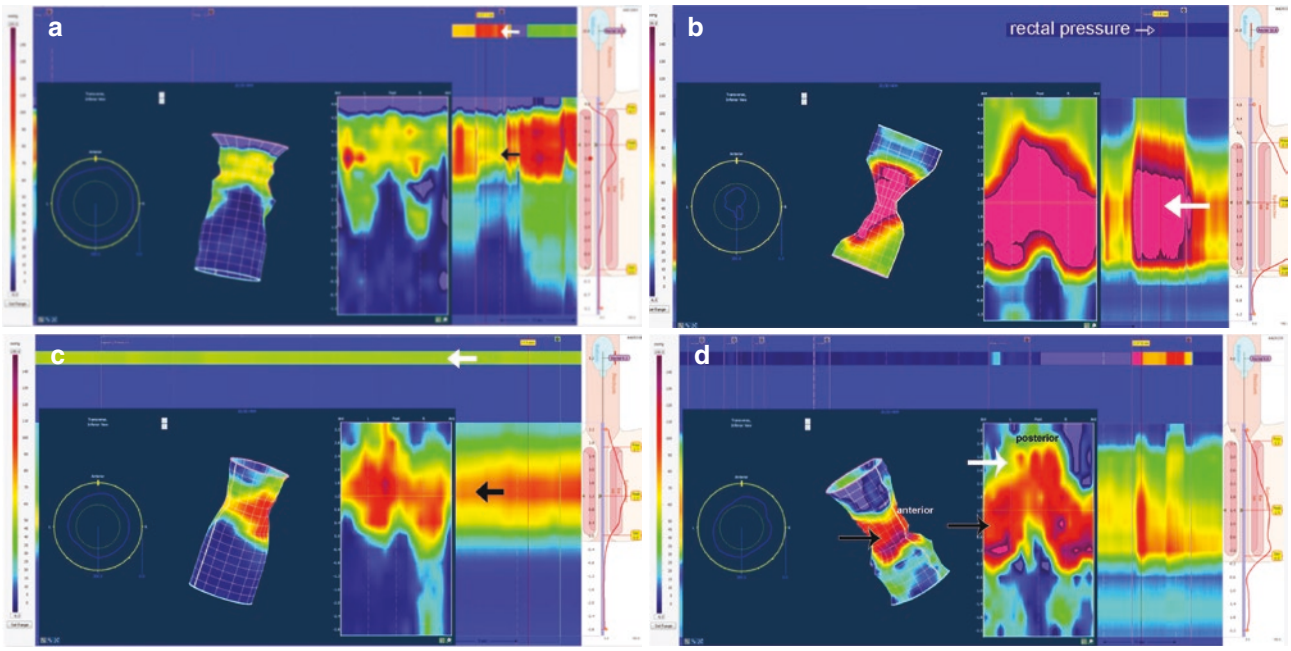

Fig. 13.2 (**a**) 3D: Resting (Baseline) anal canal during initial recoding. A moderate degree of increased sphincter pressure can be seen. This is often due to patient discomfort/anxiety. It is important to make sure the probe position does not cause discomfort and that the patient is allowed and encouraged to relax as much as possible. (**b**) 3D squeeze: Significantly increase pressure of sphincter (*large white arrow*), no pressure increases in the rectal balloon (rectal pressure, *open arrow*). (**c**) 3D bear down: an increase in pressure in the anal canal (*black arrow*) shows an increased sphincter pressure rather than relaxation, and at the same time a lack of a rectal increase in pressure (*white arrow*) signals dyssynergic defecation. **(d)** Paradoxical puborectalis: During the bear-down maneuver, a high-pressure area is seen above the sphincter (*white arrow*) in only the posterior aspect of the anal canal. This is the puborectalis sling which is not relaxing normally. The *black arrow* points toward the contracted sphincter which is below the puborectalis and is also seen in the anterior aspect of the canal

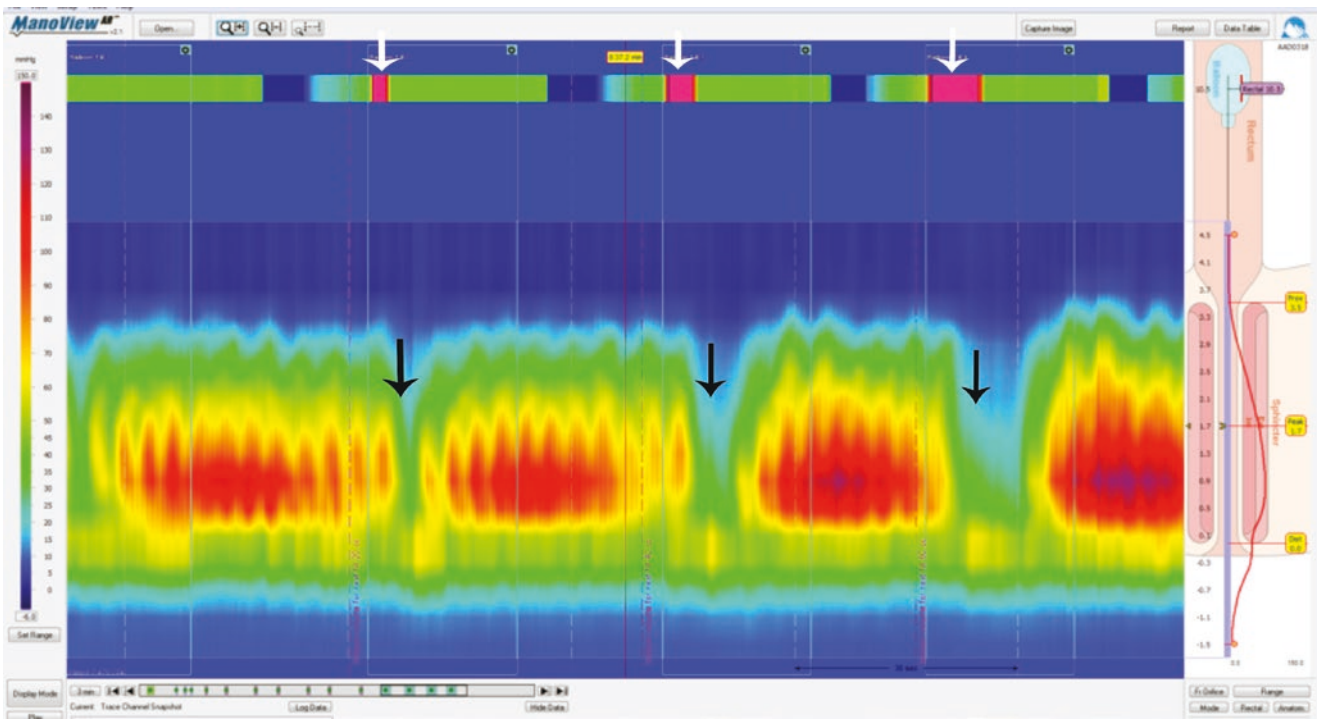

Fig. 13.3 Dose-response RAIR 3D ARM. *White arrows* point to rectal balloon insufflation (which increases rectal sensor pressure). The reflexive anal canal relaxation (sphincter relaxation) is seen after each insufflation (*black arrows*). Please note that as the rectal distention volume progressively increases as the balloon is inflated 10, 20, and 40 mL from left to right and the anal canal relaxation is proportionally greater the greater volume is infused

apparent anal canal relaxation is seen but falsely produced by the catheter migrating in and out of the sphincter region/high-pressure zone with balloon inflation by lack of digitally securing the catheter to the anal margin). The most common cause for a false-negative RAIR test (there is no anal canal relaxation seen, despite balloon insufflation) is a dilated rectum, often due to chronic stool retention. As the rectum is dilated, the balloon does not reach the needed volume to adequately stretch the rectal wall, needed to elicit an anal sphincter relaxation. Most centers recommend increasing balloon volumes up to 250–300 mL in older children if complete relaxation is not obtained [19].

Sensation: Testing the patient's sensation is an important part of the ARM exam as it provides additional information regarding the patient's perception of stool which can be indicative of anorectal dysfunction. Sensation is assessed in an awake, active participant (usually aged 5–8 years and older) by a gradual increase in balloon inflation size. First sensation is defined as the lowest balloon volume that is sensed by the patient. The urge sensation is the lowest balloon volume at which the patient develops the urge to defecate. Finally, the maximum tolerable sensation is the inflation size that is associated with severe urgency and pain. Decreased internal sensation is most often seen with a chronically dilated rectal canal due to persistent constipation.

Bear-down maneuver: The bear-down maneuver , or simulated defecation, is used to assess anorectal and pelvic floor pressure changes during attempted defecation. Similar to above, patients need to have the maturity to understand and cooperate with the testing. This ability is usually acquired around the age of 5 or 6 years. With normal defecation dynamics, there is an expected increase in rectal thrust pressure due to abdominal muscle contraction coordinated with a decrease in anal sphincter pressure. Patients in which these coordinated movements do not occur are thought to have dyssynergic defecation often resulting in outlet obstruction constipation [30]. Additionally, the puborectalis muscle can be visualized with the high-definition manometry, thus allowing for greater understanding of its contribution to defecation dynamics [31] (Fig. 13.2c).

Balloon expulsion: Once these assessments are complete, the probe is removed and a balloon expulsion test is performed. A balloon mounted on a plastic tube is inserted into the rectum and inflated to 50–60 cm^3. Some centers use air while others use saline to inflate balloon. The patient is then instructed to sit on a commode and expel the balloon in privacy. The test is considered normal if the patient is able to expel the balloon within a defined time. In adults 1 min is allowed. It is not clear if this time limit is adequate in pediatrics, as well as the right amount of balloon inflation for children, although one series report that adult volumes and time limit may be applicable [32]. The balloon expulsion test is considered an adjunct evaluation to the ARM to confirm the presence of dyssynergia but is not routinely performed at all pediatric centers [32].

Overall, ARM has been found to be a safe test with rare side effects. With insertion of any foreign object, there is the risk of colonic/anal abrasion or perforation; therefore, care should be taken with placement and removal of probes. This is especially true in younger children and with the use of the more rigid 3D manometry probe, Additionally, the study should be delayed or terminated with any abnormal symptom or sign including significant bleeding or acute onset of severe pain.

Reference Values

In general, reliable and reproducible normative values for ARM are lacking in pediatrics. Although baseline data has been reported in various publications, lack of standardization of the ARM study, different methodology, and equipment make comparing these values a difficult endeavor [7] (Table 13.1). Therefore, as concrete normative data is lacking in pediatrics, it is always important to correlate the findings with symptom presentation.

The newer modalities of HRARM and 3DHDM have been studied more extensively in the adult literature, showing that the values with high-resolution manometry tend to be higher than those with water perfusion, and there may be differences based on gender, age, and body mass index (BMI) [40–43]. Data is just now being collected in the pediatric population with these modalities [38, 44]. In the future, as these newer systems are used more frequently and studied in more depth, a greater understanding of reference values both in symptomatic and healthy individuals is expected.

Table 13.1 References for normal manometric measurements

	Technique	Healthy controls, *N*=	Ages	Anal resting tone (mmHg)	Rectal pressure (mmHg)	Anal canal length (cm)	Threshold of RAIR (mL)	Sensation threshold (mL)	Critical volume (mL)	Maximal squeeze pressure (mmHg)
Benninga [10]	WPM	13	8–16 years	55 ± 16			18 ± 10	19 ± 12	131 ± 31	182 ± 61
Hyman [33]	Not specified	20	5–16 years	67 ± 12		3.3 ± 0.8				140 ± 52
		16	>5 years				11 ± 5	14 ± 7	101 ± 39	
Kumar [7]	WPM	30	<1 month (GA 34–39 weeks)	31 ± 11		1.7 ± 0.3	10 ± 4			
		30	1–16 months	42 ± 9		1.9 ± 0.6	14 ± 10			
		30	18 months to 12 years	43 ± 9		3.0 ± 0.5	25 ± 12			
Li [34]	Not specified	10	5–15 years					28 ± 11	117 ± 46	
Sutphen [35]	WPM	27	~7–12 years					30 ± 12	96 ± 38	142 ± 47
Benninga [36]	Sleeve, WPM	22	Neonates (PMA 30–33 weeks)	32 ± 4[a]	9 ± 2		1.6 ± 0.3[b]			
De Lorijn [37]	Sleeve, WPM	16	Neonates (PMA 27–30 weeks)	25 ± 11[a]	7 ± 5		3.4 ± 1.6[b]			
Tang [38]	HRARM	180	Newborn (GA 28–42 weeks), 1–85 days old	29.7 ± 9.9		1.9 ± 0.5 cm				
Banasiuk [39]	3DARM	61	2–17	83 ± 23		2.6 ± 0.68	15.7 ± 10.9	24.4 ± 23.4		191 ± 64

GA gestational age, *PMA* postmenstrual age
[a]Anal sphincter pressure
[b]Air insufflation

Indications

The indications for ARM in pediatrics are varied [19]. A recent systemic analysis of 227 studies in pediatric populations found that ARM was most commonly performed in patients with organic conditions (e.g., Hirschsprung's disease), and specifically to asses postsurgical outcomes (versus for diagnostic purposes) [18].

Hirschsprung disease: Hirschsprung disease is caused by the arrest of migration of the neural crest cells to the colon (see Chap. 25). The length of the aganglionic gut ranges from distal colon (most common) to complete colonic aganglionosis, sometimes even involving varying lengths of small bowel. Any length of colonic aganglionosis leads to an absent RAIR on ARM. Symptoms are frequently present in infancy with delayed passage of meconium (normally in first 24 h) and explosive stool output with digital rectal decompression. Patients may also present with constipation that is refractory to medication, signs of outlet obstruction, and, at times, failure to thrive. Most children are diagnosed within the first year of life, but there is a small subset of patients, particularly those with short-segment Hirschsprung disease that won't be brought to attention until later in life.

The absence of a RAIR on ARM has been shown to have a high diagnostic specificity and sensitivity for Hirschsprung disease, particularly in those older than 1 year [45, 46]. It is important to note that false positives and negatives do sometimes occur, for example when the rectum is very dilated or when there is inflammation (e.g., milk colitis) which may cause a poorly relaxing sphincter [47–49]. The gold standard for diagnosis is a full-thickness biopsy, but the ARM is a good alternative screening test as it is noninvasive and can often be completed without anesthesia. Patients with an absent RAIR should then proceed to a rectal suction or full-thickness biopsy to confirm the diagnosis.

ARM can also be beneficial in postsurgical Hirschsprung patients to characterize the anatomy of the anorectal area, particularly as patients often have one or more surgical interventions and an altered anatomy [50]. Additionally, many patients with Hirschsprung disease continue to have symptoms postsurgically; the ARM can help to guide further management including additional necessary surgical interventions or medication therapy [51, 52].

Anal achalasia may easily be confused with Hirschsprung disease as the symptoms may be similar including chronic constipation, abdominal distention, and similar findings on

ARM: high sphincter tone and nonrelaxation of the sphincter with balloon inflation. However, these patients have a normal rectal biopsy [53, 54]. It may be that anal achalasia is the disease previously known as "ultrashort-segment Hirschsprung disease." These patients are typically treated similarly to postsurgery Hirschsprung patients, as both the anal achalasia and the post-op Hirschsprung patients have a nonrelaxing internal sphincter. Internal anal sphincter botulinum toxin injections have been very successful in improving defecation, although internal sphincter myotomy may be required in a subset of nonresponders [55, 56]. Thus, it is important to categorize these patients in order to provide them with the most appropriate therapy.

Neuromuscular: Patients with neuromuscular disorders such as myopathy or muscular dystrophy can frequently present with symptoms of anorectal dysfunction including constipation and fecal incontinence. Neuromuscular disorders can be evaluated with ARM to gain a further understanding of sphincter function in addition to the pelvic floor strength. Although there are no specific ARM findings, those with neuromuscular diseases will frequently have hypotonia leading to low resting and squeeze pressures of the sphincter. There will be a RAIR response in these patients as the neurological reflex is intact, but the dose response to increasing inflation sizes may not be present [57]. Decreased muscular strength may also lead to decreased rectal thrust during Valsalva at the time of defecation. Patients with neuromuscular diseases and anorectal dysfunction can be difficult to treat as there are no medical interventions to reverse the disease process. These patients may respond well to conventional constipation therapy including laxative use and scheduled toilet use [58]. Physical therapy may help condition and exercise the striated muscles involved.

Anatomical: Structural abnormalities should be evaluated, particularly in those with postsurgical symptoms. For example, those with imperforate anus repair who remain symptomatic should have an ARM to assess postsurgical sensory and functional capabilities as these may remain abnormal even after the anatomy is repaired [59] (see Chap. 29). Additionally, patients who have undergone colostomy/diverting ileostomy and are preparing for reversal should have ARM completed to assess functioning of the area and rule out obstructed defecation prior to surgery.

Fecal incontinence: Fecal incontinence which includes both the passage of large bowel movements into the underwear in addition to slow leakage and streaking of the underwear can be further evaluated with an ARM study (see Chap. 43). Although fecal incontinence is frequently due to constipation, the ARM study, particularly the newer modalities, can be used to evaluate for other etiologies. For example, it may be able to show abnormalities in the anal sphincter functioning which can contribute to fecal incontinence. A small pediatric study comparing HR-ARM in children with functional constipation with and without fecal incontinence found that patients with fecal incontinence had significantly lower resting pressure, particularly in anteroposterior quadrants [60]. Additionally, spinal cord abnormalities such as meningomyelocele and tethered cord can affect innervation to the sphincter, altering its ability to aid in continence. As the spinal cord lesion may produce upper motor neuron abnormalities, there can be exaggerated contractions or anal spasms of the sphincter with balloon dilation and megacolon. In case of a lower motor neuron syndrome, decreased anal tone may be found. Patients with these suggestive findings on ARM should have an MRI completed to further examine the spinal cord [35, 61, 62].

Chronic constipation: ARM can be used for evaluation in patients with chronic constipation (see Chap. 42). Studies have found that those with chronic constipation have specific ARM findings including increased frequency and amplitude of the internal anal sphincter contractions [63, 64]. As previously described, in order to appropriately pass stool, subjects need coordination of various pelvic and abdominal muscle systems. Some patients have abnormal movements in some or all of the muscle systems, leading to inappropriate muscle relaxation or contraction, thus complicating defecation [65]. This type of abnormality in defecation dynamics, called dyssynergic defecation, is thought to be the cause of some forms of constipation, particularly related to outlet obstruction [66]. Dyssynergic defecation can be classified according to abnormalities in three areas that can be assessed by anorectal evaluation during bear-down maneuvers including degree of perineal descent during defecation, perineal location at rest, and anal resting pressure [67]. The findings of dyssynergic defecation can be confirmed via an abnormal balloon expulsion test. Newer technology has provided a deeper understanding of anorectal dysfunctions and has helped to identify phenotypes in defecatory disorders and fecal incontinence in addition to providing improved classification of the puborectalis muscle and its role in outlet obstruction [31, 68]. In the London Criteria for adult patients, disorders of rectoanal coordination involve both dyssynergia on manometry and an abnormal balloon expulsion test [20]. While it is likely that the rectoanal dynamics are similar in children, it is not currently known whether this criterion applies and is useful in pediatric patients.

Dyssynergic defecation has been treated with biofeedback with varying success in the pediatric population [58, 69]. Using sensors and guidance via animated games, patients are taught to appropriately relax the pelvic floor and sphincters while increasing abdominal pressure. The intention is that with improved muscle coordination, the patient will be able to expel stool more efficiently, decreasing the rectal stool burden.

ARM can be used both to diagnose dyssynergic defecation and to guide specific biofeedback treatment, including targeting the puborectalis muscle. In a milestone diagnostic accuracy study in adults, it was found that many healthy adults had dyssynergic patterns of defecation using the 3DHDM. This is hypothesized to be in part related to the larger size and less flexibility of the probe thus possibly stretching the sphincter, leading to decreased accuracy in the results [70]. Therefore, this discrepancy must be taken into account when using the 3DARM system to analyze patients [70], particularly until more data is available in pediatrics.

Conclusion

ARM is a safe and well-tolerated procedure that provides valuable information regarding the anatomy and functionality of the anorectal canal. Symptoms related to constipation and/or fecal incontinence are common in pediatric patients and can be embarrassing and debilitating. ARM can be used to differentiate between disease processes that may present similarly but require different treatments, including Hirschsprung disease, spinal cord lesions, neuromuscular disease, and dyssynergic defecation. The advent of HR- and 3DARMs has allowed us to better describe the anorectal canal and understand anorectal pathology including asymmetric sphincter pressure and types of dyssynergic defecation. In conjunction with symptom correlation, ARM is a useful tool to understand the pathophysiology of specific disease entities and for the determination of appropriate interventions and treatments. Standardization of practice in pediatric centers should increase the clinical utility and value of these procedures.

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Functional Lumen Imaging Probe

14

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Introduction

Functional lumen imaging probe (FLIP) is a device that measures luminal parameters in the esophagus including cross-sectional area (CSA), pressure, diameter, and distensibility index (DI) using impedance planimetry. FLIP may also help identify anterograde and retrograde contractile activity in the esophageal body analyzed by the FLIP 2.0 system. This relatively new technology brings additional information to the more conventional esophagram and high-resolution impedance manometry.

Equipment

The FLIP catheter is currently available in two main configurations, each available on a distinct machine and analysis software.

The first one is the EF-325: 8 cm catheter with 16 sensors spaced 0.5 cm apart. It provides information regarding esophagogastric junction (EGJ), pylorus, and esophageal narrowing site.

The FLIP 1.0 module converts impedance recordings to cross-sectional area (CSA) measurements along the catheter while simultaneously measuring pressure with a single sensor at the distal end within the distending balloon. It provides parameters such as diameter, CSA, and distensibility index (DI). Data are displayed as a three-dimensional rendering of the esophageal lumen.

The second one is the EF-322: 16 cm catheter with 16 sensors spaced 1 cm apart. It uses distinct data display and analysis platforms. It provides esophageal body secondary peristalsis patterns (contractility) in addition to EGJ metrics. A distending stimulus in the esophageal lumen triggers a contractile response. The device uses topography to describe the diameter spacetime continuum in the digestive lumen. The change in the diameter/pressure relationship over time can be used to describe motility patterns across the distal esophagus through the EGJ. The FLIP 2.0 module uses diameter topography to display the diameter-pressure changes across a space-time continuum, using the 16-cm catheter. Using the process of interpolation, diameter changes can be displayed similar to esophageal pressure topography, and normal or abnormal propagation in the antegrade or retrograde direction can be assessed, providing an assessment of motor function that correlates with primary peristalsis on high resolution manometry (HRM) [1]. Consequently, the contractile response to volumetric distention can be formalized around four distinct categories: (i) repetitive anterograde contractions (RACs), with runs of ≥3 consecutive anterograde contractions considered normal; (ii) repetitive retrograde contractions (RRCs), an abnormal response associated often with spasm, achalasia, and postsurgical EGJ outflow obstruction; (iii) absent contractility, suggestive of aperistalsis, scleroderma, and significant ineffective esophageal motility; and (iv) other contractile patterns not fulfilling criteria for the above three categories, termed diminished or disordered contractile response, which likely represents a milder form of motor dysfunction. This classification is not currently used in pediatrics.

What Information Does FLIP Provide?

The FLIP system assesses esophageal biophysical (FLIP 1.0) and motor responses (FLIP 2.0) to distention by measuring several parameters:

- CSA is measured (in mm^2) at the level of each pair of impedance electrodes.

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- Distension pressure is measured (in mmHg) within the distended balloon.
- Distensibility index (DI) is calculated (in mm^2/mmHg) through the relationship between CSA and pressure.
- Diameter (in mm) of the luminal digestive tract along the catheter. These diameter changes can be plotted in a three-dimensional topographic manner.
- Finally, esophageal luminal distension from the balloon induces secondary peristalsis, which in turn causes changes in luminal diameter in the esophageal body. It helps to identify anterograde and retrograde contractile activity in the esophageal body analyzed by the FLIP 2.0 system.

How Is the FLIP Procedure Performed to Study Esophago-Gastric Junction?

The FLIP catheter is placed transorally after an upper endoscopy, usually under sedation or general anesthesia [2]. The endoscope must be removed to allow exact measurements. Endoscopy serves to exclude mechanical obstruction and then to estimate the distance from the incisors to the EGJ. This distance can be used to place the FLIP catheter in the correct position [3]. Although transnasal placement is possible in the sedated patient, most available normative data are based on transoral placement. It should be noted that, nowadays, an important limitation of FLIP utilization in pediatrics is the size of the device precluding any use in small children and infants (<10 kg). After the insertion of the catheter, the operator should be assured that the EGJ is clearly identified, with a few sensors in the stomach and the remainder in the esophageal lumen. The catheter is held in place by the operator, who may need to adjust the position of catheter relative to the EGJ to maintain appropriate positioning of the impedance electrodes during volumetric distension because esophageal contractions can push the balloon distally.

What Is the Standard Protocol?

FLIP protocol consists of volumetric distension of the FLIP balloon to predetermined volumes using a proprietary electrolyte solution with known conductance. Although there is no recommendation for FLIP use in pediatrics, most authors recommend the following protocol: after insertion and correct positioning, the balloon is filled with 10 mL fluid aliquots up to a target volume of 20–30 mL (8-cm catheter) is reached. An hourglass shape must be seen (waist-like constriction at the lower esophageal sphincter) on the FLIP monitor (Fig. 14.1). It is important to ensure the catheter is not withdrawn beyond the EGJ. A fill up to 50 mL is recommended if intrabag pressure does not reach greater than 50 mmHg or outflow obstruction is suspected. Wait periods of 30–60 s are recommended at each distension volume to obtain an accurate measurement. The intrabag pressure may increase and decrease in waves. Once the intrabag pressure reaches its peak, record minimal diameter (Dmin), intrabag pressure, cross-sectional area (CSA), and distensibility index (DI). Diameter, intrabag pressure, CSA, and DI are continuously recorded at each distension volume. After measurements, deflate balloon and gently remove the catheter.

Clinical Applications

Distensibility index (DI) is the most investigated and, to date, most useful metric from FLIP testing in clinical setting [4]. Distensibility of the EGJ can be described as the degree of distension of the EGJ in response to radial force. Normative values range from 3.1 to 9.0 mm^2/mmHg [5–8], reduced EGJ opening values range from 0 to 2.0 mm^2/mmHg, and values that are more difficult to interpret range from 2.1 to 3.0 mm^2/mmHg [1, 5, 9].

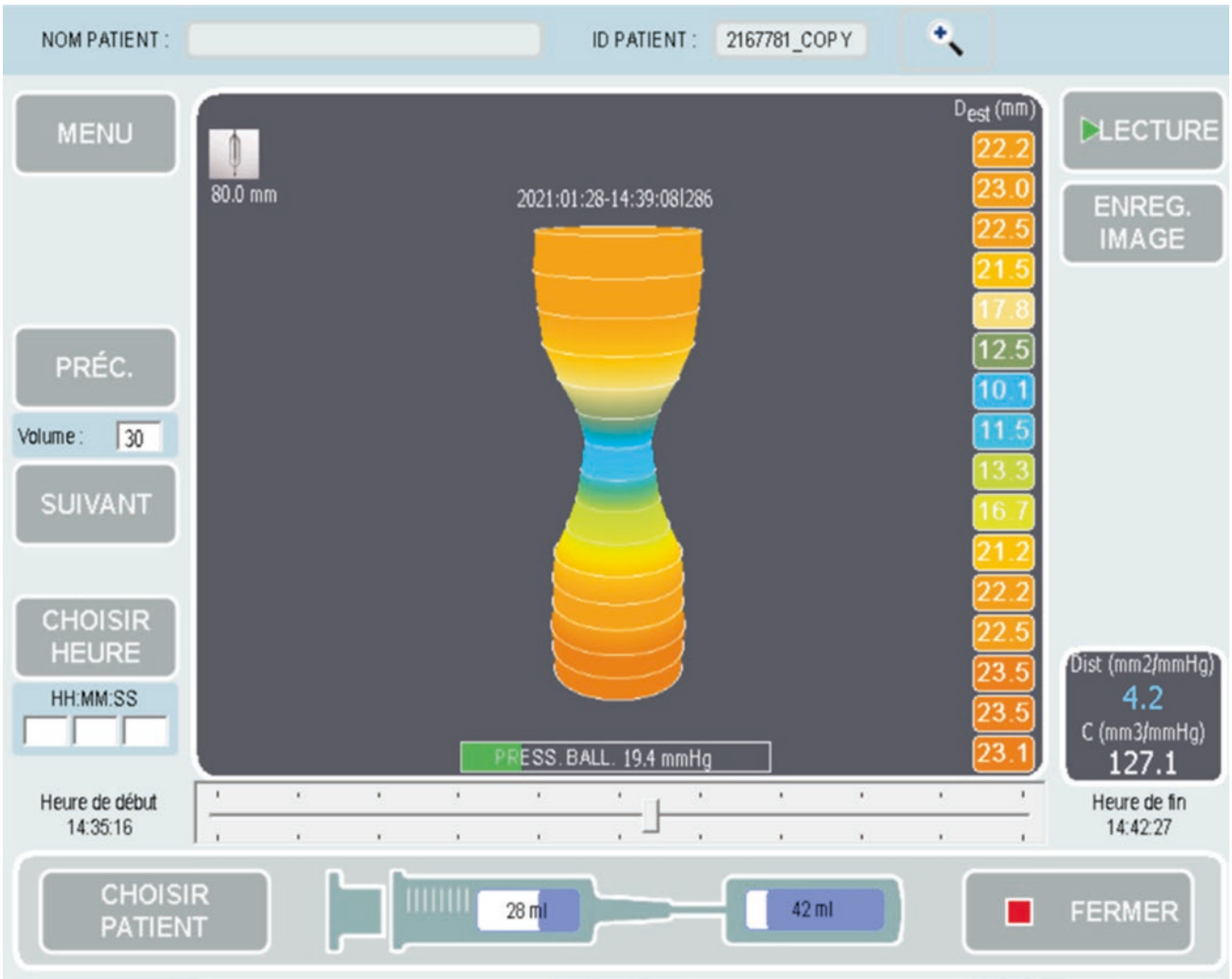

Fig. 14.1 3-dimensional FLIP view of the esophagogastric junction: the hourglass shape

Achalasia

The clinical impact of FLIP use in achalasia has been studied in the adult and pediatric populations (Tables 14.1, 14.2, and 14.3). An hourglass shape in a case of achalasia is shown in Fig. 14.2.

Several studies have reported decreased EGJ distensibility index (EGJ-DI) in treatment-naïve adults with achalasia when compared to healthy controls [6, 10]. The diagnostic EGJ-DI value in adult achalasia patients was determined to be <2.8 mm^2/mmHg [10]. However, more recent studies report a normal EGJ-DI above 3 mm^2/mmHg, abnormal below 2 mm^2/mmHg, and borderline reduced in-between [11, 12]. In children, Benitez et al. found a mean EGJ-DI of 2.07 mm^2/mmHg and Courbette et al. found a median EGJ-DI of 2 mm^2/mmHg in patients with achalasia [13, 14].

FLIP could also help discriminate achalasia sub-types based on DI values. Patients with type I achalasia had a significantly higher initial DI (median 1.7 mm^2/mmHg) than type II (0.8 mm^2/mmHg), type III (0.9 mm^2/mmHg), and variants (1.1 mm^2/mmHg; $p < 0.001$) [15]. This has not been validated in children.

EGJ-DI values correlate with radiographic retention at the barium study and the Eckardt dysphagia score [16]. FLIP has the potential to act as a useful calibration tool during operations for achalasia.

Table 14.1 Esophagogastric Distensibility Index (EGJ-DI) in achalasia cases and controls

EGJ-DI (mm2/mmHg) (1:20 mL, 2:30 mL, 3:40 mL, 4:50 mL, 5:60 mL)				
	Study	Achalasia (treatment-naïve)	Achalasia (non-naïve)	Controls
Adults	Pandolfino et al [10] (*n* = 54) Median (5th–95th)	1: 1.1 (0.9;1.6) 2: 1 (0.8;1.2) 3: 0.7 (0.5;1.1)		1: 4.2 (0.3;7.1) 2: 5.1 (0.8;21.7) 3: 8.2 (1.7;18.7)
	Rohof et al [6] (*n* = 45) Mean (± SEM)	4: 0.7 ± 0.9	0.79 (0.58;1.2)	4: 6.3 ± 0.7
	Rooney et al [11] (*n* = 240) Median (95% CI)	5: 0.88 (0.34;2.7)		5: 5.6 (2.9;9.3)
	Wu et al [17] (*n* = 54) Mean (95% CI)	1.7 (0.8;2.6)	2.5 (1.2;3.7)	4.5 (3.6;5.4)
	Holmstrom et al [15] (*n* = 34) Median (IQR)		0.8 (0.6;1.3)	
	Goong et al [19] (*n* = 23) Median (IQR)	4: 1.4 (2.4)		
	Su et al [22] (*n* = 93) Mean (± SD)	2: 1.2 ± 0.7	2: 1.2 ± 0.7	
	Verlaan et al [25] (*n* = 10) Median (IQR)	1: 1.4 (1.1;2.4) 2: 1 (0.8;1.5) 3: 1.1 (0.55;2) 4: 1 (0.4;2.3)		
	Smeets et al [35] (*n* = 41) Median (IQR)	2: 1.2 (0.8;1.6) 3: 0.8 (0.7;1.4) 4: 0.9 (0.7;1.5)		2: 2 (1.6;3) 3: 3 (2.2;4.2) 4: 3.4 (2.7;4.2)
	Yoo et al [28] (*n* = 175) Mean (± SD)	2: 3.5 ± 2.6 3: 3.3 ± 2.7		
Pediatrics	Benitez et al [13] (*n* = 43) Median (IQR)	1: 2.55 (2;3.18) 2: 2.02 (1.62;3.25) 3: 2.07 (1.56;3.22)		1: 8.28 (6.37;9.45) 2: 7.34 (6;9.39) 3: 6.4 (7;8.69)
	Courbette et al [14] (*n* = 5) Median (IQR)		1: 1.9 (1.6;2) 2: 2 (1.6;2.3)	
	Ketman et al [21] (*n* = 10) Mean (± SD)	1.2 ± 0.5		
	Rosen et al [37] (*n* = 13) Mean (± SD)	1.3 ± 0.3		6.8 ± 1.5

95% CI 95% confidence interval*IQR* interquartiles, *SD* standard deviation, *SEM* standard error of mean

Table 14.2 Esophagogastric Distensibility Index (EGJ-DI) in achalasia post treatment

	EGJ-DI (mm2/mmHg) (1:20 mL, 2:30 mL, 3:40 mL, 4:50 mL, 5:60 mL)			
	Study	Post pneumatic dilation	Post POEM	Post myotomy
Adults	Holmstrom et al [18] (*n* = 34) Median (IQR)		6.5 (5.2;10.2)	
	Holmstrom et al [20] (*n* = 46) Mean		7	5.9
	Su et al [22] (*n* = 93) Mean (± SD)			2: 4 ± 1.5
	Verlaan et al [25] (*n* = 10) Median (IQR)		1: 3 (1.4;9.4) 2: 2.9 (1.3;19.6) 3: 4 (2.9;12.7) 4: 6.7 (3.8;16.6)	
	Smeets et al [35] (*n* = 41) Median (IQR)	2: 1.6 (1.4;2.2) 3: 3.2 (2.2;4) 4: 4.2 (3;5.7)		
	Yoo et al [28] (*n* = 175) Mean (± SD)		2: 11.4 ± 6.0 3: 12.5 ± 7.4	
Pediatrics	Benitez et al [13] (*n* = 43) Median (IQR)	1: 2.98 (2.35;4.4) 2: 5.21 (3.28;6.25) 3: 6.38 (4.23;7.79)		
	Courbette et al [14, 21] (*n* = 5) Median (IQR)	2: 3.8 (2.5;4.1)		
	Kethman et al [21] (*n* = 10) Mean (± SD)		3.1 ± 0.9	

IQR interquartiles, *POEM* per oral endoscopic myotomy, *SD* standard deviation, *SEM* standard error of mean

Table 14.3 Esophagogastric Distensibility Index (EGJ-DI) in achalasia according to the therapeutic response post treatment

EGJ-DI (mm2/mmHg) (1:20 mL, 2:30 mL, 3:40 mL, 4:50 mL, 5:60 mL)			
	Study	Good treatment response	Poor treatment response
Adults	Pandolfino et al [10] (PD, HM, POEM) Median (5th–95th)	1: 1.8 (1.2;2.2) 2: 2.5 (1.3;3.4) 3: 3.4 (2.2;4.9)	1: 1.4 (1;2.2) 2: 1.1 (0.8;2.6) 3: 1.5 (0.6;2.8)
	Rohof et al [6] (PD, HM) Mean (± SEM)	4: 4.4 ± 0.5	4: 1.6 ± 0.3
	Wu et al [17] (PD) Mean (95% CI)	6.5 (5.3;7.8)	5.8 (3.8;7.7)
	Goong et al [19] (poem) Median (IQR)	5.01 (4.52)	4.91 (3.63;6.20)

95% CI 95% confidence interval, *HM* heller's myotomy, *PD* pneumatic dilation, *POEM* per oral endoscopic myotomy, *SD* standard deviation, *SEM* standard error of mean

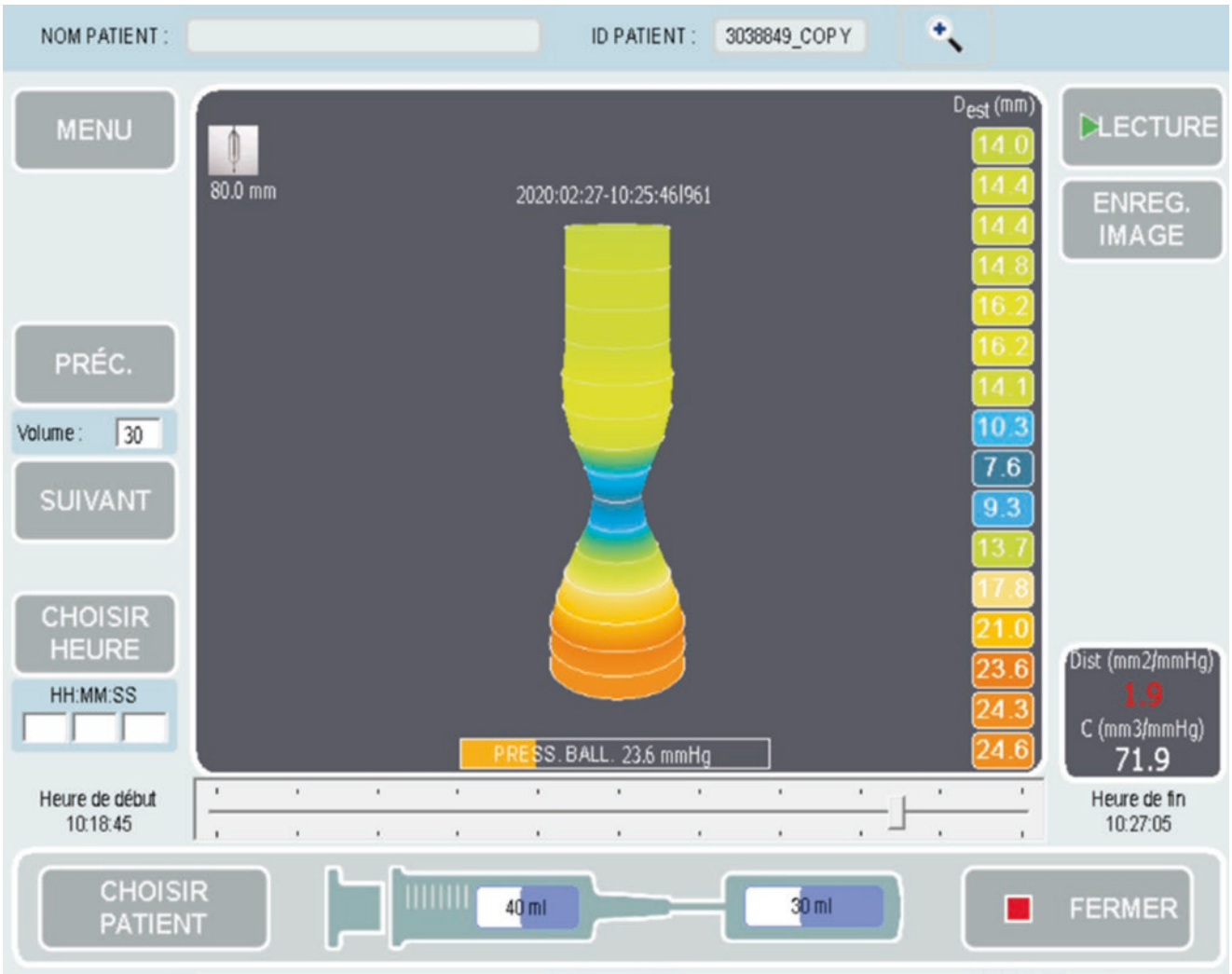

Fig. 14.2 3-dimensional FLIP view of the esophagogastric junction in case of achalasia

Pneumatic Dilation (PD)

Among the adult patients with achalasia that demonstrate an immediate response after PD, EGJ-DI increased by an average of 4.5 mm^2/mmHg (baseline 2 mm^2/mmHg, $p < 0.001$). In immediate non-responders, the EGJ-DI was unchanged by PD with a mean increase of 0.9 mm^2/mmHg (baseline 4.8 mm^2/mmHg, $p = 0.07$) [17]. Within-subject difference of EGJ-DI was highly predictive of immediate clinical response. An increment in EGJ-DI of 1.8 mm^2/mmHg after a single PD predicts an immediate response with an accuracy of 87% [17]. Patients with good treatment response had significantly greater EGJ-DI than untreated or patients with poor response [10].

In children, PD resulted in a significant increase in EGJ-DI immediately after the dilation, particularly in treatment-naïve patients with +3.72 mm^2/mmHg ($p < 0.001$), and a significant improvement in Eckardt scores with +2.5 points ($p < 0.001$) [13].

Per Oral Endoscopic Myotomy (POEM)

In an adult study, real-time data generated by the use of FLIP during POEM was incorporated into intraoperative decision making by the surgeon [18]. Clinical success rates at 1 year were higher in patients with intraoperative FLIP use. These findings suggest that a FLIP-tailored myotomy may lead to improved clinical outcomes following POEM [18]. However, the final DI did not differ significantly between good and poor post-POEM responders and the final DI did not differ significantly between post-POEM reflux esophagitis and non-reflux esophagitis groups [19]. In another study, POEM resulted in a significant increase in DI (induction 0.9 vs. post-myotomy 7 mm^2/mmHg). There was a subsequent decrease in DI in the follow-up period (post-myotomy 7 vs. follow-up 4.8 mm^2/mmHg), but DI at follow-up was still significantly improved from pre-treatment measure [20].

In a cohort of pediatric patient with a treatment success achieved in 80%, pre-treatment mean EGJ-DI was 1.2 ± 0.5 mm²/mmHg and post-treatment mean DI was 3.1 ± 0.9 mm²/mmHg [21].

Heller Myotomy

In a study with 11 adult patients, DI increased significantly after Heller myotomy (induction 1.5 vs. post-myotomy 5.9 mm²/mmHg). DI decreased in the follow-up period, but this change was not statistically significant (5.9 vs. 4.4 mm²/mmHg). Post-Heller myotomy, patients with erosive esophagitis on follow-up endoscopy had a significantly higher post-myotomy DI compared with those without esophagitis (9.3 vs. 4.8 mm²/mmHg) [20]. In another study, patients with a post-operative Eckardt score ≥ 3 were more likely to have a final DI ≤ 3.1 mm²/mmHg (p = 0.014) or a change in DI ≤ 3.0 mm²/mmHg (p = 0.010). Additionally, a final CSA > 96 mm² or D min > 11.0 mm was predictive of worse reflux at 2 years (p = 0.01) [22].

When all patients were divided into thirds based on final DI, none in the lowest DI group (<6 mm²/mmHg) had symptoms suggestive of reflux as compared with 20% in the middle third (6–9 mm²/mmHg) and 36% in the highest third (>9 mm²/mmHg). Patients within an "ideal" final DI range (4.5–8.5 mm²/mmHg) had optimal symptomatic outcomes in 88% of cases, compared with 47% in those with a final DI above or below that range [23].

EGJ Outflow Obstruction (EGJOO)

FLIP is increasingly used to adjudicate the severity and clinical relevance of the diagnosis of EGJOO [24], mostly in adults. EGJ-DI is the most studied parameter. EGJ evaluated with FLIP before and after pneumatic dilation is displayed in Fig. 14.3.

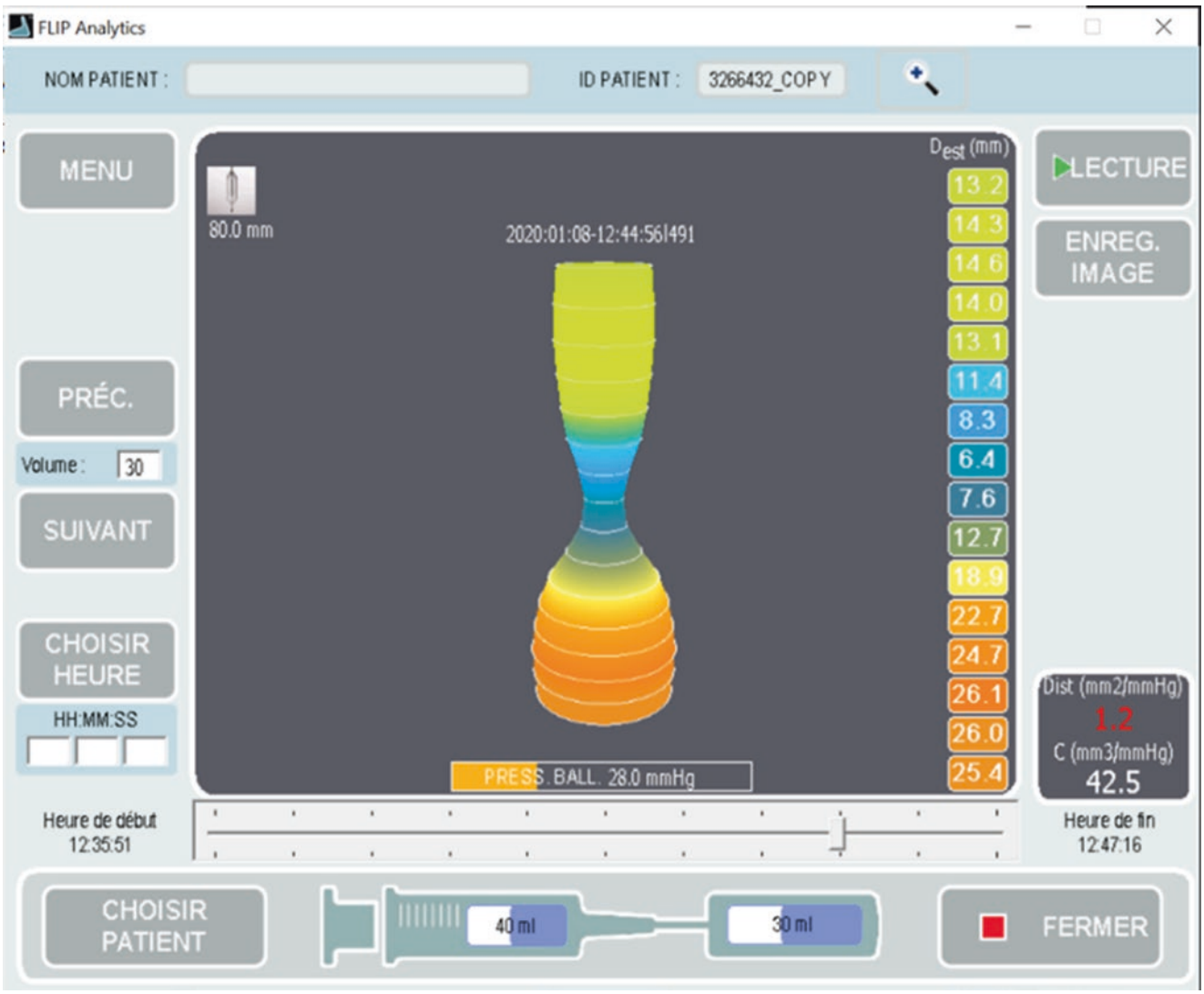

Fig. 14.3 EGJ-DI in an EGJOO case evaluated with FLIP before and after pneumatic dilation

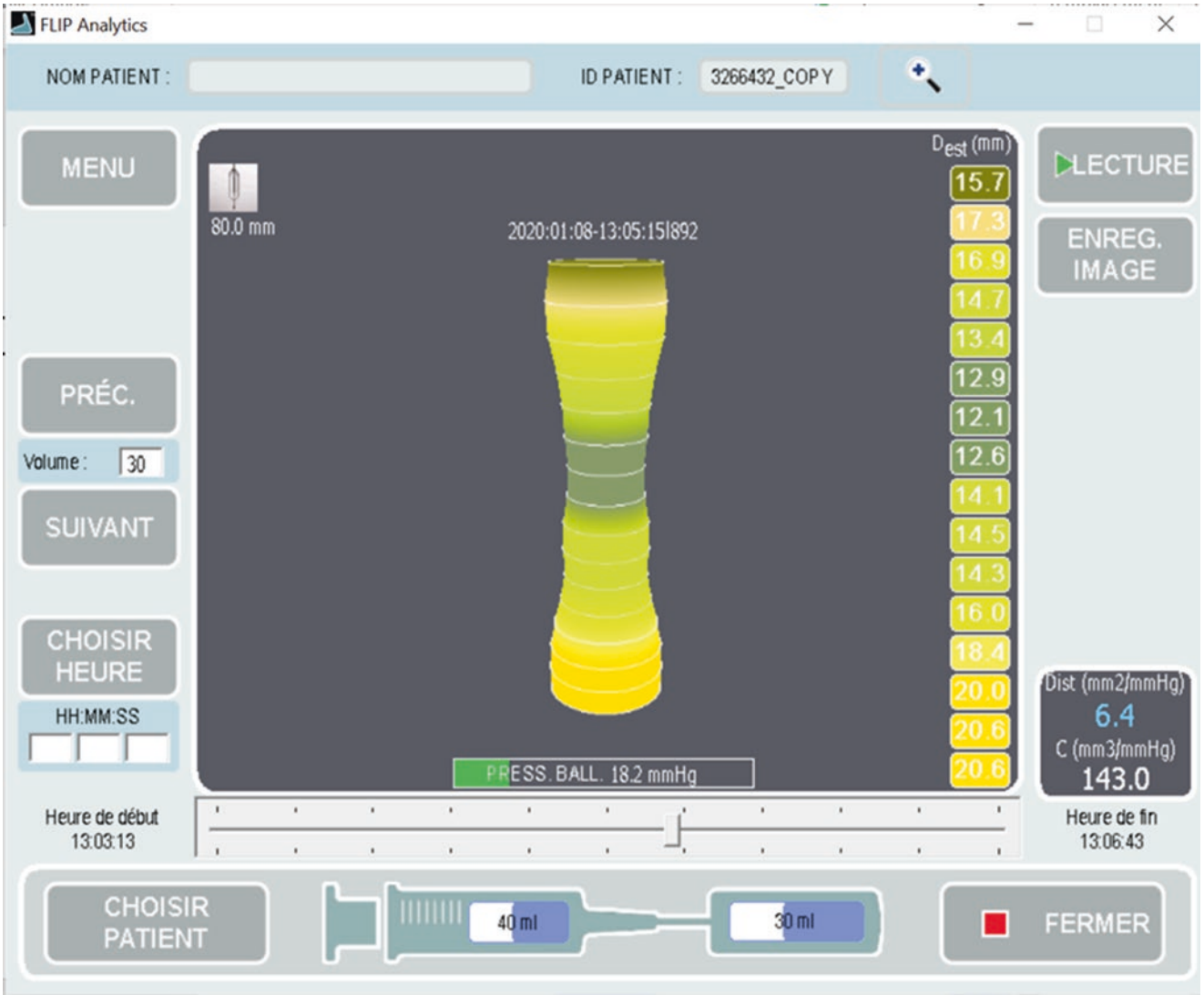

Fig. 14.3 (continued)

FLIP is useful in identifying patients with EGJOO who are most likely to benefit from achalasia-type therapy [26]. Patients with a low EGJ-DI (<2 mm^2/mmHg) responded well to achalasia-type treatment, whereas patients with normal results from FLIP (>3 mm^2/mmHg) had good outcomes from conservative management. FLIP might help select management strategies for this difficult population of patients [26].

FLIP has been shown to be of diagnostic value in the assessment of EGJOO in symptomatic patients with normal single water swallows during HRM [27].

In children, at diagnosis, median EGJ-DI was 1.7 (1.3;2.2) mm^2/mmHg at 20 mL balloon size and 1.5 (1.2;2.1) mm^2/mmHg at 30 mL. Post-pneumatic dilation treatment, good responders had a median EGJ-DI of 3.8 (1.9;9.7) mm^2/mmHg with a median increase of 2.5 (0.2;8) mm^2/mmHg [14].

Fundoplication

Patients with GERD have demonstrated a higher distensibility when compared with normal controls; this increase in distensibility allows for a greater volume of abnormal refluxate to pass through the EGJ and the EGJ to open at a lower intraluminal pressure [29, 30]. Using FLIP during a fundoplication procedure can help guide the surgeon by differentiating distensibility changes between individual operative steps.

Laparoscopic fundoplication results in decreased EGJ distensibility in patients with GERD. The EGJ following partial fundoplication is significantly more distensible than that after a full fundoplication [31]. In adults, Ilczyszyn et al. showed that the median DI at 40 mL pre-procedure was 3.75 mm^2/mmHg with a significant decrease post-Nissen

procedure of 2.39 mm²/mmHg (p = 0.0039) [32]. Other parameters have been evaluated during laparoscopic fundoplication and Turner et al. showed that a decrease in Dmin of 0.15 mm or less (area under curve (AUC) = 0.718, sensitivity: 71%, specificity: 69%) and a decrease in CSA of 1.5 mm² or less (AUC = 0.728, sensitivity: 71%, specificity: 70%) were associated with severe heartburn [33]. Furthermore, FLIP measurements correlate well with patient outcomes, with a final DI between 2 and 3.5 mm²/mmHg potentially being ideal [34]. The EndoFLIP™ can be a useful adjunct in the operating room by providing objective measurements of esophageal distensibility after crural closure and fundoplication [34]. Smeets et al. demonstrated that the best cutoff value for objective outcome was 2.3 mm²/mmHg for preoperative EGJ distensibility. EGJ distensibility decreased postoperatively from 2.0 (1.2–3.3) to 1.4 (1.0–2.2) mm²/mmHg (p = 0.014) but increased to 2.2 (1.5–3.0) at 6 months follow-up (p = 0.925, compared to preoperative) [35].

In the case of dysphagia post-fundoplication procedure, Samo et al. showed that FLIP complements HRIM and barium swallow in assessing the EGJ in the management of post-fundoplication esophageal symptoms not caused by a clear wrap herniation or other anatomical derangement, using the definition of EGJ obstruction diagnosed on FLIP as a DI < 2.8 mm²/mmHg [36].

In children, Rosen et al. showed that in fundoplication patients, there is a threshold effect, such that once a certain balloon size is reached, the distensibility and EGJ diameter increases significantly [37]. In that study, patients evaluated for dysphagia post-fundoplication had mean distensibility of 3.5 ± 1.8 mm²/mmHg. Integrated relaxation pressure (IRP) measures from high resolution impedance manometry (HRIM) were not significantly different in the intervention group from the conservative group where the treatment decision was based on distensibility measurement [36]. Courbette et al. evaluated cases of dysphagia post-fundoplication in children and showed a EGJ-DI of 1.9 (1.8;2.2) mm²/mmHg at 20 mL and 2.4 (2.1;3) mm²/mmHg at 30 mL of balloon size [14].

Gastroesophageal Reflux Disease (GERD)

The clinical impact of FLIP use in GERD has been studied in the adult population. The EGJ of GERD patients was found to be more distensible and shorter than normal subjects using concurrent esophageal manometry, fluoroscopy, and stepwise controlled barostatic distention of the EGJ [29].

The data on using FLIP for the diagnosis and management decision-making for GERD are mixed. Based on some studies, the EGJ is more distensible in reflux patients than in control subjects, and fundoplication reduces distensibility to normal levels [7, 38]. Conversely, when the FLIP was used to evaluate patients with GERD symptoms in addition to 48-hour wireless esophageal pH monitoring compared with asymptomatic control subjects, the patients with GERD were found to have a lower EGJ-DI and the EGJ-DI was not different between normal or abnormal esophageal acid exposure [8].

A more recent study demonstrated that EGJ-DI was not consistently associated with esophageal acid exposure as the EGJ-DI did not differ between abnormal acid exposure time and normal acid exposure time [39]. This may reflect the fact that the EGJ-DI is not the most important metric in assessing reflux as the opening dimensions and pressure gradient for reflux are much lower than those generated during swallowing. The dynamic relationship between openings at lower pressures may be more appropriate, and future studies in GERD should assess the rate of opening and the yield pressure for opening.

Eosinophilic Esophagitis

Adult patients with eosinophilic esophagitis (EoE) have decreased compliance of the esophageal body compared with controls [3]. Decreased distensibility using the FLIP has been shown in adults with EoE and is a risk factor for severity of rings and strictures seen endoscopically, need for dilation, and food impaction [40].

Menard-Katcher et al. studied the FLIP in a pediatric population and demonstrated that esophageal distensibility is decreased in children with EoE compared to controls [41]. In their study, eosinophil density negatively correlated with distensibility in patients with EoE. Nevertheless, those results are inconsistent. Hassan et al. found in a pediatric population that distensibility was not significantly different in the EoE group compared to the control group and it was not significantly different in patient with active versus inactive EoE either. However, there were a significant inverse correlation between the distensibility and the maximum epithelial remodeling score and a trend toward significance between distensibility and eosinophilic density [42]. FLIP could be useful to evaluate the compliance of esophageal body in EoE patients but not to make the diagnosis of EoE.

Esophageal Strictures and Stenosis

Most esophageal stenosis/strictures can be fully evaluated endoscopically, where symptoms generally guide the therapeutic decision. Fluoroscopy is usually recommended to define stricture anatomy and to facilitate guide wire placement. This is an area where FLIP could provide an alternative to fluoroscopy in providing accurate diameter assessments during index endoscopy, where dilation could also be simultaneously performed. FLIP can be useful in

such settings in providing diameter and CSA information to define stricture diameter.

In a small single-center study on 19 pediatric patients, use of FLIP hydraulic dilation (EsoFLIP™) provided a larger diameter increase compared with standard balloon dilation directed by diagnostic FLIP (4 vs. 2.2 mm), but this was not statistically significant likely because of the small cohort size [43]. In another pediatric study using EsoFLIP™ balloon to perform the esophageal dilation, median procedure time of the EndoFLIP™ + traditional balloon dilation group was longer than the median procedure time of the EsoFLIP™ group (60.5 vs. 35 min). Median diameter change in the EndoFLIP™ + traditional balloon dilation group was less than the median diameter change in the EsoFLIP™ group (2.2 vs. 4 mm) [43]. In another pediatric study, two cases of congenital stenosis were included with baseline EGJ-DI at 1.6 (1.6;1.7) mm^2/mmHg at 20 mL and 1.2 (1.1;1.2) mm^2/mmHg at 30 mL. Three cases of anastomotic stricture post-esophageal atresia repair were also included with baseline EGJ-DI of 4.3 (3;7.5) mm^2/mmHg at 20 mL and 3.2 (2.3;7.4) mm^2/mmHg at 30 mL [14].

FLIP2.0

FLIP 2.0 metrics allows to discriminate esophageal major motility disorders [1, 44]. In a cohort study of patients with normal FLIP measurements (EGJ-DI greater than 3.0 mm^2/mmHg and normal contractile response: absence of RRCs and meeting the RAC Rule-of-6 s (>6 consecutive antegrade contractions that were >6 cm in axial length and occurred at a rate of 6 (±3) antegrade contractions per minute) [45], 79% did not have a major esophageal motor disorder on HRM. Among the remaining 21% with apparent disagreement with HRM, patients with normal FLIP carried overall clinical impressions of not having a major esophageal motor disorder and subsequently were treated conservatively without the need for surgical interventions. Thus, normal FLIP results can exclude major esophageal motility disorders at the time of endoscopy, possibly negating the need for HRM in selected patients [46].

In adults, a FLIP-based classification helps discriminate achalasia subtypes based on absent contractile response, repetitive retrograde contractile pattern, occluding contractions, sustained occluding contractions (SOC), contraction-associated pressure changes >10 mmHg [47].

Use of FLIP on Other Anatomical Sites

Pylorus

Flip has been studied in adult studies in the context of gastroparesis evaluation. In healthy patients, the median pylorus distensibility index (P-DI) was 8.37 mm^2/mmHg (interquartile range, 4.22–13.04 mm^2/mmHg) at 40 mL balloon volume [48].

Several preliminary studies have shown the measuring feasibility of pyloric distensibility using FLIP. In study by Malik et al. the symptoms of gastroparesis such as post-prandial fullness and early satiety were inversely correlated with CSA and the diameter of the pylorus [49]. Significantly decreased pyloric distensibility ([8.0 ± 1.0] mm^2/mmHg) was observed in patients with delayed gastric emptying compared with individuals with normal gastric retention ([12.4 ± 1.4] mm^2/mmHg) [50]. In addition, FLIP may help to identify the gastroparesis subgroup with pylorus dysfunction who could benefit most from the pyloric intervention.

Gourcerol et al. found that fasting pyloric compliance decreased in a subgroup of patients with gastroparesis, and dilatation in these individuals improved their quality-of-life scores [51]. Ata-Lawenko et al. proposed that the cut-off value of distensibility for intervention should be <10 mm^2/mmHg [52]. Jacques et al. used EndoFLIP in a retrospective study including 20 patients to evaluate pyloric DI after endoscopic intervention. Three months after a gastric POEM the pyloric DI was favorable in patients with diabetic gastroparesis compared with those who did not have diabetes (31.6 vs. 23.6 mmHg). Furthermore, the pyloric diameter and DI improved after a gastric POEM, particularly in patients with diabetes (+4 mm^2/mmHg in mean) [53]. The results of studies on gastroparesis, however, have been preliminary.

Jehangir et al. showed that in gastroparesis patients with refractory symptoms after pyloromyotomy/pyloroplasty, pyloric through-the-scope dilation improved symptoms in about a third of the patients. Patients with symptom improvement had lower pre-dilation pyloric distensibility on EndoFLIP suggesting incomplete myotomy, pyloric muscle regeneration, or pyloric stricture. Pyloric EndoFLIP followed by through-the-scope dilation seems to be a promising treatment for some patients with gastroparesis symptoms refractory to pyloromyotomy/pyloroplasty [54].

Anus

The anal sphincter assessment using FLIP methodology can effectively distinguish anal sphincter function between fecal incontinence patients and normal subjects [55]. It has also been studied to evaluate the distensibility of the anal canal in patients with systemic sclerosis [56]. Flip has been studied to characterize the impact of sacral nerve stimulation on distension properties of the anal canal in patients with idiopathic fecal incontinence. The resistance of the anal canal to distension was significantly reduced in patients with idiopathic fecal incontinence and in fecal incontinence secondary to systemic scleroderma. It has been used to better

understand the effect of sacral nerve stimulation in fecal incontinence. FLIP has showed that the opening pressure of the narrowest part of the anal canal increased significantly during the therapy [57].

What Are the Limitations of the FLIP Procedure?

Despite accumulating evidence on the clinical utility of FLIP, limitations exist, and quality of available evidence is low. First, direct comparative studies with imaging modalities such as barium esophagography and scintigraphy are limited. Second, availability is limited, and costs are higher than other esophageal tests (i.e., barium swallow and HRM), especially because FLIP is performed during sedated endoscopy. Although many of the metrics are intuitive, training is needed for the operator and assistants, adding to the cost of adoption of the technology. Finally, an important limitation of FLIP utilization in pediatrics is the size of the device precluding any use in small children and infants (<10 kg).

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Barostat and Other Sensitivity Tests

15

Christophe Faure

Introduction

Visceral sensitivity is a complex phenomenon that is regarded as a key pathophysiological factor in children with functional gastrointestinal disorders (FGID). In recent years, techniques have been developed in adults and adapted to children making possible measures of visceral sensory thresholds of stomach and colon. This chapter reviews the barostat technique and satiety drinking tests. Functional cerebral imaging and other chemical stimulation that have not been extensively applied in pediatric subjects will not be discussed.

Barostat

Principles

The barostat is a computer-driven air pump connected to a double-lumen catheter on which a highly compliant balloon or bag is securely fixed. The balloon is introduced in a hollow organ (in children the rectum or stomach) and is used to measure tone, compliance, and sensory threshold (Fig. 15.1). The principle of the barostat is to maintain a constant pressure within the air-filled bag inserted in the organ: when the organ relaxes, the air-pump inflates the balloon to maintain a constant pressure; when the organ contracts, the system withdraws air and deflates the balloon. Because in barostat studies, the function of the bag is to isolate a segment of the digestive tract without interfering with its function and its motility, the compliance of the balloon or bag should be "infinite" and the volume must be greater than the range of volume used during the study (rectal bags: length 11 cm, maximal capacity 600 mL; gastric bags: maximal diameter 17 cm, maximal capacity 1200 mL). Polyethylene bags are recommended versus latex balloons.

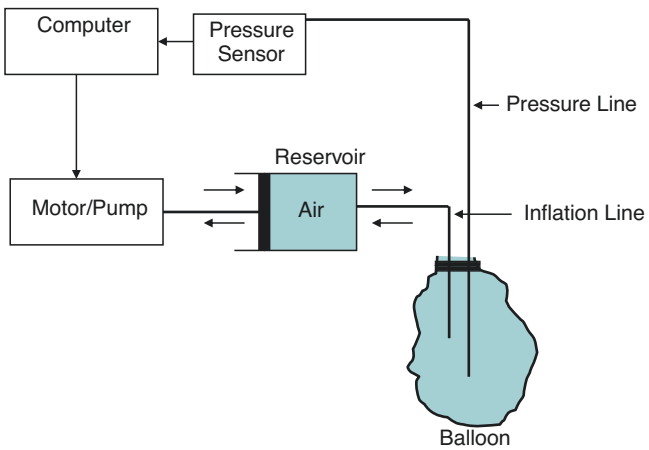

Fig. 15.1 Schematic diagram of a barostat and catheter

Because visceral sensitivity relies on wall pressure and not on volume of the organ [1, 2], sensory thresholds should be expressed as pressure. Moreover, reproducibility of pressure measurements between laboratories and between subjects is better than volumes because the pressure scale compensates for differences in bag shape, smooth muscle compliance, and contractile activity of the organs [3].

Procedure

Technical recommendations for measurements of sensory threshold and compliance have been published in adults and the general principles apply to practice in children [3]. However, sensory threshold assessment requires adequate cooperation for the reporting of sensation and feeling by the subject. Children younger than 7–8 years may not be able to adequately relate sensations experienced during the procedure. Explanation on equipment and sequence of the procedure must be given to the child and the parents. Because psychological state modulation results in changed sensation at a given stimulus in healthy adult subjects [4], environment and sequence of the barostat study should be

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as quiet as possible in order to minimize external influences and standardize the procedure.

For rectal sensitivity studies in children, most authors do not extensively clean the colon but rather suggest to the child to go to the toilet before the study. For study compliance in children with constipation, cleansing of the rectum with an enema should be conducted the day before the barostat study. Because meals may interfere with colonic and gastric tone, a 4–6-h fasting period prior to the study is recommended. All medications affecting pain or gastrointestinal motility should be discontinued at least 48 h prior to the barostat procedure.

For rectal studies, the patient lies in the left lateral position and the catheter is gently inserted into the rectum. For gastric studies, the catheter is inserted by mouth. The catheter is secured with a tape and 5–10 min are allowed for adaptation before beginning the procedure. The barostat bag is then slowly inflated with 30 mL of air and the pressure is allowed to equilibrate for 3 min. The average bag pressure during the last 15 s defines the individual operating pressure (IOP) also called the minimal distending pressure (MDP) which is the minimum pressure required to overcome mechanical forces and inflate the bag with 30 mL of air.

Various distension protocols have been described [3]. In children, the ascending method of limits (AML) without [5–7] or with [8–13] tracking has been the most applied. In the AML, the barostat is programmed to deliver phasic intermittent stimuli starting at the IOP progressively increased in 2–4 mmHg steps lasting 60 s followed by 60 s deflation. When the first sensation of pain is reported, the study can be stopped (the sensory threshold is determined) or can be prolonged (tracking) by subsequent distensions randomly adjusted up or down depending on the response of the previous distension (if the subject reports pain, the next distension will be decreased or kept the same; if the subject reports no pain, the next distension will be increased or kept the same). The threshold is determined by averaging the pressures at which pain had been indicated after a series of measures (usually 3) (Fig. 15.2). A 4 to 5-point scale [6, 10] is used as a verbal descriptor for sensation felt during the barostat procedure. The AML is vulnerable to psychological biases (fear of pain) because the stimuli are predictable to the subject. The tracking technique is believed to be more reliable because it is less vulnerable to psychological bias (the stimuli are unpredictable) and because there are multiple determinations of the threshold. On the other hand, the tracking technique necessitates delivering multiple painful stimuli that can be less acceptable in children. However, the tracking method has been used successfully without any adverse event by several pediatric groups [8–13]. Of note, the majority of children tested report that the pain sensation felt during the barostat is notably lower than the pain felt in *real life*.

Measurements

Sensory Thresholds

The visceral sensory threshold can be separated into two components: the *perceptual sensitivity* (the ability to detect intraluminal distension) and the *response bias* (how the sensation is reported). The perceptual sensitivity allows to discriminate between two distensions and reflects the ability of the organ to detect and transduce the stimulus to the central nervous system. The response bias (or perceptual response) is the reporting behavior (intensity, painfulness) that is a cognitive process influenced by past experience and psychological state. Actually, the tools currently used (distending protocols, methods for reporting subjects' response) are not able to accurately measure the two components separately. Adult studies have shown that the threshold measurement is responsive to changing environment or perturbations and psychological modulation results in changed sensation at a given stimulus in healthy subjects [4]. In children, there are few data regarding the influence of psychological state or trait on sensory threshold assessment. One pediatric study found that rectal sensory threshold did not correlate with the *state* of anxiety, suggesting that the anxiety generated by the

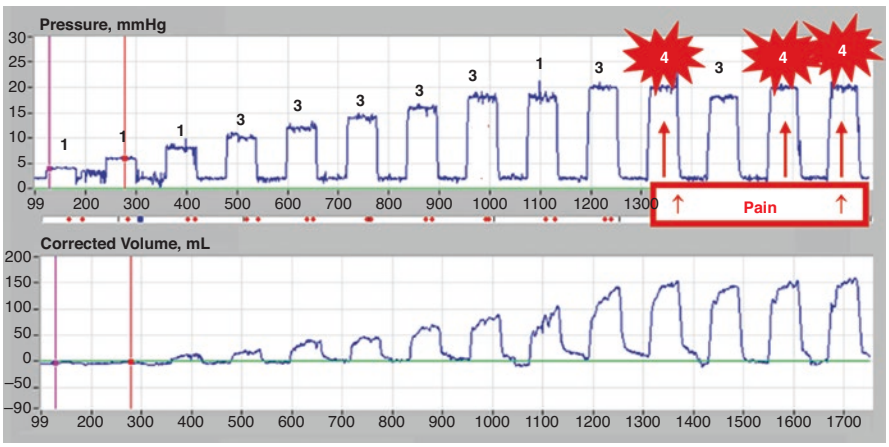

Fig. 15.2 Ascending method of limits with tracking. Rectal barostat tracing in a 11-year old girl with IBS. Verbal scale: (1) *Gas or first sensation*, (2) *Need to go to the bathroom*, (3) *Urge to go to the bathroom*, (4) *Pain*

procedure itself is not sufficient to bias the child's response to distension [10]. However, visceral sensitivity studies should be conducted in a neutral and quiet environment in order to avoid any external interference with the measurements. Results can be expressed as sensory thresholds, that is, the first pressure that triggers a given sensation (urge to defecate, pain), or in intensity of sensation triggered by stimuli at fixed pressure.

Compliance

The compliance reflects the ability of a hollow organ to adapt to an imposed distension. It is expressed in mL/mmHg. It is defined as the pressure-volume relationship whose sigmoid shape is composed of an initial reflex relaxation followed by a linear section and a final plateau phase. Practically, compliance is calculated according to a nonlinear model fitting the pressure-volume curves. Pressure-volume curves are constructed with average computed volumes during each consecutive pressure step (when equilibration of the volume is reached, typically after 30–45 s). Compliance is calculated as the maximum slope of the pressure-volume curves (Fig. 15.3) [3, 9, 12, 14–18]. Normal pediatric values have been published for rectal compliance (22 healthy volunteers 12 ± 2.6 years; 16 mL/mmHg, 12–20) [16]; 10 control children (mean age: 13.7 years; 8.7 mL/mmHg, 6.0–14) [12]. Alteration of gastric compliance has been reported in eight children after Nissen fundoplication [17, 19–21].

Tone and Accommodation

The volume of air entered into or withdrawn from the balloon is an indirect measurement of tone of the organ. Changes in volume in response to a meal (accommodation) can thus be easily measured by calculating the difference between preprandial and postprandial balloon volumes. Rectal volume response to feeding (decrease of 25 ± 3% from 88 ± 8 mL before the meal to 66 ± 7 mL after the meal) has been reported in healthy children [6]. In the stomach, data have been reported in young adults but not in children [18].

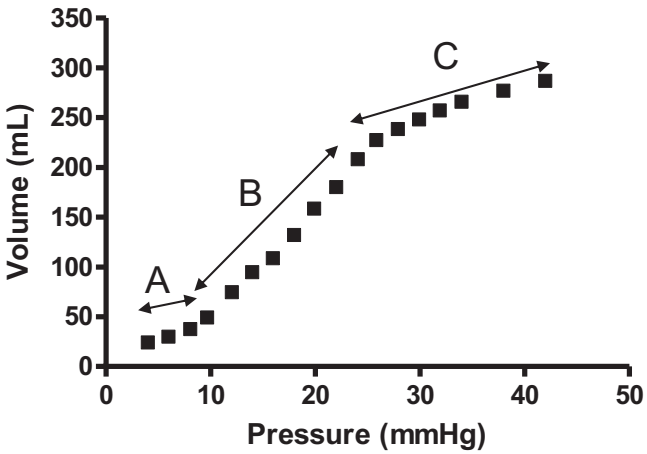

Fig. 15.3 Normal relationship volume-pressure (compliance = 9.1 mL/mmHg) in the rectum of a 12-year old IBS patient
The sigmoid curve is composed of an initial reflex relaxation (**a**) followed by a linear section (**b**) and a final plateau phase (**c**). Compliance is calculated as the maximum slope of the curve in the linear section (**b**)

Qualitative and Quantitative Assessment of the Sensations

Sensations elicited during the barostat, painful or not, must be rated (intensity) and qualitatively reported. Visual analog scales can be used by children aged between 6 and 7 years to rate sensations such as urgency or pain [9, 11, 12] and are easier to use than verbal descriptors in this population. Rating pain separately from unpleasantness is difficult in children. Qualitative evaluation of the pain has been conducted by using validated human body diagrams [10, 22] and questionnaires related to the similarity of the induced pain and the typical pain felt in real life [9, 13].

Clinical Relevance of Barostat Measurements

Pain-Associated Functional Gastrointestinal Disorders

Rectal Sensitivity Measurement

Using rectal barostat, several independent groups have reported that 75–100% of children with irritable bowel syndrome (IBS) have rectal hypersensitivity as compared to control children [6, 8–10, 13]. In adults affected by IBS, the prevalence of visceral hypersensitivity varies from 20 [23]–94% [24] across studies suggesting that rectal hypersensitivity is a more reliable diagnostic marker of IBS in children than in adults. This has been confirmed in a prospective study that included children with abdominal pain for whom rectal sensory threshold was measured prior to any other diagnostic procedures [9]. In the 51 children included, rectal sensory threshold was lower in the FGID group than in the organic disease group (25.4 mmHg vs. 37.1 mmHg; $p = 0.0002$) and 77% of the children with FGID had a rectal hypersensitivity. At the cutoff of 30 mmHg, the rectal sensory threshold of pain (RSTP) measurement for the diagnosis of FGID had a sensitivity of 94% and a specificity of 77%. Rectal compliance has not been found to be different between IBS and control subjects [6, 8, 9, 11, 13]. Children with functional dyspepsia (FD) have normal rectal sensitivity suggesting that visceral hypersensitivity is organ specific [10].

Data regarding visceral sensitivity in children with functional abdominal pain (FAP) according to Rome III criteria are less clear with discrepancies (sensory threshold similar to controls [6] or similar to IBS [10]) between authors.

Gastric Sensitivity Measurement

Because of the invasiveness of gastric barostat, the pathophysiology of FD has been scarcely studied in children. A subset of children with recurrent abdominal pain studied by gastric barostat using a latex balloon was reported to present hypersensitivity at the gastric level [13]. More recently, 16 dyspeptic children were extensively studied using gastric barostat [18]. Compliance was similar between patients and controls (69.5 ± 8.9 mL/mmHg). Pressures at the discomfort threshold were significantly lower in dyspeptic children compared with young healthy controls. Accommodation to a meal was significantly lower in dyspeptic children. Hypersensitivity to gastric distension was present in 56% (9/16) of patients and impaired accommodation in 11 patients (69%). When studied by gastric barostat, children with IBS had normal gastric sensitivity [13].

Somatic Projections and Reproducibility of the Visceral Pain

Somatic referral induced by rectal distension differs in IBS, FAP, and FD children.

In healthy children without any gastrointestinal complaints and in dyspeptic patients, rectal distension-induced sensations refer to the S3 dermatome (perineal area). In IBS and FAP, children refer their sensation to aberrant sites compared to controls, that is, with abdominal projections to dermatomes T8 to L1 [10]. However, similar results have been obtained in barostat study of children with organic disease suggesting that subjects with protracted complaints of abdominal pain not related to FGID may have, in contrast to "true" controls, an abnormal perceptual response to distension (i.e., abnormal interpretation and sensation in response to rectal distension) [9]. The reproduction of pain during rectal distension is frequent in IBS and FAP children but is not predictive of a diagnosis of FGID as compared to organic diseases [9].

Constipation

In constipated children a high rectal compliance (>20 mL/mmHg) is present in a majority (58%) of patients and explains that, to reach the intrarectal pressure threshold that triggers the sensation of need to defecate, a larger stool volume is required. Actually in contrast to previous studies, only 10% of the patients have true rectal hyposensitivity [15, 16]. Whether the abnormal rectal compliance is primitive or secondary to fecal impaction is uncertain although there is no difference in compliance between groups with and without impaction [16]. Moreover, rectal emptying by regularly using enemas does not normalize compliance [15]. Sensation of urge to defecate has been shown to be decreased in children with chronic constipation and functional non-retentive fecal incontinence with a difference between them with respect to patterns of cerebral activation and deactivation during rectal distension [25].

Less Invasive Methods to Assess Gastric Sensitivity

Because gastric barostat studies are more invasive than rectal barostat, less invasive methods of measure of gastric sensitivity have been developed.

Water Load Test

The water load test has been advocated as a means of identifying patients with gastric hyperalgesia. The water load test can be performed using 2 different techniques. The first involves the patient drinking water at a fixed rate (e.g., 100 mL/min) until she or he reports being "full." The second method, which has been used in pediatrics, is referred to as rapid water loading and involves the patient drinking water ad libitum over a 3–5 min period [26]. Practically, the child must drink from a glass as much water as possible poured from a liter bottle in 3 min or until he/she feels too full to continue [26, 27].In a non-controlled small study, the maximum water intake capacity was found reduced in children with functional dyspepsia (n = 11, median = 380 mL) as compared to patients with irritable bowel syndrome (n = 10, median = 695 mL) or functional abdominal pain (n = 10, median = 670 mL) [28]. However, the water load test seems to be a poor diagnostic test for FD because of poor sensitivity [27]. Interestingly, the water load test was used to demonstrate that obese children and adolescents have to drink 20% more water until the onset of satiety when compared with normal-weight participants [29]. This was confirmed in an independent study suggesting a possible underlying anomaly in the perception of satiety [30].

Satiety Drinking Tests

Satiety drinking test with a liquid meal has been validated in adults and is correlated to gastric barostat measurements [31]. Subjects are studied after an overnight fast. A peristaltic pump fills one of two beakers at a rate of 15 mL/min with a liquid meal (Nutridrink [32], Ensure [33]). The children are instructed to maintain intake at the filling rate, thereby alternating the beakers by filling and emptying. For every 5 min, they score their satiety using a graphic rating scale, graded 0–5 (1 = no sensation, 5 = maximum sensation). Satiety is defined and explained to the children as the opposite of the desire to eat. Children are asked to cease the meal intake when a score of 5 is reached. The maximal tolerated volume reflects gastric accommodation. This method has been used in a large group of 59 children aged 5–15 years for which normal values have been published [32]. Adolescents with FD have been shown to present increased symptoms 30 min after reaching maximum satiation [33].

Intragastric Pressure during Food Intake

Recently, using a standard catheter for high resolution esophageal manometry, the intragastric pressure during nutrient drink ingestion has been validated versus gastric barostat as a minimally invasive technique for assessment of gastric accommodation. Upon nutrient drink ingestion, intragastric pressure drops initially and gradually recovers [34]. This technique has been applied in children with FD [35].

Role of Visceral Sensitivity Measurement in Clinical Practice

By providing an objective criterion in addition to the clinical symptoms of FGID, the determination of a low sensory threshold may give a pathophysiological explanation to children and their parents, making it possible for them to understand the nature and mechanisms of the symptoms. This may be helpful to reassure patients, their parents, and physicians by confirming the clinical symptom-based diagnosis of FGID. On the other hand, children with IBS or FAP symptoms with a normal RSTP should be carefully re-examined to exclude other diagnoses. Rectal hypersensitivity has been reported in children with inactive Crohn's disease suffering from protracted abdominal pain suggesting that rectal barostat may be useful to recognize FGID in such patients [12]. Whether measurement of visceral sensitivity impacts the outcome of patients with FGID (number of procedures ordered by the physician, long-term prognosis, and response to drugs…) is unknown. Less or non-invasive means to assess visceral sensitivity are important to be validated in pediatrics to allow an easier and larger determination of this physiological parameter to further understand and treat FGID. The lactulose challenge test which allows to discriminate patients with IBS and which is correlated with rectal barostat measurements is as such a promising tool [36].

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Radionuclide Gastrointestinal Transit Tests

16

Lorenzo Biassoni and Osvaldo Borrelli

Introduction

Scintigraphic techniques in the investigation of the gastrointestinal tract (GIT) have been available for decades but until recently have been little utilized in clinical practice [1, 2], especially in pediatrics. Scintigraphic tests provide an evaluation of gastrointestinal function under physiological conditions, are cheap and easy to perform, well tolerated, and not operator-dependent [3]. The radiation burden is lower than in conventional radiology and, as γ-cameras are linked to digital computers, quantification is relatively easy.

Scintigraphy is considered the gold standard for measuring gastric motility, but its clinical applications have been limited in view of the lack of standardization of the technique. The large variety of the radiolabeled meals in use has made it difficult to define a normal range for the gastric emptying study that is applicable to all centers, thus generating uncertainties in the value of the examination. The difficulty in recruiting pediatric normal volunteers has added to the problem. Small bowel and colonic transit scintigraphic studies in children are performed only in selected specialized centers.

In the last 15 years, a new set of guidelines that standardize the radiolabeled test meal to be used for a radionuclide gastric emptying study [4, 5] in adult patients have been published. The guidelines also define the normal range in adults for a solid gastric emptying test meal based on radiolabeled egg white. As a result, many centers around the world have adopted the newly standardized radiolabeled test meal and the recommended acquisition protocol, with significant improvement in the accuracy and reproducibility of the results.

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An important recent report, based on a review of >1000 subjects studied with a 4-h gastric emptying protocol, has shown that the adult normative standards for gastric emptying are applicable in the pediatric population [6]. These same normal range can be also applied to non-standard test meal options such as cheese-based test meals and partially standard test meals. As such, the adult gastric emptying criteria, which designate percent gastric retention values of <10% at 4 h as normal, are applicable to pediatrics.

The normal range for a liquid gastric emptying study with milk or formula in children under 5 years of age has also been recently defined in a large group of individuals as similar to healthy children as possible [7]. The data suggest that the overall normal liquid gastric emptying in infants and children younger than 5 years of age is >80% of the initial gastric content at 3 h. Interestingly, the results also showed that 1-h emptying measurements are not reliable for detecting delayed gastric emptying.

The standardization of the acquisition protocol of the liquid and solid gastric emptying studies and the definition of the normal range in pediatrics have opened the way for a more widespread clinical use of these imaging techniques.

New guidelines on the acquisition and interpretation of the whole gut transit study, which includes the stomach, small bowel, and colon, have also been published [8]. A standardized acquisition protocol on how to perform these studies is presented, although the normal range, especially in children, is still broad.

Radionuclide GI Studies in Children: General Observations

Radionuclide gastrointestinal transit studies in children require great patience and skills from the radiographers and technicians who interact with the child and family. A full explanation of the procedure to both child and parents is essential, including the length of time they will need to be in

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the nuclear medicine unit. The parents should be present during the test to support the child. The cooperation of the child can also be improved using age-appropriate relaxation and distraction techniques. It is very important to keep the child as still as possible during the examination to obtain high-quality images; this is often challenging, and in some instances, sedation may have to be considered. The administered activity of the radiopharmaceutical is scaled on the child's body weight or body surface area.

Radiopharmaceuticals

The radiopharmaceuticals used in gastrointestinal motility studies must be non-absorbable and stable in gastric acid. For esophageal transit, gastroesophageal reflux (GER), and gastric emptying studies, the main radiopharmaceuticals utilized are [^{99m}Tc]Tc-sulfur colloid or [^{99m}Tc]Tc-nanocolloid. In a gastric emptying study, these tracers are used for both the liquid phase, as they bind well to milk, and for the solid phase, and they have a good affinity for the protein matrix of the egg white and the melted cheese. The maximum limit of the activity that can be administered varies according to different countries, ranging between 18 and 74 MBq [9, 10]. In the United Kingdom, the maximum limit is 40 MBq for studies evaluating esophageal motility and GER: this activity gives a maximum effective radiation burden of 0.9 mSv. For gastric emptying studies, the maximal activity is 12 MBq, which gives a radiation burden of approximately 0.3 mSv.

[^{99m}Tc]Tc-diethyl-triamine-pentaacetic acid (DTPA) is used as a tracer for the liquid phase of the gastric emptying. [^{99m}Tc]Tc-macroaggregates of albumin (MAA) can be used in the liquid phase of the gastric emptying study.

[^{111}In]In-DTPA is frequently used as a tracer for the liquid phase of small bowel and colonic transit studies. The administered activity varies between 5.5 and 18.5 MBq in an adult. The maximum administered activity in the United Kingdom is 10 MBq, which gives a radiation burden of approximately 3 mSv. The administered activity in a child is scaled down from the adult activity in proportion to body weight, with activities ranging between 1.5 and 3 MBq typically administered in a child less than 10 years of age.

Esophageal Transit

Esophageal transit scintigraphy is a non-invasive method to assess esophageal motility qualitatively and quantitatively. It is fast, easy to perform with minimal radiation exposure. However, since its introduction by Kazam and colleagues, several protocols have been used without standardization, thus limiting its widespread use [11]. Some protocols used in adults are applicable to older children able to swallow a bolus on command. Some variations have been introduced for assessing esophageal motility in young children and infants [12]. This test provides visual and quantitative data on the transit of a radiolabeled bolus through the esophagus. It can be used for the diagnosis of organic and functional esophageal disorders and is especially valuable when done sequentially to evaluate the effect of medical or surgical treatments.

The test is performed after a fast of at least 3 h in infants and 6 h in children. Any medication with a known effect on esophageal motility should be discontinued for at least 72 h. [^{99m}Tc]Tc-sulfur colloid is routinely used for esophageal transit scintigraphy. In adults, most of the studies have been performed using a liquid bolus, whereas only few studies have used a semisolid bolus [13, 14]. In infants and children, an activity of at least 150 μCi (5.55 MBq) is added to 10 mL bolus of milk or water. In the case of milk allergy, a substitute may be used.

Acquisition Technique

Infants can lie on a slightly inclined collimator. Older children can sit up with their back to the collimator. It is essential to turn the head of the bottle-fed infants to the side, to avoid superimposition of the radioactivity in the bottle over the upper esophagus. Older children can be fed with a cup or with a straw. Before the administration of the radiolabeled bolus, an external small radioactive marker is placed over the cricoid cartilage as an anatomical landmark. After a practice swallow with unlabeled liquid, the radioactive bolus is placed in the mouth and swallowed on command followed by a dry bolus at least 30 s later. Since some swallows are not completely propagated even in healthy subjects, 4–6 swallows should be obtained. The patient's position during the study can affect the results because of gravity. Performing the study with the patient in an upright position may be more physiological. Eliminating the force of gravity by performing the study with the patient in the supine position is more practical in infants and young children and more efficient in exposing motility disorders.

A large-field-of-view γ camera fitted with a low-energy high-sensitivity collimator is used when imaging due to high temporal resolution required for quantitative studies. Dynamic images in a 128 × 128 matrix must be acquired in a rapid sequence. Because many of the events occur in a short time, images should be acquired at 4–10 frames per second for 60 s. The field of view of the γ camera must include the entire esophageal tract including the mouth and the gastric fundus. An additional 10 min static acquisition is obtained when the patient is asked to dry swallow to measure the clearance from the esophagus. If a large residual remains in the esophagus, delayed static images are obtained at 30

and 60 min. A [^{57}Co]Co transmission image may be taken immediately or at 10 min following completion of the dynamic acquisition when the anatomical location of the tracer is uncertain (gastric fundus versus esophagus).

Study Analysis

Once the study has been completed, the images are reviewed in a one-to-one single-frame analysis and then played back in a cine display mode. This procedure depicts the dynamics of the swallowing and swallowing-related esophageal motor pattern and helps to identify aberrant patterns. For instance, the adynamic pattern is characterized by slow progression or even stopping of the bolus along the esophagus, such as in achalasia and scleroderma, whereas the uncoordinated pattern is characterized by random disorganized retrograde and antegrade or yo-yo contractions throughout the esophagus as occur in patients with diffuse esophageal spasm. This visual pattern corresponds to multiple peaks of the time-activity curves as determined by the quantitative assessment of the esophageal transit. Esophageal transit can be measured quantitatively with time and retention parameters. The esophagus is divided into upper, middle, and lower zones. Equal regions of interest (ROI) are placed on each zone and a fourth ROI is placed over the stomach. Time activity curves for the proximal, mid, and distal parts of the esophagus are generated. The curves allow quantitative and qualitative assessment of the bolus transit. Condensed dynamic images that summarize the whole deglutition event into one single image may also be used. A condensed dynamic image displays the profile of the swallowing event side by side on the *y*-axis, along with the time on the *x*-axis. The total transit time is usually calculated as the period between the first appearance of the tracer in the proximal esophagus and the time needed to obtain 90% radioactivity clearance from the distal esophagus. The residual 10% of the tracer is ignored in order to avoid any potential overlap with the tracer contained in the fundus. Besides total and segmental transit times, a clearance rate at time *t* is usually obtained with the following formula: $C = (E_{max} - E_t)/E_{max} * 100\%$, where E_{max} is the maximal esophageal radioactivity and E_t is the radioactivity at time 0 [12–14]. In healthy adults and in children, the pharyngeal transit is quite rapid occurring in less than 1 s. The normal transit time through the esophagus is typically less than 10 s, ranging from 3.4 ± 1 s for infants, 4.6 ± 1.9 for children aged 8–16 years, and 5.5 ± 1.1 for adults [15].

Clinical Indications

The main indications for esophageal transit scintigraphy are the evaluation of esophageal motility in patients who cannot tolerate manometry, the lack of availability of esophageal manometry, equivocal manometric results, and follow-up of patients with esophageal motor disorders such as achalasia and scleroderma (e.g., to assess the efficacy of surgical or medical therapy).

The sensitivity and specificity of the esophageal scintigraphy to detect esophageal motility disorders vary widely depending on the technique used and the esophageal disorder investigated. No diagnostic benefit of esophageal scintigraphy has been shown in patients with normal peristalsis even in the presence of severe motor abnormalities such as nutcracker esophagus or isolated hypertensive lower esophageal sphincter (LES) [16, 17]. On the other hand, several studies have shown its use in detecting abnormalities of esophageal peristalsis, such as achalasia, scleroderma, esophageal atresia, and diffuse esophageal spasm [18, 19]. It still represents an ancillary test when compared to esophageal manometry.

Gastroesophageal Reflux and Aspiration

Gastroesophageal reflux (GER) is the passage of gastric contents into the esophagus with or without regurgitation and vomiting. GER is a normal physiological process occurring several times per day in healthy infants, children, and adults. Most episodes of GER in healthy individuals last <3 min, occur in the postprandial period, and cause few or no symptoms. In contrast, gastroesophageal reflux disease (GERD) is present when the reflux of gastric contents causes troublesome symptoms and/or complications.

GER scintigraphy has been widely used for the evaluation of GER in children [20–22]. It is easy to perform, is well tolerated, and requires minimum patient cooperation. It also incurs a low radiation burden. Advantages of GER scintigraphy include the ability to detect pulmonary aspiration and to evaluate gastric emptying in the same study [23].

Technique

In young infants, the radioactive milk used for the test should replace the normally scheduled feed, while older children should fast for at least 4 h prior to the test. The tracer used is [^{99m}Tc]Tc-sulfur colloid or nanocolloid (or [^{99m}Tc]Tc-DTPA) mixed with an appropriate volume (between 30 and 240 mL) of milk, or milk formula. The amount of activity administered is 0.55 MBq/kg, with a minimum activity of 7.4 MBq and a maximum of 40 MBq. The tracer is added to a portion of the patient's feed (one third to one half of the normal milk or formula feed volume). This volume is introduced into the stomach orally, or by nasogastric tube (which should be removed after feeding), or by a gastrostomy tube if this is the method used to feed the child. A second tracer-free volume is then given to clear any residual tracer from the oropharynx

and esophagus prior to imaging. The volume of the feed varies according to the patient's age and weight. In most cases, the desired volume is like the volume given to the patient for regular meals. The start and end of the feeding should be recorded.

There is no single universally accepted protocol for this study; most protocols however share the same basic principles. After feeding, the child is positioned supine on the γ camera couch. Young infants should be burped when possible prior to imaging. Restraints such as sandbags and Velcro straps may be used to secure young children to the imaging bed and prevent motion. Dynamic images are acquired from the posterior view with the stomach and chest in the field of view at a frame rate variable between 10 and 30 s/frame for 60 min [24]. Any event during the acquisition (motion, coughing, vomiting, reflux) is recorded at the time it occurs. The dynamic images are followed by anterior and posterior static views of the chest, with the stomach out of the field of view. These images are recorded on a 256 × 256 matrix over 3–5 min. It is important to perform the dynamic study over 60–120 min because a significant number of GER episodes can be missed by limiting the study to 60 min. The supine position is more sensitive than the prone position to detect GER [25].

Analysis

New visualization of tracer in the esophagus indicates an episode of gastroesophageal reflux. Radioactive markers positioned over the shoulders, suprasternal notch, and xiphoid are helpful in determining the level of reflux in the esophagus or oropharynx and in localizing possible activity within the lungs. Time activity curves generated from ROIs drawn over the esophagus can be helpful. GER episodes are seen as sharp spikes in the curves. Patient motion during the study can introduce significant artifacts in the curves, and therefore images should always be inspected for motion and motion correction should be applied when necessary. Visual inspection of the dynamic images and cine, together with the time activity curves, provides best diagnostic accuracy.

The presence of GER can be quantified using the formula: $R = E(t) - E(b) \times 100/G0$, where R is the percentage of refluxed material in the esophagus, $E(t)$ the esophageal count at time t, $E(b)$ the para-esophageal background counts, and G0 the gastric counts at the beginning of the study. R and $E(t)$ may refer to the entire organ and the individual regions [26]. According to this formula, a reflux greater than 5% is considered abnormal [21].

Sensitivity and specificity of a 1-h scintigraphy for the diagnosis of GERD are 15–59% and 83–100%, respectively, when compared with 24-h esophageal pH monitoring [22, 27]. Interestingly, scintigraphy has been shown to be more sensitive in the detection of reflux beyond the first postprandial hour as compared to pH monitoring, which usually fails to detect some types of reflux, especially when little or no acid is present [22]. Evidence of pulmonary aspiration is usually assessed through images obtained up to 24 h after administration of the radionuclide [23], but the sensitivity is low, and a negative test does not exclude aspiration.

Clinical Indications

This test does not confirm the diagnosis of GERD and therefore it is not recommended for the routine evaluation of children with suspected GERD. The test is recommended only in individuals with symptoms of gastric retention [28]. Multichannel intraluminal impedance and pH (MII-pH) monitoring can characterize the reflux episodes as acid or non-acid, as well as the level reached by the refluxate.

Gastric Emptying Study

Clinical Indications

The most common indication for a gastric emptying study is the evaluation of gastroparesis. Gastroparesis is a condition of abnormal gastric motility which presents with symptoms suggestive of delayed gastric emptying in the absence of an anatomical obstruction. Gastroparesis in children can follow a viral infection, can be a sequela of Nissen fundoplication, can be associated with gastroesophageal reflux disease (GERD), especially if unresponsive to medical treatment, or can be idiopathic. A full list of conditions associated with gastroparesis is presented in Table 16.1.

Table 16.1 List of conditions that can be possibly associated with gastroparesis in pediatrics

• Idiopathic
• Diabetes mellitus
• Post-surgical
– Nissen fundoplication
• GI disorders associated with delayed gastric emptying
– GERD
– Functional dyspepsia
– Diffuse GI motor disorders (Pediatric Intestinal Pseudo-Obstruction—PIPO)
– Celiac disease
• Non-GI disorders associated with delayed gastric emptying
– Eating disorders (anorexia)
– Neurologic disorders (cerebral palsy)
– Collagen vascular disorders (scleroderma, SLE)
– Endocrine and metabolic disorders (thyroid and parathyroid dysfunction, CRF)
– Gastric infection (post-viral infection)
Medication associated (cancer patients)

The pathophysiological mechanisms underlining this condition are complex and still not well understood, and include exaggerated fundal relaxation, poor antral contractility, lack of coordination between antrum and pylorus, pylorospasm. Main presenting symptoms in gastroparesis are nausea, vomiting, abdominal bloating, early satiety, and postprandial fullness [4]. In a child presenting with symptoms suggestive of gastroparesis, it is essential to exclude an anatomical obstruction such as malrotation with a fluoroscopic upper GI contrast study. The radiological examination will also show the anatomy of the upper GI tract and in particular the outline of the stomach: this is helpful at the time of processing of the gastric emptying study as it guides the position of the ROI around the stomach. It also helps to better define the anatomy of the stomach, which at times can be not straightforward, especially following a surgical intervention.

Assessment of dumping syndrome, based on symptoms occurring in the initial hour after meal ingestion such as diarrhea, abdominal discomfort, nausea, bloating and vasomotor symptoms, is another possible indication for a gastric emptying study.

The test consists of a solid meal and/or a liquid meal. A solid meal is more reliable to assess gastroparesis. A liquid meal can be normal in the presence of gastroparesis. Recent reports suggest that both meals may provide complementary information [29, 30]. In very young children (<3 years), a test feed based on milk or milk formula is adequate (milk is regarded as a semisolid meal, being a nutrient feed).

Patient Preparation

Medications that affect gastric motility should be discontinued for an appropriate period prior to the test depending on the pharmacokinetics of the drugs unless the purpose of the study is to evaluate the effect of specific drugs on gastric motility. Typically, prokinetic drugs (domperidone, tegaserod, metoclopramide, erythromycin) are withdrawn for 48 h. Medications that delay gastric emptying, such as opiates and antispasmodics, are also stopped for 2 days. Serotonin receptor antagonists (5-HT-3) such as ondansetron, which have little effect on gastric emptying, can be given in case of severe symptoms of nausea and vomiting. Fasting blood glucose should be within normal range, due to the well-known effect of hyperglycemia on the gastric motor activity [31]. The child is usually kept nil by mouth for approximately 4 h. Young infants should miss a normal feed just prior to the test. Previous medical history, especially regarding the GI tract, including previous surgical procedures, as well as a history of possible allergies, must be available before the study.

Technique

Liquid gastric emptying study The feed is radiolabeled with [^{99m}Tc]Tc-sulfur or nanocolloid or [^{99m}Tc]Tc-DTPA (the range of the administered activity is 10–37 MBq; the maximum administered activity depends on the legislation of the country). The amount of feed is calculated according to the patient's age and what they can ingest. The quantity of feed is split between the radiolabeled feed, that is ingested first, and a portion of unlabeled feed, that is drunk as a chasing portion to clear possible labeled feed that might have remained stuck in the oropharynx and esophagus. If the child is fed via a nasogastric or a gastrostomy tube, the amount of test feed introduced via the tube should reflect what the child could normally tolerate for their meals.

Solid gastric emptying study The composition of the meal is a very important factor that affects the result of the study. The meal should consist of a balanced content of carbohydrates, proteins, and fat (Table 16.2). Every effort should be made to stick to the standardized meal for a gastric emptying study. If a child/adolescent is intolerant to eggs, a test feed based on melted cheese on toast or macaroni pasta is a suitable choice [32, 33].

Image Acquisition

Liquid gastric emptying study After feeding, the child is positioned supine on the γ camera couch. Young infants should be burped, when possible, prior to imaging. Restraints may be used to secure young children to the imaging bed and prevent motion. Dynamic images are acquired from the posterior view, with the stomach and chest in the field of view, at a frame rate variable between 10 and 30 s/frame for 60 min [24]. Images are obtained in

Table 16.2 Solid meal preparation (from [45])

Recommended meal:
1. 118 mL (4 oz.) of liquid egg whites (e.g., Eggbeaters [ConAgra Foods, Inc.] or an equivalent generic liquid egg white)
2. Two slices of toasted white bread
3. 30 g of jam or jelly
4. 120 mL of water
Meal preparation:
1. Mix 18.5–37 MBq (0.5–1 mCi) of 99mTc-sulfur colloid into the liquid egg whites
2. Cook the eggs in a microwave or on a hot non-stick skillet
3. Stir the eggs once or twice during cooking and cook until firm—to the consistency of an omelet
4. Toast the bread and spread the jelly on the toasted bread

the anterior and posterior projections with the child supine on the gamma camera couch using a dual head camera. Continuous data recording is preferable over recording data only at discrete time intervals, as it gives information on the lag phase and may be helpful in identifying patterns of rapid gastric emptying; moreover, episodes of gastroesophageal reflux can be detected. Any event during the acquisition (motion, coughing, vomiting, reflux) is recorded at the time it occurs. The dynamic images are recorded on a 128 × 128 matrix and may be followed by anterior and posterior static views of the chest, with the stomach out of the field of view, with the purpose to assess for possible aspiration. These images are recorded on a 256 × 256 matrix over 3–5 min. Further delayed images at 2 and 3 h are obtained, using the same acquisition parameters as the dynamic acquisition, so that the delayed images can be compared to the dynamic series.

Solid gastric emptying study With a solid phase gastric emptying study a dynamic acquisition in the first hour is not strictly necessary, although it is helpful to assess the lag phase in the initial part of the study. It can also inform on the distribution of the radiolabeled feed within the proximal and distal portions of the stomach, and on possible to- and from-motion between the fundus and the antrum during the dynamic sequence, which may be due to dysmotility. The solid phase gastric emptying study must be continued with at least a delayed image at 4 h: this is critical, as the normal range is based on that (<10% of the initial gastric content at 4 h). An acquisition at 2 and 3 hours is recommended.

Image Processing

A ROI is placed around the stomach, as seen in the immediate post-feed image. An upper GI barium contrast study with fluoroscopy is very helpful to delineate the anatomy of the stomach. A time-activity curve, corrected for decay, is generated from the stomach ROI. Motion correction should be applied when required. Care should be taken not to include bowel activity in the gastric ROI. Gastric emptying can be expressed as a percentage of the initial activity remaining at a specific time point (residual) or as the activity emptied by the stomach at these times. The pattern of the emptying curve is important, including the presence and the duration of the lag phase (seen in solid gastric emptying), which can provide evidence on abnormalities in gastric motility. Milk usually empties in an exponential or bi-exponential manner [21].

Analysis

The normal range of a solid phase gastric emptying study in the pediatric population has been recently defined. In a patients' population of children younger than 5 years of age, a gastric emptying study with a liquid test feed based on milk or formulas is normal if gastric retention at 3 h is <20% of the initial gastric content [7]. A solid phase gastric emptying study in the adult practice, with a standard test meal based on radiolabeled egg white or melted cheese, is normal with a gastric retention at 4 h of 10% of the initial gastric content or less [4–6]. A detailed normal range for a specific meal and age group has not been defined in pediatrics.

Two examples of gastric emptying study are shown in Figs. 16.1 and 16.2.

Issues Requiring Further Evaluation

There is a need for alternative meals to radiolabeled egg white and melted cheese; these will require validation and a normal range will have to be established.

The effect of the volume and the composition of the test feed in carbohydrates, protein, and fat, also have to be clarified.

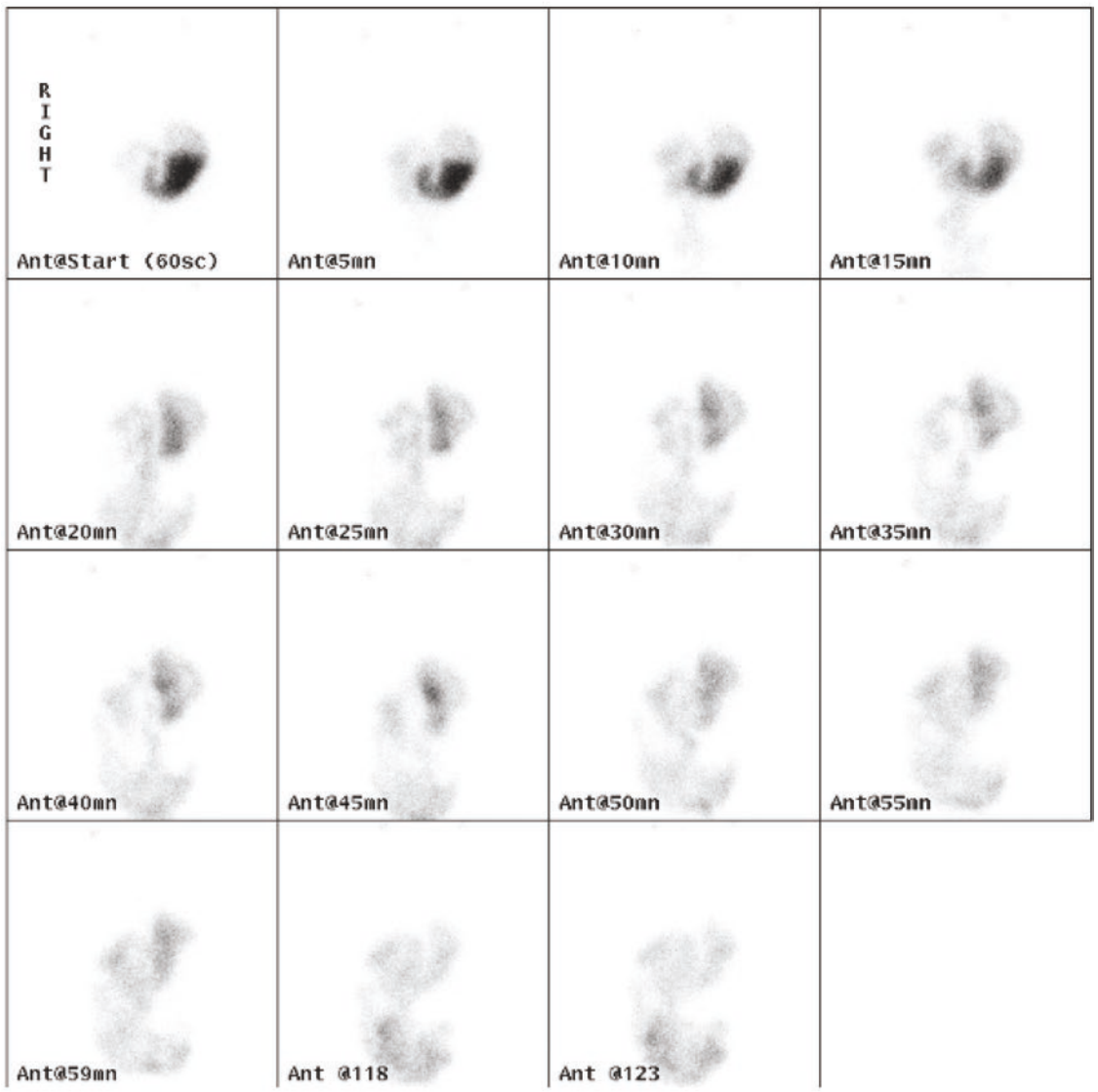
A "normal" range in post-surgical children (following Nissen's fundoplication, for example) or in children fed via a gastrostomy tube must be defined.

Also, it is not clear whether in grown up children and in adolescents a solid test feed is sufficient to estimate gastric emptying, or whether both a solid and a liquid test feed are required. Preliminary evidence in the adult practice suggests that both test feeds are required for a comprehensive assessment of gastric emptying as they explore different aspects of the pathophysiology of gastric emptying [30].

It would be also interesting to see if gastric emptying scintigraphy can demonstrate the coordination of the different portions of the stomach (fundus and antrum, with relaxation of the pylorus) and provide some insights on gastric dysmotility, as hypothesized [26].

Fig. 16.1 (**a**, **b**) Gastric emptying study in a 2-year-old child with jejunal atresia and GERD. The dynamic acquisition over 1 h (**a**) shows little distribution of the milk-based radiolabeled test feed in the fundus of the stomach, with predominant distribution in the body of the stomach. The overall timing of gastric emptying is within normal limits. The delayed images at 2 h show further gastric emptying, with only approximately 25% of the initial gastric content remaining in the stomach, as it can be seen from the time activity curve (**b**). This study suggests impaired ability of the fundus of the stomach to relax after ingestion of the feed, which fits the clinical context

a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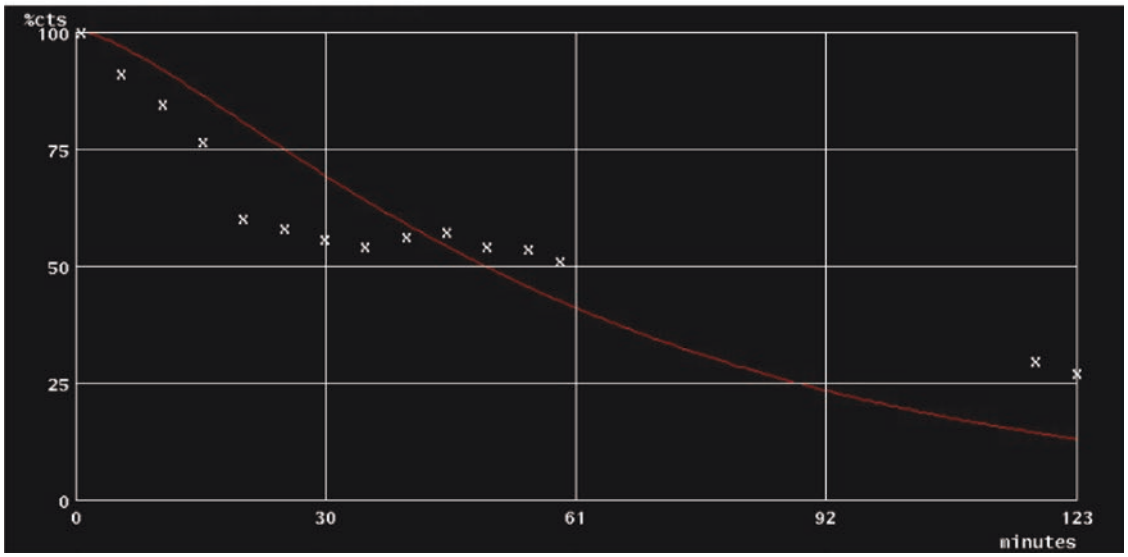
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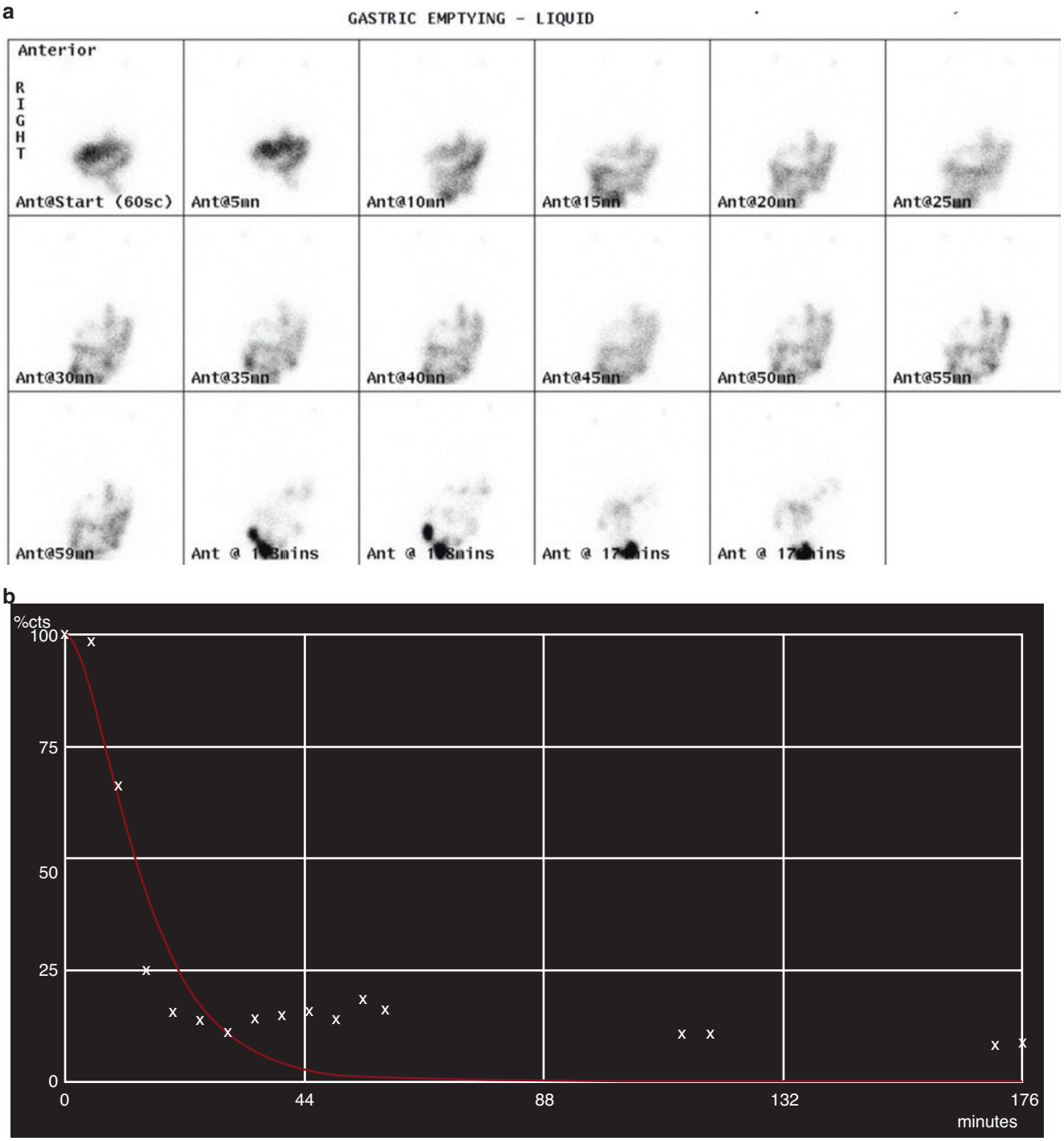

Fig. 16.2 (**a**, **b**) One month old baby with global developmental delay. The baby had a Nissen's fundoplication and was gastrostomy fed. The gastric emptying study shows a very rapid gastric emptying (**a**). The time activity curve confirms that there is no significant activity remaining in the stomach by 35 min (**b**). This case is an example of dumping syndrome following Nissen's fundoplication

Small Bowel and Colonic Transit Studies

Two imaging techniques are used to evaluate motility through the GI tract: the transit of radio-opaque (plastic) markers viewed with X-rays and the transit of a radiolabeled feed viewed by γ camera (scintigraphy). The radionuclide studies to assess intestinal transit include the small bowel transit scintigraphy, the colonic scintigraphy, and the whole gut transit study.

Clinical Indications

1. *Small bowel transit scintigraphy*: The study is indicated in a patient with suspected pediatric intestinal pseudo-obstruction (PIPO) when there is minimal intestinal luminal dilatation and when there is uncertainty regarding the motor impairment [8]. The small bowel scintigraphy may also be able to separate myopathic from neuropathic PIPO.
2. *Colonic transit scintigraphy*: This is indicated in patients with refractory chronic constipation considered for surgical management, to identify the site of abnormal colonic motility. Colonic transit scintigraphy may demonstrate a slow colonic transit involving the whole colon (colonic inertia), a hold up in a particular colonic segment, or may show normal colonic transit, or a defecation disorder or functional outlet obstruction [8, 34]. The study may also be helpful to guide biopsy: for example, in patients with ano-rectal hold up a rectal biopsy could be performed. The X-ray study with radio-opaque markers is usually performed as a gross indicator of colonic transit in patients with constipation but is unreliable to assess segmental colonic transit [34–36].
3. *Whole gut transit study*: this can be helpful in patients with suspected generalized gastrointestinal motility disorder (drug induced, idiopathic, genetic) or in the presurgical evaluation of colonic inertia in chronic refractory constipation, to exclude a delayed upper GI transit if colectomy is considered [37, 38].

Symptoms of motility disorder are often vague and nonspecific, and it may be difficult to determine whether they are caused by upper or lower gastrointestinal tract dysfunction. Therefore, a comprehensive evaluation of the motility of the whole GI tract would be clinically useful [37]. Treatment may be guided by the finding of upper, lower, or combined gastrointestinal transit abnormalities. For example, in a patient with chronic constipation considered for colectomy the finding of an associated upper gastrointestinal dysmotility may reduce the clinical response to surgery.

Patient Preparation

Medications that affect GI motility are withdrawn at least 2 days prior to the test unless the purpose of the test is to assess the efficacy of these medications. These include opiate analgesics and anticholinergic medications (which slow gastrointestinal transit), prokinetics (domperidone, erythromycin, metoclopramide), which accelerate transit. For colonic transit studies, a bowel wash-out is performed prior to the test, to remove possible impacted feces. A radiological contrast study of the upper GI tract to exclude malrotation and clarify the anatomy of the bowel is important, and this should be available prior to the acquisition of the radionuclide study.

Radiopharmaceuticals

The two main radiopharmaceuticals utilized in gastrointestinal transit studies are [^{99m}Tc]Tc-colloid to label the solid test feed for the evaluation of gastric emptying and small bowel transit, and [^{111}In]In-DTPA water to assess colonic transit. A contemporaneous estimate of gastric emptying allows a more accurate determination of pure intestinal transit, especially if gastric emptying is slow; therefore, evaluation of gastric emptying is strongly advised in association with intestinal transit scintigraphy. A dual isotope acquisition with [^{99m}Tc]Tc-nano-colloid and [^{111}In]In-DTPA water can be performed to label both the solid and the liquid components of the test feed which will be ingested as part of the same test feed: on the first day the pulse height analyzer of the gamma camera will be centered on the [^{99m}Tc]Tc photopeak to follow the gastric emptying and the small bowel transit; from the second day, the pulse height analyzer will be centered on the [^{111}In]In photopeak to follow the colonic transit.

Acquisition

The published guidelines on small bowel and colonic transit [8] suggest three options:

- A *whole gut transit study*, which includes administration of a [^{99m}Tc]Tc-colloid labelled solid test feed together with [^{99m}Tc]Tc-DTPA water, to evaluate gastric emptying, small bowel transit, and colonic transit. Imaging is performed at hourly interval on the first day and then on day 2, 3, 4 (and possibly day 5, if needed).
- A *small bowel transit study*, with [^{111}In]In-DTPA labelled water for the small bowel follow through and a [^{99m}Tc]

Tc-colloid radiolabeled solid phase test feed to evaluate gastric emptying at the same time (the solid phase meal can be given with no radiolabeling, to create mass effect in the GI tract). Imaging is acquired at hourly interval up to 6–7 h on the first day, and then at 24 h to outline the large bowel, thus helping in the identification of the cecum and ileo-cecal valve.

- A *colonic transit study* with [^{111}In]In-DTPA water: imaging is acquired at hourly intervals on the first day and then on day 2, 3, 4 (and possibly day 5, if needed).

Markers placed on the patient's anterior superior iliac spine facilitate identification of the small bowel. Imaging is performed with the patient in an upright position using a large γ-camera equipped with a medium energy collimator. During the dual isotope acquisition, images are dynamically acquired for 1 h immediately after ingestion of the meal, with a static image at 2 h to measure gastric emptying of solid and liquids. Afterwards, images are usually taken at 4, 6, 24, 48, 72, and possibly 96 h. Images at 24 and 48 h may give a sufficient summary of colonic transit with acceptable specificity and high sensitivity for detecting motility disorders, although in constipated patients it is very helpful to acquire images at 72 h and, if activity is still seen in the colon, at 96 h [34]. Anterior and posterior images are obtained for an acquisition time up to 400 s on a 256 × 256 matrix. In the initial gastric emptying phase the pulse height analyzer of the γ-camera is centered on 140 keV with a window of ±20% to detect counts from [^{99m}Tc]Tc and on two peaks (173 and 247 keV) ±20% to detect counts from [^{111}In]In. Subsequent images are acquired using the [^{111}In]In energy peak only.

Analysis

The commonest scintigraphic method for assessing small bowel transit is to measure orocecal transit time, defined as the time taken for 10% of small bowel radioactivity to accumulate into the cecum [39, 40]. This is a very laborious method since it requires multiple images taken every 10 min until 10% of the activity reaches the colon. A valid surrogate for the 10% activity is the percentage of the administered activity reaching the terminal ileum at 6 h after meal ingestion.

The analysis of colonic transit is performed drawing different colonic ROIs on both the anterior and the posterior images to quantify the geometric center (GC) of the distribution of radioactivity within the colon. This represents the weighted average of radioactivity over specific regions of the bowel and determines the median point of radioactivity for each time point. The number of ROIs varies from 5 to 7, including the segment referring to the expelled stools. For instance, Southwell and co-workers defined six colonic ROIs each with a numerical value: (1) Small Intestine, (2) Cecum-Ascending Colon, (3) Transverse Colon, (4) Descending Colon, (5) Rectosigmoid Colon, (6) Excreted Stools [34] (Fig. 16.3). A low GC indicates that the center of the activity is in the proximal colon, and a higher GC indicates that it has progressed to the left side of the colon and has been eliminated in the stool. In adults, based on this method, the normal mean (±1 SD) GC values range between 2.67 ± 1.09 to 4.6 ± 1.5 at 24 h, 3.89 ± 0.15 to 6.1 ± 1.0 at 48 h, and 6.6 ± 0.19 at 72 h [41]. In children, the normal mean ± SD GC values are 3.9 ± 1.1 at 24 h, and 5.2 ± 0.9 at 48 h [42]. Of note, as a summary of the colonic transit, some researchers

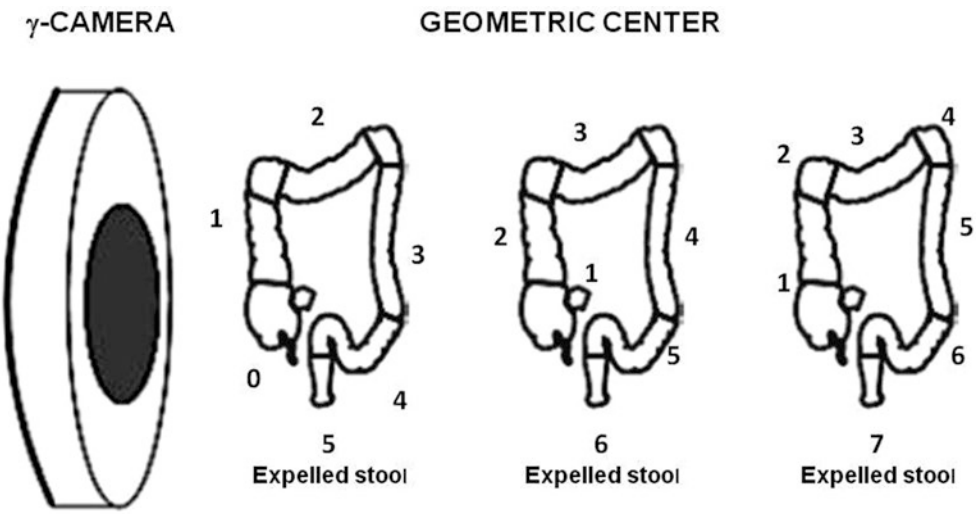

Fig. 16.3 Diagram showing the ROIs used to determine the geometric center of radioactivity in the colon

also utilize the emptying of ascending colon expressed as *t*½ (time for 50% emptying), which is significantly correlated with stool consistency.

Interpretation

Only few published reports on small bowel and colonic scintigraphy in children are available [42]. Normative data in adults are limited and the test seems to be diagnostic only if extreme values are present. Identification of abnormal small bowel transit through scintigraphy has been shown to modify both initial diagnosis and clinical management, although its analysis needs to be interpreted with caution, keeping in mind that both delayed colonic transit and gastric emptying can affect small bowel transit [37].

Three categories of colonic transit could be readily distinguished also by visual assessment of the acquired images. In normal studies, the tracer reaches the cecum in 6 h and is largely excreted by 48 h. Slow colonic transit is identified when the tracer reaches the cecum at 6 h, but most radioactivity is retained in the proximal colon and transverse colon at 24, 36, and 48 h. In children with outlet obstruction or functional fecal retention, the tracer reaches the rectosigmoid by 24–36 h but is not passed at 48 h. In children and adolescents with refractory functional constipation, slow transit in the proximal colon occurs in 20–50% and outlet obstruction in 22–55% with some children exhibiting both patterns [43].

Scintigraphy can influence management of patients with refractory constipation who might benefit from different treatment strategies. For instance, by using colonic scintigraphy the degree of efficacy of several prokinetic drugs can be evaluated. In addition, the type of surgery or stoma positioning may be determined by identifying the site of delay [44].

Examples of small bowel and colonic scintigraphy are shown in Figs. 16.4, 16.5, and 16.6.

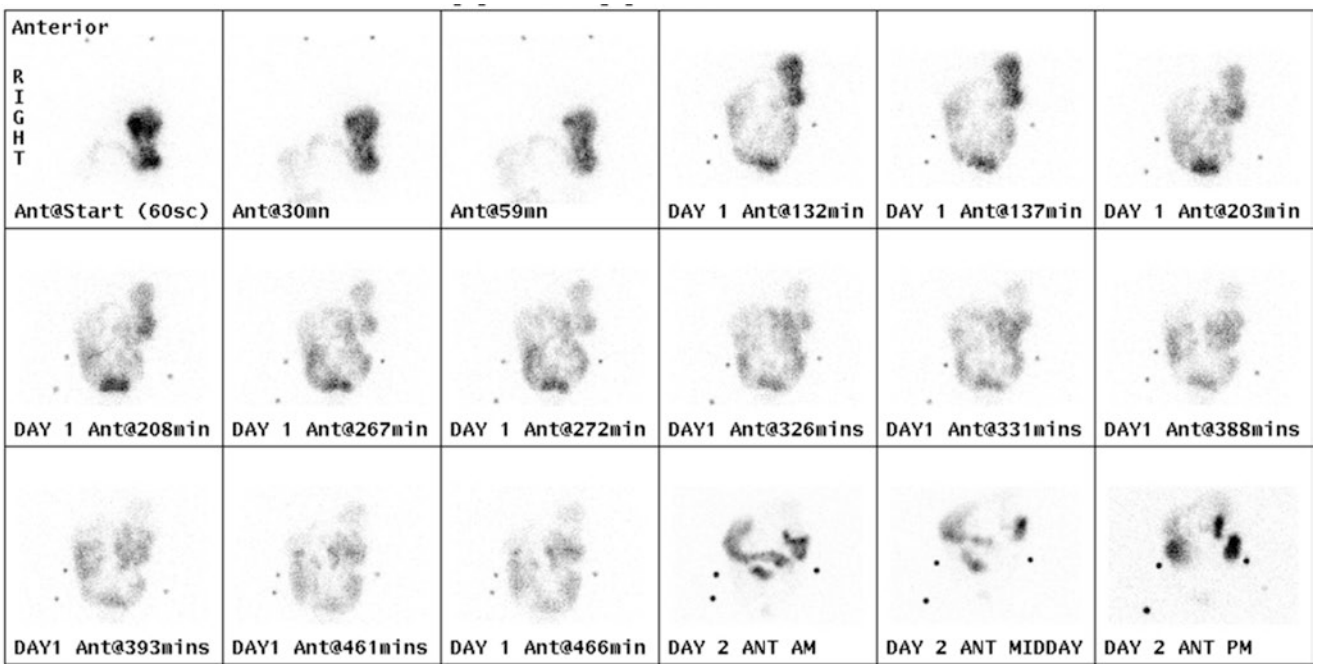

Fig. 16.4 A 15-year-old boy with a diagnosis of chronic intestinal pseudo-obstruction. Small bowel transit after ingestion of milk radiolabeled with Tc-99m-nanocolloid. Images acquired dynamically over 1 h to assess gastric emptying, followed by delayed images over 8 h on the first day, and then at 24 h to delineate the colon. The findings suggest slow transit through the small bowel

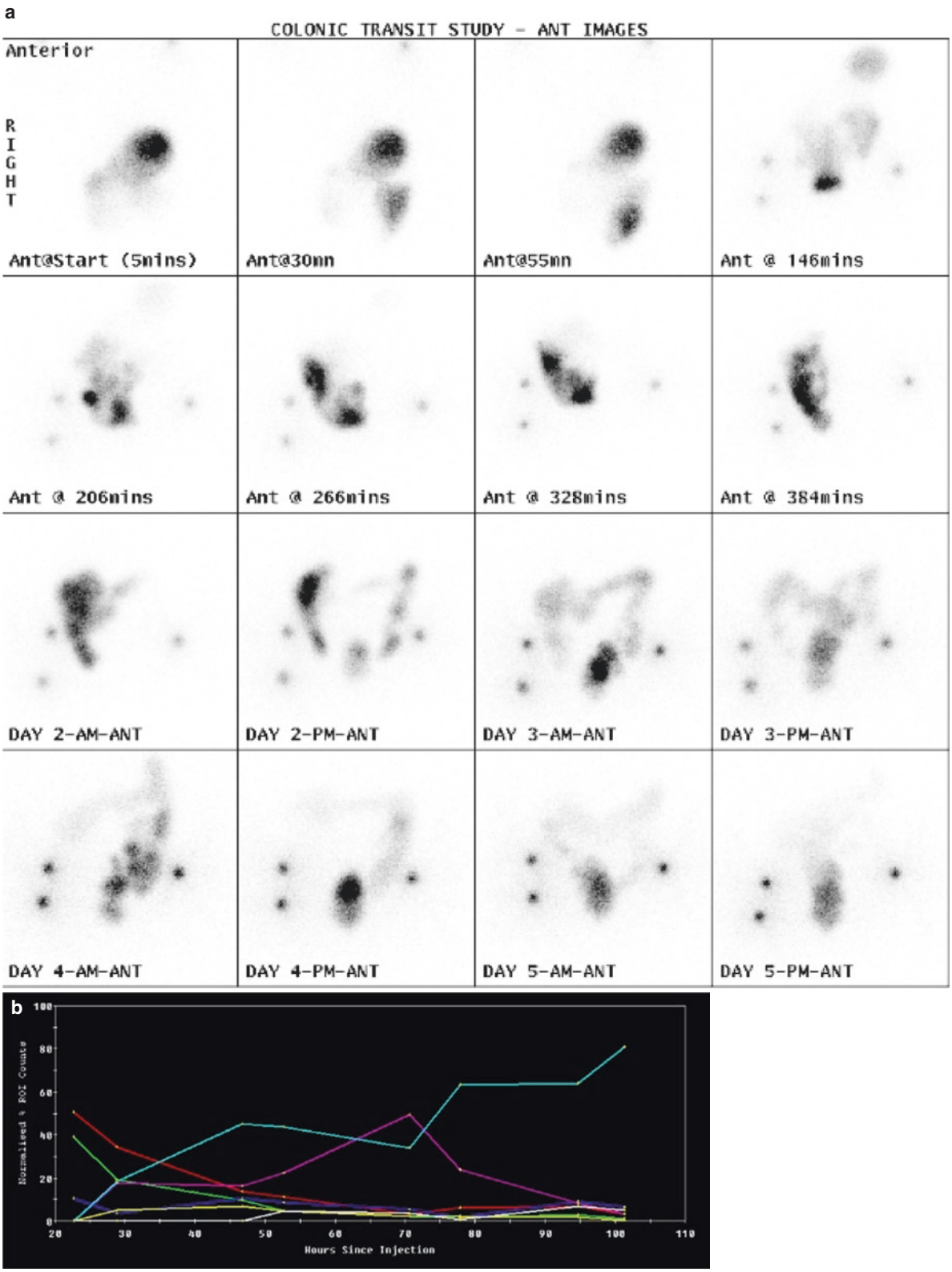

Fig. 16.5 (**a**–**c**) A 6-year-old girl with a family history of chronic constipation. Whole gut transit study following ingestion of 2 MBq In-111-DTPA labelled water and an unlabeled meal to create mass effect (**a**). The gastric emptying phase is slow; the transit through the small bowel is probably within normal limits, with activity seen in the right iliac fossa in the region of the ileo-cecal valve by 4 h. The colonic phase of the study shows hold up in the region of the sigmoid rectum, even 5 days after ingestion. This is confirmed in the time activity curve (**b**). The center of gravity is lower than expected, confirming delayed transit especially in the descending colon and sigmoid rectum

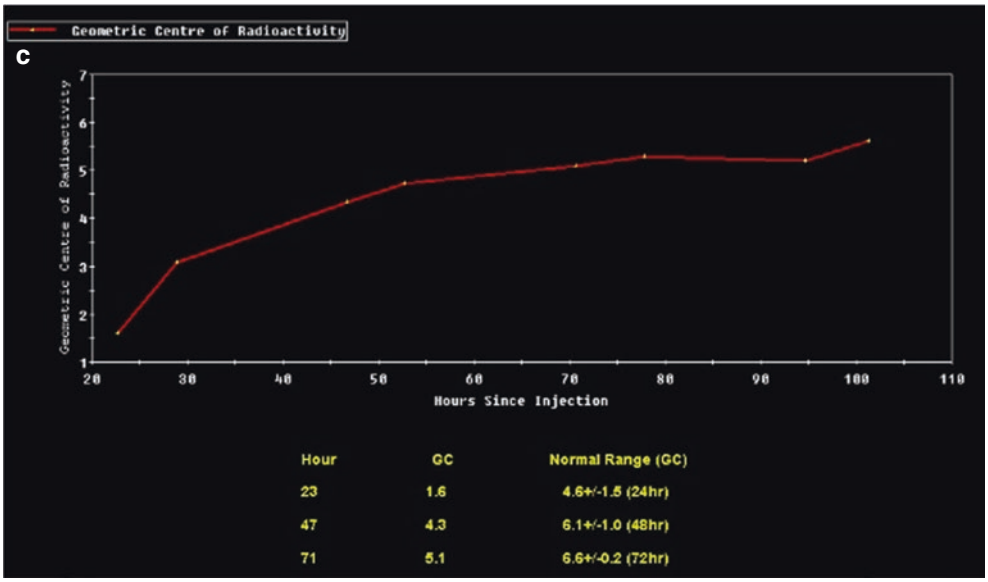

Fig. 16.5 (continued)

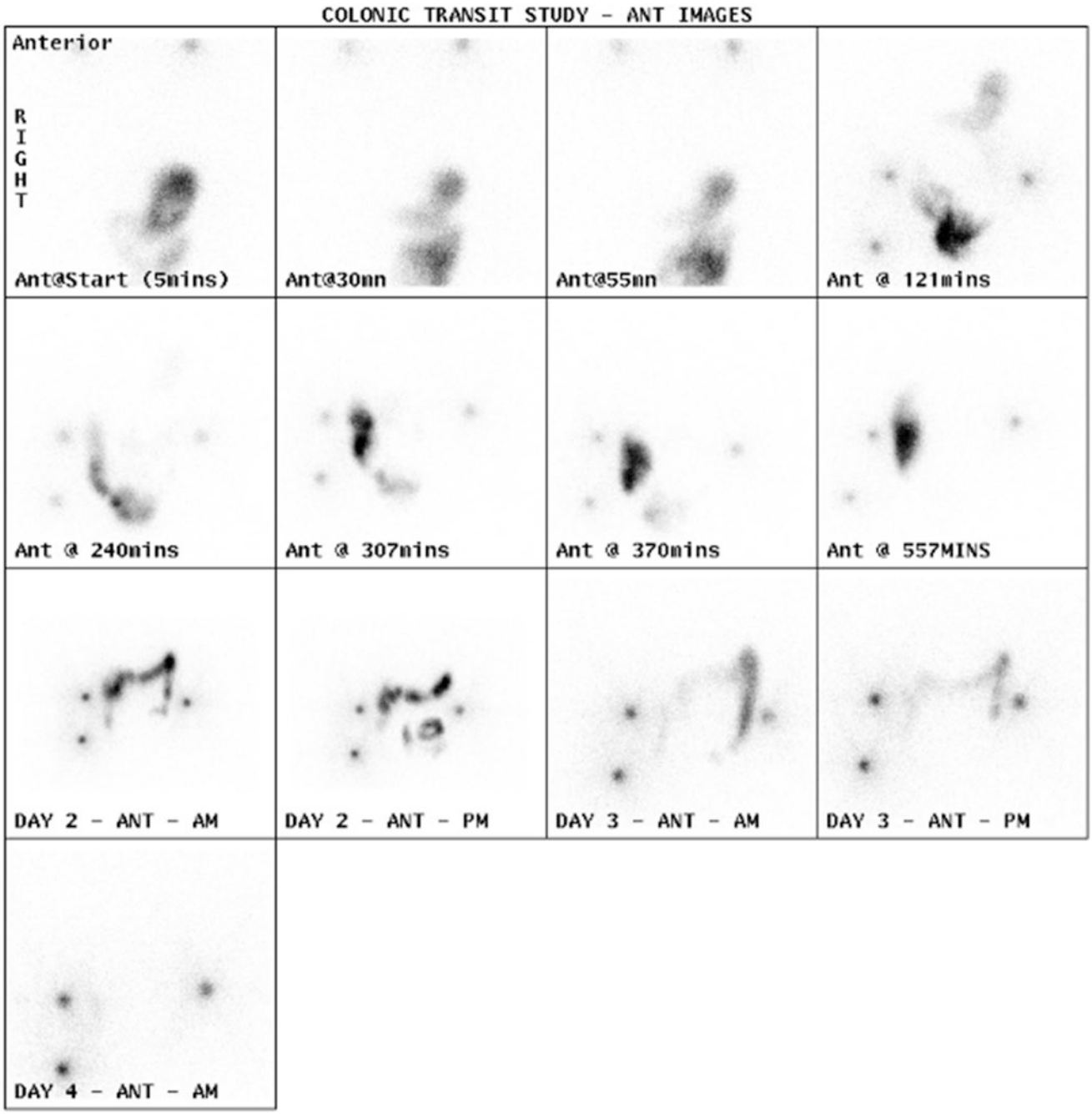

Fig. 16.6 A 12-year-old boy with severe constipation and rectal pain, had colostomy; recent history of stoma pain and rectal pain. Colonic transit study after ingestion of 2.2 MBq In-111-DTPA water. Gastric emptying is probably delayed, with activity still seen at 2 h. Transit through the small bowel is normal. Within the colon, transit is probably within normal limits. This study suggests that colostomy has been beneficial in providing relief the severe constipation the child was complaining of

Conclusion

Radionuclide studies of the GI tract provide a functional evaluation of gastric, intestinal, and colonic transit and are an effective means of complementing the radiological contrast imaging techniques and the manometry studies in the evaluation of the patient with suspected GI dysmotility. The tests are physiological, simple to do, and well tolerated. The gastric emptying scintigraphy in children with a liquid and a solid test meal has been recently standardized and the normal range clearly defined. This will allow a more widespread clinical use of the test. Further work needs to be done to better define the normal range for the small bowel transit study, the colonic scintigraphy, and the whole gut scintigraphy.

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17 Electrogastrography, Breath Tests, Ultrasonography, Transit Tests, Wireless Motility Capsule, and Cine-MRI

Ricardo A. Arbizu and Leonel Rodriguez

Electrogastrography

Electrogastrography (EGG) is a noninvasive test that records the gastric myoelectrical activity through cutaneous leads. The basis of the test is to identify the normal rhythmicity of the stomach of 3 cycles per minute (cpm), with a range of 2–4 cpm. This rhythm, which reliably corresponds to the slow waves generated by the gastric pacemaker region, has been confirmed in animal and human studies by simultaneous electrode recordings from the gastric mucosa, gastric serosa, and skin [1–3]. Values above and below this range are called tachygastria and bradygastria, respectively (Fig. 17.1). The variables evaluated by EGG include the dominant frequency, the dominant power (amplitude in decibels), the percentage of normal frequency, and the percentage of coupling. The rhythmicity from other organs (like heartbeat and respi-

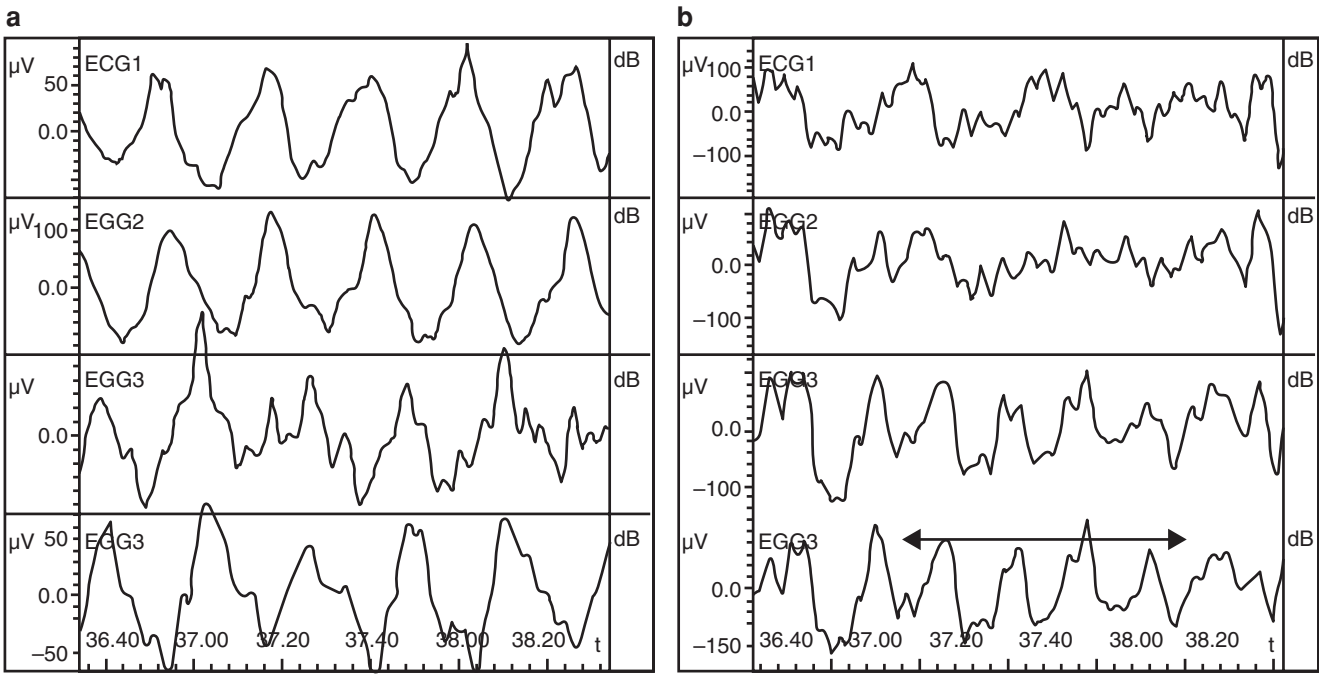

Fig. 17.1 Electrogastrogram tracing. (**a**) Shows normogastria or normal gastric rhythm of 3 cpm and (**b**) shows tachygastria with a rhythm of 5 cpm

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ration) is filtered out during the recording and motion artifact can be analyzed either visually or via a motion sensor and then manually excluded. The signal from all recordings is then selected and the EGG parameters are computed based on spectral analysis. This allows for an objective interpretation of the results. Since the first recording of an EGG in 1921 by Walter C. Alvarez [4], multiple improvements have been added to this technique.

In its early stages, most of the investigations with EGG were focused on its diagnostic role in peptic ulcer disease and gastric cancer and the physiological changes caused by gastric surgery. Over the last two decades, the focus has expanded to evaluate symptoms more than conditions. The first report of the use of EGG in children occurred in 1976, when Disembaeva et al. reported the normal EGG patterns in healthy children [5], followed by a report from Mirutko et al. describing its potential applicability in the evaluation and management of peptic ulcer disease [6]. The field of pediatric EGG exploded in the 1990s when the technique was evaluated in multiple disorders and symptoms.

Developmental Aspects

The gastric rhythm of 3 cpm seems to be irregular or absent at birth and matures over time [7, 8]. Although some have reported no difference between term and preterm infants [9], there seems to be agreement that the rhythmicity reaches adult characteristics in late childhood [7, 10].

Normal Values

Multiple studies, unfortunately following different methodologies, have attempted to develop normal values in children. The largest study was done by Riezzo et al. in 114 healthy children aged 6–12 years, which reported a gastric rhythm in the 2–4 cpm range and a significant increase in postprandial dominant frequency and power [11]. Another study with 55 healthy volunteers age 6–18 years showed a mean dominant frequency of 2.9 ± 0.40 cpm preprandially and 3.1 ± 0.35 cpm postprandially, 80% ± 13% preprandial normogastria, and 85% ± 11% postprandial normogastria [12]. These normative values were independent from age, gender, body mass index, and position [11–13]. Another study demonstrated that the adult norms reported by the American Neurogastroenterology and Motility Society can be used in children and adolescents when the same methodology is applied [14]. Among the factors that could affect the test values are the meal content and position. Breast feeding compared to formula feeding for infants [15] and solid meals compared to liquid meals for adults [16] are associated with higher dominant frequency and power.

Clinical Applications

EGG has been considered as a substitute to other invasive tests, like gastric emptying scintigraphy and antroduodenal manometry, and for other noninvasive but associated with operator-dependent downsides, like ultrasonography. However, most studies have not used the same methodology in terms of number and position of electrodes, recording time, test meals, and analytical software, limiting the validity of the test. Multiple studies in healthy adults as well as adults with specific disorders have shown no significant correlation between the findings on EGG and gastric emptying scintigraphy. Small series in children have replicated those findings [17]. EGG is not useful to discriminate between the three phases of the migrating motor complex (MMC) in adults [18], but it is helpful in differentiating children with normal or abnormal antroduodenal manometry. However, there is significant overlap in EGG results related to artifact from movement leading to inability to interpret data in up to 12% of patients [19]. Also, EGG findings do not correlate with gastric emptying and motility measured by ultrasound [20]. Rather than a substitute for these studies, EGG should be seen more as a supplement for the evaluation of patients with functional and motility gastrointestinal disorders.

Functional Gastrointestinal Disorders

Although some have reported that EGG may not be helpful in differentiating functional abdominal pain from gastritis [21], others have reported significant EGG abnormalities in children with functional dyspepsia and functional abdominal pain [22–24] particularly in patients with severe pain [22]. Also, EGG does not seem to be a helpful tool when it comes to distinguishing functional abdominal pain from peptic disease since chronic gastritis does not seem to be associated with gastric dysrhythmias [21, 25]. A comprehensive systematic review and meta-analysis by Varghese et al. analyzed the clinical association of functional dyspepsia in adults with gastric dysrhythmia on EGG and found that patients spent less time in normogastria while fasted (both brady- and tachygastria) and postprandially when compared to controls. However, no significant differences were found on the power ratio and dominant frequency meal-response ratio, and there was no correlation between EGG metrics and symptom timing [26]. A systematic review and meta-analysis in pediatric patients with gastroduodenal disorders found that patients with functional dyspepsia spent significantly less time in normogastria during the pre- and postprandial period when compared to controls. Similarly symptom correlation with gastric electrophysiology was inconsistently reported [27].

Gastroesophageal Reflux

EGG has been extensively used to assess the potential role of gastric myoelectrical abnormalities in gastroesophageal reflux disease (GERD). In children, myoelectrical abnormalities associated with delayed gastric emptying seem to be associated with severe GERD [28]. However, in a systematic review and meta-analysis, electrophysiological abnormalities were inconsistently reported in pediatric patients with GERD [27].

Chronic Intestinal Pseudo-Obstruction

In children with chronic intestinal pseudo-obstruction (CIPO), EGG has been reported to be abnormal [29] showing a significant difference in the values of either preprandial dominant frequency with tachygastria or differences in the postprandial value of 3 cpm when compared to normal subjects [30].

Eating Disorders

Gastric myoelectrical abnormalities have been related to the symptom pathophysiology in patients with eating disorders. Studies have shown that these abnormalities are more common in bulimia than anorexia nervosa [31] and in patients with long-standing disease [32]. EEG has been shown to be normal in early stages of anorexia nervosa [33].

Effect of Medications on Gastric Myoelectrical Activity

Prokinetic agents domperidone [34] and cisapride [35], unlike erythromycin [36], were effective in normalizing gastric myoelectrical activity in children. General anesthesia has been associated with significant gastric dysrhythmias that return to baseline approximately an hour after anesthesia is stopped [37]. EGG has also been helpful to elucidate the potential mechanism of chemotherapy-induced emesis. Cytotoxic chemotherapy has minimal direct effect on gastric myoelectric activity in children who receive 5-HT3 antagonist prophylaxis. However, tachygastria was noticed during emesis episodes preceded by normal myoelectrical activity [38]. On the other hand, baseline abnormalities in gastric myoelectrical activity have been observed in patients who undergo high-dose chemotherapy and autologous stem cell transplantation despite normal gastric emptying scintigraphy and absence of symptoms [39].

Surgery

Nissen fundoplication may increase gastric myoelectrical abnormalities in neurologically impaired children. In part, this could explain the postoperative retching seen in some of these patients after fundoplication [40]. A study in children with neuromuscular scoliosis found that gastric myoelectrical power increased after surgical correction of spastic scoliosis, but the effect of surgery on gastric emptying, upper gastrointestinal symptoms, and nutritional status was minimal [41].

- *Strengths*: Noninvasive, easy to perform, can be accomplished at bedside, no radiation required, not operator dependent.
- *Limitations*: Nonstandardized methodology, significant motion artifact, need for significant amplification to detect signals with low amplitude.

Breath Tests

The most common indications for breath testing (BT) include assessment for lactose intolerance and small bowel bacterial overgrowth. The first is assessed by measuring breath hydrogen levels in response to lactose ingestion and the second by measuring breath hydrogen levels after an oral challenge with glucose or lactulose.

Recently, BT has been used as a noninvasive and nonradioactive alternative to the gold standard test for gastric emptying with scintigraphy. For this purpose, ^{13}Carbon (^{13}C) isotope is used to label the substrate used for the oral challenge. The test is based on measuring the ratios of ^{12}C and ^{13}C. Both isotopes naturally exist in normal breath, 99% as ^{12}C and 1% as ^{13}C. This ratio is changed by the test meal enriched with ^{13}C resulting in expired $^{13}CO_2$. The exhalation of $^{13}CO_2$ in the patients' breath over time reflects the emptying of the substrate from the stomach. The substrates used for the evaluation of gastric emptying are ^{13}C-octanoic acid for solids and ^{13}C-sodium acetate for liquids. Recently, the ^{13}C-*Spirulina platensis* breath test has been validated and was compared to scintigraphy for gastric emptying in healthy volunteers [42–44].

BT has also been evaluated as an alternative to measuring whole gut transit (WGT). Lactulose has been classically used for this purpose. However, due to concerns of inherent transit acceleration by increasing the osmolality of the gut contents, other substrates have been used, including lactose (^{13}C-ureide breath test) and, more recently, inulin has been found to be the most reliable substrate since it does not seem to affect gastric emptying [45, 46]. ^{13}C is typically measured in breath by continuous flow isotope ratio mass spectrometry, although some have also suggested the use of nondispersive infrared spectrometry (IRMS) as a feasible method [47, 48]. The test relies on normal small intestine absorption, liver metabolism, and pulmonary function to validate the results. An important concern is the high inter- and intrasubject variability [49, 50]. There is also significant inconsis-

tency associated with the meal caloric content in healthy adult volunteers [51], although some have reported very little intrasubject variability in critically ill subjects [52], making the test particularly attractive for this patient population.

^{13}C-octanoic acid has been reported as feasible [53], reliable, and reproducible in preterm [54, 55] and term infants [56] and results seem to be relatively independent from milk amount in preterm newborns during the first hours of life [55]. In healthy children, BT has performed poorly when assessing gastric emptying of both liquids [57] and solids [58] and a high day-to-day variability has been reported in the evaluation of WGT [59]. In preterm infants, gastric emptying measured by ^{13}C-octanoic acid BT does not seem to be affected by feeding osmolality, volume, or energy density; however, reducing osmolality and increasing feeding volume increase gastric emptying [60]. It is important to take into account the meal utilized for the study in children, as human milk [56] and hydrolyzed formulas [61] empty faster than partially and nonhydrolyzed formula. Another significant concern is the potential overestimation of gastric emptying by ^{13}C-octanoic BT due to gastric processing of the substrate. A correction factor of approximately 60 min has been classically added and validated in infants [62], while others have suggested the use of the Wagner-Nelson method [63]. BT with ^{13}C-sodium acetate for liquids and semisolids [64] and ^{13}C-octanoic acid for solid meals [65] have been validated for gastric emptying compared to scintigraphy. In adults, both the ^{13}C-sodium acetate [66] and ^{13}C-octanoic acid [67] do not seem to be affected by age, gender, or body mass index (BMI). In a recent study, normal values for gastric emptying of a standardized test milk-drink in healthy children were determined using the ^{13}C-acetate BT and concluded that the technique is reliable and well accepted by the patients [68].

Clinical Applications

Gastric Emptying

Functional Gastrointestinal Disorders

BT does not correlate with scintigraphy in functional dyspepsia [69] and could not discriminate between healthy volunteers and subjects with dyspeptic symptoms [70].

Gastroparesis

In children with gastroparesis, the ½ emptying time of ^{13}C-sodium acetate correlates with the time to empty half of radioisotope [71, 72] and also discriminates between healthy volunteers and children with symptoms due to gastroparesis [71]. BT has been reported as feasible in neurologically impaired children with GER [73]. BT can be done at bedside, which makes it useful under certain circumstances like in mechanically ventilated patients in the intensive care unit [74]. In a study of adult patients with diabetic gastroparesis, ^{13}C-octanoic acid BT was useful in discriminating between subjects with normal or delayed gastric emptying measured by scintigraphy [75].

Whole Gastrointestinal Transit

BT has demonstrated a constant WGT after the first month of age when a weight adapted dose of lactulose is given [76]. The lactose-[^{13}C]-ureide breath test has been reported useful to evaluate WGT in children older than 8 months [77]. Results in healthy volunteers using lactulose BT have been reproducible [78] and this method has also been useful in the evaluation of small bowel transit (SBT) in patients with anorexia nervosa [79].

- *Strengths*: Noninvasive, low cost, safe, office based, not operator dependent, no radiation required, useful in particular situations (pregnancy, intensive care setting and infants).
- *Limitations*: Requires normal intestinal, liver, and pulmonary function, poorly reproducible in children and adults, equipment may be expensive (IRMS).

Ultrasonography

Ultrasonography (US) is a noninvasive technique that can be used to evaluate gastric emptying, receptive accommodation, antral contractility, transpyloric flow, and gastric anatomical changes (volume and wall width) during meal and therapy challenges. US has been useful to demonstrate trituration of solids to small size particles, retention of larger particles with linear emptying of liquids [80], and antral motility coordination with pylorus flow during normal conditions [81]. Antral waves noticed on US correlate with peristaltic waves seen in antroduodenal manometry, with 99% propagating aborally and 68% becoming lumen occlusive at the site of the ultrasound marker [82]. US has been used in the evaluation of duodenogastric reflux in healthy volunteers [83] as well as in subjects with gastric ulcers [84]. The reproducibility in the assessment of gastric emptying is controversial with some studies reporting significant intra- and interobserver variability [85, 86], while others report differing findings [87, 88], but there is a common agreement on the significant day-to-day variability [87]. More recently, 3D US has been used to assess gastric emptying and has shown good correlation with scintigraphy in healthy subjects [89], but more studies are needed to validate the test.

Developmental Aspects

US has been invaluable in the evaluation of fetal gastrointestinal physiology demonstrating evidence of gastric emptying by 12–13 weeks [90], gastric filling and emptying by 20 weeks, and an important change in gastric volume by 25 weeks [91]. The frequency of these emptying cycles reaches a periodicity of 35–55 min by about 35 weeks [92] and demonstrates a clear normalization along pregnancy with cycles of longer duration and stronger power along the third trimester [93]. Gastric accommodation also seems to develop over time with preterm infants showing delayed gastric distention with feeds at 26 weeks, followed by a subsequent improvement by the time full feeds are tolerated and, almost immediate gastric distention with feeds by 32 weeks [94].

Clinical Applications

Gastric Emptying

The most common technique requires measurements by the same observer after fasting and at regular 30-min intervals postprandially. The emptying time is the time at which the antral area or volume returns to a baseline value [95], although others have also reported the half emptying time. US has shown a strong correlation with scintigraphy in assessing gastric emptying of liquids in healthy adult volunteers at rest [96, 97] and after exercise [98] as well as in subjects with diabetic gastroparesis [99]. In children, US has shown good correlation with scintigraphy; however, discordances associated with overlapping of duodenum and stomach during scintigraphy and shadowing of the gastric antrum by air during US have been reported [100]. Establishing a safe preoperative fasting time has been another use of US in children after ingesting liquids [101] and in adults before undergoing anesthesia [102] and endoscopy [103]. US is reliable in assessing gastric emptying in preterm infants with a good correlation with intragastric volume [104] and particularly in very low birth weight infants with nasal continuous positive airway pressure [105]. US is also useful during pregnancy when radiation should be avoided. Another advantage is that it allows for simultaneous assessment of gallbladder emptying [106]. US reliably assesses changes in gastric emptying in response to use of prokinetic agents like domperidone [107–109], metoclopramide [110], cisapride [111], mosapride [112], and erythromycin [113].

Gastric Receptive Accommodation

US has emerged as an attractive alternative to the more invasive barostat to assess gastric accommodation. The test demonstrates no significant intra- and interobserver variability but moderate day-to-day variability in healthy adult volunteers [114]. It has been reported as a reliable tool to assess gastric accommodation in subjects with functional dyspepsia [115, 116], children with recurrent abdominal pain [114], and the effect of therapy with prokinetic agents like mosapride [117] and other medications like sumatriptan [118].

Antral Motility

A novel use of US is to characterize antroduodenal motility associated with transpyloric fluid movement in healthy volunteers [119] and in subjects with GER symptoms [120]. Some have suggested an advantage of US by allowing a simultaneous observation of antral contractions and gastric emptying and have also reported a good correlation between antral hypomotility and delayed gastric emptying in patients with dyspepsia [121].

- *Strengths*: Noninvasive, no radiation required, readily available, inexpensive.
- *Limitations*: Reliable for the assessment of liquids only, dissimilar, and nonstandardized methodologies, requires certain expertise, operator dependent, obesity and presence of air impair study interpretation (gaseous distention is common in gastrointestinal motility disorders).

Transit Studies

Several tests have been developed to assess gastrointestinal transit as an alternative to other more invasive and expensive tests associated with radiation, like scintigraphy transit studies. Here, we describe tests to assess transit in different segments of the gastrointestinal tract.

Gastric Emptying

Paracetamol Absorption Test

The rate of paracetamol absorption measured by serial serum levels after oral ingestion has been used in multiple research studies as an indirect and noninvasive test to assess gastric emptying of liquids. The test has low interindividual variability [122] with good correlation with scintigraphy [123, 124], although recent studies have questioned this correlation [125]. It is not widely used in clinical practice due to the technical requirements of frequent blood draws, the cost of the assays, and lack of sensitivity to assess gastric emptying in certain clinical situations [126, 127]. Its use has been relegated mostly to pharmacokinetic studies [128] and in special situations where radiation, mobilization, or meal intake is a limitation, like patients in the intensive care units [127] and during pregnancy [129].

Epigastric Impedance

This is a noninvasive method used for the assessment of gastric emptying/transit by measuring electrical impedance through skin electrodes. Results are comparable to scintigraphy [130]. The method has been revised and improved by adding applied potential tomography to generate tissue electrical impedance images and estimate gastric emptying and/or transit [131, 132]. Despite being an attractive noninvasive alternative, it is not widely used or recommended because of its low reproducibility due to significant motion artifact [133, 134]. In addition, the relationship between phasic contractions and phasic variations in impedance does not appear consistent enough to allow clinical application of the technique [135].

Radiopaque Markers

Radiopaque markers (ROM) have been extensively used in the evaluation of gastrointestinal transit due to their low cost, minimal radiation exposure, and uncomplicated performance and interpretation. Despite good correlation between gastric transit of ROM and gastric emptying measured by US [136], the test is not widely used due to the lack of standardization and the availability of other more reliable tests.

Intestinal Transit

Carmine dye, pellets, and ROM have been used in the evaluation of intestinal transit. Unfortunately, the correlation between these methods and scintigraphy is poor. Small intestinal transit is best assessed by scintigraphy, which is considered the gold standard, and wireless motility capsule. If these are not available, ROM should be considered.

Colon Transit

ROM studies have been used to evaluate colonic transit (CT) and several protocols exist for this purpose. The main drawback for ROM studies is the lack of standardization between the multiple methods and the centers performing the studies. The simplified protocol assesses normal versus abnormal colonic transit. It requires the ingestion of a single ROM capsule (24 markers) on the first day followed by an abdominal film on the fifth day. Retention of >5 rings is considered abnormal. The Metcalf protocol (Fig. 17.2) is used for the same purpose with the added information on segmental transit, providing a broader extent of information. In this method, three sets of distinctive ROM capsules (24 markers per capsule) are ingested on 3 consecutive days followed by an abdominal film on the fourth day. Retention of >50 markers indicate delayed colonic transit. This protocol has shown good correlation with transit values obtained with other methods that require multiple films. The normal values for the test are total colonic transit 35.0 ± 2.1 h, right colon 11.3 ± 1.1 h, left colon 11.4 ± 1.4 h, and rectosigmoid colon 12.4 ± 1.1 h with overall shorter transit in men and no effect by age [137]. In children, norms by the Metcalf protocol have been established: total colonic transit time 37.8 ± 6.2 h, 10.8 ± 3.5 h for the right colon, 12.2 ± 2.7 h for the left, and 14.7 ± 2.1 h for the rectosigmoid [138]. The Metcalf protocol has been used to discriminate between constipated and nonconstipated adolescents showing a statistically significant difference in total colonic, right and left colon transit times [139].

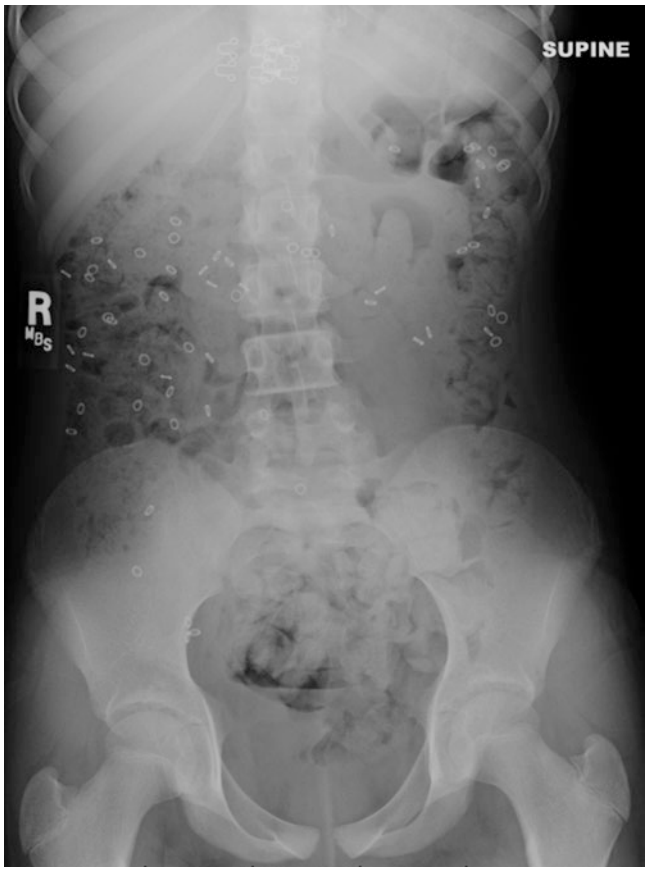

Fig. 17.2 Radiopaque marker study. This abdominal film was obtained on day 4 after ingesting three daily capsules with 24 markers each. Note the retention of all markers

Transit measured by ROM seems to be faster than colonic transit measured by scintigraphy [140]. Overall, mean colon transit time does not differ significantly between young adults and children [140]. However, there are regional differences within the colon in relation to age, with children having faster transit times in the right and left colon, and stagnation in the rectosigmoid [141]. In regard to clinical applications in children, ROM transit studies have been helpful to define pediatric slow transit constipation [142] and to demonstrate correlation between colonic transit and severity of symptoms [143], slower colonic transit in constipated children without soiling compared to those with soiling [144], rectosigmoid transit delay in low variety and global delay in high variety anorectal malfor-

mations [145], constipation in neurologically impaired children associated with slow colonic transit rather than fecal retention [146] and response to therapy for constipation [147]. Similarly, the whole colon and segmental (right colon) transit times measured by ROM and the Metcalf protocol is significantly higher in children with cystic fibrosis (CF) and associated constipation when compared to those without constipation [148].

- *Strengths*: Readily available, minimal radiation, noninvasive, easy to interpret, inexpensive.
- *Limitations*: Multiple nonstandardized methodologies.

Wireless Motility Capsule

This novel device offers the ability to simultaneously measure contractility and transit. The wireless motility capsule (WMC, SmartPill™), measures 26.8 × 11.7 mm and has three different sensors that detect pressure (to measure contractility), pH (to measure transit from stomach to small bowel and from small bowel to colon), and temperature (to assess capsule exiting the body). The capsule is ingested orally with a standard meal, then the patient is discharged and wears a recording device for 3–5 days. The most important use of this device is to record pressures and simultaneously measure transit throughout the different segments of the gastrointestinal tract. In this regard, WMC has been used to evaluate gastric residence time (GRT), small bowel transit (SBT), colonic transit (CT), and whole gut transit (WGT) (Fig. 17.3). Perhaps the most significant contribution of the WMC in gastrointestinal physiology is the reaffirmation of the concept that nondigestible solids empty from the stomach primarily with the return of the phase III of the MMC when the fed state is over and the pylorus is completely open. No less important is the novel finding of gastric emptying of nondigestible solids in some subjects in association with high-amplitude antral contractions and not with the phase III of the MMC [149]. Since the WMC is an equivalent to a nondigestible solid, in healthy volunteers the gastric residence time moderately correlates with the gastric emptying of digestible solids measured by scintigraphy and, it is not surprising that there is a stronger correlation with emptying at 4 h than at 2 h [150, 151]. The WMC has been also useful

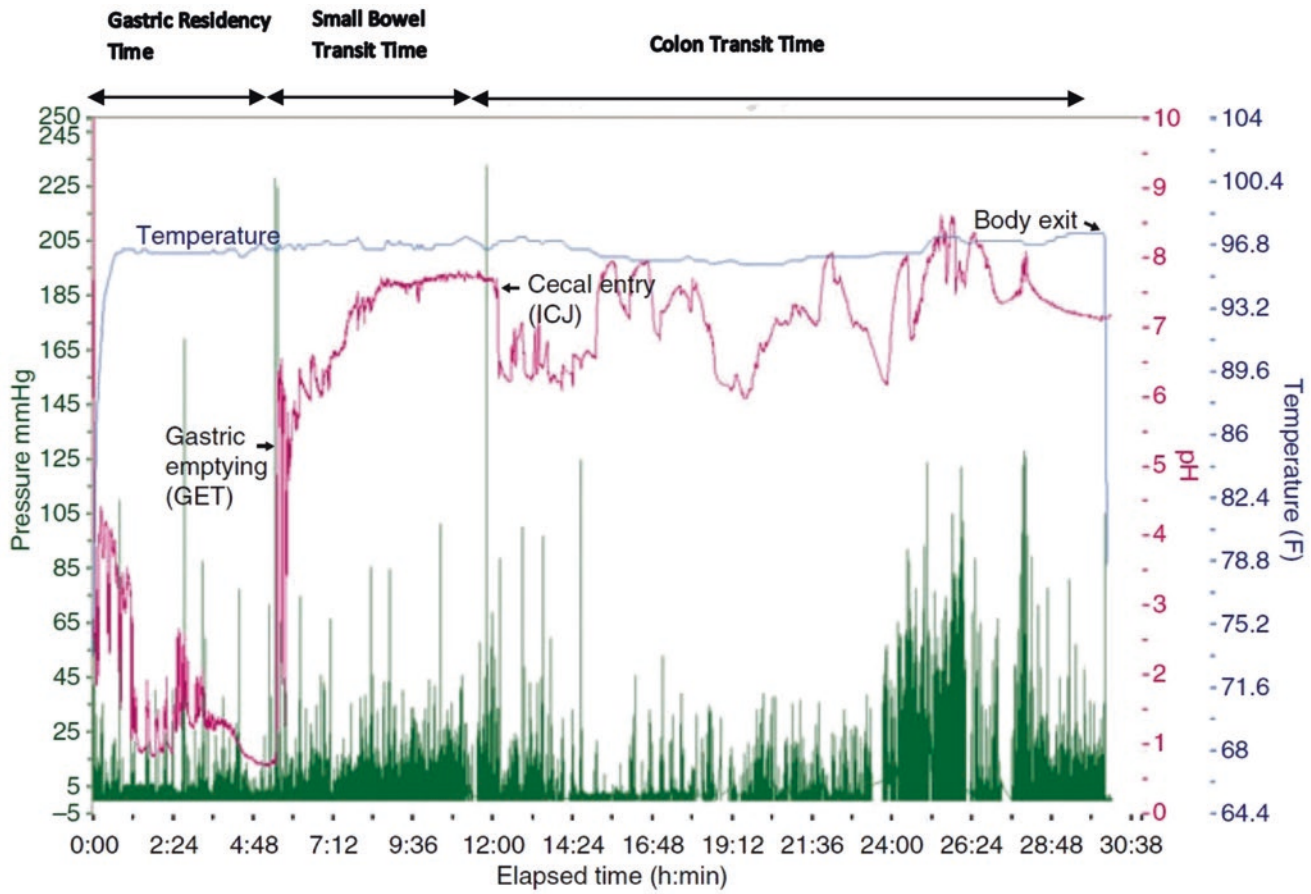

Fig. 17.3 SmartPill tracing. Notice the prolonged gastric residency time as well as significantly prolonged colonic transit. (Courtesy of Dr. Braden Kuo and Dr. Margarita Brun)

to demonstrate the lack of effect of proton pump inhibitors on antral and small bowel motility and transit [152]. A great concern with transit studies with scintigraphy is the significant daily variability, which also potentially applies to the WMC. This has not been addressed in humans, but animal studies have shown a significant variability of GRT by WMC and gastric emptying by scintigraphy with important intraindividual variability [153] and an inverse relationship between GRT and body weight [154].

Clinical Applications

Delayed Gastric Emptying and Constipation

GRT measured by the WMC correlates with the gastric emptying measured by scintigraphy with higher sensitivity at 4 h than at 2 h [151]. WMC also has been useful to discriminate between healthy subjects and patients with diabetic gastroparesis [151] and to measure contractility assessed by number of contractions and motility index in antrum and small bowel [155]. WMC has proven to be useful in classifying and diagnosing regional and generalized motility disorders with good agreement with other conventional motility studies [156]. A recent study by Green et al. compared the WMC with gastric emptying by scintigraphy and antroduodenal manometry in children with upper gastrointestinal symptoms. They reported a sensitivity and specificity of 100% and 50%, respectively, for the detection of gastroparesis by the WMC compared with the 2-h gastric emptying study. Both WMC and antroduodenal manometry were equal in detecting the presence of the MMC but the WMC was more sensitive in detecting motor abnormalities [157].

Colon contractility is poorly characterized in adult patients with constipation and irritable bowel syndrome-constipation subtype. The WMC has been proven useful to measure contractility pressures in different segments of the gastrointestinal tract in these patients. A study by Hasler et al. that evaluated colon contractility and transit in healthy adult patients demonstrated greater pressures in the distal colon when compared to the proximal colon. In the same study, constipated patients with normal or moderately delayed transit showed increased motor activity that was partly explained by IBS. The findings in this study emphasize the differential effects on transit and motility in different constipation subtypes [158].

The WMC has been validated for measurement of the CTT and WGT by the simplified and Metcalf protocol. For the Metcalf protocol, a recent large multicenter study demonstrated that although the measured transit time was significantly different between the WMC and ROM, the agreement for delayed transit was 80% and 91% for normal transit with an overall device agreement of 87% [159]. The WMC with the simplified method showed slower GRT, SBT, CTT and WGT in subjects with constipation compared to controls. Interestingly, the CTT was slower in women than in men and, more importantly, showed upper gastrointestinal transit delay in subjects with constipation [160]. In addition, the WMC has demonstrated that stool form predicts delayed versus normal CTT in adults in contrast to stool frequency [161] and, has reiterated the concept of a generalized gastrointestinal dysmotility beyond the stomach in patients with gastroparesis by evidencing delayed CTT [162]. WMC has been also validated with scintigraphy for the evaluation of gastric emptying, colonic and whole gut transit (WGT) in healthy subjects as well as patients with constipation [163]. In regard to therapy outcomes, the only available study has demonstrated a possible positive effect on CTT and WGT by increasing dietary fiber [164].

In one of the largest studies in pediatrics, Rodriguez et al. [165] prospectively evaluated the diagnostic and clinical utility of the WMC in children with functional GI symptoms by measuring the WMC transit and motility and comparing them with gastric emptying times measured by scintigraphy and colonic ROM (Metcalf protocol), respectively. The authors found fair interpretation agreement between WMC and scintigraphy and moderate interpretation agreement between WMC and colonic ROM in a good proportion of patients with upper and lower GI symptoms, respectively. Interestingly, they found a significant detection rate of abnormal and severe gastric retention with WMC when compared to scintigraphy (>35% radiotracer retention at 4-h). Also, they found a significant correlation between the colon transit time measured by both methods and although the median transit time measured by colonic ROM was higher when compared to WMC, it was not statistically significant. However, they found no association between WMC study interpretation, motility and transit parameters, and GI symptoms. Capsule retention was associated with prolonged colon transit times and not related to symptoms, age, or gender. The authors concluded that WMC is well tolerated in children as young as 8 years of age and provides additional transit information not detected by the other modalities.

Cystic Fibrosis

Patients with pancreatic insufficiency secondary to CF require optimal proximal intestinal neutralization of gastric acid for timely release of pancreatic enzyme replacement therapy. As mentioned above, the WMC has the ability to measure pH and transit in different regions of the gastrointestinal tract. A recent study by Gelfond et al. demonstrated delayed SBT and, more importantly, deficient proximal intestinal buffering capacity measured by WMC in adult pancreatic insufficient CF patients when compared to controls. This study also adds that measurement of gastrointestinal pH using the WMC may

be a method to aid in the development of pharmacological interventions for patients with CF and potentially assess individualized interventions [166].

- *Strengths*: Allows evaluation of transit of the whole GI tract and pressure measurements simultaneously, not operator dependent, ambulatory.
- *Limitations*: Cost, availability, requires expertise in interpretation, risk of capsule retention causing obstruction, capsule size limits use in children, no studies have been done in children.

Cine-MRI

Magnetic resonance imaging (MRI) is a well-known radiologic modality that utilizes strong magnetic fields, radio waves, and magnetic field gradients to generate detailed images of visceral organs, thus providing comprehensive physio- and pathophysiological information. MRI offers the advantage that it does not involve ionizing radiation, it is widely available, and is useful to monitor disease progression. MRI of GI tract function, known as dynamic or cine-MRI, was first described by Stehling et al. in 1989 in four healthy volunteers using a high-speed echo-planar imaging technique and demonstrated a detailed quantitative measurement of the peristaltic patterns in the antrum and proximal small intestine during fasting, after a feed and pharmacologic stimulation [167]. Consequently, cine-MRI became an attractive technique that continues to evolve, currently being applied to study and define GI physiology parameters including GI volumes, motility, transit, and also disease. There are, however, important limitations to its use, particularly the optimization of quantitative imaging analysis. Different quantification methods have been described, including the visual assessment, diameter measurements, displacement mapping, and GI tagging [168]. Other limitations include issues related to imaging acquisition and duration of scans; breath-hold and free-breathing protocols are being explored as potential solutions to address those problems.

Stomach

Measurement of gastric volumes by MRI is feasible, and has been utilized in studies assessing gastric emptying of Gd-DOTA (gadolinium tetra-azacyclododecane tetra-acetic acid) labeled liquid and solid meals in healthy adults with good agreement with scintigraphy [169, 170]. Similarly, this technique has allowed to simultaneously measure the diameters and the contractions per minute of both the proximal and distal stomach before and after a meal [171]. The study is reproducible (assessing the postprandial gastric volumes and gastric emptying within and in between healthy controls and adults with functional dyspepsia) [172] and has a good correlation with antral motility evaluated by water-prefusion manometry during fasting and postprandially (water intake) [173]. Cine-MRI has also been used to study the effects of prokinetic medications, like cisapride, on gastric motor function in diabetic gastroparesis [174] and, to simultaneously measure gastric accommodation, emptying and motility in patients with Ehlers-Danlos syndrome hypermobility type with dyspepsia [175].

Small Bowel

Volume assessment of small bowel by MRI continues to be challenging due to the tortuosity, length, and uneven filling of the lumen. Nevertheless, significant progress has been made in cine-MRI and small bowel motility, both in health and disease. In general, most methods require luminal distension with contrast (enteroclysis, enterography) and evaluation of both fasting and postprandial motility and volumes [168]. Breath-hold protocols that minimize motion artifacts and respiratory displacement are typically used, but may limit the amount of information obtained from the study [176]. Khalaf et al. developed a method using cine-MRI to assess pan-intestinal motility during fasting and the postprandial state during a single session [177]. In this study, healthy adult volunteers underwent baseline and postprandial MRI scans and measured gastric volume, gallbladder volume, small bowel water content, small bowel motility, and whole gut transit. In addition, serum GI peptides (glucagon-like peptide-1, polypeptide YY, and cholecystokinin) were measured and information regarding symptoms (fullness, bloating, distension, abdominal pain, nausea) were collected from the subjects following a 204 kcal liquid meal. Based on their findings, the authors established a method that assesses postprandial small bowel motility by cine-MRI and were able to correlate their measurements with known physiologic peptide response and symptoms.

The utility of cine-MRI has also been evaluated in GI disease. A prospective study using cine-MRI measured and compared the luminal diameter, contraction ratio, and contraction cycle in healthy subjects, patients with irritable bowel syndrome and chronic intestinal pseudo-obstruction (CIPO) and demonstrated that in patients with CIPO the small bowel luminal diameter was significantly higher and contraction ratio was significantly lower when compared to IBS patients and controls, with no differences in contraction cycle [178]. A retrospective study later found that luminal and motor abnormalities detected by cine-MRI are useful in predicting disease severity and outcomes in CIPO when

compared to controls [179]. Another study utilized the pan-intestinal motility technique based on motion capture MRI and compared their findings between CIPO patients and controls. Unsurprisingly, the authors found that the baseline global bowel motility index was significantly lower in CIPO. Subjects were later randomized to undergo repeat MRI and receive intravenous neostigmine or normal saline and were able to detect an increased motility in the both groups receiving neostigmine but noticed a reduced response in CIPO secondary to scleroderma, highlighting the potential utility of cine-MRI to determine treatment response [180].

Colon

The application of cine-MRI in the assessment of colon motility is very limited, mostly assessing response to medications or the simultaneous use of manometry. One study aimed to assess colon motility in healthy volunteers after stimulation with senna tea and erythromycin. Colon motility was measured according to changes in the luminal diameter at five different locations in the ascending, transverse, and descending colon and found significant changes in all segments, highest after senna tea [181]. However, the main limitation of this study was the inability to assess the sigmoid colon. A different study used cine-MRI to measure small bowel content, ascending colon motility index, and regional colonic volumes after the ingestion of a single dose (2 L on day of study) or split dose (1 L evening before and 1 L on day of study) of polyethylene glycol (PEG). The authors found a fourfold increase in small bowel water content after both single- and split-dose PEG ingestion and a significant increase in colon volumes after single-dose PEG. Most importantly, the ascending colon motility index was twofold higher after single-dose PEG [182].

Colon manometry is considered the gold standard method to assess colonic motility, but it is invasive, time consuming, requires a bowel clean out and colonoscopy. A feasibility study by Kirchhoff et al. stimulated high-amplitude propagated contractions (HAPCs) with bisacodyl and aim to measure them in the descending colon of healthy volunteers by manometry and cine-MRI. HAPCs were detected by manometry in all subjects and cine-MRI simultaneously detected colon luminal changes corresponding to these contractions [183]. Recently, a feasibility study by Vriesman et al. also assessed the simultaneous assessment of colon motility in children with functional constipation by manometry and cine-MRI. Unlike the adult study, not all HAPC recorded by manometry was noticed during cine-MRI. However, cine-MRI detected colon activity not seen in patients with absent HAPC's on manometry [184]. Both studies demonstrated that the simultaneous acquisition of colon motor activity by manometry and cine-MRI is feasible making the latter an attractive and noninvasive alternative to colon manometry.

- *Strengths*: Allows evaluation of volume, luminal diameter, motility and transit of the whole GI tract, no radiation involved, not operator dependent, ambulatory.
- *Limitations*: Cost, requires expertise in interpretation, no standardized methodology available, movement or use of sedation limits use in children, limited information available in pediatrics.

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Autonomic Nervous System Testing

18

Gisela Chelimsky and Thomas C. Chelimsky

Autonomic Nervous System (ANS) Testing

Autonomic testing increasingly contributes to our understanding of the pathophysiology and management of pediatric functional gastrointestinal disorders. At the simplest level, the ANS constitutes the link between the central control circuits for gastrointestinal function and the enteric nervous system. No clinical tests directly assess the portion of the autonomic nervous system that innervates the gastrointestinal tract. Current routine clinical testing is limited to examination of cardiac, vasomotor, and sudomotor function, and based on the results of these tests in the appropriate clinical setting, the gastroenterologists or autonomic specialists must infer the potential role of the autonomic nervous system in the pathogenesis of gastrointestinal symptoms. The goals of this chapter are as follows:

1. To describe the current available autonomic testing and discuss the portion of the autonomic nervous system assessed by each test.
2. To discuss the utility of these tests in clinical practice.

Autonomic testing in children is increasingly available, though very few centers perform more than just a tilt-table test. Tilt-table tests, typically performed by cardiologists, are seldom performed in patients with primarily gastrointestinal complaints. Some studies have shown altered electrical activity of the stomach in the upright position in subjects with postural tachycardia syndrome (POTS). In addition, treatment of the orthostatic intolerance in patients with POTS often benefits their gastrointestinal symptoms. These findings imply a significant physiologic relationship between orthostatic and gastrointestinal dysfunction, though the mechanism remains unknown. Furthermore, the electrical activity of the stomach measured by electro-gastrography (EGG) seems to relate to heart rate variability (HRV), a measurement of vagal modulation. So far, researchers have found a correlation between the power ratio of high frequency (hf) and low frequency (lf) HRV and the EGG power and also the changes in power in EGG to the changes in the hfHRV pre- and post-water ingestion [1, 2]. To summarize, reduced vagal modulation may be associated with reduced tachygastria during orthostatic tilt [3]. Although HRV is used frequently at a research level to assess vagal modulation, HRV is typically not available as a clinical tool when assessing the ANS [4].

This chapter describes the tests performed most commonly in autonomic function referral centers and the underlying physiology (summarized in Table 18.1).

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Table 18.1 Tests of autonomic function and their underlying physiology

Autonomic test	Receptor	Afferent	Integrating center	Efferent signal
Deep breathing	Pulmonary stretch J-receptors	Vagus nerve	Nucleus tractus solitarius	Nucleus ambiguus (NA) and dorsal motor nucleus (DMNX) of the vagus through vagus nerve
Valsalva maneuver	Low-pressure atrial baroreceptors	Vagus nerve	Nucleus tractus solitarius	*Phase II*:
				1. Inhibition of NA for HR
				2. Excitation VLM to descending sympathetics exiting at T1 vasoconstriction
				Phase IV:
				Reverse of 1 and 2
Tilt-table test	Low-pressure atrial baroreceptors	Vagus nerve	Nucleus tractus solitarius	1. Inhibition of NA for HR
				2. Excitation of VLM to descending sympathetics exiting at T1 vasoconstriction
Sudomotor axon reflex test	Nicotinic cholinergic	Sudomotor nerve	None	Sudomotor nerve (axon reflex)
Thermoregulatory sweat test	Temperature sensors in the anterior hypothalamus and peripheral veins	Temperature C-fibers	Anterior hypothalamus	Descending projections from anterior and lateral hypothalamus to IML cell horn preganglionic spinal neurons postganglionic sudomotor axons

DMNX dorsal motor nucleus of the vagus, *VLM* ventrolateral medulla, *IML* intermediolateral, *NA* nucleus ambiguus

Critical Steps in Preparation for All Autonomic Function Testing

Prior to testing, the patients should be asked to have a normal meal at the usual mealtime with plenty of fluid. They must also taper or stop all medications and dietary or nutritional supplements that may influence test results. This includes caffeine and passive or active exposure to nicotine. When the patient is unable to avoid taking some medications, results need to be interpreted accordingly. Each center has protocols for when and which medications should be stopped. As a general guideline, α(alpha)- and β(beta)-receptor agonists and antagonists, pro- and anticholinergics (particularly phenothiazines and tricyclic agents), and mineralocorticoids (including fludrocortisone) must be discontinued at least five half-lives prior to testing. Selective serotonin reuptake inhibitors (SSRI) Serotonin reuptake inhibitors (SSRI) and serotonin nonselective reuptake inhibitor (SNRI Serotonin nonselective reuptake inhibitor (SNRI)) agents should be discontinued 5–7 days prior to the testing.

Tests Currently Available

The most common tests can be divided in two categories:

1. Tests of cardiovascular autonomic function:
   (a) Deep breathing
   (b) Valsalva maneuver
   (c) Head-up tilt-table test
   (d) Handgrip
2. Tests of sudomotor autonomic function (sweating)
   (a) Quantitative sudomotor reflex test (QSART)
   (b) Thermoregulatory sweat test (TST)

The tests of cardiovascular autonomic function are particularly helpful in evaluating the branch of the autonomic nervous system involved (afferent baroreflex, or efferent sympathetic vs. parasympathetic), whereas the sweat tests provide information on lesion localization (central vs. peripheral nervous system). At this time, the pediatric norms are not well defined [5], and therefore, norms are inferred from adult values. Other tests of autonomic function such as pupillometry and pharmacologic evaluation of the baroreflex also exist; these are even less commonly utilized, have even less clearly defined norms, and are therefore not described in this chapter.

1. **Tests of Cardiovascular Autonomic Function**:
   (a) **Deep Breathing**

   This test assesses heart rate variability, a parasympathetic nervous system function. The test is performed by instructing the patient to breathe deeply and regularly at a rate of 6 breaths per minute for 1 min. This is repeated after a minute of rest. Values for this parameter are age dependent, and a reduction in heart rate variability is considered abnormal. The authors utilize the data published by Ingall et al. [5] and Singer et al. [6] as age-based norms in their laboratory. The presumed purpose of the reflex is to provide adequate pulmonary blood volume to receive incoming oxygen when the lung is filled with air from deep inspiration. When an individual inhales deeply, both air and vascular spaces expand and require increased lung blood volume. This need is met through an increase in heart rate during inspiration, triggered by vagal parasympathetic inhibition. When the individual exhales, the heart rate decreases, due to parasympathetic excitation [7]. In teenage

years, this heart variability may reach large values, probably due to a maturing vagal circuitry. The nucleus tractus solitarius orchestrates this response to pulmonary stretch receptor afferents (J-receptors) [8] also accounting for baroreflex responses to blood pressure changes and intrinsic central respiratory rhythms.

(b) **Valsalva Maneuver**

The Valsalva maneuver (VM) (Fig. 18.1) is probably the single most complete test of cardiovascular autonomic function as it evaluates cardiac parasympathetic, cardiac sympathetic, and vasomotor sympathetic functions in response to low-pressure baroreceptor afferents from the right atrium and the great veins. The patient generates a continuous expiratory pressure of 40 mmHg by blowing against a fixed resistance for 15 s, followed by an abrupt pressure release. The rise in intrathoracic pressure impedes venous return to the heart, reducing ventricular filling and stroke volume. Phases I and III are mechanical phases unrelated to autonomic physiology. During phase I, blood pressure rises for a few seconds as the held pressure is transmitted directly as a pressure wave through the vascular system. Phase II is a sympathetic nervous system-mediated response to the decline in cardiac output, resulting in vasoconstriction and tachycardia to restore blood pressure. The lost cardiac output is reflected in a drop in systolic pressure, while vasoconstriction causes a rise in diastolic pressure, resulting in reduced pulse pressure. Phase II may be further subdivided into early and late phases. Systolic pressure drops during the early phase, while it rises during the late phase, once vasoconstriction fully compensates for reduced cardiac output. When the subject releases pressure, blood pressure drops transiently during the mechanical phase III. The dominant effect occurs when blood fills the heart again, reaching higher levels than baseline, due to thoracic pressure normalization in the face of continued vasoconstriction. The baroreflex triggers a relative bradycardia through sympathetic withdrawal and parasympathetic excitation. Since vasodilation is slow, the blood pressure overshoots temporarily before returning to baseline. The result is usually read as a ratio of the fastest heart rate during phase II and the slowest heart rate during phase IV. If the ratio is below the age-based normal value, one must determine if this is due to an inadequate bradycardia during phase IV or inadequate tachycardia during phase II. In most centers, results of this study are repeated three times, with the two largest responses included in the dataset [7]. The values vary with age, and we currently utilize pediatric values published by Ingall et al. [5] and Singer [6].

(c) **Head-Up Tilt Test**

This test primarily evaluates sympathetic vasomotor responses. The patient must remain supine for a minimum of 10 min to obtain reliable baseline values, and is then passively tilted to 70°. The tilt duration varies across centers, as short as 10 min in some neurologic centers and up to 45 min when performed by cardiologists. Currently, in our institution, we tilt children without history of syncope for 30 min, and if there is a history of recurrent fainting, the tilt is extended to 40 min. In our clinical experience, many subjects would be diagnosed as normal had the tilt-table test been stopped at 10 min or may be erroneously diagnosed with POTS due to a cardioacceleration in the first 10 min, though this is not sustained in the ensuing time upright. The clinical significance of such findings is still unknown. A study performed by Carew et al. [9] in adolescents to adult age group (14–60 years) showed that 75% of the subjects with complaints of orthostatic intolerance develop a sustained increase in heart rate to fulfill the heart rate criteria for postural tachycardia syndrome (POTS) within the first 3 min of head-up tilt and by 7 min had developed the diagnostic criteria

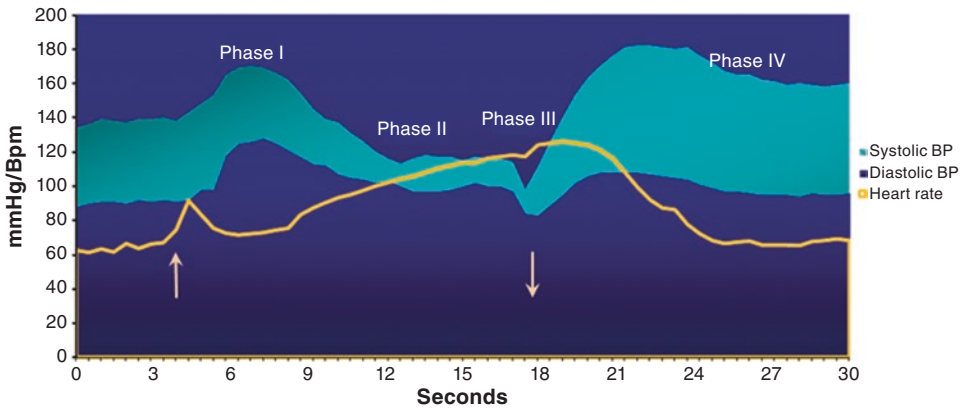

Fig. 18.1 Valsalva maneuver, showing the four phases and the blood pressure and heart rate changes of each phase

for POTS. None of the subjects in the control group (no orthostatic intolerance symptoms) demonstrated a sustained tachycardia. Reflex syncope occurred in 36% of the subjects with POTS between 7.4 and 32 min into the head-up tilt [9]. This frequency of syncope in POTS subjects is similar to that found by Ojha et al. of 38% [10]. Based on these various data sources, perhaps children should be tilted for a minimum of 30 min, and the study halted at the time of a pre-syncopal or syncopal event. Not every pediatric autonomic center agrees with this recommendation, and some tilt for 5–10 min. During the test, all symptoms should be documented (and rated on a numeric rating scale) so they can later be correlated with vital sign changes. Vital signs should be documented minute by minute for the clinical record. It is of particular importance if children replicate their gastrointestinal complaints during the upright portion of the tilt test, as these complaints may themselves improve with treatment aimed at orthostatic intolerance [11].

The tilt-table test may demonstrate four patterns (Fig. 18.2): (a) normal response, (b) postural tachycardia syndrome (POTS), (c) orthostatic hypotension (OH), and (d) reflex syncope. In our clinical experience, children seldom demonstrate true orthostatic hypotension, while POTS and POTS associated with reflex syncope is the more common finding.

• *The Normal Response to a Tilt-Table Test*

A normal tilt response includes a mild increase in diastolic pressure by 5–10 mmHg, a mild decrease in systolic blood pressure of 5–10 mmHg, and an increase in heart rate of about 10–20 bpm. A transient drop in blood pressure with reflex tachycardia within the first minute of tilt is common in adolescents during tilt test [12, 13]. Sometimes when the systolic blood pressure decreases more than 40 mmHg or the diastolic >20 mmHg **this initial orthostatic hypotension (IOH)** becomes clinically significant with symptoms of lightheadedness or vision changes. In IOH the blood pressure normalizes within the first 30 s, but the compensatory tachycardia may take a little bit longer [13]. IOH is thought to be secondary to a deficit in adrenergic vasoconstriction or hypovolemia.

Although IOH has been regarded as an expected consequence of physiological changes in response to rapid shifts of blood by gravity, IOH patients may have decreased nadir BP and

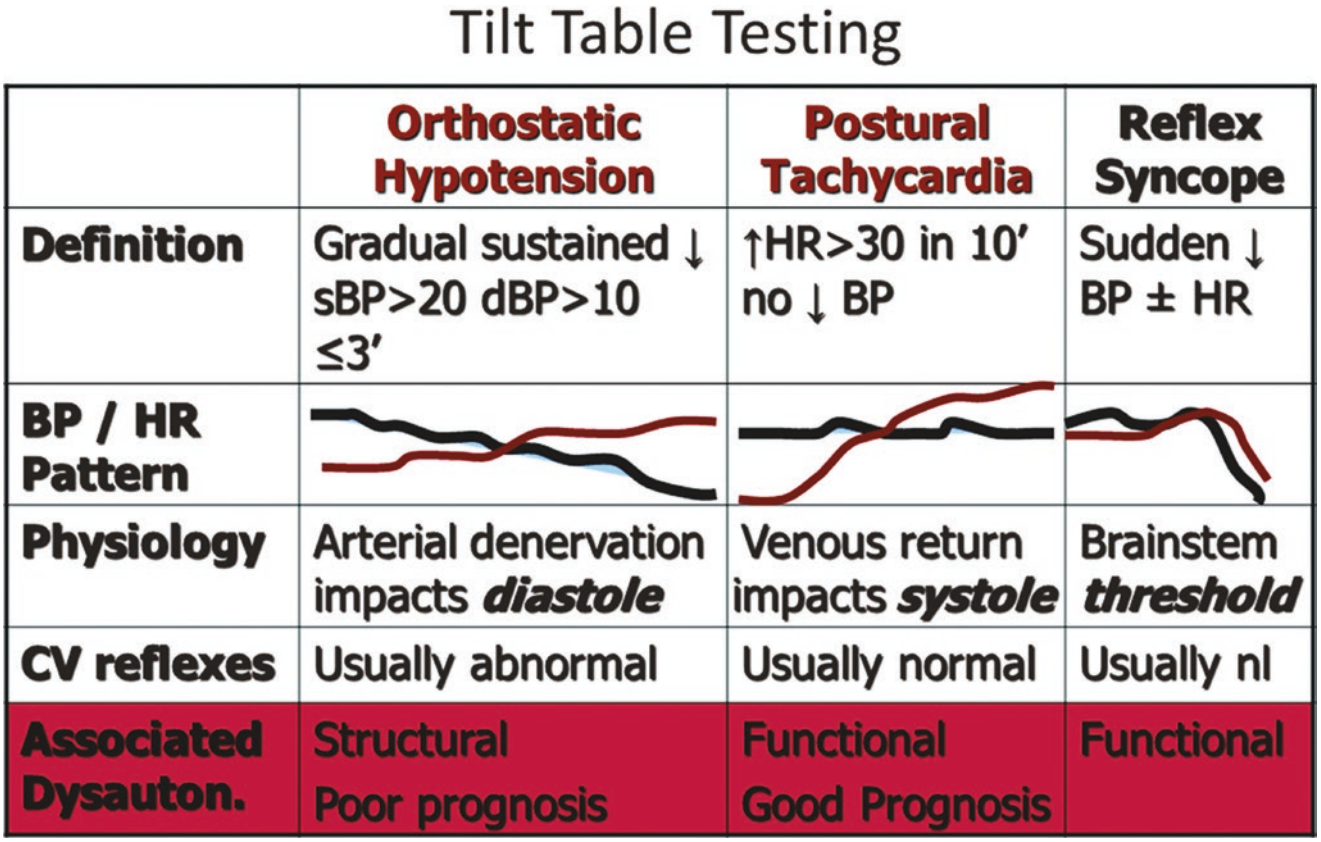

Fig. 18.2 Cartoon illustration of blood pressure (black line) and heart rate (red line) changes in the three orthostatic syndromes, their physiologic mechanism and a graphic description of the vital signs (*nl* normal)

prolonged time to BP recovery, suggesting real (though mild) deficits in adrenergic vasoconstriction or hypovolemia [14].

• *Orthostatic intolerance (OI)*

Orthostatic intolerance describes *symptoms* that occur in the upright position and resolve when supine, such as lightheadedness, feeling faint or blacking out, shortness of breath, fatigue, headaches, nausea, abdominal discomfort, and visual changes [13]. This term makes no assumptions regarding tilt-table or other autonomic test findings, and patients with OI may have or not have test findings of postural tachycardia syndrome, syncope, near-syncope, or orthostatic hypotension. Chronic OI describes symptoms lasting 3 months or more, although the symptoms may come and go, subacute OI, 1 week to 3 months, and acute OI less than 1 week [13].

• *Postural Tachycardia Syndrome*

POTS is defined in adults as an increase in heart rate greater than 30 bpm within 10 min of becoming upright or to greater than 120 bpm, without a gradual drop in BP, and associated with orthostatic symptoms [15]. Since about 42% of healthy pediatric subjects meet this criterion [6], most pediatric centers require a heart rate increase of >40 bpm from baseline during the first 10 min of upright tilt for the diagnosis of POTS, with associated orthostatic symptoms in the absence of sustained significant drop in the blood pressure (systolic BP >20 mmHg and diastolic BP >10 mmHg). In children <13 years of age, an exaggerated orthostatic heart rate response during head-up tilt should be >130–140 bpm, and in children >13 years of age, probably the adult value of 120 bpm may be applicable [6]. The pathogenesis of POTS is still unclear. Mechanistically, the final common pathway is probably excessive cardiovascular sympathetic activation due to abnormal blood volume distribution with venous pooling resulting in central hypovolemia and inadequate cardiac return [16].

• *Reflex Syncope*

Also known as neurally mediated syncope, vasovagal syncope, cardiogenic syncope, and vasodepressor syncope, these different terms emphasize different aspects of the event. A temporary loss of consciousness caused by inadequate brain perfusion, it is caused by a sudden discharge from the medullary vasomotor center, reducing sympathetic outflow and increasing vagal outflow which leads to peripheral vasodilation, hypotension, and bradycardia. Subjects usually experience a brief loss of consciousness followed by rapid recovery with a relatively clear sensorium. It is important to note that syncope is a normal reflex that may occur in all subjects if enough strain is placed on orthostatic pressure maintenance (e.g., through the application of lower body negative pressure). Its probable function is the continued perfusion of the brain through gravitational mechanisms when the individual experiences severe loss of blood volume. Syncope and POTS can coexist, being present in 30–40% of children evaluated in our center [10]. From a diagnostic perspective, it is important to distinguish the acute increase in heart rate that may precede impending syncope (typically 2–3 min) from the chronic increase (throughout the entire tilt-table study) that occurs in POTS.

• *Orthostatic Hypotension*

Orthostatic hypotension is defined as a sustained drop in blood pressure of greater than 20 mmHg systolic or 10 mmHg diastolic within 3 min of being upright, associated with symptoms. The underlying pathophysiology is an impaired efferent sympathetic signal to the arterioles with consequent vasoconstrictive insufficiency [15]. Figure 18.2 graphically summarizes the three orthostatic syndromes and their etiopathology.

(d) **Sustained (Static) Handgrip**

This test evaluates sympathetic vasomotor function and sympathetic cardiac and parasympathetic function. After baseline recording, the patient is instructed to sustain a grip at 30% of their maximal grip strength for 3 min by squeezing a hand dynamometer. Heart rate and blood pressure are monitored continuously from the contralateral upper extremity. The maneuver results in both cardioacceleration and an increase in blood pressure. In contrast to the tilt-table test and the Valsalva maneuver, the afferent signal here originates from muscle and is related to lactate accumulation, in contrast to the former two tests where the initial afferent signal originates from the right atrial low-pressure baroreceptor. An early heart rate increase is due to vagal withdrawal, and a later heart rate response is due to sympathetic activation. The blood pressure increase is due to both increased cardiac output and to sympathetically mediated arterial vasoconstriction [17].

2. Tests of Sudomotor Autonomic Function (Sweating)

(a) **Quantitative Sudomotor Reflex Test**

This study evaluates for an autonomic neuropathy through the presence and function of postganglionic sudomotor axons. The sympathetically innervated sweat gland uses acetylcholine as its postganglionic neurotransmitter. The test is performed by applying a

capsule with dual concentric chambers to the patient's skin. Acetylcholine from the outer chamber is iontophoresed into the skin and via an axon reflex stimulates axons that innervate the local sweat glands. The axon reflex stimulates more distant sweat glands whose output is then measured in the area of the central chamber of the capsule. The capsules are usually placed from distal to proximal on four sites in the upper and lower extremities [17]. A reduced response indicates postganglionic sympathetic sudomotor impairment. The sudomotor reflex is often preserved in central nervous system processes.

(b) **Thermoregulatory Sweat Test**

This study helps to differentiate a central disorder from a neuropathy or radiculopathy. It evaluates both preganglionic and postganglionic pathways. The patient dressed in a disposable swimsuit-like garment is covered with a powder that changes color on contact with moisture. The subject is placed supine in a sauna-like enclosure and kept at an air temperature of 50 °C, with a relative humidity of 50%. The skin temperature is maintained between 38.5 and 39.5 °C. The skin may also be heated with infrared heaters. The test is interpreted based on the detection of areas of lack of sweat (anhidrosis) [18]. Usually a subject with central disorder will have lack of sweating diffusely throughout the body, although sweating on hands and feet may be preserved. Reduced sweating in the toes and fingers with a distal to proximal gradient is suggestive of a peripheral process. If there is lack of sweating following a nerve root pattern, the study may suggest a radiculopathy.

Utility of Autonomic Testing in the Evaluation of Children with Functional Gastrointestinal Disorders and Motility Disorders

To date, autonomic testing in children has been deployed in limited ways, being primarily utilized in the evaluation of rare disorders such as familial dysautonomia. The utility of autonomic testing in functional gastrointestinal disorders (FGID) is emerging. More than 20 years ago, the first case series was reported of children with FGID, demonstrating a postural tachycardia in most subjects and an autonomic neuropathy in many. The cardiac parasympathetic function was preserved in all subjects [19]. A few case reports further supported this association and reported improvement of the gastrointestinal symptoms when treatment was aimed at the orthostatic intolerance [20, 21]. Sullivan and collaborators reported tilt-table results in 24 children with FGID [22]. A subsequent study in children with abdominal pain (71%), nausea (56%), and vomiting (50%) showed POTS in 4, POTS and neurally mediated hypotension (termed reflex syncope in this chapter) in 8, and neurally mediated hypotension alone in 12. In about half of the cases, the tilt-table test reproduced the gastrointestinal complaints. Follow-up was available in 18/24. Twelve children were treated with fludrocortisone (4 had also sertraline) with either improvement or resolution of symptoms [22].

A retrospective study supported the concept that children that replicate the gastrointestinal symptoms during the tilt-table test usually had POTS and often show improvement of gastrointestinal symptoms when treated with fludrocortisone [11]. Prospective data in 16 children with orthostatic intolerance and nausea (mean age 14.8 ± 2.8 years) showed that treatment with fludrocortisone 0.1–0.2 mg daily for >4 weeks significantly improved nausea, dizziness, abdominal pain, flushing, and missing school, but interestingly did not improve vomiting, syncope, constipation, and anorexia [23]. Given the high association of nausea and POTS, a few studies have evaluated the prevalence of gastroparesis in children with POTS. Patients with POTS and with FGID typically demonstrate normal or accelerated gastric emptying, delayed only in a minority [24, 25]. A pediatric study comparing the gastric emptying time in patients with FGID with POTS vs. those without POTS showed no significant difference [26].

In an attempt to further understand nausea and foregut symptoms, electrogastrographic changes were assessed in subjects with and without POTS in the supine position and during the upright portion of the tilt test. In the upright position, children with POTS developed more gastric electrical abnormalities in the locations corresponding to the fundus and the antrum, while the opposite happened in the non-POTS group [27]. These findings suggested a possible mechanism for the association between orthostatic intolerance and the gastrointestinal symptoms that occur in the upright position. Further prospective, blinded studies will determine if treatment aimed at the orthostatic intolerance is superior to "conventional" treatment of FGID or to placebo in this subgroup of children who have FGID symptoms replicated while upright. Against the concept of placebo response, most children have failed most "conventional" gastrointestinal treatments prior to referral to our center. Sullivan and collaborators reported that tilt table was performed after symptoms were present for more than a year, sometimes even 3 years (48%), and had failed gastric acid secretory blockers, antispasmodics, and prokinetics. Many of them (50%) had been referred to a psychiatrist or psychologist for their symptoms, having then resolution with fludrocortisone or sertraline [22]. One would not expect a placebo effect to be restricted to orthostatic agents.

Although POTS is clearly associated with many of these gastrointestinal symptoms, it may not be their cause. In a

recent tertiary care autonomic center study, children and adolescents showed the same comorbidities whether or not they had POTS. Comorbidities included fatigue, sleep problems, dizziness, gastrointestinal symptoms meeting Rome criteria for FGID, migraines, chronic nausea, fibromyalgia, and joint hypermobility [28].

Many patients with POTS also have Ehlers Danlos Syndrome-hypermobility (EDS-H), which is a connective tissue without a known mutation, with an autosomic dominant inheritance [29]. It is a non-inflammatory disorder with articular and extra-articular symptoms. POTS coexists with EDS-H in a great percent of affected individuals [30]. Our group did not find a higher association of POTS in children, with FGID and hypermobility [31], but Tai et al. (2020) reported a greater association of gastrointestinal symptoms in patients with hypermobility spectrum/EDS-H with POTS [32].

Furthermore, practitioners often wonder whether anxiety may be the primary cause of the increase in heart rate during tilt-table test. Masuki et al. attempted to answer that question by performing graded venous pooling with lower body negative pressure by wearing antishock trousers to −40 mmHg and sham venous pooling by inflating the trousers to −5 mmHg and vacuum pump activation without lower body negative pressure in subjects with POTS and in controls [33]. They also performed mental stress to determine if there were differences in the heart rate increase in the two groups. They demonstrated that only significant venous pooling caused a rise in heart rate in the POTS group, whereas the heart rate increase in response to "sham" venous pooling and mental stress did not differ between the two groups. These results suggest that the heart rate increase in patients with POTS is not directly related to anxiety but rather to reduced venous cardiac return [33].

Although many of these studies are either retrospective or small series, evidence is slowly mounting for the role of autonomic dysfunction in children with FGID and hence a benefit of autonomic testing in the evaluation of children with FGID. Prospective studies will compare different treatment modalities and determine if fludrocortisone, salt supplementation, and beta-blockers may benefit the gastrointestinal symptoms.

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Part III

Disorders of Digestive Motility

Pathology of Enteric Neuromuscular Disorders

19

Raj P. Kapur

Introduction

Diagnosis and management of patients with intestinal dysmotility are best conducted by a multidisciplinary team, including a pathologist with interest and experience in enteric neuromuscular disorders. While most pathologists are familiar with the key diagnostic features of Hirschsprung disease and will recognized advanced histopathological signs of visceral myopathy, many are not familiar with subtle features of that correlate with the myriad of etiologies and evolutionary stages of gastrointestinal neuromuscular pathology (GINMP). In addition, common alterations caused by tissue handling or non-specific adaptations to obstruction may be misinterpreted by the uninitiated in their zeal to explain a patient's symptoms. Even GINMP experts are unable to identify specific changes in many tissue samples from patients with profound dysmotility, in part because etiologies are diverse and likely include physiological defects that cannot be resolved with routine histological, immunohistochemical, or electron microscopic methods. The field is compounded by the fact that considerable published pathological descriptions are often anecdotal, conflicting, and confounded by ambiguous or imprecise clinical terminology. Optimal patient care necessitates that pathologist and clinician are aware of these limitations and apply an evidence-based approach to each patient, with a clear understanding that in some cases management decisions will be based on negative pathological findings and clinical "best judgement."

This chapter is written primarily for surgeons and gastroenterologists who treat patients with motility disorders, to help them formulate realistic expectations from pathological investigations and understand how such investigations impact on clinical management. The author aims to provide the basic information necessary to choose a diagnostic procedure, obtain an adequate tissue sample, and deliver it in an appropriate state to the pathology laboratory. Guidelines are presented for how tissue samples should be handled in the laboratory to resolve most types of GINMP and allow for consultation and/or special studies if indicated. Histologic features, diagnostic pitfalls, and ancillary methods are discussed for Hirschsprung disease and a subset of common causes of chronic intestinal pseudo-obstruction (CIPO), but comprehensive coverage of all forms of GINMP is not attempted. The reader is specifically encouraged to consult other references for more information on the enteric neuromuscular pathology of systemic muscular dystrophies (e.g., myotonic dystrophy, Duchenne muscular dystrophy) [1, 2], esophageal achalasia [3], gastroparesis [4, 5], and systemic connective tissue disorders [6, 7]. Although some patients with severe CIPO are treated by intestinal allograft, transplant pathology is reviewed elsewhere [8].

Rectal Biopsy and Diagnosis of Hirschsprung Disease

Rectal biopsy is one of the first diagnostic procedures performed in many patients with impaired intestinal motility, particularly when clinical signs date back to birth. The primary purpose of rectal biopsy is to exclude Hirschsprung disease (HSCR)—congenital aganglionosis of the distal rectum and a variable length of contiguous bowel (see Chap. 24). Other motility-related disorders that may be diagnosed or strongly suggested by rectal biopsy include intestinal neuronal dysplasia type B (IND), neuronal intranuclear inclusion disease, some mitochondriopathies, and some forms of visceral myopathy (requires full-thickness biopsy). Apart from HSCR and IND, rectal biopsy is not a sensitive diagnostic approach, but is less invasive than other types of intestinal biopsy.

Two types of rectal biopsy, suction and "full-thickness," are used. Suction biopsies are obtained with a special instru-

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ment designed to liberate and capture a small sample of rectal mucosa and underlying submucosa. Suction rectal biopsy can be performed without anesthesia and is the procedure of choice to exclude HSCR in patients under a year of age. For older patients, suction biopsy does not harvest as much submucosa, possibly because the tensile strength of submucosa increases with age. Therefore, many clinicians opt for a full-thickness biopsy in older children (e.g., toddlers) or adults, particularly if their laboratory relies entirely on H&E-stained sections to exclude HSCR (see below).

Surgeons are taught that a rectal biopsy should be taken 2 cm from the anorectal junction (dentate line) to avoid sampling a zone of physiologic hypoganglionosis (perhaps aganglionosis), which exists in the distal rectum of some otherwise normal infants. The basis for this recommendation dates back to an autopsy study by Aldridge and Campbell [9], which was performed in an era when microscopic identification of ganglion cells in H&E-stained paraffin sections was the only method used to exclude HSCR. Aldridge and Campbell examined H&E-stained sections from postmortem samples of distal rectum for a group of 20 individuals ranging from premature infants to age 15 years. For most of the specimens, ganglion cells were quantified in three representative full-thickness sections, whereas serial sections of biopsy-size sections were only studied for two patients. The serial sections, which were evaluated in a manner most comparable to suction biopsies, demonstrated <1 ganglion cell per mm^2 in the superficial submucosal plexus 1 cm immediately superior to anal mucosa versus ~15 ganglion cells per mm^2 in tissue 2 cm or more proximal to anal mucosa. Although these figures and data from the full-thickness sections clearly demonstrate hypoganglionosis, they are not sufficient to conclude that an adequate suction biopsy from a non-HSCR patient can appear aganglionic with generous histological sampling—sections through the entire block if necessary. In fact, a subsequent autopsy study of punch biopsies taken 0.5–1 cm from anal mucosa from 68 infants and children found ganglion cells (no false positive diagnoses of aganglionosis) in all cases, with a maximum of 25 H&E-stained sections from each biopsy [10]. This has been the author's experience as well, in that suction biopsies obtained "1 cm" from the ani of non-HSCR patients require more sections on average to find a ganglion cell than more rostral biopsies, but invariably contain a definite ganglion cell if adequate submucosa is present and the biopsy is sectioned thoroughly (more than 100 sections in rare cases).

Reluctance to biopsy the distal 2 cm of rectum is a potentially serious issue because even very short-segment aganglionosis, restricted to the distal 1–2 cm, can cause significant morbidity. Suction biopsies are performed transanally in infant who is often distressed. The dentate line is not visualized. Rather the operator notes the relative position of the biopsy instrument's aperture to the anal verge (junction between skin and anal canal mucosa). It is not uncommon for a biopsy designated "2 cm above the anal verge" to contain squamous mucosa, as evidence for potential inaccuracies inherent in the procedure. It seems equally likely that a biopsy might be 1 or more centimeter rostral to the intended location, whereby very short segment HSCR might be missed. Our laboratory and many others typically request biopsies from at least 3 sites (e.g., 2-, 3-, and 4-cm from the anal verge) [11]. This practice reduces the likelihood of inadequate sampling due to either a biopsy that is "too low" (squamous or transitional mucosa) or insufficient submucosa, and affords an opportunity to evaluate innervation of the distal-most rectum. When adequate submucosa is sampled and the biopsy is sectioned thoroughly, it is almost always possible to confidently diagnose or exclude HSCR with this approach, particularly if coupled with one or more of the ancillary methods discussed below.

The histopathological hallmarks of aganglionosis are absence of ganglion cells and hypertrophic submucosal nerves (Fig. 19.1). Hypertrophic nerves represent an increased density and caliber of cholinergic nerves that ramify through the bowel wall in the absence of intrinsic enteric neurons. Hypertrophic nerves originate from autonomic and possibly sensory ganglion cells outside the bowel wall, which enter from the mesentery and normally make up a small portion of the nerves in the enteric plexuses. Like other extra-enteric peripheral nerves, they are enclosed by perineurial cells, which express glucose transporter 1 (Glut1) (Fig. 19.1c). In aganglionic submucosa, abnormally large nerves are usually conspicuous, particularly in the distal rectum. Monforte-Munoz et al. measured the diameters of submucosal nerves in aganglionic biopsies from 20 patients with HSCR and compared them with 50 ganglionic control biopsies [12]. They reported that control nerves were never more than 40 μm thick, whereas 90% of biopsies from HSCR patients contained one or more biopsy >40 μm in caliber. This "40-micron rule" is a helpful guideline, but should not be relied on too strongly, particularly with older patients. Nerve caliber and density increase with age, and rectal submucosa from toddlers and older children often contains submucosal nerves >40 μm in diameter, particularly in deep submucosa captured with incisional biopsies [13]. Nonetheless, an experienced pathologist can usually appreciate an age-adjusted overall increase in nerve diameters and density of large nerves, which serves as the most reliable gauge of abnormal extrinsic submucosal innervation in HSCR.

The diagnosis of HSCR is firmly established when a distal rectal biopsy with adequate submucosa shows aganglionosis and unequivocal nerve hypertrophy. However, most honest pathologists will admit to some degree of nervousness rendering a diagnosis based solely on the H&E findings

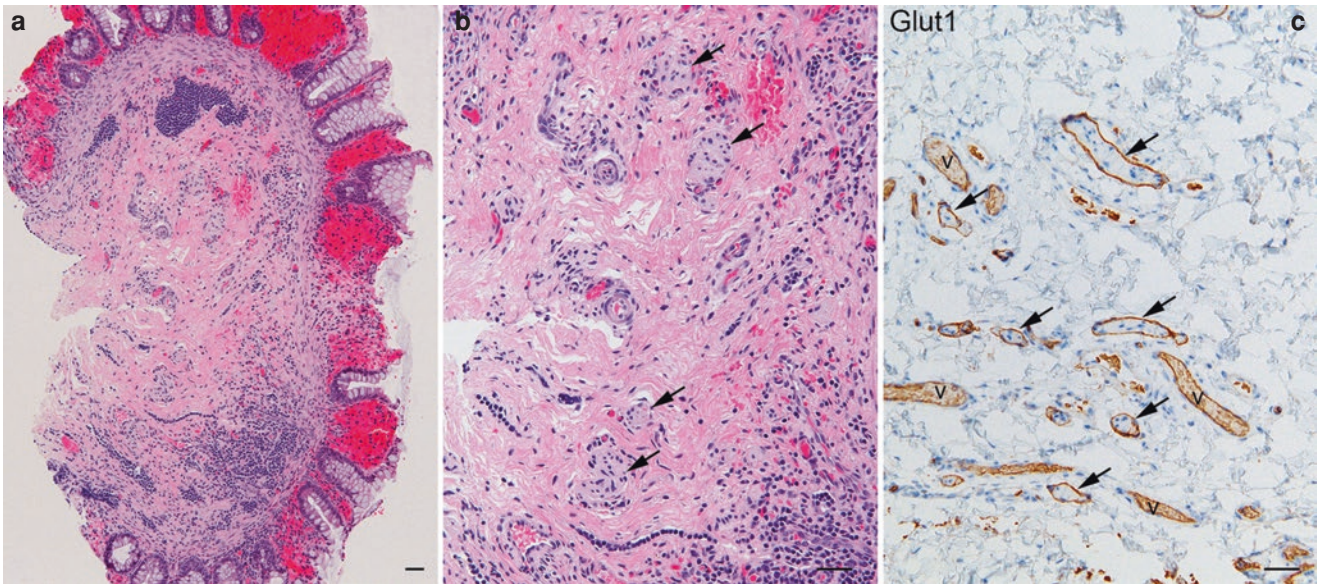

Fig. 19.1 Diagnosis of Hirschsprung disease by rectal suction biopsy. (**a**) An adequate suction rectal biopsy should be ≥2 mm in greatest dimension and contains a generous sample of submucosa. (**b**) Hirschsprung disease is diagnosed based an absence of ganglion cells in exhaustive histological sections of an adequate biopsy and the presence of crowded abnormally large caliber submucosal nerves (arrows). (**c**) Hypertrophic submucosal nerves (arrows) have Glut1-immunoreactive perineuria similar to extra-enteric (extrinsic) nerves. Glut1 also labels erythrocytes in vessels (v). Scale bars = 40 μm

in some cases. Reasons for consternation are many. Nerve hypertrophy is an inconsistent finding and the distinction between adequate and inadequate submucosal sampling is arbitrary. Ganglion cells, particularly the immature ones found normally in neonates, can be difficult to distinguish from reactive endothelial cells or lymphocytes. Inflammation, not uncommon in the setting of a constipated infant who has undergone rectal examination, barium enema, and possibly other diagnostic procedures, can obscure ganglion cells. The diagnostic challenge is compounded by artifacts like compression or tissue desiccation, which compromise histological resolution. Some of these problems are reduced by careful handling and expedient transportation/fixation. Unless enzyme histochemistry (see below) is planned, biopsies can be fixed at the bedside and sent to the laboratory in fixative. Any unfixed biopsies should be sent to the laboratory in a sealed container on a saline moistened Telfa pad and promptly fixed or frozen by laboratory staff.

The many challenges working with H&E-stained sections have led to many proposed ancillary histopathological approaches to evaluate rectal biopsies. Several papers have been published which tout immunohistochemistry to detect neuronal markers (e.g., PGP9.5) to facilitate recognition of ganglion cells [14], but very few laboratories employ these methods because in most cases ganglion cells, when present are fairly abundant and readily identified by H&E staining. When ganglion cells are rare, finding them requires evaluation of many sections from a given biopsy, which would require immunostains on an impractically large number of sections and/or destaining and immunostaining H&E sections with equivocal ganglion cells. In contrast, three ancillary approaches, acetylcholinesterase (AChE) histochemistry, choline transporter immunohistochemistry, and calretinin immunohistochemistry, detect changes in mucosal innervation which complement information gleaned from H&E sections.

Use of AChE histochemistry as a diagnostic tool for HSCR was pioneered by Meier-Ruge in the 1970s [15]. AChE is expressed on the membranes of cholinergic nerves from pelvic autonomic ganglia, which enter the distal rectum and project rostrally through all layers of the bowel wall. In the normal mucosa, these nerves are slender and sparse (Fig. 19.2a). However, in aganglionic rectum mucosal AChE-positive nerves are thick and concentrated (Fig. 19.2b) [16]. In experienced laboratories, AChE immunostaining alone appears to be a fairly sensitive and specific diagnostic approach [17, 18]. However, performance and interpretation of AChE histochemistry requires regular practice. False negative results from biopsies of premature infants or term babies less than 3 weeks of age are particularly problematic because, as with submucosal nerve hypertrophy, the density, coarseness, and extent of mucosal AChE-positive innervation increase with age [18, 19].

Multiple factors restrict use of AChE histochemistry to specific centers. Some practices, particularly those with small pediatric volumes, cannot justify the expense and

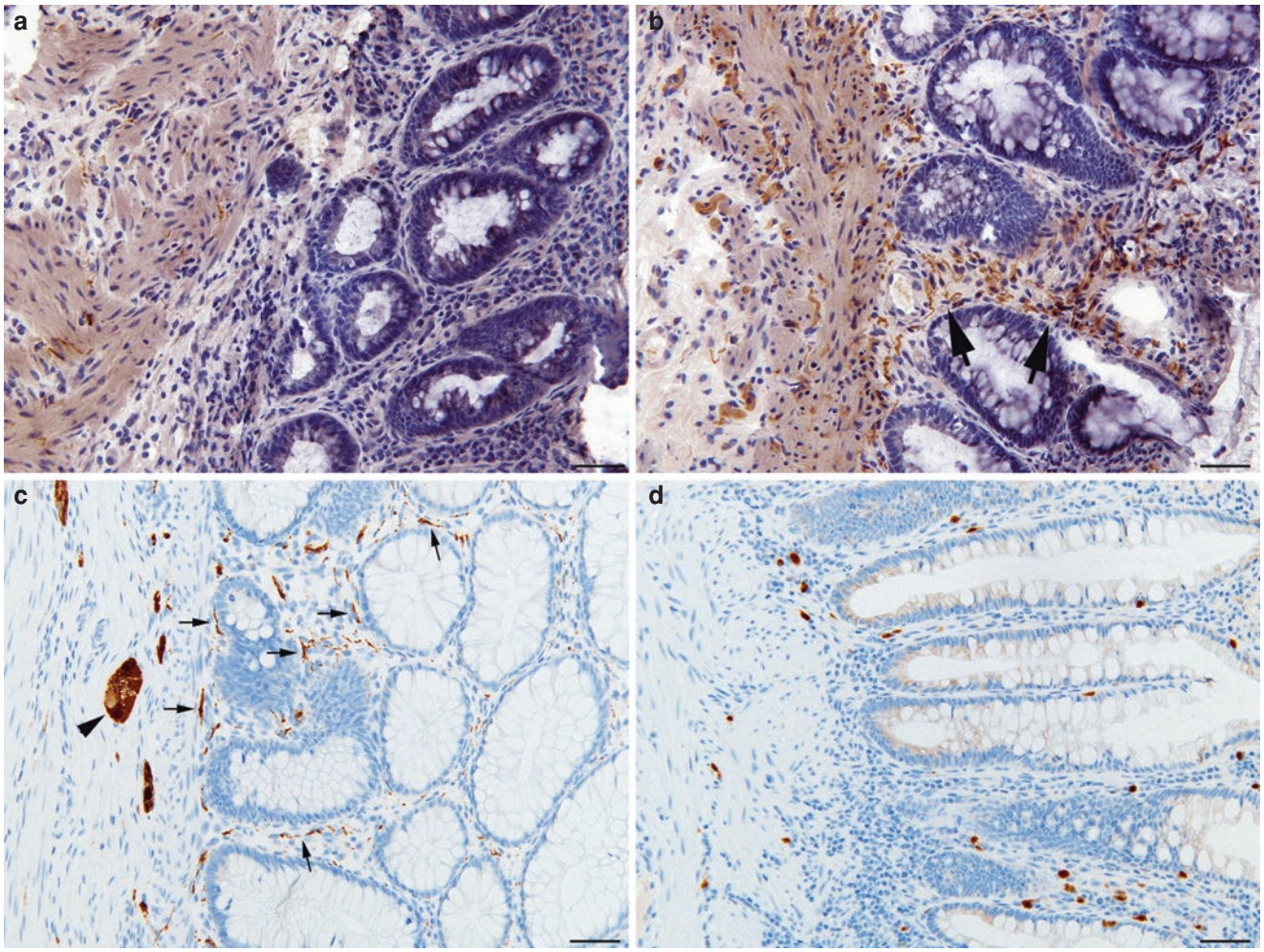

Fig. 19.2 Ancillary staining methods for Hirschsprung disease. (**a**, **b**) Acetylcholinesterase histochemistry highlights cholinergic nerve twigs which are sparse in normal mucosa (**a**), but abundant (arrows) in the mucosa overlying aganglionic rectal tissue (**b**). (**c**, **d**) Calretinin-immunoreactive ganglion cells (arrowhead) and mucosal neurites (arrows) are present in a biopsy of ganglionic rectum (**c**), but absent in mucosa overlying aganglionic rectal tissue (**d**). Round immunoreactive structures in (**d**) are mast cells. Scale bars: 50 μm

effort required to maintain a histochemical assay that is used relatively infrequently. AChE histochemistry also necessitates frozen tissue, typically an additional suction biopsy, because the enzymatic activity is lost when tissues are formalin-fixed and embedded in paraffin. Acquisition of additional tissue and appropriate handling can be impediments, especially if biopsies are performed in remote clinics. Choline transporter immunohistochemistry, which can be used with sections from formalin-fixed paraffin-embedded tissue, has been suggested as a surrogate for AChE histochemistry [20]. As with the latter, choline transporter immunohistochemistry labels cholinergic nerve terminals in the muscularis mucosae and lamina propria, which are more abundant and coarser in Hirschsprung disease.

Calretinin immunohistochemistry is another ancillary method to resolve changes in mucosal innervation that correlate with aganglionosis and has been adopted by many laboratories as an alternative or complement to AChE histochemistry. Calretinin is a calcium-binding protein expressed in a subset of submucosal and myenteric ganglion cells, including muscularis mucosae and lamina propria neurites from intrinsic neurons (Fig. 19.2c) [21]. Aganglionic bowel is devoid of calretinin-immunoreactive mucosal innervation (Fig. 19.2d), except in a 1–2 cm region immediately distal to ganglionic bowel, where neurites from the latter extend into the mucosa of the aganglionic segment [22]. Calretinin immunohistochemistry can be performed on formalin-fixed paraffin-embedded sections, so no additional biopsies or special tissue processing is required. More importantly, several studies have demonstrated equivalent or superior diagnostic specificity and sensitivity to AChE histochemistry [23–25], although rare situations exist when calretinin immunohistochemistry may be misleading (e.g., very short-segment aganglionosis) [22, 26, 27].

Incisional ("Full-Thickness") Rectal Biopsy

Incisional biopsies require anesthesia and may be associated with slightly higher rate of complications than suction biopsies but are indicated in certain situations. One frequent use is to exclude HSCR in a toddler or older patient, particularly if prior suction biopsies yielded inadequate submucosa. Other indications for incisional biopsy include results from suction biopsies that suggest possible very short segment HSCR and evaluation of a patient with chronic obstructive symptoms months to years after HSCR surgery to exclude transition zone pull through. Since full-thickness biopsies are performed under anesthesia, the surgeon is able to visualize the anorectal transition and any prior surgical anastomosis boundary and establish the exact location of the biopsy. Incisional biopsies are usually labeled "full-thickness" by the surgeon, but frequently do not extend through the muscularis interna to reach the myenteric plexus. These biopsies are usually small and fairly symmetric but occasionally are deliberately sampled longitudinal strips. For the latter, whether truly full-thickness or not, the biopsy should be oriented by the surgeon to designate the proximal and distal ends because a transition between ganglionic and aganglionic bowel may be evident along the length of a 2–4 cm-long "strip" biopsy and provide definitive evidence for very short segment HSCR. In a patient, whose obstructive symptoms persist long after a pull-through procedure, punch biopsies taken at four quadrants just proximal to the anastomosis line may be used to exclude features of transition zone pull through (e.g., partial circumferential aganglionosis, hypoganglionosis, or nerve hypertrophy), which may involve only portions of the bowel circumference [28–30]. Most full-thickness biopsies are large enough to be divided and freeze a small portion including mucosa and submucosa for enzyme histochemistry, if indicated.

Diagnosis of Intestinal Neuronal Dysplasia by Rectal Biopsy

Rectal biopsy is the principal diagnostic procedure for isolated intestinal neuronal dysplasia type B (IND). IND was first described by Meier-Ruge in patients with symptoms of Hirschsprung disease but ganglion cells in their rectal biopsies [31]. The diagnostic criteria have evolved with time, but remain based on counts of submucosal ganglion cells, as identified by enzymatic histochemical staining for lactate dehydrogenase and/or succinate dehydrogenase activities [32]. The latter, like AChE histochemistry, are performed on frozen sections, but the quantitative analysis requires a standardized section thickness (15 μm) and is subject to significant observer bias [33]. Formalin-fixed paraffin-embedded biopsies are not adequate. An overabundance of "giant" submucosal ganglia (>8 ganglion cells/ganglion in an appropriately stained section) is the primary diagnostic feature of IND. However, the proportion of giant ganglia appears to change with age [34], and the formal diagnostic criteria are not considered valid for patients under a year of age [32].

IND has also been reported in ganglionic bowel proximal to the aganglionic segment in HSCR, albeit mostly in patients less than a year of age, a finding that some studies suggest may portend a worse outcome after pull-through surgery [35–41]. Recently, we used paraffin sections, immunostaining for the neural marker Hu C/D, and colonic tissue from autopsy control infants (no history of dysmotility) to establish diagnostic criteria for IND-like submucosal hyperganglionosis (IND-SH) [42]. Based on these criteria, IND-SH (deviations >3 standard deviations from controls) were observed at the proximal surgical margin of 15% of patients with short-segment HSCR, up to 15 cm proximal to the aganglionic segment.

Considerable confusion and controversy exist regarding IND. Many have questioned the existence or clinical significance of this histopathological phenotype [34, 43–47]. Skepticism is due to many factors including lack of appropriate controls, changes in diagnostic criteria, erroneous extrapolation of diagnostic criteria to H&E-stained paraffin sections, and the possibility that hyperplasia of submucosal ganglion cells is a secondary adaptation to downstream obstruction, as opposed to a primary neuropathy. At this time, it seems prudent to regard IND as an "investigational" phenotype in need of research studies with appropriate controls to validate diagnostic features and demonstrate any clinical significance. Certainly, the diagnosis should not be rendered based solely on analysis of paraffin sections or outside the context of a reference laboratory, which has performed adequate internal validation studies.

Use of Rectal Biopsies to Diagnose Other Conditions

Rectal biopsy is primarily a procedure to diagnose HSCR or IND, and the deliberate search for other histopathologic etiologies for intestinal dysmotility is best approached with full-thickness or seromuscular biopsies from other parts of the gastrointestinal tract. Suction biopsies and many biopsies designated as "full-thickness" by the surgeon fail to extend into the muscularis propria and provide no insight into the muscularis propria or myenteric plexus. Those that truly are full thickness generally sample a very small portion of the muscularis propria and myenteric plexus. Small sample size and the normal hypoganglionic nature of the distal rectum prohibit diagnosis of hypoganglionosis and reduce the likelihood of recognizing key pathological features that are only present in a small subset of neurons or muscle cells (e.g.,

inclusion disorders). Furthermore, the neuromuscular microanatomy of the distal rectum is different from most of the rest of the intestines and mimics changes considered pathologic in other sites. The muscularis propria of the distal rectum is thickened and separated into discrete bundles by fibrous tissue, which also interdigitates between the muscularis externa and interna around the myenteric plexus. Elsewhere this pattern of fibrosis might suggest visceral myopathy or post-inflammatory scarring. Furthermore, selective atrophy of rectal muscularis interna has been described as a consequence, rather than cause, of chronic constipation [48]. As discussed above, except in infants and young toddlers, large submucosal nerves with extrinsic morphological features (e.g., conspicuous Glut1-immunoreactive perineurium) are normal in the distal rectum, but not more proximally. These nerves are identical in size to, but fewer in number than, the large caliber nerves observed in the transition zone of HSCR. In an infant with HSCR they are regarded by many as an indicator of physiologically abnormal bowel that can cause persistent obstructive symptoms if it is not resected during a pull-through procedure [49, 50]. In the distal rectum of an older patient, occasional large nerves are normal and aganglionosis or prior transition zone pull through should only be suspected if abundant large nerves are present.

Despite these potentially misleading features, occasionally findings in a rectal biopsy done to exclude HSCR actually lead to another specific diagnosis. While insensitive, rectal biopsy has led to accurate diagnosis of conditions associated with inclusions in ganglion cells such as mitochondrial disorders [51] or neuronal nuclear inclusion disease [52]. In principle, diagnostic features of some inflammatory visceral myopathies or neuropathies might also be evident in a true full-thickness rectal biopsy, which samples a generous amount of muscularis propria and myenteric plexus. Although widespread involvement of the intestinal tract is usually present in these very rare disorders, the changes can be patchy and we have no idea how often rectal tissues are affected. More typically multiple sizable laparoscopic or open surgical intestinal biopsies are considered the diagnostic standard for adequate evaluation.

Intestinal Biopsy to Evaluate a Patient with Chronic Pseudo-Obstruction

Once HSCR is excluded, most infants either resolve their symptoms or can be managed satisfactorily with dietary/medical therapy. Unfortunately, other patients continue to have debilitating dysmotility or acquire chronic intestinal pseudo-obstruction as older children or adults. Clinical findings in many of these patients are difficult to distinguish from true obstruction, and it is not uncommon for them to undergo laparotomy to exclude an anatomic etiology. After anatomic cause is excluded, the recurrent nature of their disorder coupled with a history of prior abdominal exploration prompts concerns about obstruction due to abdominal adhesions, which can lead to multiple laparotomies in some instances. Diversion enterostomy is also a common, particularly for those patients with profound colonic dysmotility. Intestinal biopsy is often considered as part of any of these surgeries or sometimes as a primary diagnostic procedure. Intestinal biopsy to identify ganglionic bowel for either a leveling ostomy or primary pull-through procedure is also an integral component of HSCR management.

Diagnostic intestinal biopsies from patients with intestinal pseudo-obstruction are performed cognizant that (a) similar clinical findings may be due to numerous etiologies, not all of which have anatomic correlates, (b) diagnostic histopathological features are often patchy and may be missed with inadequate or unlucky sampling, (c) key histological findings can be mimicked or obscured by artifacts associated with improper handling, and (d) many diagnoses have prognostic or genetic implications, but will not significantly affect clinical management. No standard exists with regard to which or how many sites should be biopsied from a patient with pseudo-obstruction. Sometimes manometric data or other clinical findings suggest more severe involvement of one part of the intestinal tract. However, it is prudent to biopsy multiple sites including large and small intestine to gain information about the distribution of pathological changes and their severity/progression. If segmental dilatation is present, at least one biopsy should be from the dilated area and another from bowel immediately downstream.

An international working group recommended full-thickness biopsies at least 1.5 × 1.5 cm, with transverse closure of the surgical defect [53]. In my experience with pediatric patients, biopsies are more often rectangular or ovoid, range from 1 to 1.5 cm in greatest dimension, and provide adequate tissue for evaluation. Priority should be given to obtaining well-oriented, undamaged, formalin-fixed, paraffin-embedded tissue sections. However, it is usually possible to save a 1 mm^3 sample of muscularis propria and enclosed myenteric plexus in electron microscopy fixative and snap freeze small full-thickness portions of each biopsy. Pre-surgical coordination between pathologist and surgeon is advisable and the surgeon should procure biopsies with gentle traction (typically applied with a nylon suture) and send the specimen to the laboratory for immediate processing. Orientation of the biopsy so that sections are cut perpendicular to the serosal surface is most important, and a biopsy should ideally be aligned in a true transverse or longitudinal plane.

As with rectal biopsies, H&E-stained sections provide the starting point for histological evaluation of intestinal biopsies. Generally, a single slide (1–3 sections per slide) is sufficient; additional sections or special stains are obtained as needed. Trichrome-stained sections provide good contrast between smooth muscle and collagen-rich fibrous tissue, and

are often helpful to resolve intramuscular fibrosis. Except as a research tool, immunohistochemistry should be guided by the clinical and H&E findings. Immunohistochemistry can help identify and quantify specific cell types (e.g., neurons, enteric glia, interstitial cells of Cajal, fibroblast-like cells, and smooth muscle) involved in enteric neuromuscular activity, and has been used to distinguish specific subtypes of enteric neurons and/or the distribution of their cell processes. However, for the most part, disease-specific alterations in the density, distribution, or intensity of immunoreactive cells have not been found.

For example, consider CD117 (c-kit) immunohistochemistry. In the gut wall, CD117 is a fairly specific marker for interstitial cells of Cajal (mast cells also express this antigen), which mediate intestinal pacemaker activity. However, CD117-positive interstitial cells are difficult to quantify, especially in tissue sections. Reduced or absent CD117-immunoreactive pacemaker cells have been reported inconsistently in multiple contexts, including diverse conditions (e.g., HSCR, post-inflammatory strictures), as what appears to be a non-specific secondary change [54, 55]. Nonetheless, many pathologists use CD117 immunochemistry in their work-up of intestinal biopsies from patients with pseudo-obstruction, with no clear idea how results of such analysis should be interpreted. Similarly, poorly understood alterations in the densities of neurochemically defined subtypes of enteric neurons or glial cells have been reported in patients with slow transit constipation, hypoganglionosis, idiopathic megacolon, transition zone of Hirschsprung disease, and congenital chronic intestinal pseudo-obstruction [56].

Some types of intestinal neuropathology that can be diagnosed from biopsies are listed in Table 19.1 and their histopathological features are briefly reviewed in the following sections.

Table 19.1 Intestinal neuromuscular pathology in intestinal biopsies

Diagnosis[a]	H&E findings	Ancillary pathology	Confirmatory studies
Congenital myenteric hypoganglionosis	Sparse myenteric ganglion cells organized as individual cells or pairs with minimal adjacent neuropil	May require multiple levels to confirm impression and determine extent of intestinal involvement; immunohistochemistry with neuronal markers (e.g., Hu C/D, PGP9.5) may help resolve ganglion cells	None (genetic basis unknown)
Degenerative enteric neuropathy (including inflammatory neuropathies)	Reduced density of ganglion cells without significant loss of adjacent neuropil; degenerating neurons; lymphocytic or eosinophilic ganglionitis; rarely neuronal nuclear inclusion disease	Immunohistochemistry to document intra-ganglionic T-cells; consider electron microscopy or immunohistochemistry to characterize intranuclear inclusions	Serology for anti-neuronal antibodies
Ganglioneuromatosis/ neurofibromatosis	Ganglioneuromatous or neurofibromatous hyperplasia of enteric plexuses with or without mucosal neuromas		Other clinical features; *RET* (MEN2B), *NF1*, or *PTEN* (Cowden) mutational analysis
Mitochondrial disorders	Eosinophilic cytoplasmic inclusions (megamitochondria) in ganglion cells; atrophy of muscularis externa	Electron microscopy to document megamitochondria ± abnormal cristae	Other clinical features; Reduced plasma thymidine phosphorylase activity in MNGIE; Mutational analysis for various established hereditary mitochondriopathies (e.g., Alpers, MNGIE)
Diffuse abnormal layering of small intestinal smooth muscle	Markedly disorganized lamination of muscularis propria (e.g., trilaminar)	Immunohistochemical demonstration of absent Filamin A	Other clinical features: *FLNA* mutational analysis
Megacystis microcolon intestinal hypoperistalsis syndrome	No consistent histopathological alterations	Possibly abnormal "clumping" of actin-gamma-2 in smooth muscle cells	*ACTG2*, *MYH11*, *MYLK*, *LMOD1*, *MYL9*, and *PDCL3* mutational analysis
Familial visceral myopathy	No consistent histopathological alterations; fibrosis and myocyte vacuolar degeneration are common, but patchy	Possibly abnormal "clumping" of actin-gamma-2 in smooth muscle cells	*ACTG2*, *MYH11*, and *SGOL1* mutational analysis[b]
Inflammatory myopathies (visceral leiomyositis)	Dense and usually diffuse lymphocytic or eosinophilic inflammation of muscularis propria	Immunohistochemistry to document intra-ganglionic T-cells	Serology to demonstrate anti-smooth muscle antibodies

[a] Based in part on the London Classification of gastrointestinal neuromuscular pathology [56]: clinical-histopathologic correlates with established etiologies as determined by consensus of an International Working Group. Excludes morphological abnormalities that may be clearly identifiable, but provide only weak evidence of the pathogenic mechanism and may not be causally related to an observed clinical entity

[b] MMIHS and FVM have heterogeneous etiologies. *ACTG2* mutations have been described most frequently, but pathogenic alterations in other genes listed have also been observed

Congenital Myenteric Hypoganglionosis

"Hypoganglionosis" denotes a reduced density of neurons relative to normal. In a literal sense, the term encompasses a wide range of possible abnormalities, including relatively small alterations in neuronal number and/or loss of selective subtypes of neurons. Even in resection specimens, such small changes are impossible to diagnose by simple analysis of H&E-stained sections and very difficult to diagnose reliably even with immunostaining and/or sophisticated types of morphometric analysis. The problem is compounded by the limited sample present in a typical intestinal biopsy, marked variation in the observed numbers of ganglion cells observed in control populations [57, 58], and uncertainty about how distension may affect ganglion cell density. For this reason, many of us only express confidence recognizing moderate-to-severe myenteric hypoganglionosis (to the best of my knowledge, submucosal hypoganglionosis per se has not been described). Myenteric hypoganglionosis can be congenital ("hypogenesis") or acquired. Acquired forms are neurodegenerative conditions and described in the next section.

The severe and readily recognized form of congenital hypoganglionosis can be recognized in H&E-stained sections, provided a generous biopsy of at least one-fourth of the bowel wall circumference or multiple affected smaller biopsies are obtained. The essential microscopic features are a predominance of small myenteric ganglia (one or two ganglion cells) with minimal amounts of surrounding neuropil (Fig. 19.3) [59, 60]. Because the entire myenteric plexus is hypoplastic, the laminae of the muscularis propria are closely apposed and ganglion cells are tightly sandwiched between the two muscle layers. Ganglion cell size and cytology may be normal or relatively immature. Submucosal ganglia are usually not affected, and their density often appears to exceed that of myenteric ganglia. Immunostains are not necessary, but neural markers may help resolve immature ganglion cells

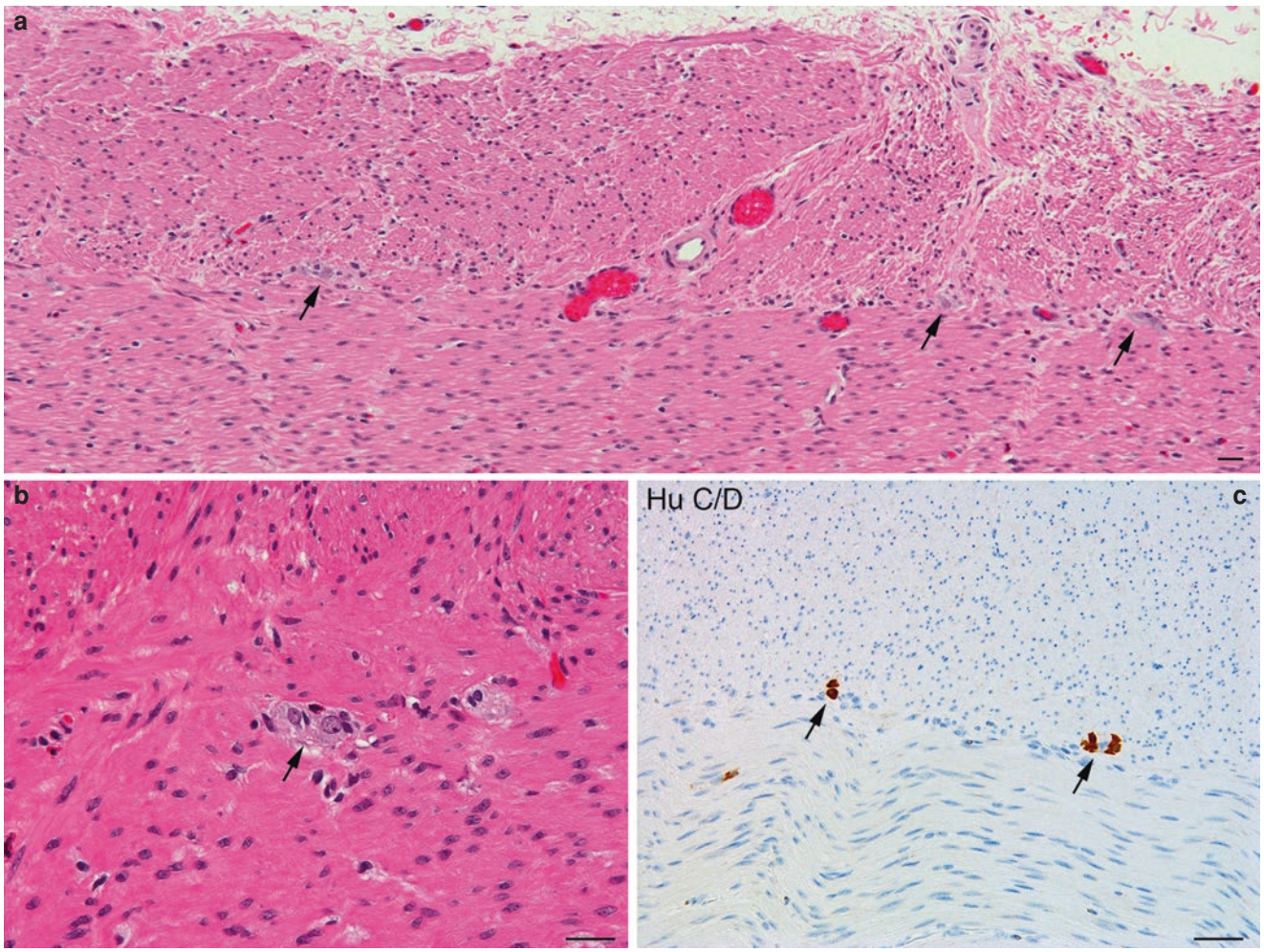

Fig. 19.3 Myenteric hypoganglionosis. (**a**) At low magnification, a "string" of very small myenteric ganglia (arrows) is found at the interface between the muscularis interna and externa. (**b**) Each small ganglion (arrow) is composed of one or two neurons with minimal neuropil. (**c**) Hu C/D immunostain highlights the sparse myenteric ganglion cell bodies. Scale bars: 50 μm

and exclude aganglionosis. Reduced AChE-positive innervation has been touted as a helpful diagnostic feature, and many published studies of hypoganglionosis are from laboratories that use this technique routinely [61]. Absent NeuN antigen expression in myenteric ganglia also has been observed in most patients [59]. Diffuse involvement of the intestinal tract is typical, but similar features may be observed in the transition zone of HSCR. In the transition zone, particularly in short-segment HSCR, hypertrophic extrinsic nerves co-exist with hypoganglionosis, whereas hypertrophic myenteric or submucosal nerves are not part of isolated congenital hypoganglionosis. The pathogenesis of congenital hypoganglionosis is unknown, but does not appear to overlap genetically with HSCR [59, 62].

Ganglioneuromatosis/Neurofibromatosis

Dysmotility due to hyperplasia and disorganization of enteric nervous system components is recognized as part of the phenotypic spectrum of at least three hamartoma syndromes—multiple endocrine neoplasia type 2B (MEN2B), neurofibromatosis type I (NF1), and Cowden syndrome [63]. Ganglioneuromatous hyperplasia can occur with any of the three conditions, whereas intestinal neurofibromas are only associated with NF1. These lesions can occur anywhere along the length of the bowel and involve mucosa, submucosa, or myenteric plexus, although pseudo-obstruction is most often associated with diffuse lesions that involve extramucosal portions of the bowel wall. Ganglioneuromatous enteric lesions have been sub-divided into diffuse ganglioneuromas, ganglioneuromatous polyposis, and solitary polypoid ganglioneuroma [64]. Diffuse ganglioneuromas are composed of variable numbers of ganglion cells, glial cells, and nerve processes, and have an infiltrative growth pattern, frequently along exaggerated neural pathways in the myenteric, intramuscular, and submucosal plexuses (Fig. 19.4a–c). Diffuse ganglioneuromas are almost invariably syndromic, and often associated with similar mucosal hamartomas (Fig. 19.4d, e), but mucosal lesions alone do not necessarily imply a syndrome. Solitary polypoid ganglioneuroma is a sporadic mucosal hamartomatous lesion, which only produces dysmotility due to anatomic obstruction or intussusception. Polypoid ganglioneuromas are formed by collections of cytologically mature ganglion cells, glia, and neuropil in the lamina propria, which displace adjacent crypts or glands. The presence of many such lesions constitutes ganglioneuromatous polyposis. A syndromic basis for at least some examples of ganglioneuromatous polyposis has been suggested, but no definite syndrome or genetic association has been identified [63]. While the ganglion cells of these hamartomas are easy to recognize, the network of neural tissue that accompanies them may be difficult to distinguish from surrounding lamina propria or smooth muscle. S100 immunostain highlights the nerve processes and associated glial cells.

Mitochondrial Disorders

Intestinal pseudo-obstruction is a frequent, sometimes severe, and occasionally initial problem for patients with hereditary mitochondrial disease. For patients with severe enteric manifestations, in addition to central nervous system pathology, the term mitochondrial neurogastrointestinal encephalomyelopathy (MNGIE) is used. Similar gastrointestinal dysfunction and pathological findings have been described in patients with mutations in at least three different genes [65], including patients with *POLG1* mutations and Alpers syndrome [66]. Histopathological features of mitochondriopathy are multifocal thinning or loss of the muscularis externa, absence of interstitial cells of Cajal [67], and megamitochondria in enteric neurons ± smooth muscle (Fig. 19.5). In H&E-stained sections megamitochondria are dense, eosinophilic cytoplasmic granules 1–5 μm in diameter. They are only observed in a minority of ganglion cells, sometimes less than 10%. Less frequently they can be resolved in smooth muscle cells. Electron microscopy can help clarify that these inclusions are giant mitochondria and sometimes resolves abnormal cristae. A thorough neurological examination and other laboratory tests may reveal extra-enteric findings that help confirm the diagnosis.

Diffuse Abnormal Layering of Small Intestinal Smooth Muscle (X-Linked Pseudo-Obstruction)

An X-linked form of familial intestinal pseudo-obstruction was recognized several decades ago and recently shown to be caused by mutations in the Filamin A gene (*FLNA*) [68, 69]. Affected males usually have one or more other congenital anomaly (e.g., cerebral periventricular heterotopias, atrial septal defect, cleft palate) and some are thrombocytopenic. All patients have intestinal malrotation and congenital short small bowel (CSSB). Alterations in the density and relative numbers of argyrophilic and argyrophobic ganglion cells have been described, albeit inconsistently, and led to the impression that the disorder is a primary neuropathy [70]. However, stronger evidence now exists for a primary myopathic basis [71]. *FLNA* is expressed in intestinal smooth muscle, not neurons, and expression is lost in males with *FLNA* mutations and pseudo-obstruction. Histologic sections of well-oriented biopsies demonstrate diffuse foci of disorganized lamination of the small intestinal muscularis propria, including trilaminar architecture (Fig. 19.6). Colonic biopsies from a teen patient showed a unique pattern of myocyte multinucleation in the innermost layers of the muscula-

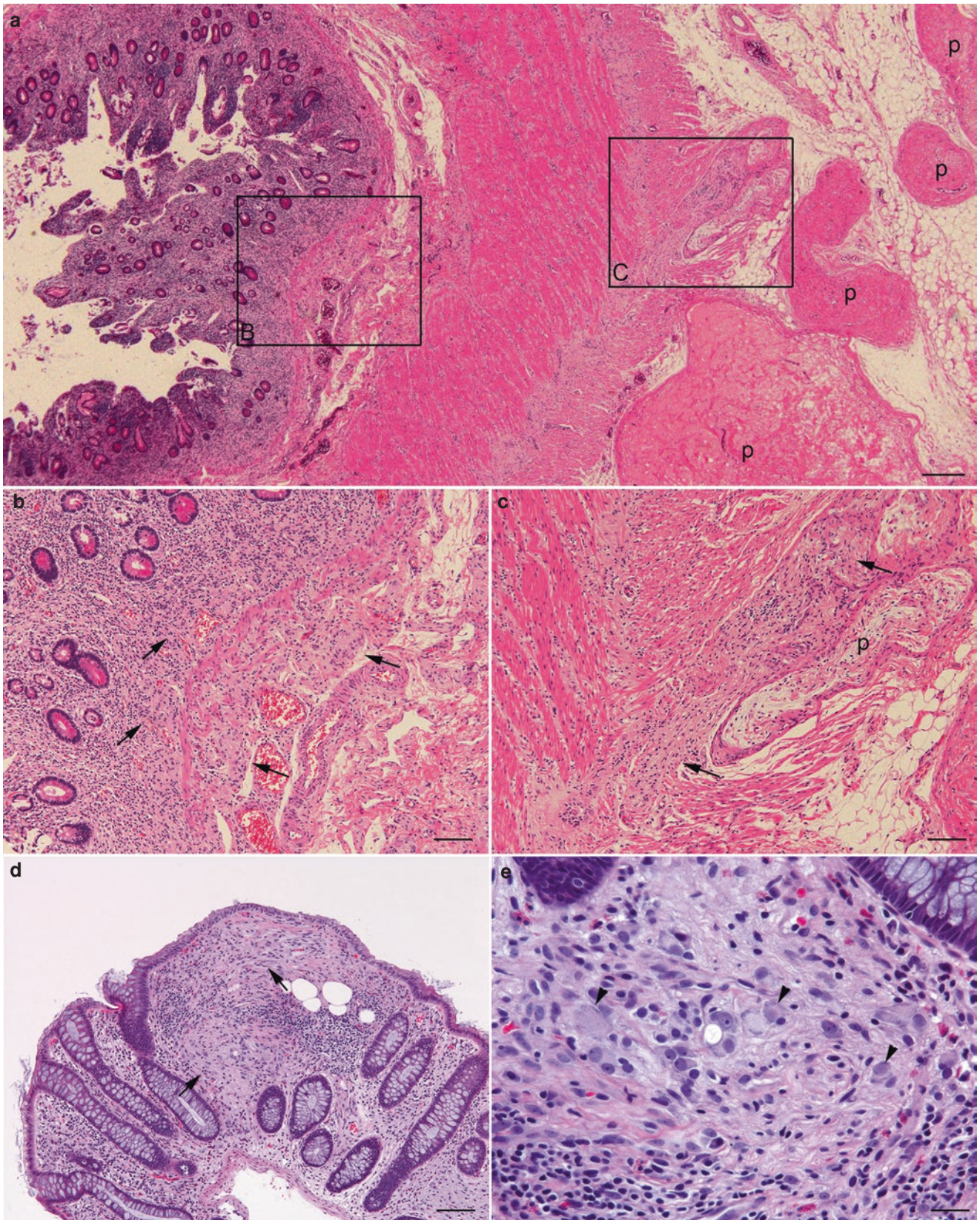

Fig. 19.4 Ganglioneuromatous hyperplasia (neurofibromatosis and multiple endocrine neoplasia type 2B). (**a**) Low magnification image shows a plexiform neurofibroma in the mesentery of the small bowel in a patient with neurofibromatosis. Ganglioneuromatous hyperplasia (arrows) is present in the underlying myenteric plexus (**b**) and submucosa/mucosa (**c**). (**d**, **e**) A mucosal ganglioneuroma (arrows) in a patient with multiple endocrine neoplasia type 2B is composed of ganglion cell bodies (arrowheads) and surrounding neuropil. Scale bars: (**a**) 250 μm; (**b**) 100 μm; (**c**) 100 μm; (**d**) 100 μm; (**e**) 25 μm

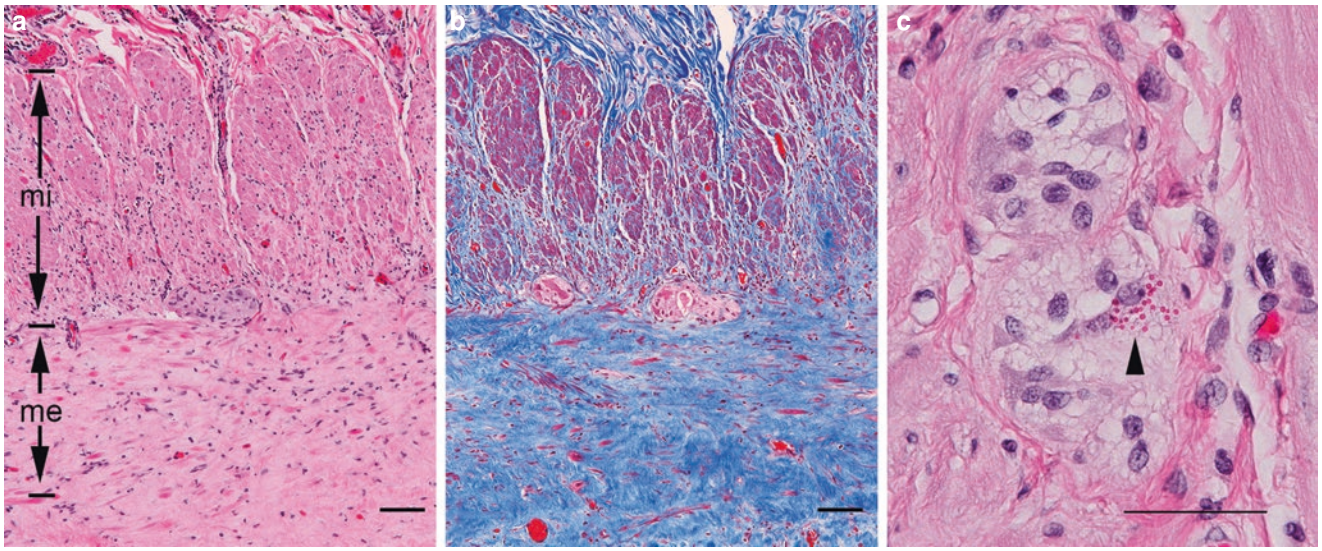

Fig. 19.5 Mitochondriopathic histopathology. (**a**) H&E- and (**b**) trichrome-stained sections show near complete effacement of the muscularis externa (me) by fibrous tissue (blue in **b**) with less severe atrophy of the muscularis interna. (**c**) Dense eosinophilic granules (megamitochondria) are present in a subset of enteric ganglion cells (arrowhead). Scale bars: (**a**) 100 μm; (**b**) 100 μm; (**c**) 50 μm

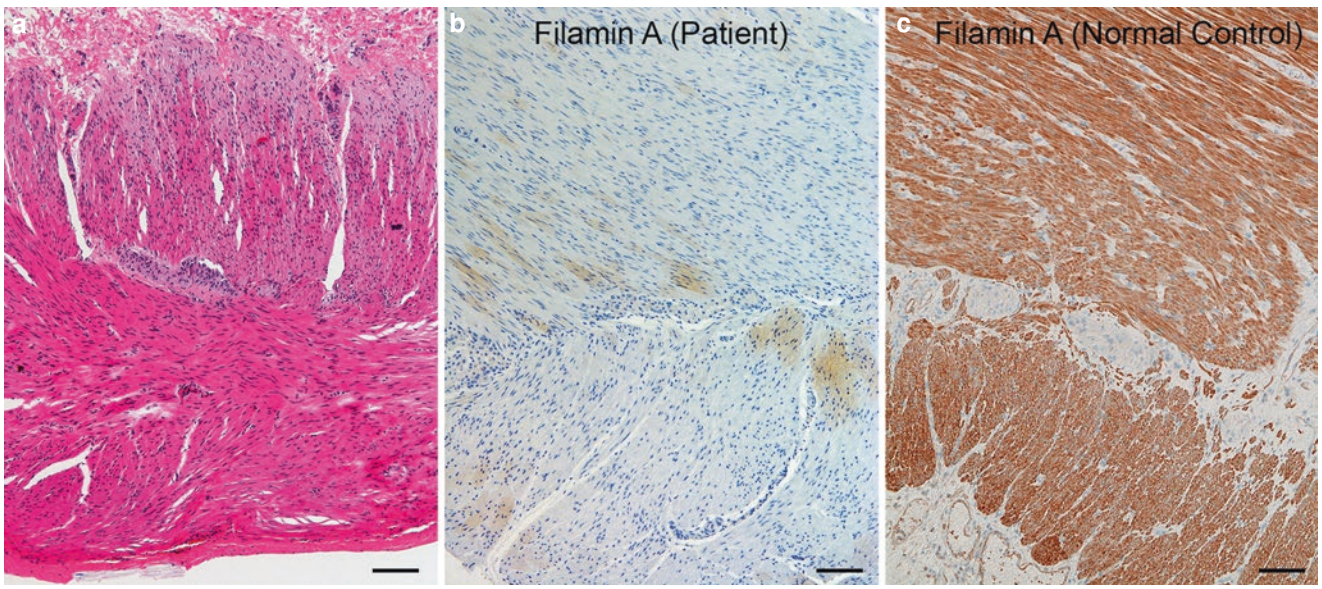

Fig. 19.6 Filamin A-related visceral myopathy (X-linked intestinal pseudo-obstruction). (**a**) H&E-stained section from an area of abnormal lamination in the small intestinal muscularis propria shows a vaguely trilaminar architecture. (**b**) Filamin A immunohistochemistry demonstrates dramatic loss of muscular immunoreactivity, in comparison to the diffuse dense cytoplasmic immunoreactivity in a section of normal control bowel (**c**). Scale bars: 100 μm

ris interna [71]. Although abnormal layering has been observed throughout the small intestine in those few cases with extensive sampling, intact lamination is present in some areas and diagnostic features could be missed with a small biopsy. Therefore, immunohistochemistry and/or mutational analysis should be considered for a male patient with CSSB.

CSSB and intestinal malrotation also result from recessive mutations in the autosomal gene, Coxsackie and adenovirus-receptor like membrane protein (*CLMP*) [72]. However, neither pseudo-obstruction nor abnormal smooth muscle lamination is part of the phenotype in *CLMP*-related CSSB.

Degenerative Enteric Neuropathy

The London classification system for gastrointestinal neuromuscular pathology recognizes neuronal degeneration with or without associated inflammation of ganglia as an etiology for intestinal pseudo-obstruction [56]. Recognition of neuronal degeneration is subjective, and one should be wary about a diagnosis based on subtle cytological changes like nuclear condensation, cytoplasmic hypereosinophilia, cellular vacuolization, or irregular cell contours. Unequivocal forms of neuronal degeneration are associated with one or more of the following: moderate-to-severe hypoganglionosis, lymphocytic, or eosinophilic ganglionitis, pathological intranuclear or cytoplasmic inclusions, and nuclear pyknosis or fragmentation. Although inflammatory cells often cluster in the periganglionic space between the muscularis interna and externa, it is rare to find lymphocytes or eosinophils within ganglia. Even in the context of transmural inflammation related to mucosal injury or inflammatory bowel disease, the proportion of inflammatory cells within ganglia is usually small. An exception is in the transition zone of some patients with HSCR, where concentrated intra- or peri-ganglionic eosinophilic inflammation may be present with minimal inflammation elsewhere [73]. As opposed to primary eosinophilic ganglionitis, these HSCR-associated infiltrates are not accompanied by degenerative cytopathology of ganglion cells and are not known to affect neuronal loss, clinical outcome or motility.

Degeneration of ganglion cells occurs due to varied primary causes, some hereditary (e.g., neuronal nuclear inclusion disease, mitochondrial disorders) and others acquired, is usually progressive, and culminates in hypoganglionosis. Acquired forms include neurodegenerative conditions of the central nervous system like Parkinson disease [74] and inflammatory neuropathies [75]. The pathological findings are widespread, although many individual ganglia are often spared. Extra-enteric findings help narrow the differential diagnosis. Histopathologically, numerous cytotoxic T-cells are present in the ganglia of lymphocytic ganglionitis, without significant inflammation in surrounding smooth muscle. Circulating anti-neuronal antibodies may be identified with lymphocytic ganglionitis, which sometimes arises as a paraneoplastic syndrome in patients with small cell carcinoma or other malignant tumors [76].

Neuronal degeneration and eventual hypoganglionosis are also observed Chagasic megacolon [77]. Early loss of neurons has been attributed to direct infection by the parasite followed by a chronic phase of lymphocytic ganglionitis and T-cell mediated neuronal apoptosis. Segmental colonic dilatation, as opposed to obvious pan-intestinal dysmotility is the predominant finding in Chagas disease, and neuronal loss is generally most severe in the dilated segment. The lymphocytic infiltrate can be mild and immunostains for CD3 or other lymphocytic markers may help distinguish lymphocytes from enteric glial nuclei. Alterations in the densities of specific neuronal subsets, enteric glia, and interstitial cells of Cajal have also been reported in Chagasic megacolon, but assessment of these details is not required to make the diagnosis [78].

Hereditary types of intestinal pseudo-obstruction and degenerative enteric neuropathy include some metabolic disorders (e.g., Fabry disease) [79], mitochondrial disorders (discussed above), and neuronal intranuclear inclusion disease (NIID) [52]. All of these are multisystem disorders that affect the brain and/or other organs, in addition to the bowel. Pathologic nuclear or cytoplasmic change in a subset of ganglion cells is the microscopic key to suspecting each diagnosis (Fig. 19.7). In NIID, hyalinized round inclusions larger than the large nuclei of ganglion cells are present, but even in advanced cases it may require examination of many ganglion cells to find this diagnostic feature. NIID is an autosomal dominant disorder caused by trinucleotide repeat expansions in the *NOTCH2NLC* gene [80]. Infantile, juvenile, and adult forms have been described, and it is possible that the phenotypes correspond to different genetic etiologies. The inclusions contain ubiquitin, SUMO-1, and other proteins found in the nuclear deposits of other "trinucleotide-repeat" disorders [81]. Electron microscopy demonstrates fine microfibrillar structures easily distinguished from nucleoli or normal chromatin.

Megacystis Microcolon Intestinal Hypoperistalsis Syndrome (MMIHS)

MMIHS is a congenital and severe form of pseudo-obstruction in which intestines and urinary bladder are affected. The bladder and small intestine are distended, but the colon is narrow because propulsion through the small intestine is incomplete. Megacystis may be recognized in utero by prenatal ultrasound examination. The same phenotype likely results from any neural or muscular defected that severely impedes smooth muscle contractility in both organs, and MMIHS has multiple etiologies. A genetic defect appears to be responsible for the majority of cases. Heterozygous mutations in a gene encoding smooth muscle actin (*ACTG2*) or biallelic mutations in other smooth muscle genes (*MYH11*, *MYLK*, *LMOD1*, *MYL9*, *PDCL3*) have been documented in some patients [82].

Despite impressive changes in gross anatomy, the intestinal and bladder histopathology in MMIHS is non-specific and underwhelming. Past descriptions have alternatively alluded to subtle changes in the enteric nervous system or smooth muscle without clear consensus [83–85]. The most

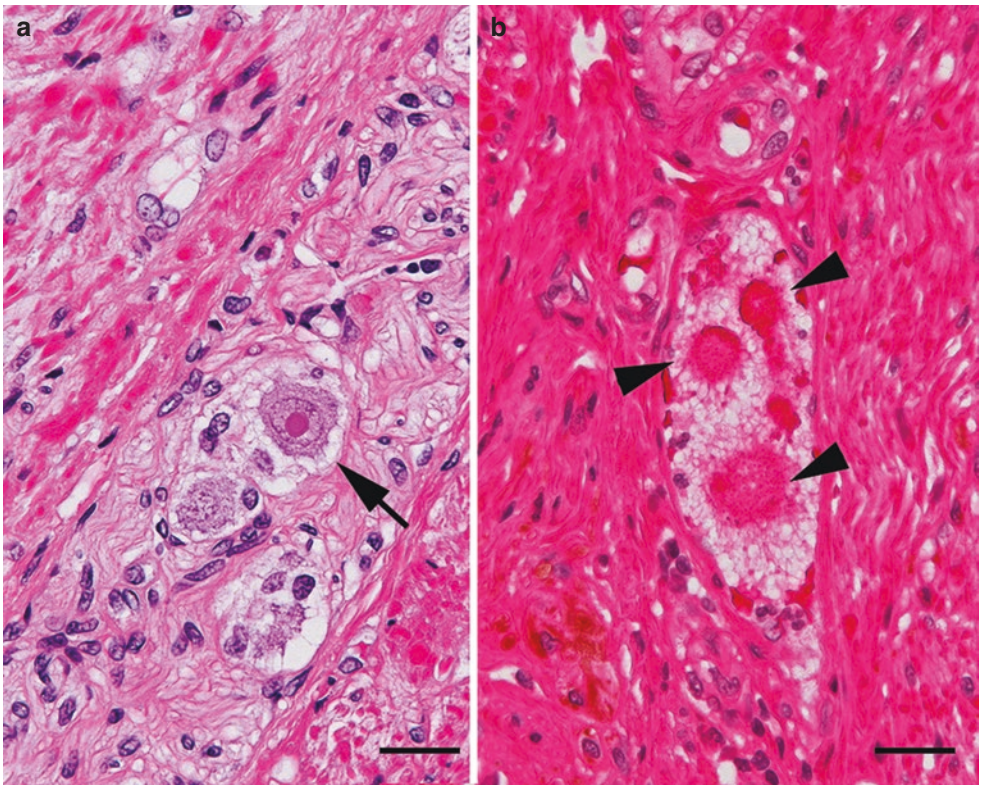

Fig. 19.7 Neuronal intranuclear inclusion disease. (**a**) Large eosinophilic intranuclear inclusions in a subset of neurons (arrow) are the diagnostic finding in this condition. (**b**) Rarely acute neuronal degeneration, as evidence by hyper-eosinophilic degenerating ganglion cells (arrowheads). Scale bars: 100 μm

frequent observations have been degeneration and fibrous replacement of smooth muscle and loss of smooth muscle actin immunoreactivity [86–89].

Familial Visceral Myopathy

Familial visceral myopathy (also termed "hollow visceral myopathy") refers to hereditary types of intestinal pseudo-obstruction with or without accompanying urinary bladder, gall bladder, or uterine hypocontractility. An effort has been made to subcategorize familial visceral myopathies based on inheritance patterns (autosomal dominant versus autosomal recessive), age of onset, and clinical–pathological features [90]. However, this scheme has limited clinical utility because of overlap between the groups and non-specificity of many of the findings. MMIHS is not included in the scheme, but should be considered a severe and early-onset form of familial visceral myopathy, a point made clear by identification of *ACTG2* mutations in children and adults with familial visceral myopathy [91–93].

Histopathological features range from no alterations to severe myocyte degeneration and fibrosis. Degenerating myocytes have condensed, crenated nuclei with perinuclear vacuoles or "halos" [7, 94, 95]. Irregular amounts of collagen accumulate between myocytes and may replace large parts of the muscularis propria. In some cases, one lamina is profoundly affected, but the other is spared. These changes are usually patchy and may be missed with a single biopsy. Inflammation is not a feature of familial visceral myopathy per se. Reduced, absent, or irregular immunostaining for smooth muscle cytoskeletal components (e.g., actin) have been described in some cases [93, 96], but are not a consistent feature. Retention of actin immunoreactivity does not exclude *ACTG2* mutation [91, 92].

A series of pediatric patients with CIPO, myopathic changes in their intestinal smooth muscle, and mutations in *SGOL1* was described recently [97]. The homozygous mutation (p.Lys23Glu) in the affected family members appears to have arisen from a common French–Canadian founder. In addition to CIPO, all affected individuals had cardiac sick sinus syndrome. *SGOL1* encodes a protein involved in the cohesin complex, which plays an important role in chromosome segregation during cell division and the regulation of gene expression. Myocyte degeneration and fibrosis were observed in these patients, along with ectopic myenteric ganglia and interstitial cells of Cajal.

Inflammatory Visceral Myopathy (Visceral Leiomyositis)

Inflammatory visceral myopathy exhibits similar myodegeneration and fibrosis to familial visceral myopathy, but in conjunction with inflammation of the muscularis propria. Severe inflammatory visceral myopathy is a rare condition which

can affect any age, including young infants. An autoimmune basis is suspected and affected infants often have elevated serum titers of antibodies against smooth muscle actin, although this may be secondary to muscle damage. A dense infiltrate of cytotoxic T-cells (CD3+, CD8+) is present in the muscularis propria and occasionally in the muscularis mucosae (Fig. 19.8) [98, 99]. Vascular smooth muscle is typically spared. The process is diffuse and not likely to be missed with a biopsy.

Although systemic autoimmune disorders (e.g., primary systemic sclerosis) injure enteric muscle and produce dysmotility, inflammation of the bowel wall is usually absent or mild. Fibrosis, likely secondary to vascular injury and secondary muscular ischemia, predominates without myocyte vacuolar degeneration [7]. Other forms of inflammatory visceral myopathy include eosinophilic leiomyositis and diffuse lymphoplasmacytic inflammation of the small intestine without myocyte degeneration [90, 100].

Non-specific Changes

Non-specific histological changes and artifacts created by tissue handling or processing extend an open invitation for misinterpretation in the pathologist's earnest desire to find clues to the etiology of intestinal pseudo-obstruction. In the muscularis propria, swelling or contraction of smooth muscle cells, possibly related to osmotic changes or delayed fixation, results in a variety of interesting cytological changes. Contraction bands can produce hyper-eosinophilic, actin-

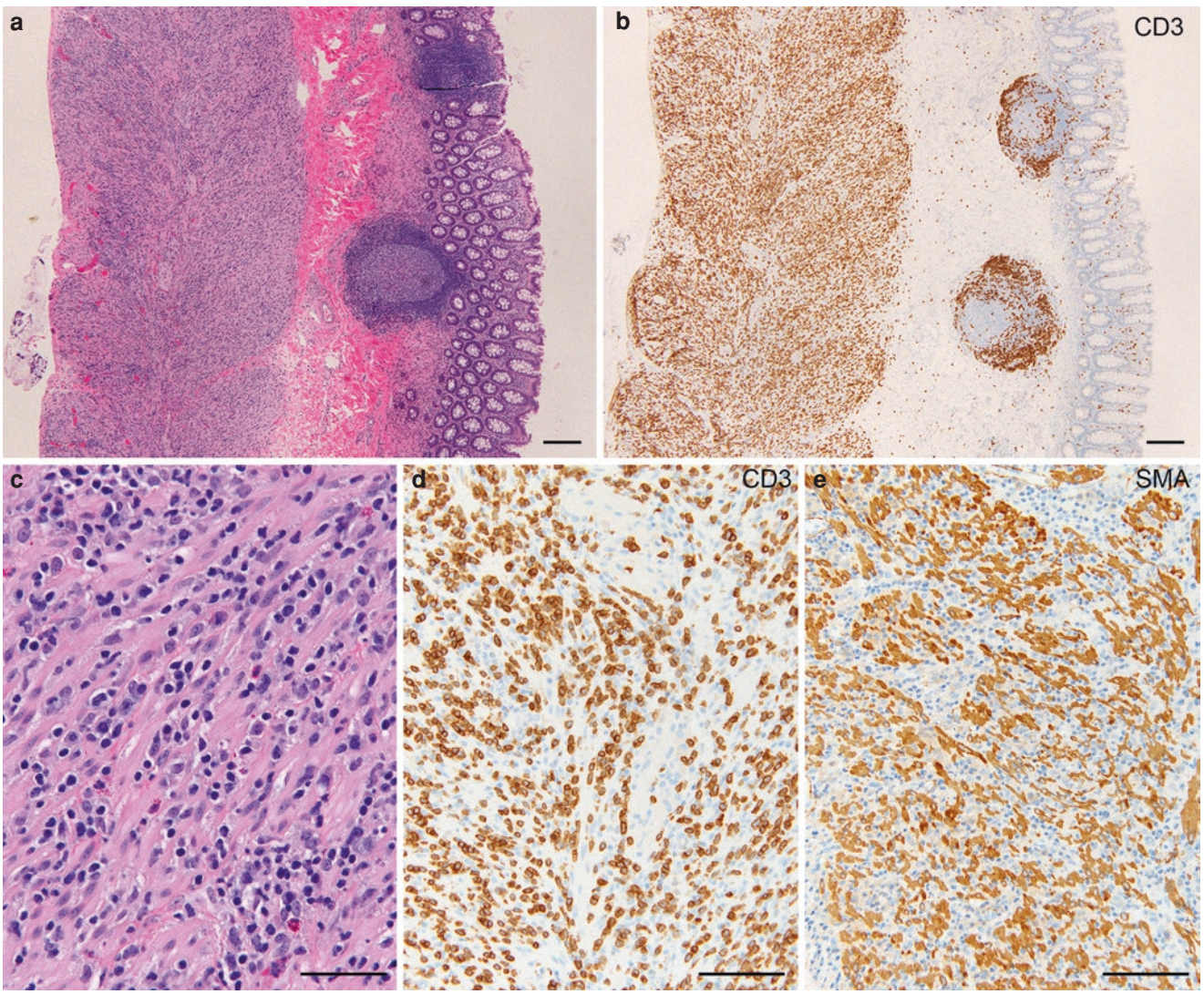

Fig. 19.8 Inflammatory visceral myopathy. (**a**) The muscularis propria (higher magnification in **c**) is diffusely infiltrated by a dense population of mature lymphocytes. (**b**) CD3 immunostaining demonstrates that the lymphocytes are primarily T cells (higher magnification in **d**). (**e**) Smooth muscle actin immunostaining demonstrates smooth muscle fibers, which are widely separated from each other by the inflammatory infiltrate. Scale bars: (**a**, **b**) 200 μm; (**c**–**e**) 100 μm

rich cytoplasmic globules in individual smooth muscle cells or align nuclei in clusters of adjacent cells to create a pattern of "nuclear stripes" in sections parallel to the long axis of a smooth muscle layer (Fig. 19.9a, b). Pale subsarcolemmal cytoplasmic foci, devoid of actin, can be difficult to distinguish from myodegeneration or increased extracellular matrix, especially without a trichrome stain. Muscular hypertrophy is a common response to chronic increased downstream resistance, and is presaged by increased mitotic activity, as evident in the transition zone of Hirschsprung disease (Fig. 19.9c). Similarly, distension can lead to myocyte damage and patchy fibrosis, which is usually more focal and confluent than the patchy or diffuse interstitial fibrosis of primary visceral myopathies. Secondary loss of CD117-immunoreactive interstitial cells of Cajal was discussed above. Similarly, one has to cautiously interpret smooth muscle actin-immunoreactivity, particularly in the distal small intestine, where weak staining of most of the muscularis interna, excluding the innermost layers, is normal [101–103], but has been interpreted as abnormal in some contexts [104–106].

Eosinophilic inflammation of the muscularis propria is a common non-specific reaction, particularly in distended bowel with bacterial stasis and mucosal injury. In contrast to primary eosinophilic leiomyositis, the muscle does not show degenerative changes and the eosinophilic infiltrates are generally mild and irregularly distributed.

Non-specific alterations of the myenteric plexus include cytoplasmic hyper-eosinophilia of individual neurons without karyorrhexis, interstitial fibrosis (ganglliosclerosis), lipofuschin accumulation, cytoplasmic vacuolization, and eosinophilic inflammation in the context of Hirschsprung disease. Ganglliosclerosis (Fig. 19.9d, e) occurs primarily with chronic distension and may represent a response to

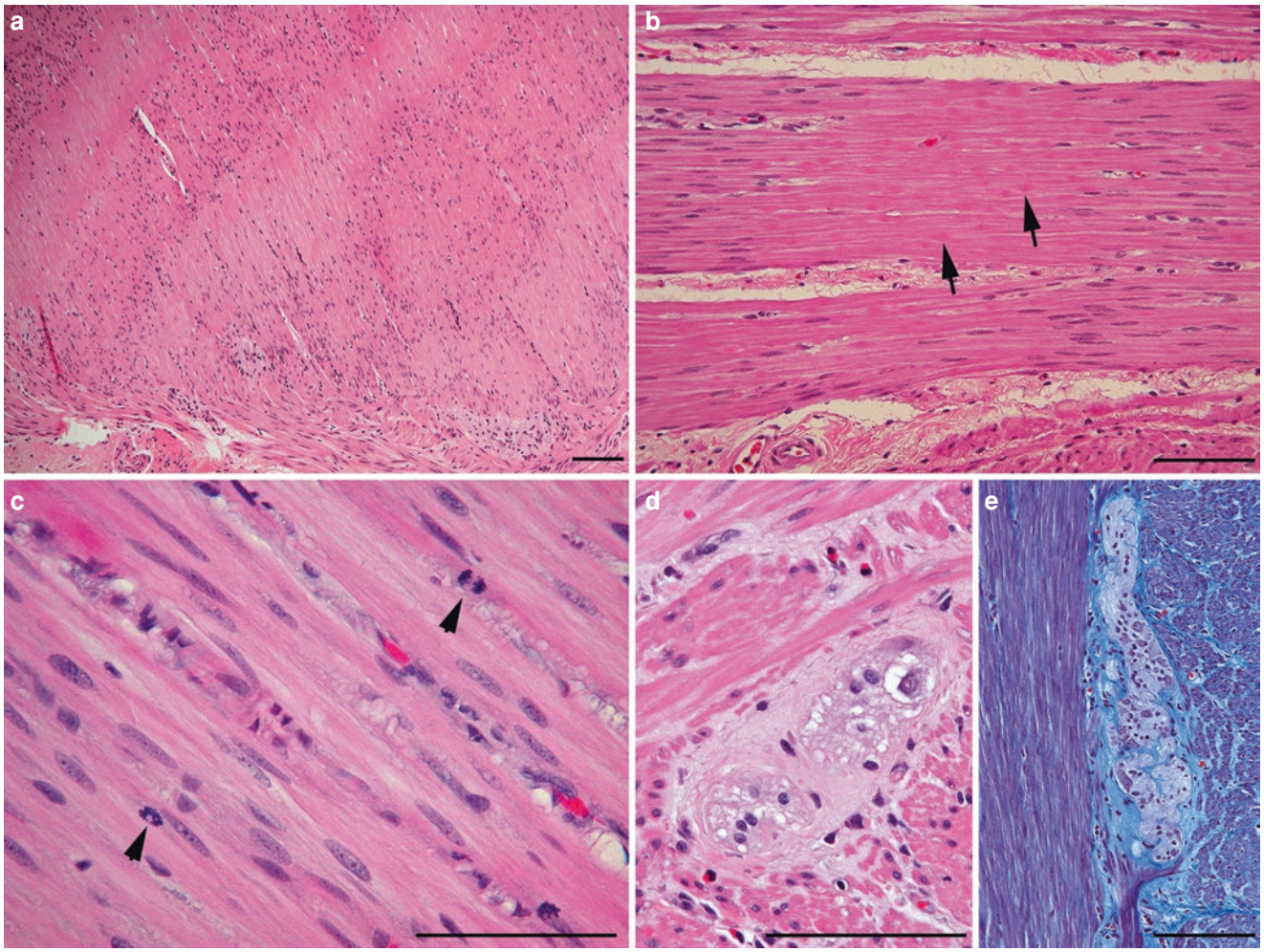

Fig. 19.9 Non-specific histopathology. (**a**, **b**) Nuclear palisading is occasionally observed in the muscularis propria, probably as a consequence of peri- or post-resection contraction bands. Alternating stripes of nucleus-rich zones are separated by eosinophilic smooth muscle cell cytoplasms, which may contain globular aggregates of contractile filaments (arrows in **b**). (**c**) Mitotic figures in the muscularis propria (arrowheads) are often observed proximal to obstructive processes, particularly in neonates. (**d**, **e**) Excessive and hyalinized deposition of collagen (blue in **e**) leads to sclerosis of myenteric ganglia, likely as a non-specific response to distension or inflammation. Scale bars: 100 μm

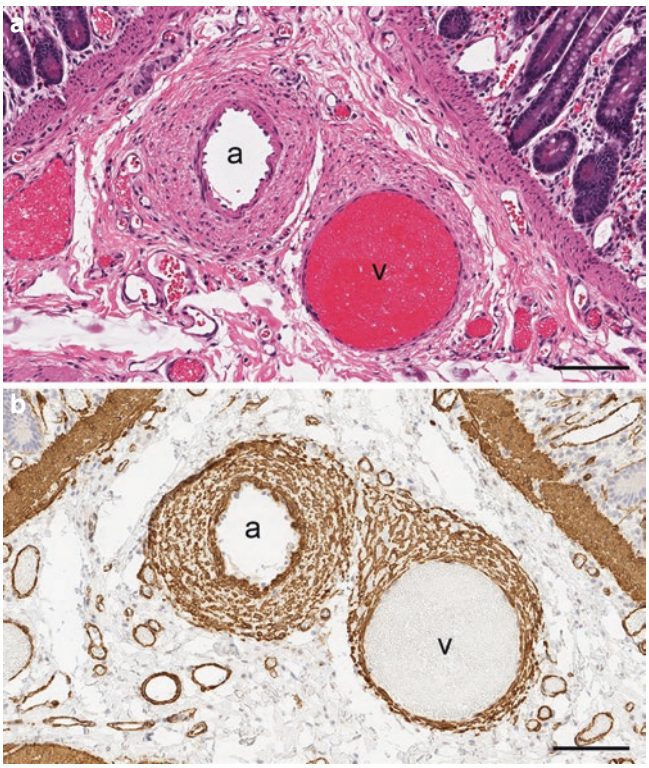

Fig. 19.10 Adventitial fibromuscular dysplasia. (**a**, **b**) In this submucosal artery (a) and vein (v) pairing, the arterial adventitia is expanded by a mixture of mature smooth muscle (highlighted by smooth muscle actin immunohistochemistry in **b**) and fibrosis. The images are from 7-month-old infant with a dilated segment of small intestine secondary to focal, downstream congenital stenosis. Scale bars = 100 μm

inflammation or stretch-related trauma. Dense bands of collagen are found around and within ganglia. Although abnormalities in the density of enteric glial cells have been reported in a variety of contexts [107, 108], specific clinical–pathological correlations for myenteric gliosis are not well established.

Adventitial fibromuscular dysplasia of intestinal wall arteries is frequently observed in patients with chronic intestinal pseudo-obstruction and probably represents a consequence of chronic distension [109]. Affected arteries may in the submucosa, muscularis propria and/or serosa. Proliferation of plump myofibroblasts in the adventitia is found in early stages with progression of mature smooth muscle and fibrosis as the vascular lesions mature (Fig. 19.10).

Intestinal Resections

Resections of bowel from patients with motility disorders are performed in several different contexts. Some of the most common include pull-through procedure (one- or two-stage) for Hirschsprung disease, segmental resection for volvulus, perforation, segmental dilatation, intussusception or atresia, total colectomy for idiopathic chronic slow transit constipation, and intestinal transplantation for generalized enteric myopathies or neuropathies. For most of these specimens, the pathologist's aims are to (a) document any pathological findings, (b) identify or confirm the underlying disease or at least exclude as many conditions as possible from the clinical differential, (c) ascertain whether the disease process extends to the surgical margin(s) and (d) collect and store samples appropriately for ancillary studies or research. The histopathological findings will be similar to those encountered in full-thickness biopsies.

Hirschsprung Disease Pull-Through Specimens

The definitive therapy for Hirschsprung disease is a resection of the neuroanatomically abnormal bowel with anastomosis of normoganglionic bowel a centimeter or so above the anus, usually done transanally by a pull-through procedure. Most of the time, surgery is scheduled after the diagnosis is established by rectal biopsies. Sometimes, the diagnosis is made because of an exploratory laparotomy for spontaneous perforation or intestinal atresia. In rare instances (e.g., healthcare systems in which arrangement for sequential visits is impractical), an intraoperative rectal biopsy is examined by frozen section to establish the diagnosis with an option to move directly to a leveling ostomy or pull-through. Given the challenges associated with accurate diagnosis, this practice should be discouraged unless no other option exists. Where the approach is used, rapid AChE histochemistry may be helpful [110].

Whether the pull-through procedure is done in one stage or preceded by a diversion enterostomy, intra-operative frozen section analysis is required to identify ganglion cells and thereby determine an appropriate site ("level") for bowel transection. An appropriate leveling biopsy is at least 3 mm long (>5 mm is ideal) and contains serosa and the full-thickness of muscularis propria with or without submucosa/mucosa. It should be sent immediately to the laboratory on a moist Telfa pad.

The biopsy should be oriented in the laboratory such that sections are cut perpendicular to the serosal surface. Most laboratories stain sections with H&E or Diff-Qwik, either of which is fine provided the pathologist has experience with the method. I usually begin with five slides, two sections per slide. In a well-oriented, adequate size, nicely sectioned seromuscular biopsy this is almost always sufficient to identify unequivocal myenteric ganglion cells in normoganglionic bowel. Under no circumstances should the pathologist conclude that ganglion cells are present, unless unequivocal ganglion cells are identified. One or more large nerve with extrinsic features in the myenteric plexus is a suggestive, but

neither obligatory nor pathognomonic, finding in aganglionic bowel. If necessary, the entire biopsy should be exhausted until an unequivocal ganglion cell is found. If the biopsy is suboptimal (i.e., too little tissue, poorly oriented, crushed, and desiccated) the pathologist and surgeon should have a low threshold for re-biopsy at or near the same site. If no ganglion cell is found, additional biopsies should be performed more proximally until ganglion cells are identified by frozen section. Distances between leveling biopsies are at the discretion of the surgeon and may be influenced by considerations of vascular supply and bowel mobilization. Although frozen section of an appendectomy can be used to document appendiceal involvement, aganglionosis of the appendix does not necessarily indicate total colonic aganglionosis, because skip areas (segments of intact colonic innervation) are almost invariably distal to an aganglionic appendix ± contiguous cecum and distal ileum [26, 111].

It is important that the surgeon resects the entire length of the aganglionic segment and the transition zone of neuroanatomically abnormal bowel found immediately upstream. In truth, anatomic pathology in the transition zone is graded and it is unrealistic to identify subtle differences in neuronal density that may distinguish normal bowel from proximal transition zone. However, moderate-to-severe histopathology is present in the distal part of the transition zone, typically 3–5 cm proximal to the aganglionic segment [30, 112]. Specific abnormalities to exclude are partial circumferential aganglionosis (absent ganglion cells along ≥1/8th of the circumference), hypoganglionosis (as described above), and/or hypertrophic submucosal nerves (abundant large submucosal nerves with extrinsic features; two or more submucosal nerves >40 μm in caliber). To improve the likelihood of adequate transition zone resection, I recommend resection of at least 5 cm of ganglionic bowel proximal to the aganglionic segment and evaluation of the full-circumference of the proximal resection margin (so called margin "donut") by intraoperative frozen section [30]. Orientation of the full-circumference frozen section can be difficult unless one cuts the "donut" into segments and lines them up in the embedding medium similar to books on a shelf.

Once the pull-through resection has been obtained, the minimal work-up must include the following. The length of the specimen should be recorded along with the positions of intraoperative biopsy sites. I prefer to open and fix the entire specimen flat before sampling for histology, so as to get well-oriented full-thickness sections. After fixation, a transverse section at or near the distal margin should be examined to confirm the diagnosis of aganglionosis. A full-circumference transverse section from the proximal margin should be evaluated to establish a normal density and distribution of ganglion cells, absence of hypertrophic submucosal nerves, and document any other pathology findings likely to be present in the unresected bowel. If an intra-operative frozen section of the proximal margin was performed, permanent sections of the thawed and fixed residual tissue are useful. However, as these sections are seldom well-oriented, I prefer to also submit an immediately adjacent section from the proximal margin of the fixed specimen. Finally, sections should be submitted to document the length of the aganglionic segment, either by transverse full-circumference sections at close intervals (e.g., 1–2 cm) or a longitudinal strip from the entire length of the specimen (Fig. 19.11). Some

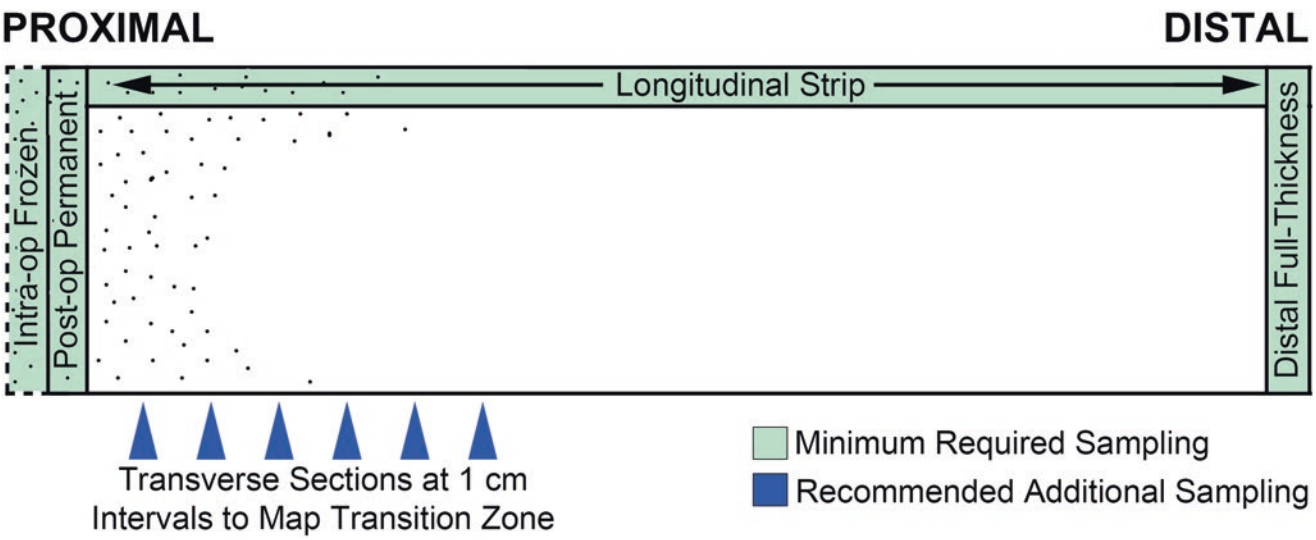

Fig. 19.11 Histological sampling of a Hirschsprung disease pull-through resection specimen. Sections shown in light green should be obtained at a minimum in order to document distal aganglionosis, exclude neuromuscular pathology at the proximal margin, and determine the approximate length of the aganglionic segment. Additional transverse sections at 1 cm intervals through the transition zone (blue triangles) may be useful to delineate the length and histopathological features of the transition zone

pathologists prefer to submit a longitudinal strip as a "jelly roll," whereas others prefer to cut it into segments and use ink to mark the proximal or distal end of each segment. Either approach should resolve the length of the aganglionic segment to within 1–2 cm, recognizing that the interface between ganglionic and aganglionic bowel is irregular, but typically deviates by no more than 3 cm around the bowel circumference [28, 29]. Immunohistochemistry probably has no role in the contemporary work-up of most HSCR pull-through specimens, although some research suggests that prognostically significant abnormalities, only resolvable with immunostains, may exist is the ganglionic bowel of HSCR patients [113].

Colectomy for Idiopathic Slow Transit Constipation

For some patients with lengthy histories of idiopathic slow transit constipation, colectomy may be the only therapeutic option [114]. Idiopathic slow transit constipation is usually diagnosed in patients with delayed passage of markers through the large intestine, no megacolon, and ganglion cells in their rectal biopsies. In my experience, pathological evaluation of these colectomy specimens has been a great disappointment. Despite clinical indications of morbid pathophysiology, anatomic changes are minimal and non-specific. Chronic laxative use and melanosis coli are common. Otherwise, no consistent histopathological phenotype has been established. Hyperganglionosis, hypoganglionosis, and deficient CD117-positive interstitial cells of Cajal have each been reported, but not reproducibly [115, 116]. Some researchers have observed reduced densities of specific subtypes of myenteric neurons (e.g., substance P-immunoreactive), but the pathophysiological relevance of such changes is unclear [117]. My approach is to snap-freeze a few representative full-thickness pieces of colon for possible future use, store small seromuscular samples in electron microscopy fixative, and then obtain representative full-thickness sections at 10–15 cm intervals through the length of the specimen. The aim of histological studies is to exclude recognizable neuromuscular disorders, with immunohistochemistry only if indicated. In most cases, no diagnostic alteration is found.

Conclusions

Our understanding of intestinal neuromuscular pathology continues to advance, in part because of the application of a combination of traditional and new methods larger sets of patients with similar clinical phenotypes. In line with the heterogeneous nature of intestinal motor disorders, the pathology of these conditions is heterogeneous and incompletely defined. The best opportunity for a definitive diagnosis requires good collaboration between clinician and pathologist with particular attention to proper handling of tissue samples. Many intestinal neuromuscular diseases are rare and may require expertise and/or ancillary studies only available in reference laboratories. Even then, links between histopathological findings and pathophysiology may be speculative or non-specific. Nonetheless, for an individual patient, sound pathology may lead to a specific diagnosis with clear prognostic and/or therapeutic implications, or at a minimum will exclude many disorders in the clinical differential.

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Allergy and Neurogastroenterology

20

Frances Connor

Introduction

Definition, Overview, Importance

Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food [1]. Rates of food allergy are rising exponentially across the world. Up to 10% of children in developed countries are affected, costing an estimated $25 billion annually in the United States alone. Although in the general community, many people mistakenly believe they have food reactions, the opposite is true in gastroenterology clinics, where many patients have undiagnosed food allergy causing their presenting symptoms. Eliminating the offending food is more effective than treating the equivalent idiopathic functional conditions. Typically, children have endured years of symptoms before being diagnosed and this can compromise nutrition. Addressing food allergy not only benefits our patients but also allows appropriate allocation of scarce neurogastroenterology resources. This is particularly important given increased wait times and service disruptions during the coronavirus disease 2019 (COVID-19) pandemic.

This chapter aims to empower gastroenterologists to recognize the many ways food allergy can present to clinics and to give practical information on diagnosis and treatment. Food protein- induced gastrointestinal allergies have been considered difficult to characterize due to delayed symptom onset and absence of simple diagnostic tests [2]. However, an allergy-focused history and supervised, time-limited elimination diet with challenge is frequently effective [3]. This is especially the case in conditions with high rates of underlying food allergy such as diarrhea (30–80% of cases), chronic constipation (28–78%), and reflux (16–59%).

The focus will be more on gastroenterology than immunology. This chapter gives a brief overview of immune mechanisms for different conditions. However, it also introduces exciting new research pointing to a role for *localized* mucosal IgE-mediated mechanisms in the gut, underlying what were previously labelled as non-IgE-mediated conditions. This research, demonstrating that local IgE-based immune responses drive food-induced abdominal pain, has profound implications for clinical management of functional pain-related gastrointestinal disorders. There is a paradigm shift underway where many functional conditions are being recognized as having an allergic or immunologic basis. The overlap of food allergy and neurogastroenterology is fertile ground for future research.

Gastroenterology clinics see a wide variety of food-allergic symptoms, representing 5–12% of patients. Food allergies can masquerade as motility disorders, reflux or functional constipation [4] and can also exacerbate symptoms in children with other underlying motility problems such as Hirschsprung's disease (HSCR).

Motility Effects of Allergen Ingestion

Since barium studies in the early 1900s, it has been recognized that allergen ingestion can trigger motility disturbance in sensitized individuals [5]. Allergen ingestion can cause cricopharyngeal spasm [6], preventing food from entering the stomach at all. Allergens can trigger esophageal dysmotility, including spasm and dysphagia, by fueling eosinophilic esophagitis or myositis (EoE or EoM). Once in the stomach, allergen degranulates mucosal mast cells, disrupts normal myoelectrical activity, and prolongs gastric emptying

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times. The offending allergen can be vomited [5] or regurgitated back up or can progress down the gut. Once in the small intestine, it can cause mucosal breaks, and rapid transit due to both increased motility and massive outpouring of secretions. In the large bowel, vigorous contractions push the allergen towards the anus, often resulting in diarrhea [5]. However, in some cases, anal spasm occurs, causing outlet type constipation, often associated with cramping abdominal pain. Both small and large intestine can display generalized or segmental atony. Alternatively, edema or painful segmental contractions can cause localized narrowing at any level. These findings are not restricted to patients with IgE-mediated food allergies. Many of these changes have been demonstrated in patients with presumed non-IgE-mediated food allergies, who have reproducible food reactions, but negative tests for IgE-mediated food allergy, for example, skin prick (SPT) and radioallergosorbent tests (RAST). A combination of upper and lower gastrointestinal (GI) dysmotility is a feature of food allergy.

Animal models of food allergy show dysmotility and visceral hypersensitivity analogous to irritable bowel syndrome (IBS) in humans.

Allergy Risk Factors in Motility Patients

Motility patients are at particular risk for food allergies for multiple reasons. These include environmental risk factors, drug exposures, and vitamin D deficiency. Alterations in the microbiome are believed to be central to increasing rates of food allergy, with higher rates associated with antibiotic exposure, cesarean birth, and urban environments. Conversely, exposure to other children (older siblings, day care), pets, and rural environments is protective. During the COVID-19 pandemic, hygiene measures and isolation are expected to exacerbate the decline of microbial diversity needed for healthy immune development. Also, many of our sickest patients lack exposure to siblings, day care, pets, and nature, due to prolonged hospitalizations. Other allergy risk factors in gastroenterology patients include vitamin D deficiency, delayed introduction of weaning foods, and exposures to drugs such as proton pump inhibitors (PPI) and antibiotics [7–10]. Many of our motility patients have a history of antibiotic use perioperatively (e.g., HSCR, short gut, chronic intestinal pseudo-obstruction [CIPO], and esophageal atresia) or in the newborn period (ex-premature babies especially). Early exposure to antibiotics increases the rate of food allergies by 40% as well as functional gastrointestinal disorders (FGID). Similarly, PPI therapy increases food allergy risk by impairing digestion of dietary antigens. A history of PPI use is ubiquitous in children with functional gastrointestinal and motility conditions, including patients with reflux, dyspepsia, esophageal atresia, eosinophilic esophagitis (EoE), and intestinal failure. Vitamin D deficiency, common in children with gastrointestinal disorders, is associated with early, prolonged, and multiple food allergies. Many gastroenterology patients have a history of eczema. Eczema is a risk factor for the development of food allergies, due to epicutaneous sensitization. An awareness of these common risk factors may improve recognition of food allergies in motility and surgical patients. Diagnosis of allergy in these complex patients can provide the missing piece of the puzzle, enabling control of previously intractable symptoms.

Children with allergy commonly have symptoms in more than one area of the body. Typical examples are combined upper and lower GI symptoms (e.g., reflux and constipation), or cutaneous (e.g., eczema) or respiratory (e.g., sneezing) symptoms. This combination of symptoms is useful in diagnosis. It has been formalized and validated in a symptom-based scoring tool for the identification of infants at elevated risk of having cows' milk allergy (CMA), termed COMISS™. Currently, there is no similar tool to assist diagnosis in older patients; however, the same clues apply (see Box 20.1).

Box 20.1 Red Flags: Factors Associated with Food Allergy

1. Previously diagnosed with food allergy (e.g., CMA) in infancy
2. History of irritability, formula intolerance, colic, or reflux in infancy
3. Very early onset constipation
4. Symptom onset or aggravation on changing from breast to bottle feeds [11]
5. Gastroesophageal reflux disease, especially medication-resistant
6. Medication resistant/medication-dependent constipation
7. Persistent, severe irritability and straining during defecation even when stools soft and unformed (dyschezia)
8. Perianal erythema and/or fissures
9. Other atopic diseases (eczema, asthma, rhinitis)
10. Rashes on contact with food or vomit
11. Rashes/urticaria during/after feeds
12. Self-reported dairy intolerance or other reproducible food reactions
13. Voluntary dairy restriction [12]
14. Recurrent infections, for example, otitis media, history of tympanostomy, or adenoidectomy
15. Enuresis
16. Joint hypermobility
17. Developmental delay [13]
18. Autism [14, 15]
19. Vitamin D deficiency

20. Family History:
    (a) Atopy [16]
    (b) Food allergy
    (c) Infants whose symptoms improved on soy, goat or prescription formula
    (d) Autoimmunity (maternal family, organ-specific)

Overall, 73% of young children with food allergies have a history of eczema, as do nearly ½ the children with food allergies in gastroenterology clinics [2]. Persistent food-related symptoms in later childhood are twice as likely in children with any history of eczema, rhinitis, asthma, parental allergy, and in males. A history of any food-related symptoms in infancy triples the risk of having food-related symptoms in later childhood. A formal diagnosis of food allergy in infancy increases the risk sevenfold. Children with food allergies have high rates of extraintestinal symptoms including fatigue (53.0%), allergic shiners (49.1%), mouth ulcers (39.0%), joint pain/hypermobility (35.8%), poor sleep (34.4%), night sweats (34.4%), headache (22.7%), and bed-wetting (17.7%). Some describe specific foods triggering enuresis or migraine. Many of these symptoms, such as headaches and poor sleep, have also been identified in non-celiac gluten sensitivity (NCGS) and FGIDs. Therefore, it is important to bear in mind a possible allergic etiology and take an allergy-focused history before concluding symptoms are functional.

In gastroenterology clinics, recognition and treatment of food allergy have the potential to improve patient experience and health care utilization vastly. Children with food reactions regularly present with conditions such as intractable vomiting, diarrhea, or constipation. Infants may have symptoms even during exclusive breastfeeding, due to maternal dietary antigens in breast milk. This can worsen on exposure to formula [11]. Symptoms can be indistinguishable from primary motility disorders and FGID, recently renamed disorders of gut-brain interactions (DGBIs). Food allergy is also a commonly overlooked, but eminently treatable factor in children with other more obvious diagnoses, such as neurological conditions, dysmorphic syndromes, and after surgery.

Unrecognized food allergy can affect surgical patients with Hirschsprung's disease, anorectal malformations, intestinal atresia repairs, short gut, and tracheoesophageal fistula repair. Symptoms include distension, vomiting, apnea, diarrhea, and increased stoma losses. Food allergy can also mimic surgical conditions such as Hirschsprung's disease [17]. Failure to recognize underlying food allergy can lead to surgery, such as Soave procedure [17], fundoplication, feeding stoma, ileostomy [18], colostomy, and appendicostomy procedures. Ongoing exposure to trigger foods is a common reason for persistent symptoms and complications after such operations. Conversely, elimination of offending allergens is a powerful tool to address intractable symptoms in many patients, including reducing or eliminating the need for parenteral nutrition.

Diagnostic Tests

As the role of food antigens triggering GI motility disturbance is increasingly recognized, there is an urgent need for readily available, reproducible, and non-invasive tests for non-IgE-mediated disease. Double-blind placebo-controlled food challenge (DBPCFC), considered the gold standard, is unreliable, labor intensive and often unavailable [19–21]. Lack of sensitivity and specificity may be due to inadequate dose, delayed reactions, placebo/nocebo effects, or antigen alteration during preparation for challenge administration [19]. Various laboratory tests have been explored, but none have yet proved reliable or universally applicable.

Symptom-Based Diagnosis

Lacking reliable, accessible screening tests, some gastroenterologists have been reluctant to assess patients for food allergy. However, the neurogastroenterology community is uniquely skilled in the application of symptom-based criteria for diagnosis. Many functional and motility conditions are diagnosed solely on symptomatic criteria rather than laboratory tests. For example, the Rome diagnostic criteria are invaluable for the identification of FGIDs based on symptoms [22, 23]. Similarly, motility clinicians use patient-reported outcomes (PRO), such as symptom calendars and diaries, rather than laboratory tests, to evaluate patients' response to treatment. In the absence of reliable, non-invasive laboratory tests for gut allergies, diagnosis rests on symptom-based criteria to clearly define response to food elimination and challenge, as per European Academy of Allergy Clinical Immunology (EAACI) guidelines.

Overlap of Allergy and Functional Gastrointestinal Disorders (FGID)

A growing body of evidence shows that what we currently call FGID are syndromes, with a diverse range of underlying pathophysiologies. Worldwide, efforts are increasing to phenotype patients precisely, to enable personalized treatment and meaningful research [24]. In adult IBS, particular attention is now being paid to atopy and dietary history, self-diagnosed reactions, and self-imposed restrictions. A

fundamental principal in the diagnosis of FGIDs is that symptoms cannot be explained by another organic disease. Food allergy is a prevalent and treatable organic disease that should be excluded before labelling a child as functional.

Therapeutic Diets

Correctly supervised diet is fundamental. Many children with motility and FGID symptoms describe trigger foods for their symptoms, and many avoid suspect foods. For instance, 93% of children with IBS report food reactions, the commonest triggers being dairy (53%) and grains (31%). These self-reported food reactions are associated with more severe symptoms and worse quality of life. Despite reactions, many patients continue to consume foods containing the same allergens as the self-reported trigger food. Conversely, some children may be restricting their diet unnecessarily, avoiding foods to which they do not currently react. They may have outgrown an intolerance. Delayed reactions may cause confusion, or they may be avoiding foods on principle, based on internet research or well-meaning advice.

The nutritional, social, and financial consequences of unsupervised elimination diets are considerable. Delayed exposure to weaning foods or strict avoidance may predispose to the development of allergies including anaphylaxis.

Conversely, failing to recognize allergy triggers for symptoms has equally damaging consequences. Unrecognized cows' milk allergy is a common cause of failure to thrive. Patients with unrecognized food allergies causing motility symptoms may spend years consulting various health practitioners, returning to motility clinics, taking ineffective treatments, and undergoing unnecessary investigations and procedures. Therefore, it is imperative to clearly define what foods a child does or does not react to, in order to liberalize the diet as much as possible while avoiding foods that cause harm.

Therapeutic trials of elimination diets need rigorous implementation. They should be time limited. EAACI guidelines recommend that the duration of the avoidance should be no longer than necessary to achieve a significant relief of symptoms, usually 2–4 weeks for IgE-mediated symptoms and longer for non-IgE ones (e.g., up to 6 weeks for eosinophilic esophagitis (EoE)). Salerno criteria for non-celiac gluten sensitivity (NCGS) also recommend 6 weeks. Most motility symptoms respond within 2–4 weeks when the trigger food is eliminated. Target symptoms should be defined a priori. Symptoms must be objectively monitored and recorded before, during and after the elimination diet is imposed. Excluded nutrients such as calcium should be proactively supplemented. Elimination diets in breastfeeding mothers, targeting allergic symptoms in infants, require particular care and should follow EAACI guidelines.

Whenever possible, food reactions must be verified with challenge following elimination. If there is IgE-mediated allergy, elimination and reintroductions should be guided by allergy testing. Formal oral food challenges within an allergy service and guided by SPT/sIgE are recommended. This strategy is cost-effective and improves quality of life compared to restriction of allergens based only on skin prick or blood tests [25]. Allergist supervision with or without oral food challenges is also recommended for children with food protein induced enterocolitis syndrome (FPIES), due to the risk of acute, severe symptoms. If the challenge confirms that symptoms are food-induced, the food is eliminated to the extent required for symptom control. Ideally all diets are monitored and implemented by trained dieticians. However, simple, single food elimination diets in well-nourished children can be administered effectively from the gastroenterology clinic, using appropriate patient information and education. Ongoing supervision is required. For children with non-IgE-mediated reactions that are not acute and severe, parents can be reassured that most cases improve with time. Anticipatory guidance for families is important to build confidence to periodically reintroduce the trigger food, starting with minimal amounts and advancing as tolerated.

Much research is still needed to clarify the ideal food/s to eliminate and diet duration in different clinical scenarios. This represents an enormous opportunity to improve early diagnosis of food reactions in motility patients.

Pathophysiology: Immune Mechanisms

Food Allergy Versus Intolerance

Adverse reactions to food are summarized in (Fig. 20.1). Food reactions are divided into food allergy, which is due to immunological reactions and food intolerance. Food intolerances are non-immunological and diverse. They include malabsorption from disaccharidase deficiencies, symptoms from fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs), reactions to benzoate or sulfite preservatives, lectins, biogenic amines and activation of food chemical sensors such as transient receptor potential (TRP) receptors by foods such as chilli and ginger. Some foods, such as wheat, contain multiple compounds which can cause allergy, intolerance, or autoimmune (celiac) disease. These include gluten proteins, lipopolysaccharides, amylase/trypsin inhibitors (ATIs), wheat germ agglutinins, and FODMAPs. Individual patients may react to one or more of these agents. Some patient groups are particularly susceptible to food reactions. These include children with esophageal atresia repair experiencing dumping syndrome triggered by high osmolar loads or worsening of symptoms by lipids in functional dyspepsia (FD) and gastroparesis. While intolerances are clinically significant, they are not the focus of this chapter.

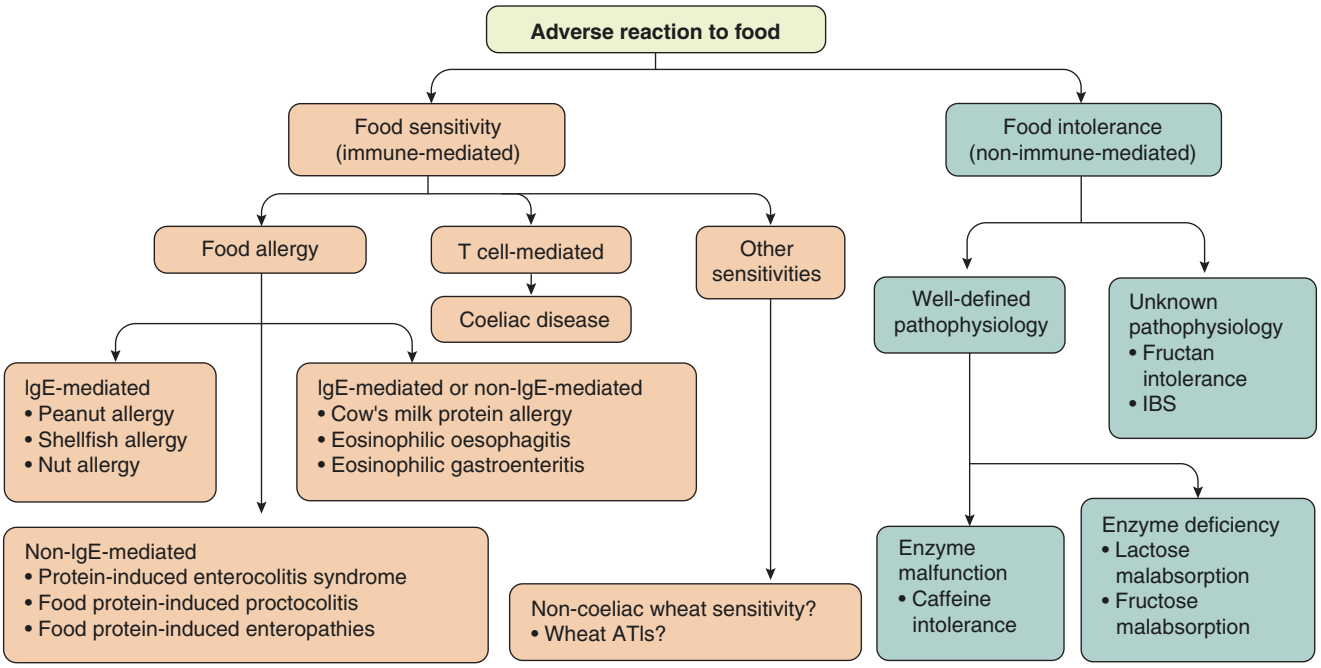

Fig. 20.1 Classification of adverse reaction to food according to underlying pathophysiology. Adverse reactions to food can be divided into food intolerances (non-immune mediated) and food sensitivities (immune mediated). Both types can be subclassified into specific diseases based on their pathophysiology. *ATI* α-amylase-trypsin inhibitor, *IgE* immunoglobulin E [26]. (With permission from Caminero A, Meisel M, Jabri B, Verdu EF. Mechanisms by which gut microorganisms influence food sensitivities. Nat Rev Gastroenterol Hepatol. 2019;16(1):7–18)

Gastrointestinal Food Allergy: Role of IgE

Gastrointestinal manifestations of food allergy may be due to IgE-mediated, non-IgE-mediated, or mixed reactions [1, 27]. IgE-mediated allergy is well recognized. Symptoms are acute, reproducible, and often occur after even tiny doses of the trigger food. Diagnosis is easily confirmed with objective testing using skin or blood tests for food-specific IgG. These include skin prick test (SPT) and blood tests (either radioallergosorbent tests (RAST) or ImmunoCAP). Typical examples of IgE-mediated food allergy in the gastrointestinal tract are oral allergy syndrome and food-induced anaphylaxis. Non-IgE-mediated reactions usually have a more delayed onset. These include dietary protein proctitis, colitis, enterocolitis, enteropathy, gastroesophageal reflux disease, dyspepsia, food-protein–induced enterocolitis syndrome, chronic constipation, and infant colic. Both IgE and non-IgE-mediated reactions contribute to eosinophilic esophagitis and gastroenteropathies. Non-IgE-mediated and mixed reactions can be particularly difficult to diagnose as symptoms can occur hours to days after ingestion.

It is now believed that some disorders currently classified as non-IgE-mediated may actually be mediated by localized IgE in the gastrointestinal mucosa, which is not circulating in sufficient levels to be detected by traditional tests such as skin prick or radioallergosorbent tests (RAST). In recent years, local allergic reactions have been documented as a common cause of rhinitis, negative to systemic-specific IgE (sIgE) tests such as skin prick testing or RAST. Local allergic rhinitis (LAR) to seasonal or dust mite allergens is now recognized in up to 25% of patients who were previously labelled as non-allergic rhinitis on the basis of negative skin prick or RAST tests. LAR is diagnosed with intranasal challenges with specific allergens, eliciting reproducible symptoms. Local production of antigen-specific IgE has been documented, as has local class switching of B cells within respiratory epithelia. Localized reaction to specific allergens triggers the release of histamine and other inflammatory mediators.

Local allergic reactions in the gut have long been suspected. Often, patients with chronic or recurrent gastrointestinal symptoms describe specific food triggers. Many also have allergic disease in other organ systems such as allergic rhinitis or contact allergic reactions to adhesive tapes.

The lack of readily available tests for gastrointestinal food reactions has been a major barrier to appropriate management. Testing for systemic levels of antigen-specific IgE is frequently negative in patients presenting with GI symptoms. However, children with cows' milk allergy have evidence of local IgE producing cells in the gut mucosa [28]. Research shows that just like skin tests for contact allergic dermatitis, or intranasal allergen challenge for LAR, localized provocation tests in the gut elicit reproducible results, corresponding to patients' symptoms. Endoscopic administration of the trigger food, either topically or by injection, causes immediate mast cell degranulation in the stomach, duodenum, jejunum, and colon.

In adult IBS patients with specific food triggers, colonic mucosal injection with dietary antigens produces localized erythema and swelling, resembling the wheal and flare of skin prick testing (see Fig. 20.2). There is an increased density of IgE-positive mast cells in biopsies from such patients. In a separate study, a significant correlation was found between the appearance of symptoms after exposure to trigger foods and the duodenal presence of IgE-bearing cells, activated eosinophils, and T cells in patients with negative SPT results and negative s-IgE Ab to the offending food.

Intragastric challenge with cows' milk in children with milk-induced dyspepsia triggered prompt mast cell degranulation, even among those with negative tests for systemic-specific IgE. Inflammatory mast cell products coat the mucosal enteric nerves, disrupting normal myoelectric function, as captured on electrogastrogram (EGG), see Figs. 20.3 and 20.4.

Post-infectious Onset

Post-infectious onset of childhood FGID [31] and food allergies is well recognized. While most childhood food allergies are present from infancy, gastrointestinal infections can trigger new onset food allergy later in life [32]. Epithelial disruption due to gastroenteritis increases the absorption of intact food proteins [33] resulting in loss of oral tolerance [26]. This may trigger allergy symptoms which are indistinguishable from post-infectious irritable bowel syndrome (PI-IBS), but triggered by specific food/s, as shown in Fig. 20.5. This landmark series of experiments supports the concept that PI-IBS results from a breakdown of oral tolerance to food antigens during infection. These authors used a mouse model of PI-IBS. Food allergy was elicited by feeding ovalbumin during bacterial colitis. The mice developed post infectious food reactions to egg, trig-

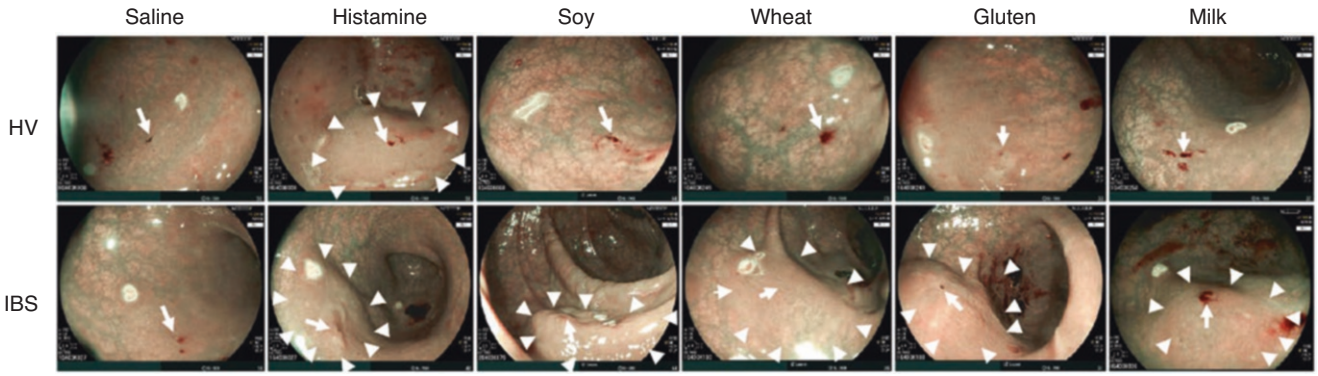

Fig. 20.2 Colonic mucosal injection of food antigens induces an immediate mucosal response in patients with IBS. Arrows: antigen injection sites; arrowheads: reaction areas and diameters of reactions to food antigens injected into healthy volunteers (HV) and individuals with IBS [29] (with permission from Aguilera-Lizarraga J, Florens MV, Viola MF, Jain P, Decraecker L, Appeltans I, et al. Local immune response to food antigens drives meal-induced abdominal pain. Nature. 2021;590(7844):151–6)

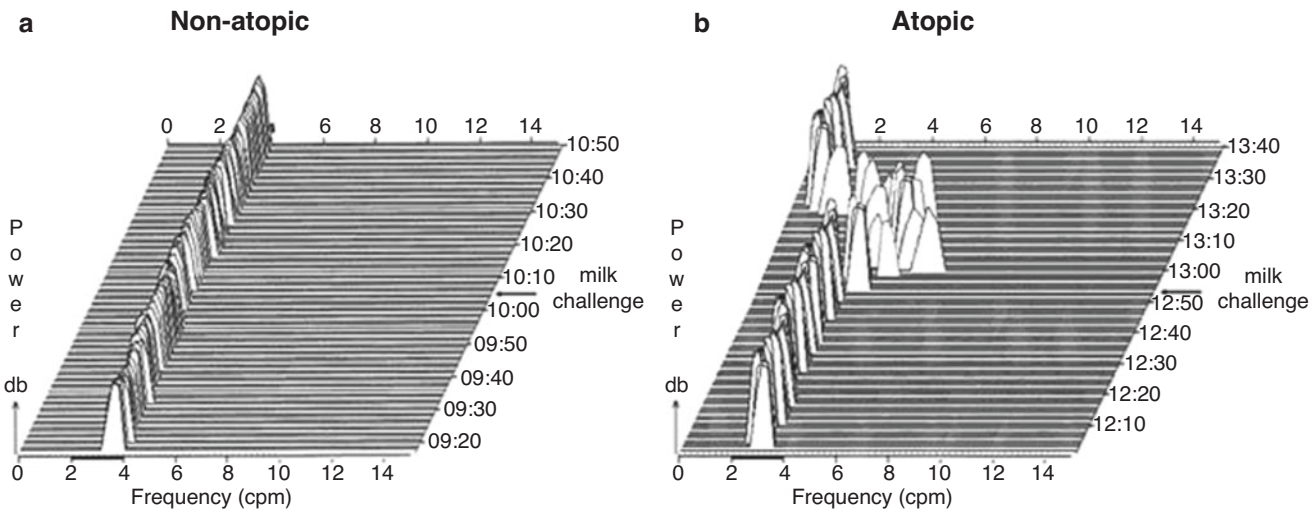

Fig. 20.3 Electrogastrography recordings from (**a**) a nonatopic and (**b**) an atopic subject with a history of dyspepsia after cows' milk, showing the rapid (within 2 min) effect of milk provocation in the atopic individual. Derangement of gastric rhythm is shown on pseudo three-dimensional running spectral analysis plots [30]. (With permission from Schappi MG, Borrelli O, Knafelz D, Williams S, Smith VV, Milla PJ, et al. Mast cell-nerve interactions in children with functional dyspepsia. J Pediatr Gastroenterol Nutr. 2008;47(4):472–80)

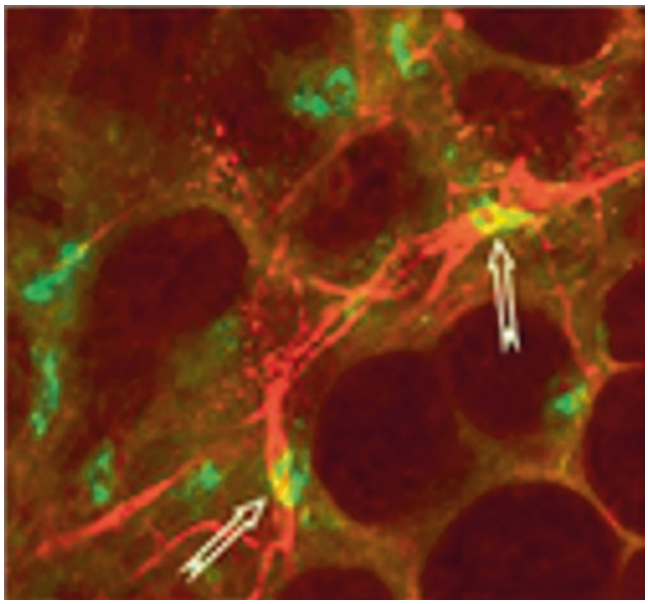

Fig. 20.4 Double immunostaining of gastric antral mucosal biopsy from a dairy intolerant child for mast cell tryptase (green) and protein gene product 9.5 (red) showing mast cell tryptase granules colocalizing (yellow) with nerve fibers. Original magnification 100 [30]. (With permission from Schappi MG, Borrelli O, Knafelz D, Williams S, Smith VV, Milla PJ, et al. Mast cell-nerve interactions in children with functional dyspepsia. J Pediatr Gastroenterol Nutr. 2008;47(4):472–80)

gering visceral hypersensitivity. Colonic infection generated mucosal IgE to egg, which was compartmentalized in the gastrointestinal tract. Echoing findings in human IBS patients, mucosal mast cell numbers were not persistently elevated in the sensitized mice, once they recovered from the gastrointestinal infection. However, the mast cells remained activated. In humans with IBS, mast cell density was not increased, but mast cells were coated with more IgE and were located closer to enteric nerves. Similar findings are present in children with food-allergic constipation and dairy-induced dyspepsia.

Subtle Immunodeficiency and Recurrent Infection

IgA and IgG antibodies to foods form the basis of oral tolerance and immunodeficiency is a risk factor for the development of allergic disease. A history of frequent infections is common in children with food allergies underlying gastrointestinal symptoms such as reflux, constipation, and diarrhea. This tendency to recurrent infection may be aggravated by concurrent PPI therapy. More than a third of children with multiple food protein allergies have deficiencies of IgA or

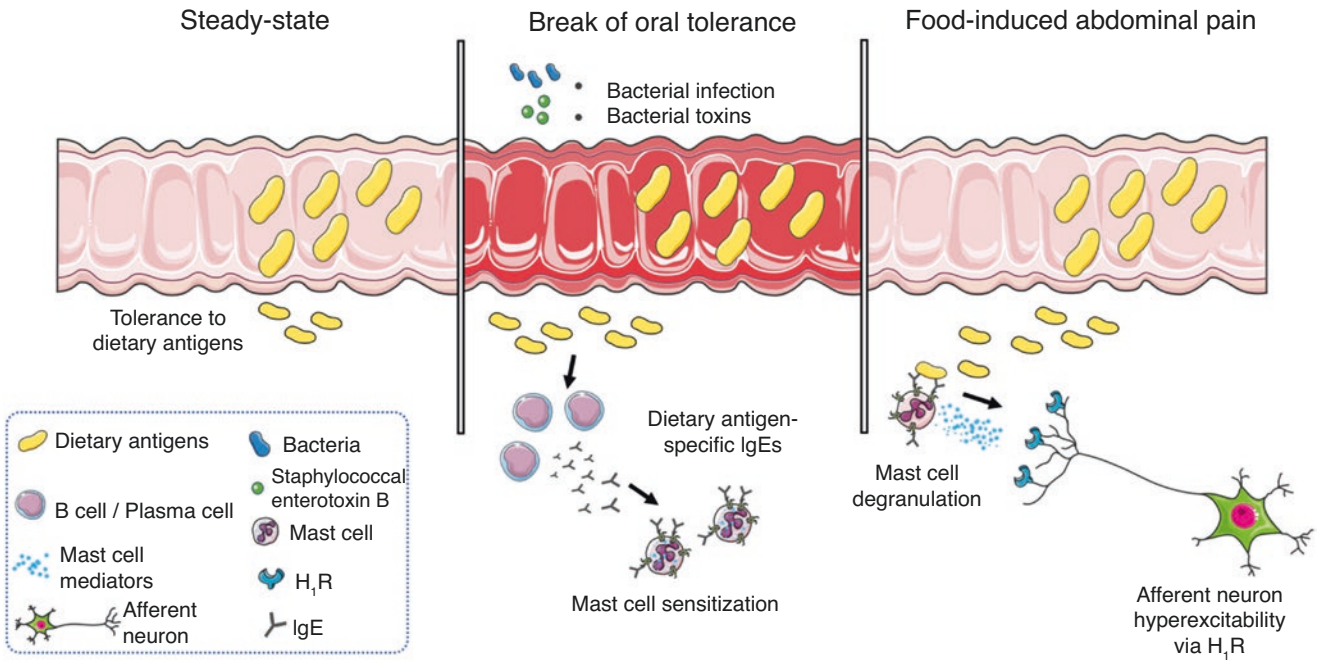

Fig. 20.5 Graphical representation of the mechanism proposed: local immune response to dietary antigens triggered by bacterial infection leads to food-induced abdominal pain. Bacterial infection (or bacterial toxins) can trigger break of oral tolerance to food antigens leading to food-induced visceral hypersensitivity upon food-antigen re-exposure. Ovalbumin-specific IgE antibodies bind to and sensitize tissue-resident mast cells, which are activated upon re-exposure to ovalbumin during feeding and release mediators that sensitize afferent neurons via H1R-mediated pathway [29]. (Components of this figure were created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com (with permission from Aguilera-Lizarraga J, Florens MV, Viola MF, Jain P, Decraecker L, Appeltans I, et al. Local immune response to food antigens drives meal-induced abdominal pain. Nature. 2021;590(7844):151–6))

IgG. In many cases, this improves with time. While this had been ascribed to "late-turn on" of immunoglobulin production [32], in some cases it may be secondary to protein losing enteropathy from the allergy itself.

The Role of Stress and Infection

In the current model of functional abdominal pain, visceral hyperalgesia can arise after sensitizing medical events (such as inflammation, distension, trauma, stress, and motility disorders), often in combination with genetic predisposition or early life events. Progression from visceral hyperalgesia to disability is determined by individual coping styles, family roles, parenting and other stressors.

Stress creates a milieu conducive to the development of allergy, dysmotility, and visceral hypersensitivity [21]. As is illustrated in Fig. 20.6, there are extensive neuroimmune interactions and bidirectional communication between enteric nerves and mast cells. Stress activates mast cells. In vitro stimulation of nerves in descending pathways (mesenteric nerve) degranulates mast cells. In animal models, stress predisposes to the development of both food allergies and visceral hypersensitivity. In humans, psychological stress acutely worsens symptoms in patients with FGID and is also a risk factor for their development. In children, stress also predisposes to the development of allergic diseases and delays recovery. PI-IBS is more likely to occur in people who were under psychological stress at the time of the infection.

Common Allergens

Cows' milk is the most common food allergy in children [35] and the most widely studied allergen affecting motility. However, many other foods have been implicated. Wheat is also widely reported. The burgeoning literature on wheat reactions seeks to distinguish between allergies and intolerances to fructans (FODMAPs), gluten, other proteins, tryptase, etc. Non-celiac gluten sensitivity (NCGS) is defined using the Salerno criteria as gastrointestinal and extra-intestinal symptoms related to the ingestion of gluten-containing food, in subjects who have neither celiac disease

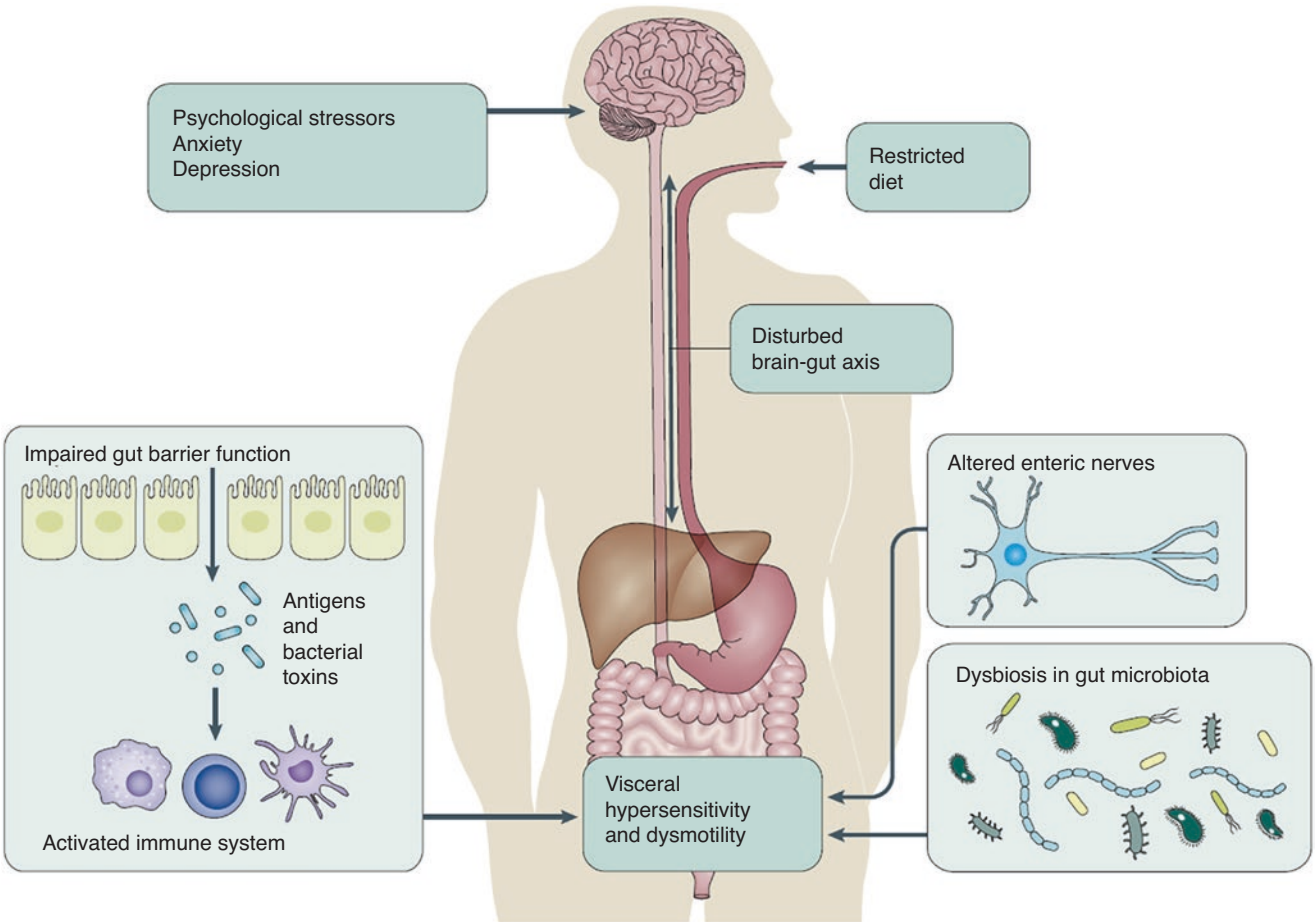

Fig. 20.6 Interplay between stress, infection, food allergens, microbiome, immune system, and gut brain axis in IBS [34]. (With permission from Spiller R, Major G. IBS and IBD - separate entities or on a spectrum? Nat Rev Gastroenterol Hepatol. 2016;13(10):613–21)

or wheat allergy. The criteria include a strict 6 weeks elimination diet, followed by blinded challenge (ideally DBPCFC) with moderate doses of gluten (approximately ½–2/3 the normal daily intake). It is not clear that gluten is the trigger in all cases of NCGS, due to the diverse range of potentially irritant components in wheat. NCGS is distinct from FODMAP sensitivity, but the two can coexist. Based on the frequency of non-IgE-mediated wheat allergy in children, as well as the local IgE-mediated wheat reactions seen in adults with IBS, it is likely that at least some patients currently labelled as NCGS have an underlying allergic mechanism.

Gluten-free diet benefits a proportion of adults with FGID. However, prospective studies in children are lacking. In the largest study to date, 1114 children with symptoms of FGID were assessed for persistent, self-reported symptoms after gluten ingestion. Children with coeliac disease or positive skin or blood tests suggesting wheat allergy were excluded, leaving 31 with suspected NCGS. These underwent 2-week gluten-free diet and crossover DBPCFC challenges with washout. Symptoms improved on the gluten-free diet in 28 (90%). However, only 11 (39%) responded to gluten on DBPCFC. This illustrates the difficulties in characterizing this group, in the absence of reliable biomarkers. Whether the intake of other allergens (such as dairy) dropped during the gluten-free diet was not reported.

Gastrointestinal food allergies to multiple foods are common. For example, 55–75% of children with CMA develop allergies to other foods, commonly egg (30%), soy (14–70%), wheat (30%), and beef (20%). Almost 1/4 of children with CMA have coexisting egg and wheat allergy. Mechanisms of multiple allergies vary. In *co-allergy*, coexisting allergies develop with separate sIgE to unrelated food antigens (such as fish and shellfish). Whereas *cross-reactivity* refers to sIgE that bonds to similar epitopes in different foods or substances. Common examples of co-allergy are dairy and soy, dairy and gluten, soy, and gluten [32]. Common patterns of cross-reactivity are mammalian milks (cows'/goat/sheep), gluten-containing grains (wheat/rye/barley), legumes (soy/peanut), multiple tree nuts (e.g., pistachio/cashew), bovine proteins (cows' milk/beef), and shrimp/dust mite.

Co-allergy may affect FODMAP response. The considerable overlap between low FODMAP and oligoantigenic diets may confound research into FODMAP effects. Specifically, low FODMAP diet excludes wheat, regular cows' milk, yoghurt, and most soy products. The reduction in dairy and soy intake is reflected in lower calcium intake of patients on FODMAP restrictions. In children with gastrointestinal allergies to wheat, dairy and/or soy, a low FODMAP diet would improve dose-dependent symptoms from those foods. Additionally, FODMAP malabsorption can be a secondary symptom of underlying food allergy. Children with CMA develop diarrhea on exposure to dairy, with lactose malabsorption despite (generally) normal lactase enzyme levels. Lactose malabsorption in this scenario is likely due to rapid transit. Food protein enteropathy is also associated with malabsorption of dietary sugars due to disaccharidase deficiency.

The low FODMAP diet is restrictive, costly, and compliance is difficult. Multiple fruits and vegetables are eliminated. Adverse effects on the gut microbiome have been documented. It is nutritionally hazardous. Studies in adults demonstrated reduced intake of key nutrients while on FODMAP restriction, including iron, calcium, vitamin D, sodium, folate, thiamine, and riboflavin. This was in addition to pre-existing, self-imposed restrictions of trigger foods in IBS patients, who had deficient intake of vitamins C, D, E, folate, calcium, magnesium, and potassium even before FODMAP restriction. Such a restricted diet poses concerns in children due to potential impacts on nutrition, healthy eating habits and risks the development of eating disorders. A "FODMAP-gentle" ("FODMAP-lite") diet has been proposed, restricting wheat, milk, yoghurt, soy, various fruits, vegetables (apple, pear, dried fruit, stone fruit, watermelon, onion, leek, cauliflower, mushrooms, beans), and legumes. This is still a very restrictive diet. Given the nutritional hazards and limited evidence for FODMAP restriction in children, it may be worthwhile to simplify intervention diets in pediatric FGIDs further, starting with only wheat, dairy, and soy. In any case, multiple food elimination diets must be time-limited, closely supervised and appropriately supplemented with micronutrients.

Classic GI Allergic Disease Phenotypes

Immediate IgE-Mediated Food Allergies

Pollen Food Allergy Syndrome (PFAS)

Pollen food allergy syndrome (PFAS), also known as oral allergy syndrome (OAS) is an immediate IgE-mediated response to food and aeroantigens. In pollen-food allergy syndrome (PFAS), patients sensitized to airborne pollens cross-react to similar epitopes in foods. For example, patients sensitive to birch tree pollen may have oral or abdominal symptoms after soy, kiwi fruit, mango and/or orange [36]. A wide variety of fruits, grains and nuts can be involved, including kiwi, pineapple, apple, banana, peach, orange, celery, carrot, wheat, soy, peanut, hazelnut, walnut and wheat. Importantly for medical procedures, patients may be latex allergic [37]. PFAS is common, and the incidence appears to be increasing. It is thought to affect 2–13% of the general population, 5–20% of atopic children [37], and 26% of EoE patients [38]. The typical symptom is oropharyngeal pruritis ("itchy throat"). Other symptoms include blisters in the mouth, throat tightness, dysphagia, dysphonia, nausea, and itching inside the ears. There may be swelling of the lips,

oral cavity, and perioral or periorbital rashes. Up to 3% of patients with PFAS experience serious systemic symptoms without oral symptoms and 1.7% experience anaphylactic shock. OAS may coexist with EoE or eosinophilic gastrointestinal disorders (EGIDs) [37]. Symptoms may be worse if the food is uncooked, after exercise, or while on PPI therapy [37]. Oral or abdominal symptoms to fruits, vegetables, and nuts are commonly reported in gastroenterology clinics. It is essential to be aware of OAS as a cause of dysphagia and as a red flag for possible eosinophilic disease affecting motility. Currently, there are no reports of manometry studies documenting the mechanism of dysphagia in this group of patients.

Immediate Gastrointestinal Hypersensitivity and Anaphylaxis

Immediate gastrointestinal hypersensitivity is a type I, IgE-mediated food allergy. Upper GI symptoms such as vomiting may occur within minutes, and lower GI symptoms may occur either immediately or with a delay of up to several hours. It is a common feature of anaphylaxis. Symptoms can be life-threatening. IgE-mediated food allergy requires allergy testing, patient education, strict antigen avoidance, written emergency plan, and adrenaline auto-injector prescription. Symptoms are usually easily recognized as allergic due to their acute onset.

Non-IgE-Mediated Food Allergies

Food Protein-Induced Enterocolitis Syndrome (FPIES)

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated disorder that may be confused with anaphylaxis. It usually occurs in infants, but rarely can develop in adult life. FPIES manifests acutely if exposure is intermittent, or chronically if exposure is ongoing [39]. Acute severe symptoms may occur on first exposure to a food or after a period of elimination. They include repeated vomiting, often with diarrhea. This can progress to dehydration, lethargy, shock, and methemoglobinemia.

Symptoms of FPIES are non-specific, frequently causing diagnostic delays. There may be bilious vomiting, abdominal distension, air-fluid levels on X-ray, and bloody diarrhea. Acute or intermittent symptoms may be mistaken for gastroenteritis, necrotizing enterocolitis (NEC), intussusception, sepsis, or anaphylaxis. Chronic FPIES from regular exposure to a trigger food manifests as chronic emesis, diarrhea, and failure to thrive. FPIES typically begins at around six months on exposure to weaning foods, but onset may be neonatal. Symptoms may occur during exclusive breastfeeding due to maternal dietary antigens. Common food triggers vary by geographic area [39]. Milk, soy, and weaning foods such as rice, oat, or other cereal grains are frequently implicated. Vomiting within 1–3 h of ingestion of the trigger food is required for diagnosis, along with the absence of classic IgE-mediated respiratory or skin manifestations and a selection of other minor criteria [39]. A minority of patients have IgE sensitization. This is termed *atypical* FPIES and may have a more protracted course or morph into other IgE-mediated diseases [39].

Food Protein Enteropathy

Food protein enteropathy is a non-IgE-mediated, non-celiac enteropathy presenting in infancy with chronic diarrhea and malabsorption. Often there is steatorrhea, weight loss, and growth failure. Food protein enteropathy is a histological diagnosis, characterized by patchy villous atrophy and intraepithelial lymphocytosis (IEL), with a relative paucity of eosinophils [40]. The finding of IEL should prompt a search for causes, particularly celiac disease. Apart from the common causes, food allergy, and celiac disease, duodenal IEL may also be seen in autoimmune disorders, inflammatory bowel disease, tropical sprue, peptic duodenitis, parasitic and viral infections, as well as lymphoma [41].

The prevalence of food protein enteropathy is unknown. While food allergy is increasingly common as a cause of chronic diarrhea, especially in infants (rising from 11.5% to 80% of cases over the last four decades), not all allergic diarrhea is associated with enteropathy. Many cases are due to changes in motility and secretion. In fact, diagnosis rates of allergic enteropathy appear to be falling. This may be due to reduced requirement for endoscopy and biopsy in the evaluation of infants with chronic diarrhea. Current international consensus guidelines recommend a 2–4-week trial of dairy exclusion for infants with chronic diarrhea [42]. Guidelines also allow for the non-endoscopic diagnosis of coeliac disease in many cases.

Food Protein-Induced Allergic Proctitis/Proctocolitis (FPIAP)

Food protein-induced allergic proctocolitis (FPIAP) typically presents in infants who seem healthy but have visible specks or streaks of blood mixed with mucus in the stool. Although it is non-IgE-mediated, IgE sensitization develops in a minority of cases. The diagnosis of FPIAP requires that the child be well, without features of other gastrointestinal food allergies, such as vomiting, diarrhea, or growth failure. FPIAP is believed to be the commonest cause of blood in the stool in infants. The condition may spontaneously resolve without intervention in 2–4 weeks. However, if symptoms persist, EAACI guidelines recommend elimination diet and challenge. Invasive testing is not required to make the diagnosis of FPIAP. Endoscopic and histologic features are patchy and inconsistent. Allergic proctitis a risk factor for the development of food-allergic constipation.

Mixed Reactions

Eosinophilic Esophagitis (EoE)

Eosinophilic esophagitis (EoE) is a unique form of food allergy, restricted to the esophagus, characterized by esophageal eosinophil predominant inflammation and dysfunction. Prevalence of EoE is increasing. It is the commonest cause of dysphagia and food impaction in children and the commonest cause of upper GI symptoms in children after reflux disease. Almost all cases of EoE are due to food allergies, which are frequently multiple. Dairy and wheat are the commonest. More than 90% resolve on elemental diet.

A wide variety of motility disturbances have been described in EoE, including aperistalsis, ineffective peristalsis secondary to simultaneous contractions, and high amplitude esophageal body contractions, hypotonicity of the LES, as well as patterns consistent with achalasia, diffuse esophageal spasm, nutcracker, and jackhammer esophagus. In a meta-analysis of 77 patients with EoE, Furuta et al. reported abnormal esophageal manometry in 53% of patients with the commonest pattern being impaired peristalsis. However, in recent series, most patients with EOE had normal motility [43–45]. Dysphagia in these cases may be related to decreased distensibility [46], abnormalities of longitudinal muscle contraction, or intermittent esophageal dysmotility not captured on stationary testing. Symptoms correlate with wall thickness and distal contractile index (DCI). Wall thickness and DCI are correlated. Both improve on treatment. There are anecdotes of children whose esophageal dysmotility is acutely triggered by a specific food; however, none are published.

EoE treatment is pharmacological or dietary. Due to the chronic nature of the condition, drug therapy with PPI or topical steroids is usually first-line [47]. Dietary elimination is used for drug-resistant cases or where there is a desire to minimize drug use. Allergy testing has poor sensitivity and specificity for identifying dietary triggers and empiric elimination diets are now standard of care [48].

Eosinophilic esophagitis associated with eosinophilia elsewhere in the gut is considered part of the spectrum of primary EGID, which are discussed below.

Eosinophilic Gastritis, Gastroenteritis, and Colitis

Primary eosinophilic gastrointestinal disorders are inflammatory disorders defined histologically by eosinophilic infiltrate at any level of the gastrointestinal tract. Secondary causes of tissue eosinophilia such as parasitic infections, hypereosinophilic syndromes, inflammatory bowel disease, reflux disease, primary immunodeficiency (e.g., XIAP deficiency), connective tissue disorders, inflammatory fibroid polyps, or drug reaction must be excluded. Eosinophilic esophagitis without involvement of any other part of the gastrointestinal tract is considered separately. In contrast to EoE, which has a prevalence of 10–57 per 100,000, EGID are rare, with estimated prevalence of 2.1–5.1 per 100,000. However, rates of recognition and diagnosis are increasing.

EGID may involve mucosal, muscular/mural, and/or serosal layers. It is unknown how many cases involve only mural or serosal disease, as these are only diagnosed in the rare situations where surgery is required. Mucosal disease may present with reflux, vomiting, diarrhea, bleeding, anemia, or pain. Mural disease has been associated with obstructive symptoms, perforation, or fistula formation [49]. Manifestations include achalasia, delayed gastric emptying [50], and intestinal obstruction. Serosal disease may present with ascites.

More than one area of the gut may be involved. Symptom profiles vary with region affected. Typical symptoms of eosinophilic gastritis are nausea/vomiting (54%) and abdominal pain (48%). For eosinophilic gastroenteropathy, the commonest symptoms are nausea/vomiting (52%), abdominal pain (50%) and diarrhea (32%). Eosinophilic colitis presents with abdominal pain (60%), diarrhea (52%), nausea/vomiting (38%), and bloody stools (24%)., In addition to motility disturbances such as reflux (22%), diarrhea, and obstruction, EGIDS may cause gastric or duodenal ulceration that may be deep and intractable. Of pediatric peptic ulcers which are Helicobacter-negative and unrelated to gastrotoxic drugs, EGIDS make up 10%.

Diagnosis of EGID is histological, typically on biopsies from gastroscopy or colonoscopy. Criteria vary. Recently, the Consortium of Eosinophilic Gastrointestinal Researchers (CEGIR) published a large pediatric series using thresholds of 30 eosinophils per high powered field (HPF) (stomach), 50 per HPF (small intestine) and 60 per HPF (colon). As with EoE, the mucosa may be macroscopically normal and mucosal eosinophilia may be patchy, requiring multiple biopsies (8 gastric, 4 duodenal) for detection. Cell counts do not correlate with symptoms at diagnosis but improve in parallel with symptoms on treatment.

As EGIDs are rare, randomized controlled trials are lacking. Management is guided by case reports and small series. There is no consensus on treatment, which may involve diets, drugs, or both. Conventional allergy testing including skin prick and RAST testing is usually unhelpful [51]. Therefore, elimination diets have generally been empirical. Elemental formula is effective in 75–100%. Various elimination diets, typically removing multiple foods, are used, with improvements in almost 90% of patients. In a recent case of drug-refractory EGID-related peptic ulcer, endoscopic lavage demonstrated locally produced IgE to several foods. Tailoring the patient's diet using this information enabled resolution of the ulcer. In future, this technique may help define patho-

physiology in other gastrointestinal manifestations of allergy. However, the technique is in its infancy and research is required to standardize methods and define clinical utility.

Drug treatment may be employed alone or in combination with diet. Common agents are PPI, steroids (topical, systemic, or delayed release), mast cell stabilizers (cromolyn or ketotifen), or leukotriene inhibitors such as montelukast. Aminosalicylic acid drugs may be used in colitis. These may be effective as monotherapy or in combination. Treatments targeting other parts of the immune pathway such as interleukin 5 and antibodies to IgE are being developed.

Symptoms of EGIDS overlap with conditions in which eosinophil counts are normal or mildly elevated such as allergy-induced reflux, functional dyspepsia, IBS, diarrhea, and constipation. Like EGID, these conditions may have coexistent peripheral eosinophilia and atopy. Red flags for EGID include hematochezia, anemia, or low albumin and persistence of symptoms for more than 6 months.

Common Gastrointestinal Symptoms Which May Have an Allergic Basis

In addition to the specific allergic diseases discussed above, there is increasing recognition that food allergies can trigger or exacerbate gastrointestinal symptoms which present to motility clinics. These include dysphagia, reflux, vomiting, gastroparesis, diarrhea, and constipation. These will be discussed below.

Dysphagia: Cricopharyngeal

CMA can cause cricopharyngeal spasm [6]. In this case report, the child had additional symptoms consistent with FPIES to cows' milk. In a second reported case, CMA was diagnosed in a child with cricopharyngeal achalasia, when apnea and vomiting persisted after balloon dilatation and symptoms resolved on dairy-free diet. In our center, we have seen a similar infant, who developed severe swallowing difficulties requiring nasogastric feeding. Dairy formula feeds provoked severe eczema. Videofluoroscopy showed almost complete failure of the upper esophageal sphincter to open during swallows. A change to non-dairy formula resulted in resolution of swallowing difficulties and almost complete resolution of eczema.

Currently, it is unknown what percentage of children with upper esophageal sphincter dysfunction/cricopharyngeal dysphagia would be cured with elimination diet, as there have been no prospective studies. Given the serious nutritional consequences of this condition and the potential for invasive testing and destructive treatments, research is needed urgently.

Dysphagia: Esophageal

Both reflux esophagitis and eosinophilic esophagitis (EoE) can be associated with dysphagia, and both are often associated with food allergy. Some types of motility disturbance are broadly similar in patients with EoE and gastroesophageal reflux disease (GERD). Pan-esophageal pressurization was documented in 17% of EoE and 2% of GERD patients, while compartmentalized pressurization was present in 19% of EoE and 10% of GERD patients.

Gastroesophageal Reflux Disease (GERD)

Food allergy can cause secondary GERD which is clinically and histologically indistinguishable from primary GERD. Where present, factors such as retching, constipation, diarrhea, hematochezia, rashes, or rhinitis help point to an allergic cause [52–59]. However, these features may be absent. The only way to distinguish allergy-induced GERD from primary GERD is dietary elimination and challenge. Studies of cows' milk elimination show response in 16–59% of infants and older children with reflux.

Pediatric data on other allergens are lacking, but a DBPCFC study in adults demonstrated reflux and indigestion on exposure to wheat in patients with NCGS. In this study, wheat consumption was associated with increased reflux and indigestion symptom scores in at least half the NCGS cases. Other symptoms associated with wheat included abdominal pain, diarrhea, and constipation. Wheat-related reflux symptoms were not due to FODMAPs, as they did not occur on a FODMAP-containing gluten-free placebo [60]. Also, FODMAP challenge does not alter lower esophageal sphincter (LES) pressure, or increase gastroesophageal reflux in healthy volunteers. It seems more likely that the patients whose reflux symptoms worsened on wheat had an immunological reaction to wheat. This could cause altered gastric motility (gastric dysrhythmia, delayed gastric emptying, prolonged gastric distension) and increased number and proximal extent of reflux events after dairy exposure, as documented in children with dairy-induced upper gastrointestinal symptoms. Interestingly, in the above adult study, many of the other participants had worse symptoms while consuming the placebo flour, which contained dairy, potato, and corn. Currently, there is no direct evidence of the immunological mechanism for food-allergic GERD.

Both allergies and GERD are associated with regurgitation, food aversion, and FTT in infants. However, prospective studies of infants with food refusal for food allergies are lacking. Regarding the benefits of hydrolyzed formulas on GER and gastric emptying in infants, there is debate over the relative contributions of the physicochemical properties of the formula, as distinct from its allergen content [61].

Persistent crying in infancy may be associated with GERD, allergies, or both. Of 50 infants with persistent crying, 14 were found to have CMA. In these infants, dairy elimination significantly improved GERD symptoms, esophageal peristaltic function, reduced acid reflux, and increased esophageal mucosal baseline impedance, in keeping with improved or restored mucosal integrity [62].

The distinction between primary and food-allergic GERD is important. Failure to recognize food-allergic GERD can lead to inappropriate prolonged acid suppression treatment, invasive testing, and inappropriate surgery. Therapy with PPI is associated with several side effects, increasing susceptibility to fractures, infections, and allergic diseases. In particular, children with GERD who were treated with acid suppression experienced more food allergy compared to untreated GERD children (hazard ratio [HR]: 1.68, 95% confidence interval [CI]: 1.15–2.46). In adults with COVID-19, PPI therapy has been associated with an increased risk of severe disease and secondary infection [63]. Therefore, identifying children whose reflux symptoms are due to allergy and avoiding unnecessary PPI therapy is important.

The 2018 NASPGHAN/ESPGHAN guidelines on GERD recommend a trial of extensively hydrolyzed formula or amino acid–based formula in infants who have not responded to conventional GERD therapies. In a separate paper, elemental formula and oligoantigenic diet were found to be effective in children with cerebral palsy and severe intractable reflux disease, resistant to medical and surgical therapies. Alternatively, tube-fed children with intractable reflux or vomiting on formula may benefit from blenderized diet given through a gastrostomy, gastrojejunal, or jejunostomy tube. Compared to commercial formulas (dairy or elemental), blenderized diet is associated with a marked reduction in hospital presentations and admissions, with a trend to reduced respiratory illnesses. Blenderized diets are thicker, reducing regurgitation. Compared to formula, blenderized diets are associated with less nausea and vomiting, abdominal pain, diarrhea, and fewer total symptoms. They are also less dairy intensive and can be dairy-free. There are many potential explanations for the observed improvements. However, one mechanism may be reduced exposure to antigens such as dairy, soy, rice, and corn found in commercial formulas.

Post-fundoplication Complications

While beneficial in well-selected cases of severe or complicated GERD, fundoplication has a host of potential complications [64]. Infants and patients with neurological impairment have particularly high complication rates, including wrap failure and dumping syndrome [65, 66]. Long-term, wrap failure occurs in up to 25% and dysphagia affects 13%. Health-related quality of life improves temporarily but declines thereafter. ESPGHAN/NASPGHAN guidelines recommend that before anti-reflux surgery, it is essential to rule out non-GERD causes of symptoms, including CMA. The guidelines also point out that symptoms of CMA and GERD are indistinguishable and recommend a two-week trial of dairy elimination in infants with persistent troublesome symptoms. Elimination diet is recommended before PPI therapy. There is no clear direction on how to exclude CMA in older children before fundoplication. This is despite the fact that 38–59% of older children with GERD respond to dairy elimination. The figure may be even higher in refractory esophagitis in neurologically impaired children, with 78% responding to elemental formula. It has been suggested that all cases of intractable GERD should be suspected of CMA and investigated accordingly.

Interestingly, rates of fundoplication have fallen dramatically in recent years [67]. The drop is likely multifactorial. It coincides with the increased use of PPI in children as well as the recognition that dairy allergy is a common reversible cause of reflux symptoms. The 2009 and 2018 NASPGHAN and ESPGHAN guidelines may well have contributed by highlighting the paucity of high-quality evidence for fundoplication in children and the potential role for milk allergy. The majority of patients undergoing fundoplication are infants, so recommendations on trials of milk free diet in this age group may have been particularly impactful.

Accurate case selection for fundoplication is imperative. Some children continue to present for fundoplication without any prior assessment for dairy allergy. Both CMA and EoE can be mistaken for refractory GERD. Features of food allergy such as delayed gastric emptying and reflex vomiting [52] are risk factors for retching after fundoplication. Also, PPI-responsive EoE may be misdiagnosed as GERD in children whose initial gastroscopy was performed while on PPI therapy. Fortunately, many children being evaluated for fundoplication are referred preoperatively for reflux testing (e.g., pH-impedance testing) or esophageal manometry. Therefore, neurogastroenterology clinicians are well placed to detect these cases and intercede. Symptoms such as retching and vomiting, rather than regurgitation, are a contraindication to fundoplication as they indicate other pathologies and predispose to post-operative complications. Other symptoms such as altered bowel habit (diarrhea, constipation, alternating) or eczema are important clues to underlying food allergy.

Unfortunately, some children with undiagnosed food allergies or EoE do receive fundoplications inadvertently. Such cases are often referred for neurogastroenterology input postoperatively for retching or other symptoms. Up to 8% of children with persistent retching after fundoplication have food allergy. Persistent gagging and retching may dis-

rupt the fundoplication or create a paraesophageal hernia, leading to recurrent reflux, dysphagia or surgical revision [68]. Children with retching or dysphagia are often placed on diets that contain large amounts of dairy, including soft foods and supplemental formula feeds. This exacerbates symptoms in dairy sensitive patients. Prompt treatment of underlying food allergy or EoE can prevent breakdown of the wrap from repeated retching. It reduces the need for invasive tests or further surgery. In an excellent study using a heuristic treatment algorithm to manage post-fundoplication retching, Cook et al. dramatically reduced or eliminated retching in 97% of patients, many of whom were medically complex [69]. Food allergy was associated with combination symptoms in the lower gastrointestinal tract (diarrhea/constipation) and skin (eczema). The authors reiterated the maxim "retching is rarely reflux." Another effective strategy for tube-fed children with post-fundoplication retching is the use of blenderized diet. It has the advantage of reducing dairy intake by replacing commercial dairy-based formula with pureed food.

Despite the frequency with which food allergy causes regurgitation, reflux, and vomiting in children, there are no studies of the rate of food allergy in children referred for fundoplication or in those with complications post fundoplication other than retching. The potential benefits of routine trial of dairy-free diet before fundoplication have not yet been systematically explored.

Allergy is reported as a predisposing or coexisting factor in a wide range of pediatric FGID. The pathogenesis of both conditions is complex. Various mechanisms, including dysmotility and hypersensitivity, might contribute to clinical manifestations.

Food allergy can mimic FGID. Forty-five percent of young children with CMA satisfy ROME IV criteria for a functional GI disorder, with significantly higher rates of reflux, functional diarrhea, dyschezia, and constipation than controls [70]. Children with functional symptoms on a background of CMA who are treated with dairy elimination respond better than control children with similar symptoms given conventional treatment for functional GI disorders [70]. Individual FGID will be discussed below.

Functional Abdominal Pain Disorders (FAPD)

Functional abdominal pain disorders (FAPD) and food allergies have similar prevalence in children, affecting 8–13.5% [71–73]. There is considerable overlap in clinical presentation, and the two can occur concurrently. Pre-schoolers with any allergic or atopic diseases have an increased risk of IBS at school age. The greater the number of allergic disorders earlier in childhood, the higher the risk of in IBS diagnosis subsequently. Both adults and children with a history of food allergy are more likely to receive a diagnosis of FGID, especially IBS, FD, and FAP. Elimination diets are effective in both adults and in infants with food allergies presenting with symptoms of FGID.

Despite these observations, data supporting the possible role of food allergies in the pathogenesis of FAPDs in children are limited. Based on follow-up questionnaire studies, prior food allergy has been proposed as a cause of post-inflammatory FAPD in children [74, 75]. In a retrospective study, children with a history of CMA as babies had four times more abdominal pain than controls when studied at school age. In that study, all the children who met Rome III criteria for FAPD had a background of CMA. None of the control children had FGID. Overall, 20% of children with CMA history met Rome III FGID criteria at school age [74]. In a recent, prospective study, 15% of children with a history of FPIAP met symptom criteria for FGID four or more years later [75]. However, neither study included data on how many children were still limiting their intake of dairy or other foods. Neither study included dietary elimination/challenge to exclude ongoing allergy. Importantly, almost 50% of children who had CMA as infants continue to have dose-dependent symptoms to cows' milk at age 10, even after their original systemic IgE-mediated symptoms or allergic proctitis have resolved [76, 77]. It has been proposed that local hypersensitivity mechanisms may remain active even after the general reactivity to small doses has disappeared [77]. Evidence for local mucosal IgE-mediated reactions has begun to accrue (see section "Gastrointestinal Food Allergy: Role of IgE" above). In particular, children with dyspeptic symptoms provoked by dairy showed prompt mast cell degranulation and gastric dysrhythmia to milk applied down the gastroscope. However, there are no systematic studies of each of the FAPD in children using allergen elimination and challenge to evaluate what proportion have underlying dose-dependent food allergy.

There is considerable overlap between FAPD and NCGS. Twenty percent of adult NCGS fulfil Rome III criteria for IBS. Conversely, 19–46% of adults diagnosed with IBS have NCGS. Previously intractable symptoms can be controlled with adherence to gluten-free diet. In a recent randomized controlled trial, 35% of adults with treatment-resistant functional dyspepsia responded to gluten-free diet, with 6.5% meeting Salerno criteria for NCGS. Extra-intestinal symptoms such as fatigue, musculoskeletal pain, and headache also improved. Studies of gluten-free diet in children with IBS or FD are virtually non-existent. Further research is needed to better delineate the prevalence and mechanisms of gluten/wheat sensitivity and their significance before recommending gluten restriction in children with FAPD whose history does not identify wheat containing foods as triggers for symptoms.

Gas and distension are potent triggers for symptoms in FAPD. In adults, a low FODMAP diet improves many symptoms of IBS [78]. In children, there is limited evidence for

the benefit of a low FODMAP diet. While a low FODMAP diet may benefit some children with IBS, it was not found to be helpful in functional abdominal pain [79]. This discrepancy may be due to the increased prevalence of food allergies in children compared with adults, and the restriction of wheat, dairy, and soy intake on a low FODMAP diet.

Functional dyspepsia in childhood is commonly triggered by foods, including spices, caffeine, fatty foods, and cows' milk protein. Rome guidelines recommend avoiding trigger foods, but there are no specific guidelines on the role of diet to identify these [23]. Suspected non-IgE-mediated food allergy in children with FAPDs requires careful evaluation, with a time limited elimination diet followed by oral food challenge.

Chronic Non-infectious Diarrhea

Food allergies are the commonest cause of chronic diarrhea in infants and children in developed countries. They can be mistaken for functional conditions and can complicate the management of children with motility disorders such as Hirschsprung's disease. In babies under 6 months, CMA causes more than 80% of non-infectious diarrhea, whereas in older children the figure is 30% [80, 81]. Children with multiple food protein allergies make up a further 10%. Because of the frequency with which food allergy causes non-specific chronic diarrhea in infants, consensus guidelines recommend a trial of dairy elimination. However, this has not yet been codified for older children. Current Rome criteria do not require a diet trial before the diagnosis of functional diarrhea or IBS [22, 23]. The distinction is important because treatment of CMA is more effective than treatment for equivalent symptoms due to FGID [70].

Children with comorbidities are at particular risk for missed diagnosis of food-allergic diarrhea. A family history of celiac disease, or a personal history of short gut syndrome, Hirschsprung's disease, etc. can divert attention from the role of allergy. In neurogastroenterology clinics, an awareness of the role of CMA in diarrhea is particularly helpful in children with incontinence after anorectal surgery for conditions such as Hirschsprung's disease and anorectal malformations. Also, food allergy may exacerbate diarrhea in children with repaired esophageal atresia, who are already at risk for dumping syndrome.

In children with chronic non-infectious diarrhea, it is worth performing a brief (2–4 weeks) trial of dairy-free diet before escalating to invasive testing. Upper endoscopy and colonoscopy are not required prior to diet, as histological changes of enteropathy or colitis are neither sensitive nor specific for the diagnosis of food allergy.

In patients with diarrhea and normal histology or non-specific changes, foods may induce diarrhea through effects on secretion and motility. Fasting antroduodenal manometry in food-allergic adults with diarrhea shows abnormalities of activity fronts, clusters of simultaneous contractions, and giant jejunal contractions. Allergen challenge induces duodenal hypermotility with a clustered pattern and sometimes giant contractions [19]. Hypercontractility has also been documented with barium and ultrasound. Intestinal ultrasound is increasingly utilized by pediatric gastroenterologists to assess children with inflammatory bowel disease. Potentially, this non-invasive technique could directly visualize intestinal responses during provocation testing, allowing diagnosis of non-IgE-mediated gastrointestinal food allergy in children, but more research is needed. Preliminary studies in symptomatic children with non-IgE-mediated food allergy have shown small intestinal changes, including wall thickening, dilation, mesenteric thickening, and poor peristalsis.

In adults with food allergy manifesting as IBS, duodenal exposure to the trigger food administered through an endoscope caused rapid onset mucosal breaks, detected on confocal microscopy during the procedure. Immediate intestinal barrier disruption was associated with widened intervillous spaces, eosinophil degranulation, and increased intraepithelial lymphocytes. In this study, more than half of the adults with IBS were found to have immediate mucosal injury by food antigens, labelled as atypical food allergy. The commonest trigger food was wheat. Pediatric studies are awaited.

Constipation

In infants with CMA, the prevalence of constipation is 4.6%. In contrast, diarrhea affects 61% [82]. Many children with functional constipation give a history of diarrhea in early infancy, followed by a switch to constipation in later childhood [83]. Constipation can be the sole manifestation of cows' milk allergy. It can present identically to functional constipation, including withholding behaviors which often begin at toilet training. Any cause of painful defecation can set up a pattern of behavioral stool retention, and CMA is a common trigger.

Back in 2014, the ESPGHAN–NASPGHAN recommendations on functional constipation reported that the causal relationship between CMA and functional constipation is controversial. However, there is mounting evidence that dairy elimination is effective in a large proportion of children presenting with apparent functional constipation. There are now 14 prospective studies from 8 countries involving 529 children with functional constipation (see Table 20.1). Dairy-free diet was effective in 61% of case overall. Taking only studies where the diagnosis of CMA was confirmed with dairy challenge, 285 of 469 (61%) constipated children

Table 20.1 Prospective clinical trials of cows' milk elimination diet in functional constipation in childhood

Year	Author	Number of cases	Study type	Maximum age (years)	Responders to dairy elimination (%)	Response confirmed with challenge (%)	Treatment resistant or dependent	Setting (primary care, secondary, gastro)
1995	Iacono [85]	27	Prospective, open challenge	3	78	78	Either	ped GE
1998	Iacono [86]	65	Prospective crossover RCT DBPCFC	6	68	68	Resistant	ped GE
1999	Shah [87]	14	Prospective	7	79[a]	n/a	Resistant	ped GE
2001	Daher [88]	25	Prospective, open challenge	11	28	28	Resistant	ped GE
2004	Turunen [89]	35	Prospective, open challenge	15	83	34	Either	ped GE
2005	Carroccio [90]	52	Prospective with DBPCFC	Not reported	46[a]	52	Resistant	ped GE
2006	Iacono [91]	36	Prospective with DBPCFC	10	39[a]	39	Resistant	ped GE
2008	Simeone [92]	11	Prospective	6	0	n/a	Resistant	Primary
2009	El-Hodhod [93]	27	Prospective, long follow-up	4	78	78	Resistant	ped GE
2009	Borrelli [94]	33	Prospective with DBPCFC	11	30[a]	30	Resistant	ped GE
2010	Irastorza [13]	69	Prospective, open challenge	14	51	39	Either	ped GE
2012	Dehghani [95]	70	Prospective, cases controlled RCT	13	80	34	Resistant	ped GE
2013	Crowley [84]	30	Prospective crossover RCT with DBPCFC	12	81	33	Resistant	Secondary
2021	Mohammadi Bourkheili [96]	35	Prospective case controlled RCT	14	71	n/a	Resistant	ped GE

[a] Some children were allergic to other foods (commonly wheat, egg, soy, corn) as well as or instead of dairy, manifesting as constipation. Figures given are for dairy allergy only

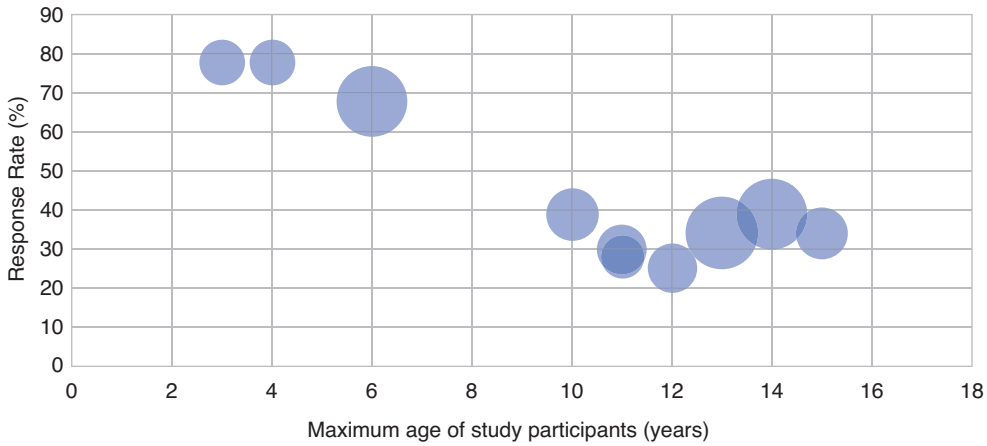

Fig. 20.7 Response rates to elimination diet children referred to secondary and tertiary clinics for constipation vary by age. *Y* axis indicates response to diet as a percentage. *X* axis indicates maximum age of study participants in years. Bubble size indicates number of participants. Studies detailed in Table 20.1

responded to dairy removal initially, with 46% relapsing on challenge. Taking only those confirmed with DBPCFC, the figure is 102 of 216 children or 47%. The research setting is important. Studies in pediatric gastroenterology clinics report challenge-proven response rates of 28–78%. In a hospital-based general pediatric clinic, the response rate was 33% [84] and in primary care, the response rate was zero of 11 patients. This was the only study of the 14 which did not show a benefit of dairy-free diet in functional constipation but given the small case numbers, it is difficult to generalize. It is likely that the children referred to pediatric gastroenterologists represent a treatment-dependent or treatment-resistant population who have not responded to conventional laxatives and behavioral management.

Response to dairy elimination for constipation varies by age, see Fig. 20.7. In children under three years of age,

response rates are as high as 78%. In older children, rates of food allergy/intolerance underlying constipation drop to 30%. These figures refer to secondary and tertiary referral populations. Rates of dairy allergy as a cause of constipation were much lower in a community-based study.

These studies are of medication-resistant or medication-dependent children from secondary and tertiary clinics, mostly pediatric gastroenterology clinics. A primary care study of 11 children with treatment-resistant constipation failed to find any responders to dairy-free diet.

The majority of studies used a 4-week elimination diet. Most used diet as add on therapy with conventional laxative or enema treatment, rather than as sole therapy [88, 90, 91].

Responders improve within days of starting elimination diet [13]. Symptoms usually return within days of reintroduction of dairy. Delay from ingestion to onset of symptoms increases with age [86], in some cases taking 2–4 weeks [16, 94].

Dairy-free diet improves all components of Rome criteria for functional constipation. This includes symptoms traditionally considered pathognomonic for behavioral or functional constipation, such as stool withholding behaviors [96].

Foods other than dairy can also cause intractable constipation, including multiple food reactions in a small percentage of children. The commonest food allergens after dairy were wheat, soy, corn, egg, and rice. However, a wide range of foods have been reported to trigger constipation including tomato, fish, cocoa, goats' milk, soy, oranges, and legumes.

Constipation in food allergy is designated as non-IgE mediated, due to negative skin prick and RAST testing in most cases. Allergy tests are not indicated.

In food-allergic constipation, delay in fecal passage is a consequence of retention of stool in the rectum and not of a generalized motility disorder [87]. Colonic transit may be more rapid than normal [97]. The pattern of rapid transit to the rectum is common in children with chronic constipation, occurring in 29% of 1000 undergoing transit studies for chronic constipation in one series. However, allergy was not evaluated in this study [98]. Transit studies normalize on elimination diet [87].

Food intolerance-related constipation is often associated with proctitis, with increased eosinophils in rectal mucosal biopsies and a raised anal sphincter resting pressure on manometry testing. These factors are reversible with elimination diet in such children. However, proctitis is not a reliable sign, being absent in up to 40%. MAST cell density and proximity of MAST cells to enteric nerves in rectal biopsies were found to be a marker of food-intolerance constipation. These MAST cell indices reduced in response to elimination diet.

Data on prognosis are limited. In a small study of 21 children under 4 years of age with constipation due to cows' milk, 77.7% remained intolerant when challenged after 6 months of elimination diet, whereas 89% could tolerate cows' milk at 12 months. Older children with food allergies causing constipation tend to improve after 2 years. Sometimes, food-allergic constipation persists into adult life.

There are now multiple adequately powered, prospective studies supporting a time-limited trial of dairy-free diet in patients with apparent functional constipation. A personal or family history of atopy or allergy are not universally present in children who respond to dairy elimination [13, 88]. Given the mounting evidence for allergic constipation, the case has been made for trying milk elimination as second-line therapy in all medication resistant/dependent cases regardless of allergy history [4]. This differs from the 2014 ESPGHAN/NASPGHAN guideline, in which children could progress as far as nuclear transit studies, colonic manometry, and surgery without prior dietary trials.

Given the high response rates in tertiary centers, the trial of dairy-free diet in all cases labelled intractable functional constipation could be considered before referral to gastroenterology/motility clinics. Response to dietary elimination would prevent unnecessary escalation of therapy and invasive investigations. This would reduce clinic waitlists and improve access for children with other motility disorders requiring specialist neurogastroenterology input. More stringent diets, such as elimination of dairy, soy and wheat simultaneously, may be considered in consultation with a pediatric gastroenterologist. Extreme oligoantigenic diets are hazardous without intensive dietetic support. Such diets are probably best left to research settings with multidisciplinary support.

It was recently proposed that dairy-free diet be used as *first-line* for the treatment of functional constipation in high-risk cases. These include pre-school children, those with a personal or family history of atopy and those with a previous diagnosis of CMA [4].

Another high-risk group may be those children with developmental delay, who were more likely than other children to respond to dairy elimination for constipation [13]. Children with developmental delay and cerebral palsy were explicitly excluded in most studies of food allergy in constipation. Children with neurodevelopmental conditions such as developmental delay, autism, and cerebral palsy are over-represented in constipation clinics. Mechanisms of constipation in these groups are yet to be defined and likely complex. Neurodiverse and developmentally delayed children often have high dairy intake. Many rely on soft diet or formula feeding. Some also have restricted dietary preferences due to factors such as autism. Autistic children have high rates of food reactions. They are twice as likely to have food allergies than other children. However, there is virtually no specific literature on food allergy in children with developmental

delay, cerebral palsy, or other neurological disorders. Tube-fed children with apparent functional or motility symptoms are a particularly amenable group for research, given the ease of eliminating dairy with a formula change.

Fecal Incontinence

Fecal incontinence may have devastating impacts on quality of life. An awareness of the possible role of food allergy can assist management of cases unresponsive to standard initial management, or who have obvious food allergy-associated conditions at presentation, such as eczema or patient-recognized food triggers.

Fecal incontinence presenting to gastroenterology clinics is usually due to underlying constipation and responds to standard management. As outlined above, elimination diets are effective in 28–78% of children with chronic or treatment-resistant functional constipation, with resolution of incontinence [96].

In 20% of cases, functional fecal incontinence is non-retentive. Treatment consists of education, a non-accusatory approach, and a toileting program with bowel diaries and reward systems. Special attention is paid to psychosocial and behavioral problems since these frequently occur in affected children. Behavioral problems may be secondary and resolve if incontinence is successfully treated [99]. Functional non-retentive fecal incontinence (NFI) often requires prolonged therapies with incremental improvement on treatment and frequent relapses. Laxatives can be counterproductive and enemas or suppositories may be required. Only 29% recover after 2 years of intensive treatment and 25% are incontinent as adults [100]. These poor outcomes drive the search for treatment options for this patient group [101].

Abdominal imaging is not indicated to diagnose NFI, as it can be diagnosed on Rome criteria [23]. However, sometimes imaging is performed to confirm the diagnosis or investigate intractable cases [102]. A subgroup of patients with NRI have rapid oro-anal transit [101]. This is a hallmark of allergy [5]. Patients with food allergy also display reduced tolerance of rectal filling. In NFI, barostat studies show rectal contractions associated with unnoticed fecal loss, echoing findings in adults with idiopathic diarrhea and incontinence [101]. Adults with NFI identify food triggers such as dairy and fatty foods [103]. A low FODMAP diet (wheat-free, low dairy/soy) improves FI associated with diarrhea in adults, but there are no studies in children. Unlike the extensive literature on food allergies and constipation, there are currently no studies evaluating the relationship between allergies and NFI in children. Given the severe impacts of NFI on quality of life, it is essential to consider organic pathology such as food allergy before assigning a functional or psychological cause. Similarly, before escalating to rectal therapies or invasive testing such as anorectal manometry, potential food allergy should be considered as a treatable cause for incontinence.

Infant Dyschezia

Dyschezia was described in 1957 as a self-limiting condition exclusively affecting infants with a personal or family history of allergic disease, especially CMA [104]. Since then it has continued to be recognized as a common symptom in infants with CMA [70]. Monosymptomatic dyschezia in otherwise well infants has been labelled as a functional disorder. In the absence of manometric studies, it has been ascribed to immature coordination of pelvic floor muscles during defecation [22]. However, food allergy is known to cause high tone, poorly relaxing anal sphincter, reduced tolerance of rectal filling and proctitis. Dyschezia is more common in formula-fed infants than those who are exclusively breastfed. It is also more common in babies born by cesarian section, a risk factor for allergy and dysbiosis. To date, there have been no prospective series of infants presenting with monosymptomatic dyschezia to determine the pathophysiology, such as response rate to dairy elimination. If infant dyschezia is monosymptomatic, this is categorized as a functional disorder by Rome IV criteria. Reassurance and expectant management are recommended [22]. However, before making a diagnosis of functional infant dyschezia, it is important to rule out CMA. Questionnaire-based tools such as the COMISS™ score are useful and can be administered to parents in the waiting room. If the COMISS™ score highlights possible CMA, elimination diet with challenge is indicated to clarify the diagnosis.

Infant Colic

Infant colic is defined as recurrent and prolonged periods of crying without an obvious cause or evidence of failure to thrive or illness in infants younger than 5 months [22]. It is common, affecting more than 20% of babies. Underlying food allergy is present in some cases. However, pathophysiology is multifactorial. Other proposed contributors include gut inflammation and dysbiosis, gastrointestinal immaturity, dysmotility, increased serotonin secretion, poor feeding technique, maternal anxiety, and maternal alcohol and nicotine intake. Parental anxiety and infant crying can amplify each other, setting up a vicious cycle. Although colic itself is time-limited, it significantly impacts quality of life, health care utilization, and parental mental health. It can be a trigger for child abuse. Guidelines recommend screening for organic disease and emphasize the importance of parental reassurance and support.

Approximately 5% of infants presenting to a hospital emergency department with excessive crying have a serious underlying organic disease, the commonest being urinary tract infection. "Silent reflux" has been proposed as a cause of excessive crying. However, PPIs have no value for infant crying and are not indicated.

Evidence supports a food-allergic basis in at least a proportion of infant colic. Many children with colic go on to develop other allergic diseases in later childhood. A 2018 Cochrane review found several studies showing benefits of antigen restriction, either by restricting maternal diet if breastfeeding, or changing formula to soy or semi-elemental in bottle-fed babies. However, evidence was sparse, and studies differed significantly in their methodology, preventing meta-analysis [105]. Since then, a randomized trial of low FODMAP diet in breastfeeding mothers significantly reduced infant crying, despite no change to the FODMAP/lactose content of the breast milk. This raises the possibility that food allergens such as wheat, dairy, and soy, which are restricted in the low FODMAP diet, may have a role. In a separate study, lactose-free formula was ineffective for infant colic; so benefits of dairy elimination for colic are likely due to CMA.

All colic guidelines recommend screening for underlying diseases, of which CMA is very common. Using evidence-based tools for screening infants for risk of CMA is likely to improve rates of detection. The COMISS™ score has been recommended for this purpose. In many cases, symptoms such as sneezing, rashes, or defecation difficulties will be present and point to a diagnosis of CMA. For cases of infant colic that are truly monosymptomatic, elimination diet is controversial. US guidelines include it but not those in the UK or Ireland. A time-limited trial of dairy antigen reduction, with semi-elemental formula or maternal dairy-free diet if breastfeeding, is often useful [106–108]. Symptoms generally respond within 1–2 weeks [105]. Therefore, any diet should be brief, with target symptoms defined in advance and objectively monitored. Only if symptoms respond should the diet continue. Subsequently, attempts should be made to liberalize the diet to include more dairy every few months [107]. Other aspects of colic management, including parental reassurance and regular support, are vital.

Food Allergies in Disorders Associated with Dysmotility

Food allergy may coexist with other disorders which affect motility. Attention to food reactions can optimize function in such children and improve quality of life. This section highlights areas where food allergy may play a role. Further studies are needed in all areas to clarify the role of allergy in these conditions.

Achalasia

Immune mechanisms are thought to be central to the pathogenesis of achalasia [109]. Both autoimmune and atopic diseases are associated with achalasia. Viral triggers have been proposed, but evidence is conflicting. EoE can also masquerade as achalasia, with lower esophageal sphincter function restored after steroid therapy. Histological studies in achalasia show various findings, with a proportion showing eosinophilic infiltration of the muscular layers. In a recent small study, almost all achalasia samples showed profound mast cell degranulation in myenteric plexus nerves, supporting the hypothesis that achalasia might be allergy driven.

Other Esophageal Motility Disorders

Using cutting-edge technologies of endoscopic muscle biopsies taken at peroral endoscopic myotomy (POEM), correlated with high-resolution manometry findings, Japanese researchers demonstrated severe eosinophilic infiltration confined to the muscle layer in four of five cases with jackhammer or nutcracker esophagus. There was no mucosal eosinophilia. This condition has been termed eosinophilic esophageal myositis (EoEM) and responds to systemic steroid treatment. This may correlate with anecdotal reports for specific food triggers and earlier case reports of steroid-responsive distal esophageal spasm and jackhammer esophagus (in the absence of EoE). As yet, there are no studies of elimination diets in spastic esophageal disorders.

Esophageal Atresia

Children with esophageal atresia (EA) are at high-risk for food allergies due to exposure to PPI and antibiotics, disrupted infant feeding and repeated hospitalization affecting microbiome development. Patients with EA are at increased risk of EoE, which can be overlooked. EoE can worsen dysphagia and lead to stricture development or inappropriate fundoplication [110]. Another under-recognized condition in patients with EA is dumping syndrome, which affects up to 29% [111]. This can contribute to fecal incontinence, especially in patients with VATER or VACTERL association who also have repaired anorectal malformations. The combination of allergy and dumping can result in severe incontinence triggered by certain foods.

Gastroparesis

In susceptible food-allergic children, ingestion of the offending food causes mast cell degranulation, immediate reduction

in gastric motility and profound delay in gastric emptying, mimicking gastroparesis. Electrogastrogram and impedance tomography studies in infants with CMA show that cows' milk induces severe gastric dysrhythmia and delayed gastric emptying. This may exacerbate GER and induce reflex vomiting [52]. Dysrhythmia has also been observed in older children with dyspeptic responses to dairy, when exposed to milk introduced through a gastroscope. (Fig. 20.3 above in section "Gastrointestinal Food Allergy: Role of IgE") Total IgE need not be elevated. Ninety percent of children were seronegative to cows' milk on RAST. However, mucosal biopsies show IgE-positive mast cells, which degranulated on exposure to cows' milk (Fig. 20.4 in section "Gastrointestinal Food Allergy: Role of IgE").

Despite the frequency with which food allergies cause regurgitation, vomiting and delayed gastric emptying, no studies have systematically evaluated elimination diets in gastroparesis. Adult patients with gastroparesis note symptoms are worse after dairy than soy milk, and after wheat bread than gluten free [112]. In children, the presence of delayed gastric emptying should alert the clinician to the possibility of underlying food allergies. It is essential to take a detailed allergy history and enquire about current or previous food reactions. Often a treatable dietary cause for symptoms can be identified. This prevents inappropriate, invasive testing and unnecessary treatments.

Necrotizing Enterocolitis

Questions of motility frequently arise in children with a history of necrotizing enterocolitis (NEC) due to persistent or recurrent obstructive symptoms, high stoma losses or feed intolerance in later childhood. The pathogenesis of NEC is related to hypoxic/ischemic insult, mucosal immaturity, and its interaction with the intestinal microflora. There is increasing awareness that a proportion of children presenting with NEC may have underlying food protein allergies. Breastfeeding confers protection against NEC. Most cases are linked to formula feeding, often occurring soon after introduction. Babies with NEC have exaggerated immune responses to dairy proteins in vitro. Although some cases of NEC have been linked to CMA, overall, there is no increase in rates of allergic diseases in older children with a history of NEC.

FPIES can affect newborns and has even been reported in utero. FPIES can masquerade as NEC. Differentiation is vital, to avoid inappropriate diet or surgery. Clinical presentations of NEC and FPIES can be similar, with vomiting, abdominal distention, diarrhea, bloody stool, feeding difficulties, lethargy, apnea and even shock. X-rays may show dilated loops of bowel, pneumatosis intestinalis (PI) and portal venous gas in both conditions [113]. A recent study using ultrasound highlighted important differences. While features such as pneumatosis, portal venous gas, bowel wall thickening, focal fluid collections and hypoechoic gallbladder wall occurred in both conditions, all are more frequent and persistent in cases of NEC. While pneumatosis and portal gas were found in nearly half the cases of FPIES, they were detected only on acute imaging performed within 2 h of symptom onset. In contrast, extraluminal gas was more persistent in NEC. FPIES features were more localized, and intestinal motility was better preserved. Motility was reduced only in an affected segment of the intestine in FPIES, with other areas showing normal or increased peristalsis. In contrast, intestinal motility was generally reduced or absent in NEC [114]. FPIES should be suspected even in breastfed infants and a trial of elimination diet considered whenever diagnostic tests for NEC are inconclusive.

Short Bowel Syndrome and Intestinal Failure

Children with short bowel syndrome are predisposed to food allergies. They have multiple risk factors for allergies, including antibiotic exposure, PPI therapy and impaired digestion of food antigens due to rapid transit. Their underlying cause for short bowel syndrome may have related to CMA, as in some cases of NEC. It is worth examining the role of dairy proteins and peptides in patients with short bowel syndrome struggling with feed intolerance or high gastrointestinal losses. A switch to elemental formula may assist in weaning parenteral nutrition support, reducing gastrointestinal losses, improving enteral uptake of nutrients, tolerance of oral diet and growth. In other children with short gut, identification of EGID or IgE-mediated food allergy can result in dietary changes which reduce GI losses.

Pseudo-Obstruction

Multiple food intolerances can be mistaken for chronic intestinal pseudo-obstruction (CIPO) [115]. Symptoms include vomiting (occasionally bilious), distension and diarrhea. However, normal fasting motor patterns (migrating motor complexes and postprandial response) are retained. Nonspecific qualitative abnormalities of antroduodenal manometry may be present in patients with food allergies. These include sustained duodenal phasic activity during fasting, clustered contractions, high amplitude waves and simultaneous onset of phase III of the migrating motor complex. Similar changes have been observed in animal models and can persist for some time after the offending food has been removed. Such manometry findings do not indicate a primary motility disorder and should not be over-emphasized [115]. Before referral for antroduodenal manometry, patients

should undergo an extensive diagnostic workup to exclude conditions that can mimic pseudo-obstruction, including factitious disorder by proxy, malrotation, inflammatory bowel disease, coeliac disease, congenital diarrheas and food reactions.

Hirschsprung's Disease

More than 50% of patients with Hirschsprung's (HSCR) suffer from incontinence [116]. Patients with HSCR suffering incontinence are more likely to have rapid colonic transit. and propagation of high amplitude propagating contractions (HAPC) through the neorectum to the anus [117]. Some have increased numbers of HAPC, and this "hyperactivity" of the colon further contributes to incontinence. Colonic hyperperistalsis is a feature of food allergy [5]. In children without HSCR, rapid transit is a marker of food allergy and improves on elimination of the offending antigen [87]. In HSCR children with non-retentive fecal incontinence, food intolerances were identified in 3.5% [118]. In another study, children with Hirschsprung's disease and incontinence were found to have fast colonic transit resembling that seen in food allergy. Assessment and management of food intolerances led to resolution of incontinence in 9/10. In most patients, fructose or lactose were identified as trigger foods, based on breath hydrogen testing. Low FODMAP diet was effective. In one child gluten and dairy were felt to be triggers and symptoms improved on elimination. Dairy allergy is known to cause rapid transit and exacerbate sugar malabsorption [119]. However, whether sugar malabsorption was due to underlying CMA was not assessed in this study.

In another study of patients with HSCR, 64% reported food reactions. The commonest symptoms were diarrhea (56%), abdominal discomfort (17%), perianal discomfort (13%), and constipation (11%) Trigger foods included fruit (59%), vegetables (28%), dairy products (28%), grains/breads/cereals (26%), fatty or fast foods (44%), meat (2%), and others (28%). Many of these are high FODMAP foods which would increase water delivery to the colon and possibly overwhelm the absorptive capacity of the shortened gut. However, dairy and wheat are also the top two antigens causing gastrointestinal food allergies. Of course, allergy and FODMAP intolerance can coexist, with rapid transit due to underlying allergy reducing the ability to cope with dietary FODMAPS. Constipation was reported after dairy, grains, and fatty/fast foods. Forty-four percent of the patients either totally or partially excluded trigger foods from their diet. The most frequently restricted food groups were fruit (24%), fatty or fast foods (19%), grains/breads/cereals (17%), vegetables (11%), and dairy (11%).

Immediate food allergies and EGIDS have been reported in children with long segment Hirschsprung's disease due to Shah-Waardenburg Syndrome.

Enterocolitis affects children with HSCR pre-operatively in 15–50%, and postoperative enterocolitis occurs in 2–33%. CMA is a possible risk factor for enterocolitis. In a recent study of 24 patients, post-operative enterocolitis occurred exclusively in patients with laboratory markers suggesting food allergy. Thirty-six percent of 14 children with mucosal eosinophilia, positive lymphocyte stimulation test or both developed enterocolitis, compared to none of the children with negative allergy tests ($p = 0.05$).

CMA can also mimic HSCR, with abdominal distension, vomiting, PR blood, and constipation. Barium enema can be identical to HSCR, with rectal narrowing and a caliber change to dilated colon above (see Fig. 20.8).

Manometry may not distinguish CMA and HSCR. In CMA, anal sphincter tone can be high and recto-anal inhibitory reflex impaired. Rectal biopsy remains the gold standard for diagnosis of HSCR. Occasionally biopsy features may be confusing. Patients with CMA without HSCR may have hypertrophic nerve fibers with increased acetylcholinesterase staining. However, the key finding of submucosal ganglion cells excludes HSCR in CMA, mucosal eosinophilia is often present, pointing to an allergic cause, and symptoms resolve on dairy elimination.

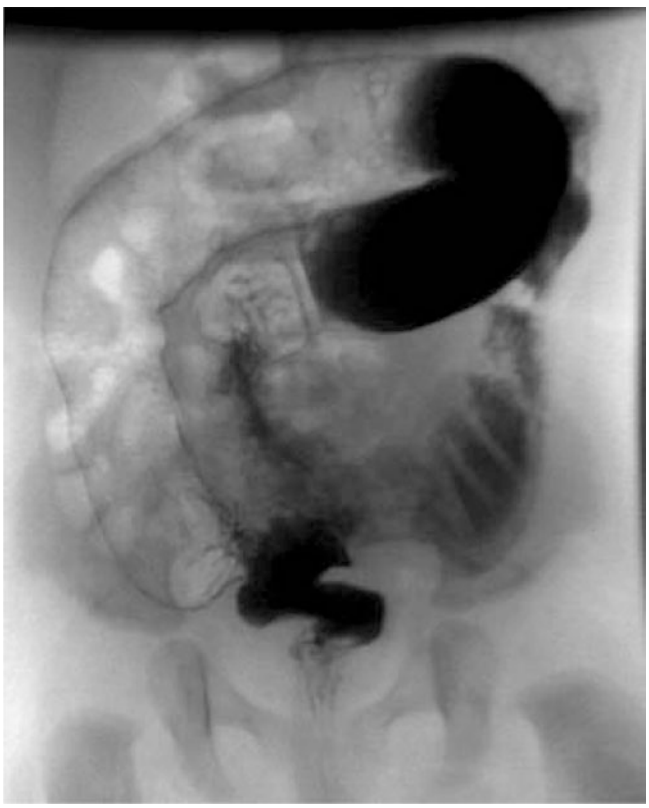

Fig. 20.8 Allergic proctitis mimicking Hirschsprung's disease on barium enema. This shows contracted rectum and colon in a 3-month-old girl with allergic proctitis [120]. (With permission from Lee JH, Choe YH, Lee SK, Seo JM, Kim JH, Suh YL. Allergic proctitis and abdominal distention mimicking Hirschsprung's disease in infants. Acta Paediatr. 2007;96(12):1784–9)

Hypermobility

Joint hypermobility is increasingly recognized in patients with motility and functional disorders, including gastroparesis, functional dyspepsia, and IBS, although this association was not found in a community-based study [121]. Young patients presenting to a hospital neurogastroenterology clinic were ten times more likely to have hypermobility than the general population and 68% met diagnostic criteria for both FGIDs and hypermobility. In a separate study, 38% of children presenting with slow transit constipation had hypermobility, which was double the rate of controls. Children with hypermobility have high rates of upper GI symptoms and may present to motility centers for pH-metry or esophageal manometry. Reflux (especially supine reflux) and subtle abnormalities of esophageal peristalsis are commonly found on pH-metry and high-resolution manometry and are more likely in patients with postural orthostatic tachycardia syndrome (POTS).

Joint hypermobility syndrome and Ehlers-Danlos syndrome are associated with food allergy. Almost 40% of children with gastrointestinal food allergies have joint pain and/or hypermobility. Hospitalized patients with Ehlers-Danlos syndrome (EDS) have a fourfold increase in food allergy [122]. Dysphagia is a common symptom in hypermobile patients. Importantly, children with hypermobility disorders have an eight-time increased rate of EoE. Such children are more likely than other EoE patients to have eosinophilic gastritis, duodenitis, and colitis.

As noted above, FGID are frequently associated with hypermobility, with milder phenotypes common in clinics. Occasionally, severe cases present with a complex range of inter-related conditions. These include food allergy and extraintestinal conditions such as autonomic dysregulation and postural orthostatic tachycardia syndrome (POTS) as well as joint instability, musculoskeletal pain, psychological dysfunction, psychosocial impairment, and emotional problems. These severely affected patients with multisystem involvement are some of the most difficult patients to treat. Symptoms can be disabling and severely affect quality of life. However, meticulous attention and specific management of each aspect (musculoskeletal instability, deconditioning, food allergy, POTs, psychological comorbidities) can markedly improve symptoms and quality of life. Multidisciplinary teams are vital for managing such complex patients. Both food allergy and hypermobility are probably underdiagnosed in motility clinics. Recognition can enable specific care and better patient outcomes.

Some hypermobile children presenting to gastroenterology services with allergy and dysmotility have underlying inherited conditions with potentially life-threatening complications. These include Marfan's, some types of EDS, Loeys Dietz syndrome, and Filamin A mutations. Such patients require careful assessment and surveillance [123]. Awareness of the association between joint hypermobility syndromes, dysmotility, and allergy is essential to enable appropriate management, as well as to detect those rare hypermobile cases with potentially serious systemic manifestations.

Implications for Manometry and Transit Studies

Dairy, egg, and wheat are common ingredients in test meals for gastrointestinal transit and motility studies, including nutrient drink tests, nuclear gastric emptying and colonic transit tests, ultrasound assessment of gastric emptying, EGG, antroduodenal, and colonic manometry. This poses a risk of overdiagnosis of primary motility disorders, given the high rates of food allergy in the community and even higher rates in motility patients. Low allergen alternatives exist but are yet to be widely adopted. An awareness of the potential confounding factor of food allergens in test meals is vital for motility and transit testing, both in clinical and research practice. Future research is urgently needed.

Prevention of Food Allergies

Primary and secondary prevention of food allergies are the subject of intense research. EAACI guidelines recommend against cows' milk formula in the first week of life and for introduction of egg and peanut between 4 and 6 months of age. Research is ongoing regarding timely introduction of other allergenic foods at weaning, emollient protection against epicutaneous sensitization, optimization of vitamin D status, fish oil, probiotics, prebiotics, vaccines, immunotherapy, and allergen-modified foods. A detailed discussion of these measures is beyond the scope of this review.

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Disorders of Deglutition in Infants and Children: Etiology and Management

21

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Abbreviations

BPD	Bronchopulmonary dysplasia
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
TLESR	Transient lower esophageal sphincter relaxation
UES	Upper esophageal sphincter
VFSS	Video fluoroscopy swallow studies

Education Gap

1. To clarify the basics for swallowing difficulties in infants and children.
2. To clarify the reasons for symptoms and signs of deglutition disorders.
3. To describe diagnostic testing and approaches to management of deglutition disorders.

Introduction

Deglutition or swallowing is the process of ingesting a bolus safely and efficiently from oral cavity to stomach, while protecting the airway. This process involves movement and coordination of multiple groups of neural elements as well as skeletal and smooth muscles within the aerodigestive tract. Disorders of deglutition are increasingly prevalent in infants and children as a result of advances in medical care, and more so in premature and high-risk infants [1, 2]. Potential underlying factors can be due to anatomic, genetic, maturational, neuropathological, and systemic abnormalities. Some of these abnormalities can be prolonged due to airway or digestive inflammatory processes that occur in diseases such as chronic lung disease or gastroesophageal reflux disease (GERD), respectively. Most healthy infants and children execute the swallowing reflex multiple times throughout the day or night, in wakeful or sleep states, volitionally, or reflexively with minimal to no effort [3]. Such reflexes facilitate movement of any swallowed material away from airway and are thus protective mechanisms.

The process of swallowing includes four distinct phases: oral preparatory phase, oral phase, pharyngeal phase, and esophageal phase. An essential component to each of these phases includes airway protection during the movement of bolus. Dysfunctions can result from the inability to properly coordinate across any of the anatomic structures involved with swallowing and/or breathing leading to possible dysphagia and resultant consequences [2, 4]. In this chapter, we discuss the etiology, differential diagnosis, and therapies for disorders of deglutition, which will permit parents and providers anticipatory guidance and definitive management strategies that will lead to superior, clinically meaningful outcomes.

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Prevalence and Burden of Disorders of Deglutition

The exact prevalence of persistent swallowing disorders in children is not known, although they appear to have become more prevalent in infants and children. Undoubtedly, this is due to consequence of technological and surgical advances with improved survival across the pediatric age spectrum, increased recognition of the importance of these disorders, improved diagnostic methods, and greatly improved survival rates among premature and high-risk neonates [5]. The resulting feeding difficulties can often prolong hospital stays and require active management after discharge [1]. Despite the impact of swallowing disorders on families and rather than being more accurately treated based on symptoms or test results, many children continue to be misdiagnosed and recommended therapies that do not effectively treat the condition causing the swallowing disorder. Symptomatic management of swallowing problems alone may not fix the underlying primary etiology and can lead to newer problems related to treatment such as growth disturbance (undernutrition or overweight), aspiration syndromes, chronic airway and lung disease, feeding aversion, all of which may prelude chronic tube feeding. Every patient with a swallowing disorder has a feeding disorder, which can be due to the abnormalities of the dynamic swallowing process, the process of how the disorder is diagnosed or how feeding is managed. On the other hand, every patient with a feeding disorder does not necessarily have a swallowing problem. This fundamental distinction needs to be made by the physicians and providers in seeking history during clinical evaluation. In doing so, targeted approaches can be developed. Earlier diagnosis and management of swallowing disorders will decrease short-term and long-term patient morbidity using holistic, multidisciplinary approaches [6–8].

Clinical Presentation of Disorders of Deglutition and Challenges with Diagnosis

Maintenance of safe breathing and adequate ventilation is a necessary pre-requisite to the swallowing phases. There are a wide range of swallowing disorder symptoms, shown in Table 21.1, ranging from trivial discomfort to severe complications [9–17]. Trivial discomfort during swallowing phases is rapidly overcome by autoregulation of breathing-swallowing phases along with postural adjustments to facilitate safe breathing during the act of bolus transit. Some overt symptoms of anterograde aspiration, that is, aspiration during feeding, can range from gagging, choking or coughing to bradycardia, apnea, or cyanosis. On the more subtle end of the spectrum, the symptoms include arching/irritability or fussiness during feeds, noisy or wet breathing after feeding, or signs such as delayed swallowing, voice changes, tearing, nasal congestion, wheezing, or facial redness [4, 18]. Symptoms therefore result from physical movement, respiratory changes, and autonomic changes [19, 20]. Furthermore, it can be difficult for providers to diagnose swallowing disorders because the symptoms are often absent, subtle, nonspecific, and heterogeneous [21], and it is especially difficult if the patient is experiencing silent aspiration. Silent aspiration

Table 21.1 Symptoms and signs in relation to dysphagia and comorbidities

	Comorbidities							
Symptoms/signs	Dysphagia	Prematurity	GERD	BPD	Reflex abnormalities	Intra-ventricular hemorrhage	Hypoxic-ischemic injury	Prolonged NG Tube
Gagging	X		X		X	X	X	X
Emesis	X		X		X			X
Choking	X		X	X	X	X	X	
Coughing	X		X	X	X			X
Apnea, bradycardia, desaturations	X	X	X	X	X	X	X	X
Delayed swallowing	X				X	X	X	X
Arching and irritability	X		X	X	X	X	X	X
Noisy or wet breathing	X	X	X	X	X			X
Voice changes	X		X	X	X			X
Tearing	X			X	X			
Nasal congestion	X		X	X	X			
Wheezing	X	X	X	X	X			
Facial redness	X		X	X	X			
Recurrent pneumonia	X		X	X		X	X	X

Diagnosis and treatment for dysphagia may be unsuccessful if only based on the symptoms that the infant is displaying because symptoms of dysphagia are nonspecific and heterogeneous, especially when other comorbidities are present (see references in text)
GERD gastroesophageal reflux disease, *BPD* bronchopulmonary dysplasia

is common in children with neurological disorders [22–24], which can be associated with varying severity of chronic aspiration that is likely due to dysregulation of the swallowing and glottal closure reflexes along with the inability to coordinate the pharyngeal and esophageal phases of swallowing [25]. The significance of silent aspiration in those infants who are thriving well without any aerodigestive, neurological or cardiopulmonary diseases is unclear.

It is important to understand retrograde aspiration that may occur during gastroesophageal reflux (GER) events if secretions reach the airway introitus. Such problems are often the result of more proximal events and failure of aerodigestive reflexes at multiple levels [26]. Transient lower esophageal sphincter relaxation (TLESR) is the most common cause of GER in infants [27, 28], as shown in Fig. 21.1a. A TLESR is characterized by prolonged relaxation of the LES followed by retrograde bolus movement [29]. The white impedance lines, in Fig. 21.1a, show whether air or liquid is passing through the different esophageal regions. A drop in impedance indicates that liquid is present, and a rise in impedance, indicates the presence of air. If a GER event is occurring, the drop in impedance will begin in the distal esophagus and end in a more proximal region of the esophagus. In Fig. 21.1a, the left arrow shows a reflux event where the impedance drops as the liquid travels up the esophagus. Reflux in a healthy infant is not a cause for concern if they can stimulate protective swallowing reflexes following the GER event to prevent aspiration and/or emesis from occurring. In Fig. 21.1a, the patient demonstrates the protective swallowing reflex, secondary peristalsis [30, 31], after a reflux event. The arrow on the right shows the direction of the liquid traveling anterograde into the stomach. Development of these protective reflexes is critical in safe oral feeding as shown in Fig. 21.1b. For a child to feed safely, they must perform pharyngeal reflexive swallowing [32, 33] during feeding (four swallows are shown in Fig. 21.1b). After a distinct pharyngeal contraction pushes the bolus towards the UES, relaxation must occur so it can enter the esophagus. This will often occur multiple times before a terminal swallow.

Nevertheless, the diagnosis of aspiration can be challenging as no reliable method exists and symptoms, as alluded earlier, are often over-interpreted in favor of the aspiration diagnosis. Therefore, empirical diagnostic and therapeutic

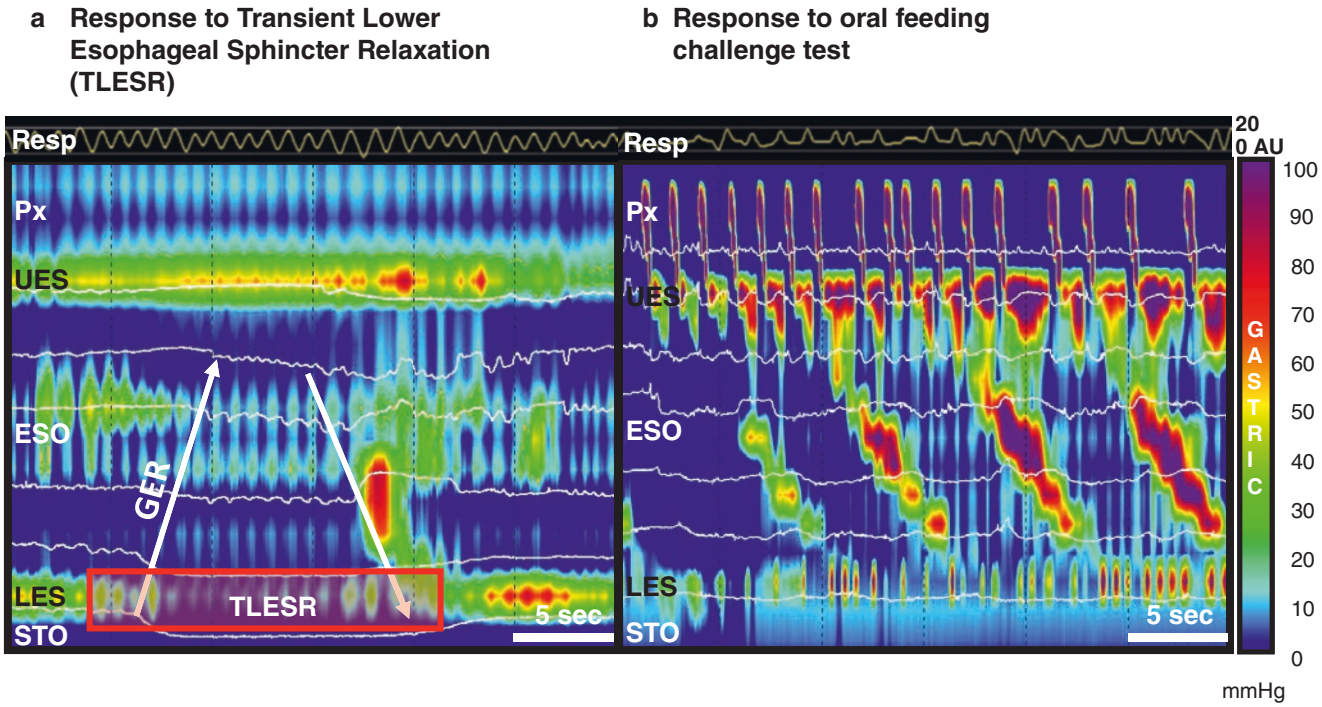

Fig. 21.1 Effect of TLESR and oral feeding challenge test. *GER* gastroesophageal reflux, *TLESR* transient lower esophageal sphincter relaxation, *GI* gastrointestinal, *Resp* respiratory, *DA* deglutition apnea, *Px* pharyngeal, *UES* upper esophageal sphincter, *ESO* esophageal body, *LES* lower esophageal sphincter, *STO* stomach. This high-resolution manometry recording represents mechanisms of gastroesophageal reflux disease and oral feeding in infants. The white impedance lines are a measurement used to detect bolus direction and the colored plot shows pressures in the patient's pharynx, esophagus, and stomach. (**a**) GER is characterized by TLSER which allows retrograde bolus movement detected by the drop in impedance in the upper GI tract. The oblique arrows demonstrate the direction of bolus movement. The GER arrow shows retrograde bolus movement and is followed by a terminal swallow, shown by the second arrow. (**b**) During oral feeding, multiple pharyngeal reflexive swallows are necessary for safe swallowing. There are four complete swallows in the figure; each is characterized by a pharyngeal contraction, followed by peristalsis that includes UES relaxation, esophageal contraction, and LES relaxation

approaches are considered. Such approaches may include but are not limited to the use of video fluoroscopy swallow studies (VFSS), upper gastrointestinal fluoroscopy studies, the use of thickeners in the diet, and acid suppressive strategies. Pharyngo-esophageal manometry studies with or without provocation can provide clues to the underlying integrity of reflexes especially when coupled with cardiorespiratory measures of infant safety [32–36]. Thus, based on the strength of reflexes, one can consider initiation of controlled and well-regulated feeding therapies.

Causes of Oropharyngeal Dysphagia

Swallowing disorders and aspiration can result from developmental issues, neuromuscular conditions, and anatomic abnormalities as seen in Table 21.2 [37]. When a patient is suspected of having aspiration or a swallowing disorder, it is important to consider all factors that may contribute to the disorder such as an unstable cardiorespiratory status, state of alertness, neurologic functioning, postural stability and control, gastrointestinal tract function, hunger and satiation, developmental abilities, oral-motor skills, oral/pharyngeal reflexes, and airway protection/secretion management [38].

Developmental Disorders

For an infant to survive and grow, they must be able to perform one of the most neurologically complex reflexes, reliant on a sequence of well-timed reflexes in the airway, regulation of breathing, deglutition sequences, and other ameliorating reflexes (e.g., signs and symptoms). When an infant has abnormal swallowing either clinically or via a documented video fluoroscopic swallow study, in the presence of a normal upper airway and absence of major associated neurological, anatomic, cardiorespiratory, or craniofacial abnormalities, such a condition can be characterized as neonatal swallowing dysfunction [39]. This dysfunction is likely due to immaturity, delayed development of basal and adaptive reflexes, and/or impaired neuromuscular coordination necessary for safe swallowing [4]. Evidence suggests that a noninvasive, cautious feeding therapy will likely result in successful oral feeding in some infants [6, 7]. In older children, dietary alterations (by altering viscosity, composition, frequency, texture, etc.) can have better outcomes. The intent of using such approaches is to prevent chronic tube feeding while facilitating the development of sensory-motor-regulatory functions as related to safe swallowing. In extreme cases of dysfunction or when no improvement occurs based on evidence-based feeding therapies, gastrostomy may be helpful as a long-term feeding strategy [40].

Table 21.2 Pathobiology of deglutition disorders: major causes

Developmental origins	Anatomic abnormalities	Neuromuscular abnormalities
• Prematurity • Polyhydramnios • Neonatal swallowing dysfunction • Inborn errors of metabolism, Hypothyroidism • Bronchopulmonary Dysplasia, Chronic Lung Disease • Congenital Heart Disease • Congenital birth defects, Genetic and Chromosomal Disorders • Post-hemorrhagic Ventriculomegaly, Congenital hydrocephalus, Maldeveloped and Underdeveloped aerodigestive reflexes, hypotonia, birth injuries, and poor neuromuscular regulation and coordination • Malrotation of intestine, Hiatal Hernia, Diaphragmatic Defects, Pyloric Stenosis	• Brain structure abnormalities • Craniofacial anomalies – Velo-Cardio-Facial Syndrome, Cleft-lip, Cleft-palate • Airway anomalies – Choanal atresia – Laryngeal cleft – Vocal cord paralysis • Defects in Oropharynx – Cleft lip and/or palate – Macroglossia – Lingual ankyloglossia – Pierre-Robin malformation sequence – Cleft larynx – Retropharyngeal mass or abscess • Defects in Esophagus/Stomach – Achalasia, Esophageal spasm – Tracheoesophageal fistula – Esophageal atresia/strictures – Esophageal stenosis – Esophageal mass or tumor – Foreign body, Vascular rings – Gastroparesis	• Arnold Chiari malformation • Evolving cerebral palsy • Cerebral vascular accidents • Other neuromuscular disorders – Bulbar palsy – Brain stem tumors – Myelomeningocele – Familial dysautonomia – Tardive dyskinesia – Post diphtheritic and polio paralysis – Mobius syndrome – Infant botulism – Congenital myotonic dystrophy – Muscular dystrophies and myopathies – Cricopharyngeal achalasia

Neurologic Disorders

Neurodevelopmental delays in premature infants cause swallowing difficulties that range from the inability for sensory nerves to recognize a stimulus (physical and chemical properties of the bolus), and the inability to send afferent and efferent signals to evoke regional reflexes. Problems with the peripheral and central nervous systems can result in swallowing dysfunction involving skeletal or smooth muscles of the foregut. Peripheral neuromuscular disorders affect tone of muscles involved in swallowing as well as poor coordination of the swallowing stages and decreased ability to clear the airway [4]. Some neurologic swallowing disorders are a result of central nervous system insults that include conditions such as cerebral palsy, Arnold-Chiari malformation, and cerebral vascular accidents [2]. Cerebral palsy is a neurologic disorder that begins in early life and can result in severe swallowing and feeding difficulties. Patients with this disorder should be monitored closely because swallow function may worsen over time [4]. Arnold-Chiari malformation occurs when the brain stem and cranial nerves are compressed by low lying cerebellar tonsils [41]. This can be surgically repaired and, in some cases, will completely resolve upper esophageal sphincter (UES) dysfunction causing dysphagia and aspiration risk [42]. More importantly and pertinent to premature infants, the consequences of intra-ventricular hemorrhage of varying severity can be associated with swallowing and aerodigestive problems. Potential mechanisms may underlie in cranial nerve and brain stem dysfunctions that are especially pertinent to the functions of sucking, swallowing, peristalsis, and airway regulation [14]. On the other hand, infants with perinatal hypoxic ischemic encephalopathy can have varying severity of lesions in cortical areas and basal ganglia, which are relevant to eating. Consequences of both these neonatal neurological injuries are seen over the life course of the child.

Anatomic Abnormalities

Defects in the nasopharynx, oropharynx, larynx, esophagus, and trachea can cause aspiration in patients. A very severe form of nasopharynx obstruction is known as choanal atresia. In young infants, this can lead to difficulties with the coordination of the oral and pharyngeal swallowing phases. Infants with allergic rhinitis, adenoid hypertrophy, and congenital masses of the nasopharynx experience similar swallowing difficulties with symptoms such as aspiration, slow eating, and aversion to textures [2]. For children experiencing chronic nasal congestion, ineffective suck, recurrent sinus disease, and nasal voice quality, an exam of the palate is critical because palate abnormalities can result in nasal reflux, aspiration, and food avoidance. Failure of tracheoesophageal fusion to occur can result in a laryngeal cleft. Recent studies suggest that this congenital malformation is a more common cause of aspiration than originally thought [43]. Even after repair of the malformation, some patients will continue to have aspiration which suggests that the dysfunction is multifactorial [44]. Vocal cord paralysis is another anatomic abnormality; it decreases sensation and limits airway protective mechanisms resulting in aspiration [45]. A noninvasive approach is preferred over a permanent feeding tube to treat this paralysis if the vocal cord function is expected to improve over time.

Dysmotility Mechanisms and Management

Any disorders of motility or esophageal inflammation can cause dysphagia making it difficult for patients to swallow, digest food of certain consistencies, and cause gagging, among other symptoms. Upper esophageal dysfunction is another condition that can cause aspiration in infants. Any issues with uncoordinated pharyngeal contraction or the inability of the upper esophageal sphincter to relax can make an infant at risk for aspiration [46]. Children with abnormalities in the suck-swallow-breathe cycle that stem from a respiratory problem or other underlying medical issues are likely to have laryngomalacia [2]. A normal nonnutritive and nutritive suck burst in coordination with respiratory signals are shown in Fig. 21.2. In a nutritive suck, that occurs during feeding, the child sucks the nipple with greater force than they do if they were sucking on a pacifier (nonnutritive suck). The respiratory signal shows the pauses in breathing that demonstrate the glottal closure that occurs during a swallow to protect the airway. However, prolonged deglutition apnea or an irregular respiratory rate after swallowing may demonstrate abnormalities in the suck-swallow-breathe cycle.

In a study with adults who were tube fed and had UES dysfunction, there was evidence that botulinum toxin injection to the UES allowed most patients to transition back to full oral feeding [47]. Balloon dilation is another therapy that has been successful in many adults with UES dysfunction [48]. These are promising therapies, but more research needs to be done to determine their effectiveness in children. Before considering any therapies, it is important to understand the patient's history and present conditions because they may have an impact on the child's normal swallowing reflexes.

Therapies for aspiration are dependent on the diagnostic testing, the severity of the dysfunction and its complications as well as the expected natural history of the underlying cause for this dysfunction [49]. There are a variety of treatment options, which include feeding and swallowing therapy, thickening of feeds, gastrostomy and gastrojejunostomy tubes, fundoplication, and pharmacologic approaches [50–

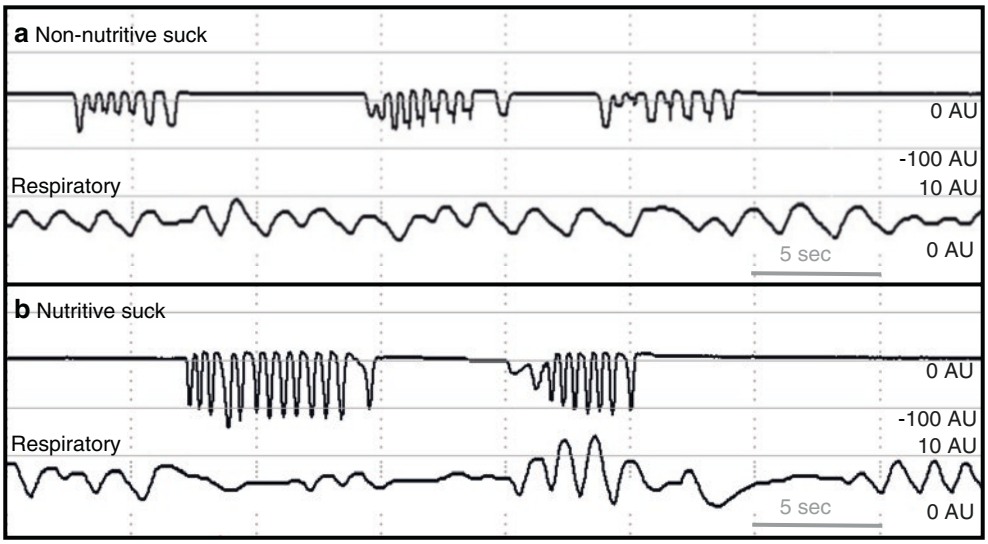

Fig. 21.2 Suck swallow breath pattern. Suck and respiratory signals in a subject during nonnutritive and nutritive sucking methods. A short pause in breathing can be a normal process and occurs during a swallow to protect the airway; this is called deglutition apnea which cannot be appreciated without pharyngo-esophageal manometry (see Fig. 21.3). (**a**) Nonnutritive suck occurs when the infant latches and begins sucking on a pacifier/nipple with no fluid delivery. Note the lower amplitude and narrower suck signals. (**b**) Nutritive suck occurs when the infant latches on and begins sucking to extract milk from bottle or breast. Note the greater amplitude of suck signals and wider bursts

53]. Feeding and swallowing therapy is an ideal way of treating patients that have oropharyngeal dysphagia with aspiration [49]. However, there are other minimally invasive approaches such as thickening of feeds which can allow the bolus to pass through the digestive tract at a slower velocity, increase the duration of pharyngeal contractions, and prolong the opening of the upper esophageal sphincter [50]. For patients that continue to aspirate with thickened feeds and feeding therapy, a nasogastric or gastrostomy enteral tube is utilized for feeding. The nasogastric tube is preferred over a gastrostomy tube, but if the condition does not improve, the gastrostomy tube may be necessary [51]. These therapies exist to prolong time for maturation and adaptation for the patient so they can develop more mature swallowing reflexes. A manometry recording of mature swallowing responses in the upper gastrointestinal tract of infants when given pharyngeal and esophageal infusions to stimulate bolus formation is shown in Fig. 21.3.

For patients that experience intractable aspiration, fundoplication is an additional surgical option to reduce aspiration. However, there is conflicting evidence on whether the surgery is a viable treatment for aspiration pneumonia [52]. Some pharmacologic approaches include the use of proton pump inhibitors, erythromycin and azithromycin [53–55]. Proton pump inhibitors, used to treat GERD, have been associated with a significant risk of gastrointestinal and pulmonary infections in the pediatric population [56]. Pro-motility medications such as erythromycin and azithromycin do not seem to influence the occurrence of oropharyngeal aspiration. However, these medications have been able to decrease proximal reflux and increase gastric emptying which may decrease the occurrence of gastric aspiration [54, 55]. Swallowing disorders are complex and often the result of underlying or interacting conditions in the patient. In order to effectively treat children with swallowing disorders, a multidisciplinary team including pediatricians, neonatologists, gastroenterologists, speech language pathologists, pulmonologists, otolaryngologists collaborating with radiologists and nutrition specialists are necessary [57].

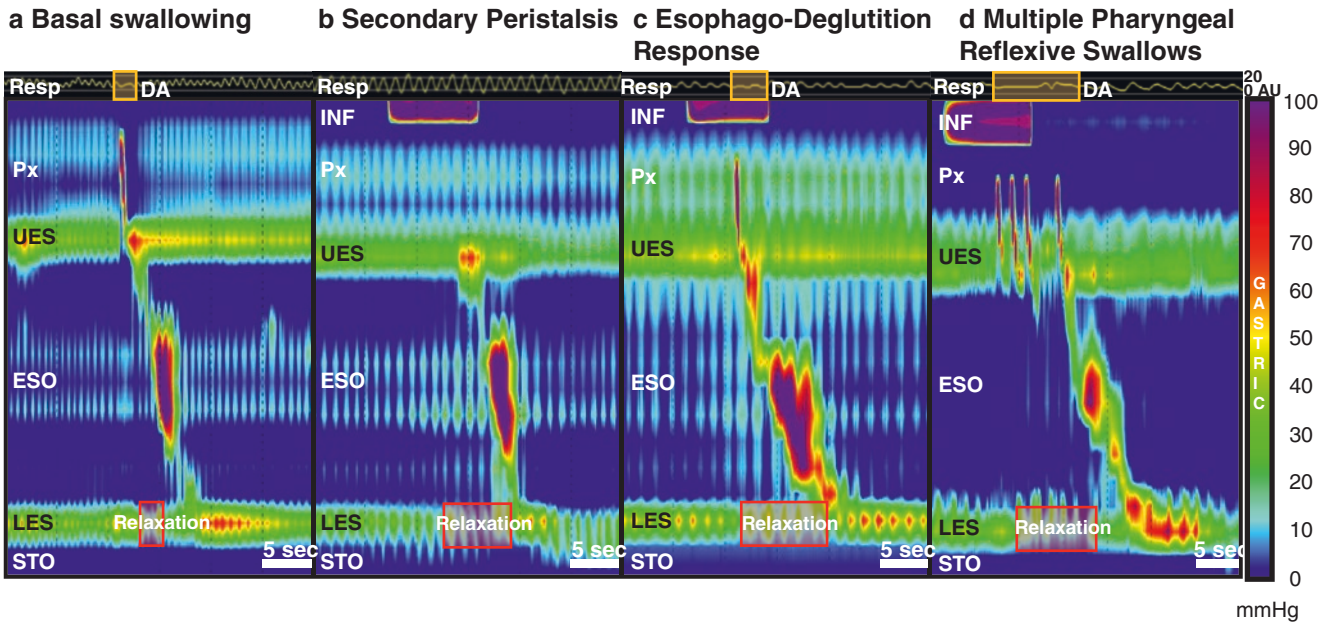

Fig. 21.3 Protective mechanisms. *SP* secondary peristalsis, *EDR* esophageal deglutition response, *PRS* pharyngeal reflexive swallow, *Resp* respiratory, *DA* deglutition apnea, *INF* infusion, *Px* pharyngeal, *UES* upper esophageal sphincter, *ESO* esophageal body, *PE* proximal esophagus, *DE* distal esophagus, *LES* lower esophageal sphincter, *STO* stomach. Yellow shaded boxes denote DA and red shaded boxes denote the LES relaxation that occurs during the different response types. This manometry recording shows pressures in the patient's pharynx, esophagus, and stomach. (**a**) A basal swallow (spontaneous swallowing) occurs when no stimulus is given. It is characterized by pharyngeal contraction, followed by UES relaxation, esophageal contractions (normally beginning at the PE and ending at the DE), and LES relaxation. Note the respiratory pause during pharyngeal contraction, the deglutition apnea. (**b**) In the event of an esophageal provocation, there can be no response or EDR, or SP [30, 31]. Note in **b**, the occurrence of SP along with UES contraction, and LES relaxation. (**c**) Note in **c**, the EDR which is commonly seen in premature infants; it is characterized by a pharyngeal contraction followed by relaxation of the UES, esophageal contractions, and LES relaxation. Also, note the deglutition apnea. (**d**) Multiple PRS [32, 33] is a common response during bottle feeding or during pharyngeal stimulations. It is characterized by multiple pharyngeal contractions, followed by a terminal swallow that includes UES relaxation, esophageal contraction, and LES relaxation. Also, note the deglutition apnea

Summary and Conclusions

In summary, a child with a feeding disorder may present with deglutition disorder symptoms even though the feeding difficulties are the result of a process problem or comorbidity of the deglutition disorder. Due to the heterogeneity of symptoms in disorders of deglutition, patients are often misdiagnosed and as a result, the true prevalence is unknown. The misdiagnosis of children with deglutition disorders can often lead to ineffective recommendations and therapies that do not treat the root cause of the feeding difficulty. In infants and children, deglutition disorders are often mistaken for GERD because patients present with similar symptoms. Manometric studies are useful in differentiating GERD and deglutition disorders because they allow providers to test the esophageal reflexes; impedance channels are useful for determining if reflux is occurring. Depending on the severity of the deglutition disorder, there are a wide range of approaches. A minimally invasive approach such as feeding therapy or thickening of feeds is preferred, but under certain circumstances invasive surgeries may be necessary to treat intractable aspiration. To effectively treat children with deglutition disorders, it is vital that providers take an interdisciplinary approach to diagnosis and management. Adoption of this approach will benefit children and their families by preventing the use of chronic enteral tubes.

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Conflicts of Interest None of the authors have any conflicts of interest to disclose.

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Esophageal Achalasia

22

Camille Plourde and Ann Aspirot

Epidemiology and Incidence

Achalasia is an infrequent adult disease with an incidence of 1.63/100,000 and a prevalence of 10.82/100,000, according to a Canadian population-based study [1]. Mean age at diagnosis is 53.1 years, and the survival is less than age-matched healthy control. Because of the relative rarity of childhood and adolescent achalasia, much of the literature has been based on the adult population but high-quality evidence on the pediatric aspects in increasing. The incidence of achalasia before 16 years is low but is rising. An incidence of less than 0.1/100,000 per year has been found in children in England and Wales in 1988 [2], compared to at least 0.18/100,000 per year in a study published in 2011 [3]. A mean incidence of 0.1/100,000 per year was also found in the Netherlands [4]. In children, as opposed to adults, achalasia seems to be slightly more frequent in boys than in girls, and most of the cases are diagnosed between 7 and 15 years [5–7]. Infantile achalasia is described as case reports in the literature [8, 9]. In a worldwide survey, diagnosis in infants occurred in 6% of cases, but symptoms were present during the first year of life in 18% of the children [10]. Diagnosis may not be as rigorous in young children as it is in adults [2, 7], as many published cases were not confirmed by esophageal manometry, the gold standard diagnostic test. Indeed, manometry can be technically challenging in children: a study reported 62% of the patients were unable to tolerate the procedure [11].

Pathophysiology

Acquired degeneration of the Auerbach's myenteric plexus is the primary mechanism of achalasia. Loss of nitrergic inhibitory enteric neurons occurring prior to loss of cholinergic neurons results in an imbalance between excitatory and inhibitory input, leading to ineffective esophageal peristalsis and incomplete lower esophageal sphincter relaxation [12, 13]. Nitric oxide (NO) is the predominant inhibitory neurotransmitter but others have been described such as vasoactive intestinal peptide (VIP). Studies on resected specimen have demonstrated decreased number of myenteric ganglia, lymphocytic infiltrate, and collagen deposition within ganglia. Some specimen had normal number of myenteric ganglion cells, but myenteric fibrosis was observed. Preservation of cholinergic excitatory neurons could explain the occurrence of vigorous achalasia which has been hypothesized to be an earlier form of the disease [14]. These findings suggest a progressive immune mediated destruction of neuronal cells. The pathologic findings could be different in childhood achalasia where less neuronal inflammation was found [15]. A decrease or absence of NO synthase-containing nerve fibers has also been described in children with achalasia [16].

Etiology

Achalasia can be primary (idiopathic) or secondary. Chagas disease is the prototype of secondary achalasia that is caused by the flagellate protozoan *Trypanosoma cruzi*. The disease is common in South and Central America, but a decline in the number of younger patients has been observed, most likely because of better sanitary measures aimed at controlling the transmission of the parasite [17]. Whether the disease is similar to idiopathic achalasia remains controversial [18]. In Chagas megaesophagus, there is not only denervation of inhibitory neurons, but also of excitatory cholinergic neurons. These differences do not seem to have therapeutic

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implication. Pseudoachalasia is also a secondary form of achalasia. Possible causes include primary malignancy of the esophagus or esophagogastric junction (EGJ), secondary malignancies (lung, breast, pancreas, liver, kidney, etc.), benign tumors, amyloidosis, sarcoidosis, central or peripheral neurological disorders, postoperative complications (after antireflux surgery, vagotomy, bariatric surgery, thoracic endovascular aneurysm repair) [19], and paraneoplastic syndromes in the context of small-cell carcinoma, bronchial carcinoid, gastric carcinoma and pleural mesothelioma [20]. These conditions are, however, uncommon in children. Esophageal leiomyomas, leiomyomatosis [21, 22] and other benign tumors such as bronchogenic cysts [23] have been described as a cause of pseudoachalasia in the pediatric population.

The etiology of primary achalasia remains unknown. Numerous hypotheses have been proposed including infection, autoimmunity, and hereditary. All three hypotheses may all be linked together [24]. Chagas disease is the proof that achalasia can be caused by infective agents. In idiopathic achalasia, viruses have been suspected because of the associated inflammatory infiltration mainly composed of lymphocytes. Herpes simplex virus 1 (HSV-1), varicella-zoster virus, measles, and human papillomavirus have been proposed. Presence of such viruses in esophageal samples has been difficult to demonstrate [25, 26], possibly because the reservoir of the virus, the myenteric ganglia, is destroyed. HSV-1-reactive lymphocytes have been identified in lower esophageal sphincter muscles of achalasia patients [26, 27]. HSV-1 DNA, RNA, and virus were also detected in the lower esophageal sphincter biopsies from achalasia patients [28]. A cause-effect relationship between viruses and achalasia has yet to be identified, but these infective agents could trigger an autoimmune-mediated ganglionitis [14, 28, 29]. There is evidence that achalasia has an important local and systemic inflammatory autoimmune component with the presence of anti-myenteric autoantibodies [28]. The significance of the antineuronal antibodies has been questioned [12, 30], but in another study, the serum of achalasia patients reproduced the phenotype and functional changes that occur with achalasia in an ex vivo human model [31]. Since not all the infected patients develop the autoimmune cascade leading to achalasia, a genetic predisposition is strongly suspected. Achalasia has been associated with specific human leukocyte antigen (HLA) class II molecules [32, 33]. The genetic link is also suggested by studies reporting association between achalasia and trisomy [29, 34, 35], Hirschsprung's disease [36], Allgrove's syndrome [37–42], Rozycki syndrome (deafness, short stature, vitiligo, muscle wasting and achalasia) [43], growth hormone deficiency [44], CS/CISS1 syndrome (facial contractions, hyperthermia and camptodactyly) [45], achalasia-microcephaly syndrome [46], and autism [47]. However, familial history is the exception in achalasic patients even in the pediatric age [10, 48]. Few case reports of monozygotic twins without multisystem disorders have been published [49, 50].

Most of the familial occurrences described in the literature are due to Allgrove (or triple A) syndrome, a rare autosomal recessive disorder caused by a mutation in the AAAS gene on chromosome 12q13, encoding the nuclear pore protein ALADIN (for ALacrima, Achalasia, aDrenal Insufficiency, Neurologic disorder) [51, 52]. Allgrove syndrome is characterized by the clinical triad of achalasia, alacrima, adrenal insufficiency, and progressive neurological signs [53]. The appellation 4A syndrome has been suggested since most patients also experience autonomic dysfunction [54]. Alacrima is the most consistent finding and is present from birth in almost all patients [55]. Although it occurs in up to 99% of cases, it is often overlooked by caregivers and rarely leads to diagnosis [53, 56, 57]. The syndrome usually presents during the first decade of life with dysphagia, hypoglycemic or hypotensive attacks. Achalasia has up to 93% prevalence, while AI is found in 85–90.1% [57, 58]. Progressive neurological disease is common but typically occurs later in life [55] with a broad range of symptoms such as optic atrophy, distal weakness and atrophy, cerebellar ataxia, motor neuron disease, and intention tremors [51, 56]. A histopathologic study revealed fibrosis of the intermuscular plane and a lack of neuronal NO synthase, explaining the defective cardia relaxation [39]. Because of the rarity of achalasia in childhood and the fact that most cases of Allgrove syndrome have no family history, it is important to refer young patients with suspected achalasia to genetics and screen for adrenal insufficiency [55]. Patients with Allgrove syndrome seem to present a more severe course than those with idiopathic achalasia despite early diagnosis with family screening. Higher LES pressure has also been noted in some patients with this syndrome [59]. Similar associations of achalasia, alacrima, and neurological deficits (without adrenal insufficiency) have been linked to mutations in the GMPPA (alacrima, achalasia and mental retardation (AAMR) or triple A-like syndrome) [60] and TRAPPC11 [61] genes.

Clinical Presentation

Achalasia presents with progressive dysphagia (first for liquids and eventually for solid food), chest pain, and regurgitation of undigested food, not mixed with gastric secretions [62]. Nurko and Rosen [63] summarized the clinical symptoms in 528 pediatric patients from 23 series. The most common symptoms are vomiting (80%) and dysphagia (75%). Weight loss is reported in 64% and failure to thrive in 31%. Chest pain and odynophagia are sometimes present (45%), but less common in younger children. Diagnosis is often

delayed in young children because of multiple factors including lower incidence of achalasia, incapacity to verbalize complaints, and unspecific symptoms, such as food refusal and failure to thrive. Parents will sometimes report that their child is a slow eater. Children additionally present nocturnal symptoms such as choking and regurgitated food on the pillow (21%). Respiratory symptoms occur in 44% which is more frequent than in the adult population. In young children, regurgitation, respiratory problems, and failure to thrive are easily attributed to gastroesophageal reflux (GER) which is much more predominant than achalasia in this population. Extraesophageal complications of achalasia include recurrent pulmonary aspirations and tracheal compression by the megaesophagus. Sudden death has also been reported.

Differential Diagnosis

Achalasia symptoms are similar to more prevalent problems in childhood such as GER, feeding aversion, asthma, and eosinophilic esophagitis (EoE) [64]. Because EoE has been associated with achalasia and other obstructive motility disorders, patients who are not responding to standard treatment should be investigated for achalasia [65]. Differential diagnosis includes mechanical obstruction by foreign body, intrinsic esophageal pathology (esophageal stenosis, leiomyomas), and extrinsic compression of the esophagus (foregut duplication, mediastinal tuberculosis). Malignant neoplasms are more frequently seen in the adult population but need to be included in the differential diagnosis even in children. Megaesophagus has been described in a case of H-type tracheoesophageal fistula [66]. Although uncommon in young children, Chagas disease is a possibility in patients coming from endemic regions [67]. Achalasia has also been mistaken as eating disorders [68, 69], emphasizing the importance of a thorough evaluation of the upper gastrointestinal (UGI) tract anatomy and function in patients suspected of having primary anorexia nervosa.

Diagnosis

Diagnosis is first suspected by the history but is often delayed because of the non-specificity of the symptoms and the confusion with other more frequent pathologies such as GER disease. Eckardt clinical score [70], which is the sum of symptom scores for dysphagia, regurgitation, chest pain, and weight loss (Table 22.1), could be used as part of the initial and follow-up assessment, although not well-adapted for children [71]. The specific workup for achalasia includes radiographic studies, upper endoscopy, and esophageal manometry. Although studies are limited in children, the 2018 ISDE guidelines recommend that children with a provisional diagnosis of achalasia undergo the same diagnosis pathway as adults [71].

Table 22.1 Eckardt clinical score for assessing the severity of achalasia symptoms (total maximum score is 12) [70]

Score / Symptom	Weight loss (kg)	Dysphagia	Retrosternal Pain	Regurgitation
0	None	None	None	None
1	Less than 5	Occasional	Occasional	Occasional
2	5–10	Daily	Daily	Daily
3	**More than 10**	**Each meal**	**Each meal**	**Each meal**

Radiography

Plain chest radiograph may show an air-fluid level in the lower chest, a widened mediastinum, and an absent gastric bubble [72]. Contrast esophagogram will demonstrate the stagnation of contrast in the distal esophagus and possibly absent or tertiary peristalsis. The typical dilated esophagus tapering smoothly at its distal end ("bird's beak") is not necessary to make the diagnosis, but is highly suggestive of the disease. Using manometry as the gold standard, Parkman et al. found a positive predictive value of 96%, a sensitivity of 100%, and a specificity of 98% [73]. However, the correlation of severity as assessed by esophagogram and patient's symptoms is poor, which can also lead to a delayed diagnosis [74]. Timed barium esophagogram (TBE) has been described to assess esophageal emptying [75, 76] and is now favored over the traditional barium esophagogram because of its very high reproducibility [71, 77]. Radiographs are taken 1, 2, and 5 min after barium intake and the distance from the distal esophagus ("bird's beak") to the top of a distinct barium column is then measured to assess esophageal emptying [78]. Although not yet widely adopted, this test is also a good predictor of treatment failure [71, 78]. In end-stage achalasia, barium swallow is considered the most accurate investigation as manometry can be technically challenging in a dilated, tortuous, and fluid-filled esophagus [71].

Endoscopy

Upper endoscopy may show retained food in a dilated esophagus. The gastroesophageal junction (GEJ) may appear tight (difficult to distend with air insufflation), but it is usually possible to reach the stomach. The main goal of upper endoscopy is to rule out mechanical obstruction at the gastroesophageal junction (pseudoachalasia) [71, 79]. Although some authors believe endoscopy is not necessary in children with a clear profile of achalasia [5], benign tumors such as

intramural esophageal bronchogenic cysts mimicking achalasia on contrast esophagogram and high-resolution manometry (HRM) [23] have been described and should be excluded. Biopsies of the GEJ are mandatory in adults but can be avoided in the pediatric population with a normal appearing esophagus given the low risk of malignancy [71]. If pseudoachalasia is suspected, further investigation with ultrasound, endoscopic ultrasonography, and other imaging studies will help to differentiate between the numerous neoplastic and non-neoplastic causes of pseudoachalasia [80].

Manometry

The diagnosis of achalasia is confirmed by esophageal manometry. Absence of peristalsis in the esophageal body is the sine qua non criteria to diagnose esophageal achalasia [62]. High-resolution manometry (HRM) has permitted a better understanding of the motility abnormalities found in achalasia and a classification in three subtypes [81]. HRM imaged with color pressure topography plots has become the gold standard for categorizing the esophageal motility disorders (Figs. 22.1, 22.2, and 22.3). Pressure topography metrics that are necessary to characterize achalasia are the median integrated relaxation pressure (IRP), the distal contractile integral (DCI), and the intrabolus pressure pattern (20 mmHg isobaric contour referenced to atmospheric for supine wet swallows with the Medtronic system). In the latest version of the Chicago Classification (CCv4.0) published in 2021 [82], achalasia is included in the disorders of esophagogastric junction (EGJ) outflow obstruction [82, 83]. The disorders of peristalsis (absent contractility, distal esophageal spasm, hypercontractile esophagus, and ineffective esophageal motility) are beyond the scope of this chapter and will not be reviewed here. In CCv4.0, all disorders of EGJ outflow require an abnormal median IRP in the primary position (either supine or upright). Achalasia also requires 100% absent peristalsis (all swallows with failed peristalsis or premature contraction) for diagnosis. The definition of EGJOO was updated in CCv4.0 to help distinguish between an underlying pathologic motor disorder versus a simple manometric observation with no clinical correlation. The criteria are as follows:

- Type I achalasia (classic achalasia): Elevated median IRP (more than 15 mmHg for Medtronic systems and 22 mmHg for Laborie/Diversatek in the supine position vs. respectively 12 and 15 mmHg in the upright position.), 100% failed peristalsis (DCI less than 100 mmHg s cm).
- Type II achalasia (with panesophageal pressurization): Elevated median IRP (more than 15 mmHg for Medtronic systems and 22 mmHg for Laborie/Diversatek in the supine position vs. respectively 12 and 15 mmHg in the upright position.), 100% failed peristalsis (DCI less than 100 mmHg s cm), panesophageal pressurization with at least 20% of swallows.
- Type III achalasia (spastic achalasia): Elevated median IRP (more than 15 mmHg for Medtronic systems and 22 mmHg for Laborie/Diversatek in the supine position vs. respectively 12 and 15 mmHg in the upright position), no normal peristalsis, premature (spastic) contractions with DCI more than 450 mmHg.s.cm with at least 20% of swallows.
- EGJ outflow obstruction (EGJOO): Elevated median IRP in the primary and secondary position and ≥20% swallows with elevated intrabolus pressure in the supine posi-

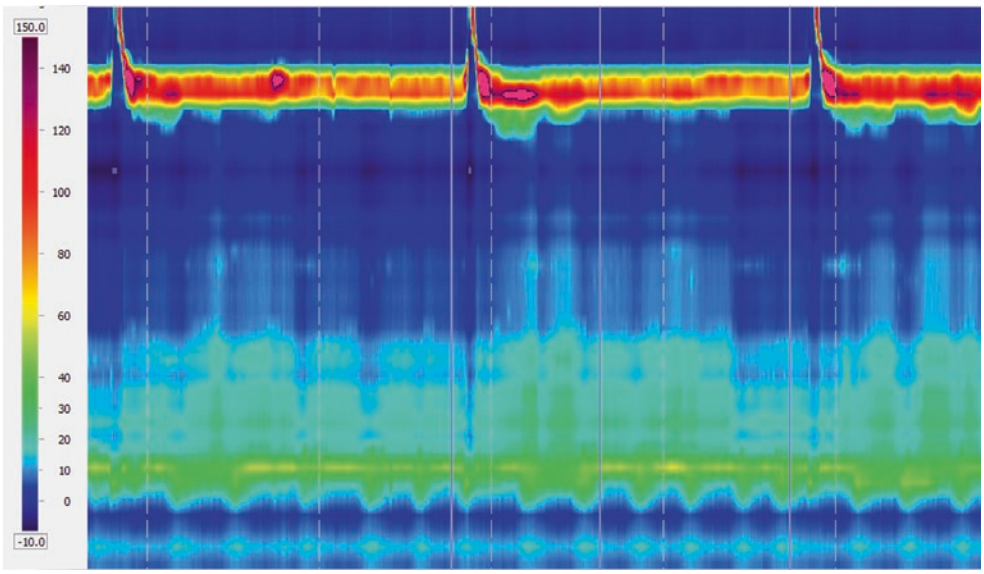

Fig. 22.1 Type I esophageal achalasia (IRP 33 mmHg)

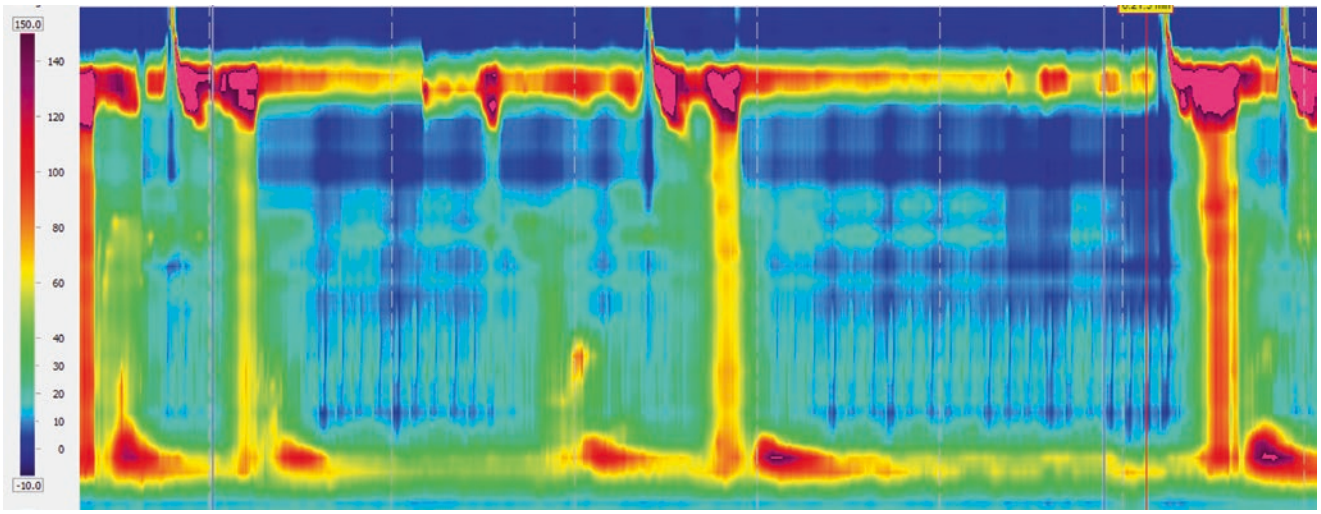

Fig. 22.2 Type II esophageal achalasia (IRP 43 mmHg)

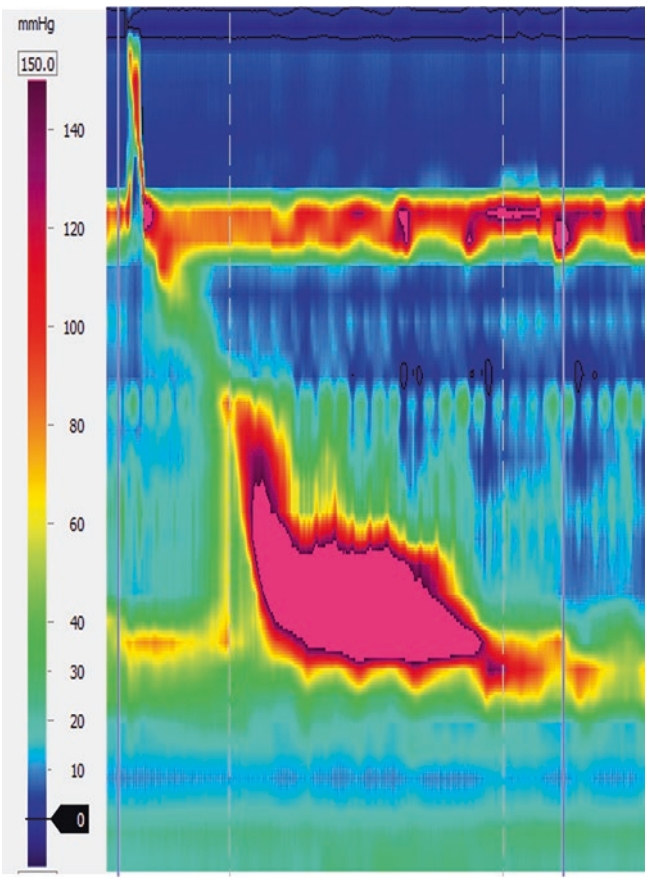

Fig. 22.3 Type III esophageal achalasia (IRP 55 mmHg, distal latency 3.9 s)

tion, with evidence of peristalsis. A manometric diagnosis for this condition is always considered inconclusive. The diagnosis requires relevant symptoms (dysphagia and/or non-cardiac chest pain) with at least one other investigation supporting obstruction (TBE and/or FLIP).

The prevalence of the different subtypes is quite variable between the studies (type I: 11–47%; type II: 32–52%; type III: 6–57%) [81, 84, 85]. EGJOO could be an incompletely expressed achalasia or an early achalasia. In adults, it should be further investigated by endoscopic ultrasound to rule out a subtle infiltrative disease or cancer [86]. It is sometimes complex to measure relaxation of the lower esophageal sphincter in cases of absent contractility. In these cases, bolus retention on a barium esophagogram will suggest achalasia [87].

In children, HRM is easier to perform than conventional manometry and is also required to establish the diagnostic. The same subtypes are seen in children (39% of type I, 50% of type II, 11% of type III). Different responses to the administration of multiple liquid swallows are seen depending of the subtypes [88]. Although pediatric studies have shown that achalasia can be reliably differentiated from non-achalasia using CC and HRM recordings, the CC diagnostic criteria should be used with caution in children as it relies on adult-derived criteria. Small pediatric studies showed CC metrics (integrated relaxation pressure [IRP] and distal latency) are age and size dependent [89]. According to Morera et al. [90], LES function in children is heterogeneous (different responses in swallows). In their cohort of 29 patients with achalasia, partial relaxations were common, and normal relaxations were possibly present. These findings suggest a different physiopathology in pediatric achalasia.

Endoluminal Functional Lumen Imaging Probe (EndoFLIP or FLIP)

EndoFLIP (Crospon Medical Devices, Galway, Ireland) is a recent technology involving impedance planimetry and allowing the measurement of EGJ distensibility in real time

[5]. The probe measures intra-luminal cross-sectional area and pressures changes during volume-controlled distension [91]. EGJ distensibility is reduced in achalasia patients, and failure after treatment has been associated with persistently low distensibility. EndoFLIP has been mostly used to assess recurrent symptoms after treatment and as a calibration method during myotomy. In a prospective case series of ten children undergoing peroral endoscopic myotomy (POEM), a significant improvement in esophageal distensibility after POEM was demonstrated using intra-operative EndoFLIP [91]. The device is also emerging as a useful diagnostic tool [92], but is not yet widely used. In adult, the diagnostic EGJ-DI for achalasia was determined to be <2.8 mm^2/mmHg [93], although some studies have considered values between 2 and 3 to be "borderline," with a "definitely" abnormal cutoff of <2 mm^2/mmHg and a normal threshold of >3 mm^2/mmHg [94, 95]. Recent data suggest EGJ-DI values in children with achalasia can differ from reported measurements in adults: Benitez et al. [96] found a mean EGJ-DI of 2.07 mm^2/mmHg, while Courbette et al. [97] reported a median EGJ-DI of 2 mm^2/mmHg. Using adult threshold could lead to misdiagnosis in up to 30% of pediatric patients [96].

Treatment

Treatments for achalasia, similar to other esophageal disorders, focus on relieving symptoms [98] as there is no curative therapies. Improving esophageal emptying to prevent the development of megaesophagus is another goal of therapy [99]. The three primary types of treatment are pharmacologic, endoscopic, and surgical. They all are directed at improving esophageal emptying by decreasing the LES pressure. The therapy of choice in children is still debated [100], but myotomy (surgical or endoscopic) has been suggested as the procedure of choice in recent guidelines [71]. A survey distributed in 2017 on the clinical management of pediatric achalasia targeted gastroenterologists from 24 different countries [6]. The treatment of choice was considered to be Heller myotomy in 58% of respondents, pneumatic dilation (PD) in 46%, while POEM was the initial choice when available in 29%. Proper treatment of achalasia is important to prevent progression toward dilated mega-esophagus where esophagectomy may become inevitable.

Pharmacologic treatments include nitrates, calcium channel blockers, and phosphodiesterase inhibitors. Although significant decrease of lower esophageal sphincter pressure has been observed by manometry, symptom improvement occurred in 53–87% of patients [101]. There is no convincing evidence that medical treatment with either of these pharmacologic options is effective for symptomatic relief in adults with achalasia [71, 77]. Experience in children is limited to calcium channel blockers and nitrates and consists mainly of case reports [102–104]. Frequent side effects such as headache, dizziness, and hypotension also limit their use in children [5].

Botulinum toxin injection (BTI) into the LES was first reported by Pasricha et al. in 1994 [105]. This potent neurotoxin blocks the release of acetylcholine at the neuromuscular junction, leading to decreased LES pressure. A systematic review and meta-analysis including 730 patients reported clinical success in 77% of patients 1–6 months following the procedure, but durability was limited to months [92]. The response decreases with repeated injections [106] and there is no evidence that using increasing doses of botulinum toxin (BT) improves outcome [71]. Pneumatic dilation has consistently been shown to have a higher remission rate than BTI at 1 year follow-up [71]. In a randomized clinical trial (RCT) comparing laparoscopic Heller myotomy (LHM) with BTI, only 34% of BTI patients were asymptomatic at 2-year follow-up, compared to 87.5% of LHM patients [107]. BTI has been used as a diagnostic tool in patients with early and unclear diagnosis. However, although it remains controversial, submucosal fibrosis resulting from intrasphincteric injections may complicate a subsequent surgical myotomy [108]. The 2020 ASGE adult guidelines recommend against BTI as definitive therapy unless patients are not candidates for other more effective therapies [92]. BTI could, however, be used as a bridge to more effective therapies or for symptom management in poor surgical candidates.

Experience in children is once again limited to retrospective case series [109–112], but shows similar results of good initial clinical response and high rate of recurrence. Its use is limited since other treatment strategies have been proven more effective. The 2018 ISDE guidelines recommend against BTI as a first-line therapy in very young children, unless they are not fit for other procedures [71].

Esophageal dilation is the oldest treatment modality [62]. Balloon pneumatic dilation (PD) is preferred over rigid bougienage. The technique is usually performed with fluoroscopic guidance, starting with the 30 mm balloon and serially progressing to 35 and 40 mm as needed [71]. It is less invasive than surgical treatment and is considered the most effective non-surgical treatment of achalasia in adults [113, 114]. PD is effective as initial treatment in relieving symptoms, but success rates decrease over time with long-term efficacy ranging from 40% to 60% [115, 116]. A recent meta-analysis comparing outcomes of pneumatic dilation and LHM showed significantly higher success rate with LHM at 3 months and 1 year, but similar success rate at 2- and 5-year follow-up [117]. The main complication of PD is esophageal perforation which has been reported in 2.8% to 4.9% of patients [92, 117], compared to 0.8% in LHM patients [117]. Guidelines [71, 92] suggest PD has long been considered the procedure of choice in pediatric achalasia and

is still the first-line treatment in some pediatric centers [6]. However, PD's efficacy also appears limited in the pediatric population as 30–75% of children need subsequent surgery due to recurrent symptoms [118]. Pediatric studies comparing LHM to PD show conflicting results [72, 100, 148–153]. Despite the lack of conclusive evidence, high success and low complication rates associated with LHM have made it the preferred approach [6, 119]. Early LHM and fundoplication have also been suggested as a more definitive option to prevent growth retardation, an important consideration specific to the pediatric population [120]. Offering PD dilation remains an acceptable first option as long as the family understands the limited durability of the technique [121].

Temporary self-expanding metallic stent and endoscopic sclerotherapy using ethanolamine oleate or polidocanol have been described as therapeutic options, but are not recommended [71].

Surgical treatment usually consists of a longitudinal division of the muscle fibers of the LES and proximal stomach, a procedure called the Heller myotomy, first described by Ernest Heller in 1913 [98]. Laparoscopic Heller myotomy (LHM) is now the most commonly performed surgical treatment of achalasia. The laparoscopic technique is less morbid but as effective as the open approach [122] and has been shown to be superior to the thoracoscopic approach [123, 124]. Robotic Heller myotomy has also been described both in adults and children with good outcomes, but data is limited [125]. Clinical deterioration over time has been associated with gastroesophageal reflux (GER) [126] which has led to randomized controlled studies comparing Heller myotomy with and without fundoplication [127]. The standard approach is now to extend the myotomy at least 6 cm into the esophagus and 2–3 cm into the stomach as measured from the GEJ, and to perform a partial (posterior or anterior) fundoplication in order to reduce the risk of subsequent GER [71, 128]. The different types of fundoplication have also been discussed and compared in randomized clinical trials. There is no evidence of superiority between the Dor (180° anterior) and the Toupet (270° posterior) fundoplications, but a complete 360° wrap (Nissen) should be avoided as it can lead to an increased rate of postoperative dysphagia [128, 129]. A recent meta-analysis [130] including 5834 patients in 53 studies (5 were randomized controlled trials) reported dysphagia improvement in 87.7% of patients after LHM with a mean follow-up of 40 months. The best outcomes for LHM are achieved in Chicago type I and II achalasia patients.

A meta-analysis of PD, BTI, and HM concluded that LHM with fundoplication was the most effective technique [113]. It was shown to provide better symptom relief than all other endoscopic and surgical approaches available at the time with a low complication rate (6.3%). Several randomized controlled trials compared favorably LHM to PD [131–134], although it has been suggested that a more aggressive balloon dilatation approach is comparable to myotomy [135, 136]. A large multicentric randomized controlled trial in Europe comparing PD versus LHM with Dor fundoplication found no differences in terms of success rate, post-treatment LES pressure, esophageal emptying, or quality of life [137]. Based on long-term success rates of 47–82% at 10 years, LHM with partial fundoplication is considered by many the surgical procedure of choice [113, 138, 139]. However, a study has reported that up to 30% of myotomized patients will require re-treatment within the first 12 years [140]. Both PD and LHM are accepted first-line options for type I and II achalasia [92].

LHM has also been found safe and effective in children [119, 141, 142]. Rates of good to excellent results of 90.9% have been published [143–145], but recurrent symptoms have been reported in 16–28% of patients 3–5 year after surgery [72, 100, 141, 142, 146–153].

Complications after LHM include esophageal perforation, phrenic nerve paralysis, hemorrhage, herniation of stomach, persistent dysphagia, and GER. The intra-operative use of endoscopy [154], esophageal manometry [155], dilation under image guidance [156], and EndoFLIP [157] has been suggested to decrease the rate of incomplete myotomy. It is important to emphasize that while myotomy should improve the bolus transit by reducing the LES pressure, ineffective peristalsis still remains an issue [158].

Peroral endoscopic myotomy was first performed by Inoue in 2008, in Yokohama, Japan. He called it POEM in his presentation at Digestive Disease Week 2009 [159]. The technique consists of a flexible endoscopy with CO_2 insufflation to perform an esophageal mucosotomy followed by a submucosal tunnel all the way to the gastric cardia to realize a longitudinal incision in the inner circular muscle. The mucosotomy is closed with endoscopic clips. The technique requires general anesthesia, advanced endoscopic expertise, and availability of surgical back up. Since the first reported experience, multiple centers started to use this technique worldwide and the experience is growing exponentially. Serious adverse events are rare, and most can be identified intra-operatively and addressed endoscopically with no adverse outcomes. Common perioperative complications include mucosal injury (4.8%), esophageal perforation (0.2%), bleeding (0.2%), subcutaneous emphysema (7.5%), pneumothorax (1.2%), pneumomediastinum (1.1%), pneumoperitoneum (6.8%), and pleural effusion (1.2%) [92]. Accumulating data suggest POEM efficacy is at least equivalent or slightly superior to that of LHM with universally reported short-term success rates of over 90% [71, 160–163]. Akintoye et al. [163] performed a meta-analysis including 2373 patients and reported clinical success, defined as Eckardt score $\leq$3, in 98% of cases. Although long-term data is limited, 88.5% overall success rate at 3 years [164]

and 83% at 4 years have been reported [165]. Multiples studies compared LHM to POEM. Awaiz et al. [166] carried a systematic review and found that the rate of adverse events, GER, length of hospital stay, and postoperative pain scores was similar in both groups, but LHM had a higher short-term clinical treatment failure than POEM. Another study [130] reported higher efficacy for POEM at 12 and 24 months. Previous treatment, either PD, BTI, or LHM [167, 168], does not seem to reduce the technical feasibility of the technique. POEM is now recognized a first-line option in the treatment of achalasia in numerous international guidelines [71, 77, 92, 169]. As opposed to the laparoscopic procedure where the myotomy is limited to the part of the esophagus that can be reached through the hiatus, POEM can be extended to the entire esophageal smooth muscle if necessary, and therefore is considered by some the procedure of choice in the management of type III achalasia patients [92].

All treatments for achalasia are directed towards decreasing the LES pressure to improve esophageal emptying, which predisposes patients to GER. The association of an antireflux procedure to LHM has decreased the GER rate from 20–100% to 0–44% [24, 113]. Even with the absence of hiatal attachments dissection and disruption of the angle of His, post-treatment gastroesophageal reflux has been frequently associated with POEM (14.8–29%) [170, 171]. In a meta-analysis by Schlottman et al. [130], although GER symptoms were similar in the POEM (18.5%) and the LHM (17.5%) groups, a much higher incidence of pathologic reflux was found on routine postoperative pH-metry after POEM (47.5% vs. 11.1% for LHM). Clinical remission of esophagitis and symptomatic GER is usually achieved with standard proton pump inhibitor (PPI) therapy [170, 171]. This possibly higher rate of GER after POEM, however, remains a matter of debate as other data suggest similar short and long-term rates after LHM or POEM [166]. The 2020 ASGE guidelines [92] suggest counseling patients undergoing POEM regarding an increased risk of postprocedure reflux compared with PD and LHM. In a study using the EndoFLIP device intraoperatively, 88% of patients with distensibility index between 4.5 mm^2/mmHg and 8.5 mm^2/mmHg had optimal symptomatic outcomes without GER [157]. Although more data is needed, intraoperative FLIP measurements could be an interesting calibration method to decrease the rate of postoperative GER in POEM patients.

Several case series of successful POEM have been reported in the pediatric population [172–175]. The largest pediatric prospective study of 27 children (aged 6–17, mean 13.8) treated with POEM reported feasibility of 96.3% and treatment success in all cases with a mean follow-up of 24.6 months [174]. A systematic review [176] including 742 patients (aged 3 months to 17 years) reported higher success rate with POEM (99.3%) compared to HM (44.9%) and PD (44.9%), with a mean follow-up of 43.7 months. The most recent systematic review and meta-analysis [177] focusing exclusively on POEM in the pediatric population included 11 studies for a total of 389 children (mean age range 5.5–15.2 years). POEM was achieved successfully in 97.4% of patients. The pooled clinical success rate, defined as a decrease in Eckardt score to ≤3, was 92.4%. The long-term efficacy at 3 years' follow-up was 95%. Postoperative GERD was diagnosed based on 24-h pH monitoring or EGD in 17.8% of patients. Although POEM is a safe and efficient technique for treating achalasia in children, it's availability remains limited: only 11/38 pediatric centers across the world had access to this technique in a recently published survey [6]. The high incidence of postoperative GER is concerning for future complications such as peptic strictures and Barrett esophagus. Further studies with long-term data are needed to determine the most effective treatment modality in pediatric patients.

Approach to End-Stage Disease

Untreated achalasia can lead to a severely dilated sigmoid-shaped esophagus. While esophagectomy is the only definitive treatment in those patients, it is associated with a high morbidity and an increased risk of mortality. The 2018 ISDE guidelines [71] suggest that standard treatment (LHM, POEM, or PD) should be attempted, and esophagectomy should be reserved as a last resort option in case of failure of first-line therapy. There is no study comparing outcomes of esophagectomy versus Heller myotomy. However, a recent systematic review and meta-analysis has shown good outcomes with HM, with only 16% of patients requiring reintervention, most of which were pneumatic dilations [178]. Although studies have suggested good feasibility of POEM in theses advanced cases [179, 180], they appear particularly challenging and should only be performed by highly experienced operators [181].

Outcome

The different subtypes of achalasia seem to have a prognostic value [84, 182]. Patients with type II have the best response (96%) to PD or LHM; patients with type I have 81% success but this decreases as the pre-treatment esophageal dilatation increases; patients with type III have the worst response (66%) [182]. The longer myotomy length with POEM could improve the rate of success to greater than 90% in patients with type III achalasia [183]. Others have questioned the clinical implication of the subtypes both based on clinical relief of symptoms and on improvement in esophageal clearance [184]. In children, correlation between the subtypes and the outcome is also not clear [88].

Different validated scoring systems have been developed to evaluate the treatment response. There is no standard definition of treatment failure, which makes comparisons between studies difficult. Although most use a clinical Eckardt score of ≤3 to define clinical success [71, 92], outcome assessment is heterogenous with objective measures sometimes used in only 39.4% [176]. Furthermore, Eckardt score has never been validated in a postoperative population, and some authors question its validity in children, since growth stagnation or insufficient weight gain are more reliable features than absolute weight loss in the pediatric population [5]. Physiologic tests are the best predictors of long-term success of treatment [24]. LES pressure ≥10 mmHg on HRM is a risk factor for treatment failure [185]. However, TBE is easier to tolerate than manometry and is a better predictor of success than LES pressure [71, 78]. More recently, Rohof et al. [185] found a strong correlation between EndoFLIP measure of EGJ distensibility and clinical response to treatment in adults. Abnormal EGJ distensibility (DI <2.9 mm^2/mmHg) was present in 92% of patients with recurrent symptoms, while only 42% had an elevated LES pressure. Patients with a DI <2.9 mm^2/mmHg were in fact 12-fold more likely to have persistent symptoms [185]. In a pediatric case series of ten patients who underwent POEM with 80% success (Eckardt score ≤3), pretreatment mean EGJ-DI was 1.2 ± 0.5 mm^2/mmHg and post-treatment mean DI was 3.1 ± 0.9 mm^2/mmHg [91].

Regardless of the elected therapy, patients must continue with regular follow-up. Periodic evaluation of symptoms, nutrition status, and growth is essential, especially in children and adolescents. Recurrent or persistent symptoms should be assessed starting with a good clinical history and followed with objective testing including UGI endoscopy, barium swallow (or TBE), HRM, and 24-h pH monitoring [71]. Differential diagnosis of this problem includes esophageal dysmotility, incomplete myotomy, fibrosis at the distal end of the myotomy, obstructive fundoplication, esophageal stricture, and preoperative misdiagnosis [186–188]. In patients with myotomy (LHM or POEM) failure, PD or repeat myotomy using the same or an alternative technique has been recommended [77, 92]. Several studies have reported the use of POEM after failed LHM, with clinical success rates varying between 92% and 100% [92].

Routine endoscopic surveillance is not indicated, but the threshold for upper endoscopy should be low in patients with long-standing achalasia (more than 10–15 years) because of the rare, yet possible development of squamous cell carcinoma of the esophagus [77, 189, 190]. It is thought to result from chronic inflammation of the esophageal mucosa due to stasis and uncontrolled bacterial growth [191]. Based on a review of the literature, Dunaway has reported a mean prevalence of 3% which represents of 50-fold increased risk over the general population [192]. Chronic gastroesophageal reflux resulting from the successful treatment of achalasia is also a risk factor for the development of adenocarcinoma [193, 194]. More recently, a prospective cohort study of 448 achalasia patients reported esophageal cancer in 3.3% with an annual incidence of 0.34 and, despite structured endoscopic surveillance, most neoplastic lesions were detected at an advanced stage [195]. Up to now, no cases of esophageal carcinoma have been reported in patients who had achalasia diagnosed as children [63]. The ISDE guidelines [71] recommend that achalasia patients should be informed that male carry a moderately increased risk of squamous esophageal cancer 10 years or more from the initial treatment of the disease. The overall life expectancy of patients with achalasia does not appear to be significantly decreased [196], but the quality of life in adulthood is decreased [4, 197]. Some have found that children with achalasia have a significantly lower quality of life compared to children with inflammatory bowel disease and healthy children [198]. Others did not find a difference [4].

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Other Esophageal Motility Disorders

23

Hayat Mousa and Adam Paul

Diffuse Esophageal Spasm and Nutcracker Esophagus

Diffuse esophageal spasm (DES; also known as distal esophageal spasm), nutcracker esophagus (NE; also known as hypertensive peristalsis), and hypercontractile esophagus (or jackhammer esophagus) are benign and very rare, with the former two clinical entities representing less than 10% of abnormal adult manometry tracings [1–3]. The incidence in children is not known and the literature is scarce, limited to case reports and small case series [4, 5]. In a retrospective study of 278 children who underwent esophageal manometry, 36 patients (13%) had DES, with the most common complaint among children under 5 years old being food refusal [6].

With the development of high-resolution manometry (HRM) and specific metrics to characterize esophageal motility, the *Chicago Classification* has become the gold standard for the diagnosis of esophageal motor disorders in adults [7, 8]. It still requires adjustments to apply to the pediatric population [9]. Initially, using conventional manometry, DES was diagnosed when there were simultaneous esophageal contractions in more than 20% of liquid swallows, with other swallows showing normal peristalsis. These were always nonspecific findings, but HRM and esophageal pressure topography (EPT) have led to a more robust definition. Premature contractions with normal esophagogastric junction (EGJ) relaxation are more specific for DES. *Chicago Classification version 4.0* defines DES as having normal lower esophageal sphincter (LES) relaxation pressures and at least 20% of swallows with premature contraction, in addition to symptoms of dysphagia and/or non-cardiac chest pain [10]. On HRM, nutcracker esophagus (or hypertensive peristalsis) is characterized by prolonged, hypertensive contractions in the context of normal propagation of the swallow waveform and normal lower esophageal sphincter relaxation [8, 11]. By standard manometric definition, average distal esophageal peristaltic pressures measure over 220 mmHg in at least 20% of swallows [10, 12]. HRM in nutcracker esophagus shows a distal contractile integral (DCI) of over 5000 mmHg s cm but pressures do not meet criteria for hypercontractile esophagus. Also known as jackhammer esophagus, hypercontractile esophagus DCI is generally greater than 8000 mmHg s cm. *Chicago Classification 4.0* defines jackhammer esophagus as having normal sphincter relaxation, but with hypercontractility in at least 20% of swallows [10]. Barium esophagograms are often normal in DES and NE patients [13], but do show typical corkscrew appearance in a minority of DES patients.

Both DES and NE share symptoms of intermittent dysphagia and chest pain, with or without swallowing [1, 13–15]. Symptoms are usually experienced while eating or drinking [1, 13]. DES tends to present comorbidly in infants and children [6]. Infants may additionally present with apnea and brachycardia and younger children with aspiration pneumonia; symptoms in older children mostly resemble those observed in adults [16]. Because symptoms are intermittent, it is easy to distinguish these two conditions from more progressive diseases (i.e., achalasia and esophageal cancer) [13].

The etiology and pathogenesis of both conditions remain unknown [1], and due to insufficient understanding of the pathogenesis, treatment remains difficult. Several reports have described patients with DES, nonspecific esophageal motor disorder (NSEMD), nutcracker esophagus, and gastroesophageal reflux disease (GERD) progressing to achalasia [17–19]. Although no causal relationship has been identified, these reports suggest that the different esophageal motor disorders represent a spectrum rather than unique and

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Table 23.1 Analysis of selected esophageal motility disorder treatment methods

Method of treatment	Associated disorders	Advantages	Disadvantages	Success
Acid suppression	DES, NE, NEMDs, SSc	Relieves GERD symptoms	May only treat GERD symptoms	Low success in children
Antibiotics	Caustic ingestion, CIIP, SSc			
Botox injection	Achalasia	Suitable for long-term use	May contribute to fibrosis at injection site	
Elemental diet	Caustic ingestion, EoE, DES, NE, SSc	Quick resolution of symptoms	Formulas not palatable	Compliance difficult for children
			Lower quality of life	
			Cost/insurance coverage	
Elimination diet	EoE, CIIP	Still allows for some food intake by mouth	Requires careful review of all food choices for allergens	Must continue elimination for long-term resolution
			Does not always indicate specific food allergen at fault	
Esophageal dilation	Achalasia, caustic ingestion, DES, EoE, NE	Highly effective when strictures are also present	Chest pain	Common treatment in adults
			Esophageal perforations	
Other surgical procedures	Achalasia, caustic ingestion, DES, HD, NE		Complications may further complicate disease	Usually successful with rare complications
Systemic or topical corticosteroids	EoE, SSc	Direct administration to eosinophilia (topical)	Low bioavailability	Satisfactory symptom resolution
		Variety of administration (swallowed or inhaled)	May not fully penetrate eosinophilia (topical)	High rate of symptom relapse upon discontinuation

CIIP chronic idiopathic intestinal pseudo-obstruction, *DES* diffuse esophageal spasm, *EoE* eosinophilic esophagitis, *GERD* gastroesophageal reflux disease, *HD* Hirschsprung's disease, *NE* nutcracker esophagus, *NEMDs* nonspecific esophageal motility disorders, *SSc* systemic scleroderma

stable disorders. Studies have suggested that DES represents a disorder of loss of neural inhibition. Experimental works in both animal and human studies have found that inhibition of nitric oxide (NO) results in simultaneous contractions in the distal esophagus, a pattern that characterizes DES, while replacement of NO reverses the defect [20, 21].

In nutcracker esophagus, endoscopic ultrasound studies show that there is an incoordination between the contractions of the circular and longitudinal muscle layers [22]. This incoordination was reversed with atropine, suggesting a hypercholinergic state is important in pathogenesis [22, 23]. Both conditions also have coexisting GERD or visceral hypersensitivity [24, 25]. Treatment strategy thus usually involves first identifying whether GERD is present via pH monitoring, thereby identifying a need for anti-GERD therapy [26]. Medical therapy also includes the use of nitrates, calcium channel blockers, and sildenafil, which allow prolongation of muscle relaxation, though esophageal function is further complicated when the LES becomes too relaxed due to medication [26–28]. Anxiolytics may be used in DES patients diagnosed with anxiety or depression [13, 15]. The use of visceral analgesics (tricyclic antidepressants, serotonin reuptake inhibitors) improved global symptom scores in individuals with esophageal contraction abnormalities and DES and has shown improvement in nutcracker esophagus as well [29]. Botox is being used increasingly for both conditions. A recent study examined 22 patients with DES or nutcracker esophagus who had primarily dysphagia and gave them blinded saline or botulinum toxin injections in a crossover study design. Results showed that symptom scores and weight loss improved after the botulinum injections, not the saline injections, and this benefit was sustained for over a year in almost half of the patients [30]. Medical and surgical approaches are intended to alleviate pain and decrease severity of symptoms [13]. Patients may undergo pneumatic dilation to relieve symptoms, but the procedure is not consistently effective because the balloon can be difficult to place. Surgery is usually reserved for those patients with dysphagia and hypertensive sphincter. Selecting a treatment option should be based on bolus transit and manometry findings [14] (Table 23.1).

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a condition in which the esophagus becomes inflamed due to infiltration by eosinophils. It is a clinicopathological disease characterized by clinical symptoms of esophageal dysfunction, detection of >15 eosinophils/high power field (HPF) on esophageal biopsy, and exclusion of other disorders associated with similar clinical, histological, or endoscopic features, especially GERD [31, 32]. Other histologic features include eosinophil microabscesses, superficial layering of eosinophils to upper third to half of the squamous epithelium, and basal zone hyperplasia with the basal zone occupying more than 20% of

the epithelium [33–35]. Endoscopic features include linear furrowing, white exudates, specks or nodules, circular rings, linear shearing/crepe paper mucosa with passage of endoscopy, and esophageal structuring [33, 36–40]. Although none of these are pathognomonic for EoE, the finding of one or more, in the appropriate clinical context, is strongly suggestive of EoE.

The exact incidence and prevalence of EoE is likely underestimated given that the knowledge of, and screening for, EoE is increasing. Noel et al. reported an incidence of ~1:10,000 children per year in the Midwest United States occurring over a period from 2000 to 2003 [41]. In an analysis of a large administrative pathologic database, the period incidence of EoE from 2015 through 2019 in the United States increased from 0.01 to 3.16 cases per 100 persons [42]. EoE has a higher prevalence in males than in females; 16 studies identified 754 pediatric patients, 66% of which were males [31]. It is postulated that 10% of children with GER, unresponsive to acid suppression therapies, have EoE [43]. Overall, prevalence tends to be higher in individuals with a history of dysphagia and pre-diagnosed/existing cases of GERD, reflux esophagitis, and food impaction [44].

Symptoms experienced by patients differ by age, with adults experiencing dysphagia and food impaction [45–48] and children experiencing feeding refusal or intolerance, GERD-like symptoms, failure to thrive, chest pain, emesis, and abdominal pain [31, 48–50]. The difference in symptoms is attributed to pediatric patients being unable to verbalize what they are experiencing, as well as a longer disease duration leading to fibrosis [51]. This is reflected in endoscopic changes as disease course progresses, with features of EoE shifting away from those that reflect inflammation, such as plaques, toward those that reflect remodeling such as concentric rings, narrowing, and strictures [52].

Etiopathogenesis of the eosinophils remains unknown, but is thought to be related to allergen hypersensitivity, with inflammation resulting from repeated exposure to food and aeroallergens in genetically susceptible individuals [53–55]. Allergic responses have been strongly implicated in the etiology of EoE based on several lines of evidence. The majority of patients with EoE (50–80%) [55] are atopic based on the coexistence of atopic dermatitis, allergic rhinitis, and/or asthma and the presence of allergic antigen sensitization based on skin prick testing or measurement of plasma antigen-specific IgE. Also, most patients improve on allergen-free diets, providing supportive evidence that antigen is eliciting the disease.

EoE is characterized by Th2-mediated inflammation. The activated Th2 response leads to the recruitment and activation of eosinophils and mast cells, which degranulate, releasing products that instigate tissue damage, remodeling, and fibrosis. Interleukin (IL)-5, IL-13, and transforming growth factor (TGF)-β1 are master regulators of EoE [56–59]. They can induce other profibrotic agents in the lamina propria [5]. Mechanisms responsible for esophageal dysmotility associated with EoE are somewhat uncertain, though it is likely that esophageal remodeling is the molecular scaffold responsible. The bulk of remodeling changes occur in the subepithelial compartments [56]. Remodeling includes basal zone hyperplasia, epithelial–mesenchymal transition (EMT), fibrosis, angiogenesis, and smooth muscle hypertrophy/hyperplasia [60]. Tissue fibrosis results in decreased esophageal compliance, increased esophageal stiffness, smaller esophageal diameter, and increased smooth muscle mass with smooth muscle dysfunction. Complications, such as esophageal rigidity, dysphagia, food impactions, and esophageal strictures, seem to be secondary to tissue remodeling. There are limited techniques to evaluate and monitor for tissue remodeling and fibrosis. To date, studies have relied on radiographic and endoscopic surrogates to qualitatively assess degree of fibrosis and compliance of the esophagus [61]. Endoscopic ultrasound or computed tomography (CT) scan has confirmed that substantial thickening of the entire esophageal wall occurs in approximately 50% of cases [62], whereas longitudinal muscle dysfunction with abnormal peristalsis has been identified on both ultrasound and manometry [63].

There are few studies utilizing high-resolution manometry (HRM) in EoE patients, particularly after treatment. Studies show that HRM is able to identify esophageal motility disorders in only some EoE patients, despite them having symptoms and eosinophils present on esophageal biopsies [64, 65]. The observed motility disorders resolve after successful treatment in almost all of these patients. Panesophageal pressurization and weak or failed peristaltic integrity are more often present in adult EoE patients than in healthy controls [65, 66]. This can also be seen in GERD patients. However, it was shown that a longer disease duration increased the prevalence of manometric abnormalities in EoE patients [66]. A recent study in adults found achalasia and obstructive motor disorders in 15% of adult patients with EoE, with 50% requiring pneumatic dilation or myotomy for symptomatic relief [67]. Similarly, studies in children show that patients with both EoE and GERD have findings of peristaltic dysfunction (i.e., failed peristalsis, aperistalsis, and esophageal spasm features) and lower distal contractile integral adjusted for esophageal body length, with patients with EoE having a higher prevalence of abnormal findings [68]. The same study also evaluated children with multichannel intraluminal impedance (MII)-pH and found that the great majority of EoE patients have a normal MII-pH profile, while patients with GERD have a markedly higher number of abnormalities picked up. Use of esophageal pressure topography (EPT) yielded the same results—that abnormal esophageal motility was sometimes picked up in patients with EoE who were similar in frequency and type to patients

with GERD, and patients with EoE were more likely to have abnormal bolus pressurization patterns thought to be a reflection of reduced esophageal compliance [69].

The current tools of manometry and endoscopy lack the ability to test distensile properties of the esophageal wall, as the pressure–geometry relationship of the esophageal lumen cannot be measured. Kwaitek et al. demonstrated the utility of measuring esophageal body distensibility by high-resolution impedance planimetry (EndoFLIP—endoscopic functional luminal imaging probe) to calculate multiple adjacent cross-sectional areas (CSAs) within a cylindrical bag while simultaneously measuring intraluminal pressure during controlled volumetric distension [61]. Patients in whom EoE was confirmed by biopsy were found to have decreased distensibility of the esophageal body and gastroesophageal junction compared with healthy controls. Neither mucosal eosinophil count, age, and gender, nor current proton-pump inhibitor (PPI) treatment predicted this limiting caliber of the esophagus. The same group later investigated the EndoFLIP as a tool to predict the risk of food impaction in EoE [70, 71]. They concluded that EoE patients had a lower maximal reachable CSA, termed the distension plateau, than controls and that this measure predicted the risk of food impaction. More recent data also showed decreased esophageal distensibility by EndoFLIP in pediatric EoE patients, with distensibility in this group negatively correlated with eosinophil density. Healthy patients in this cohort had increasing distensibility with age, while EoE patients did not, suggesting that tissue remodeling in EoE patients contributes to abnormal distensibility [72]. In a study assessing the improvement in EndoFLIP measures by Carlson et al., there was significant improvement in esophageal body distensibility with medical and dietary therapies without dilation in EoE. Additionally, improvement in the distensibility plateau in this group was a better indicator of patient-reported symptom improvement than eosinophil count [73]. Thus, EndoFLIP may prove a valuable outcome measure in EoE.

EoE is a chronic and progressive disease. If left untreated, complications, such as food impaction, esophageal stricture, narrow-caliber esophagus, and esophageal perforation, are common. Therefore, once the diagnosis is confirmed, it is important to treat the eosinophilic inflammation not only to control the presenting symptoms but also to preserve the morphological and functional integrity of the esophagus. Besides medications that are geared toward decreasing inflammation, diet avoiding culprit foods is an important therapeutic option [31]. Systemic steroids, while effective, have the downside of systemic symptoms. In a retrospective study of 20 children, oral viscous budesonide mixed with Splenda to create a topical steroid slurry resulted in a 3–4-month resolution or improvement of symptoms in 85% of patients [74]. This provides a suitable alternative to children who have difficulty with inhalers. Dietary options come in three forms: elemental diet, elimination diet that is determined by identifying trigger foods, or a six-food elimination diet that eliminates the six most common allergens. Esophageal dilation is reserved for symptomatic esophageal strictures.

Esophagogastric Junction Outflow Obstruction

Esophagogastric junction outflow obstruction (EGJOO) is a motility disorder comprised of multiple underlying etiologies. Its diagnosis is made by identifying evidence of obstruction at the EGJ during HRM. Characteristic elevation in integrated relaxation pressure (IRP) with preserved peristalsis (Fig. 23.1) sets this clinical entity apart from achalasia. With achalasia, the IRP is elevated, but there is evidence of failed or absent peristalsis. There are multiple conditions that can produce the manometric findings of EGJOO including anatomic or mechanical processes such as hiatal hernia, stricture, tumor, esophageal varices, extrinsic vascular compression, fundoplication, bariatric surgery, paraesophageal hernia, central obesity, opiate effect, and disorders impacting esophageal wall stiffness such as esophagitis, fibrosis, or malignancy. Functional EGJOO is diagnosed when no structural or anatomic abnormality is identified. Given the vast array of clinical entities that cause EGJOO findings on HRM, it is important to critically appraise diagnostic records or consider repeat endoscopy and/or imaging when making the diagnosis. Symptoms of EGJOO include dysphagia, chest pain, heartburn, and/or regurgitation.

Chicago Classification 4.0 recommends that clinically relevant conclusive diagnosis of EGJOO requires a manometric diagnosis with at least one additional test supporting obstruction, preferably timed barium esophagram (TBE) and/or EndoFLIP [10]. TBE with barium tablet administration has been shown to be useful in differentiating non-treated achalasia from EGJOO, and it has been shown to be well tolerated in the pediatric population [75, 76]. In addition to HRM, endoscopy, barium esophagram, and EndoFLIP, imaging tests such as endoscopic ultrasound and CT or magnetic resonance imaging (MRI) may assist in identifying the particular etiology of EGJOO [77]. Cross-sectional imaging and endoscopy can identify most cases of obstruction; however, endoscopic ultrasound can be considered where available when a submucosal lesion is detected [78].

Treatment strategies for EGJOO are as diverse as the clinical entities that cause it; therefore successful outcomes are predicated on the careful and accurate diagnosis of the underlying etiology. For mechanical EGJOO, treatments may include proton-pump inhibitor use for esophagitis, dietary or steroid therapy for EOE, weight loss for obesity, dilation of EGJ strictures, or revision of fundoplication. Treatment strat-

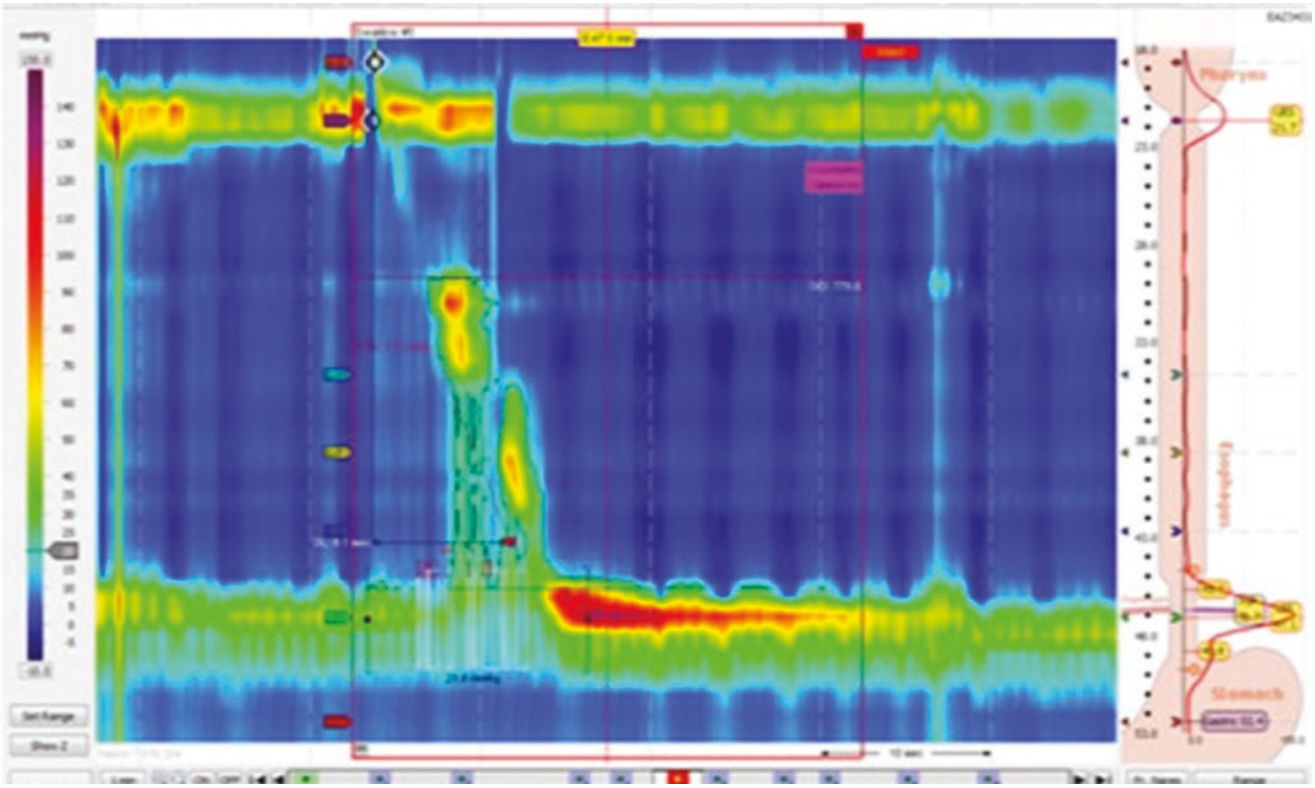

Fig. 23.1 EGJ outflow obstruction. High-resolution manometry showing elevated mean integrated relaxation pressure (IRP) of 22.1 mmHg (normal <10.0 mmHg) and some instances of weak peristalsis with 70% failed bolus clearance and an intrabolus pressure of 8.3 mmHg (normal <8.4 mmHg), consistent with EGJ outflow obstruction

egies for EGJOO should be tailored to match a patient's symptom severity, as it often has a benign course [79]. The intact peristalsis associated with EGJOO often overcomes or compensates for the lack of EGJ relaxation, and thus invasive therapies are often unnecessary and should be reserved for severe cases in which patients have a significant impact on quality of life. Spontaneous resolution of symptoms has also been observed in up to 1/3 of patients with EGJOO, and symptoms of GERD and/or epigastric pain are noted to be predictors of a favorable outcome [79]. Another study suggests that without intervention, greater than 72% of patients are asymptomatic at 2-year follow-up [80]. Given this outcome, close follow-up and repeat manometry may be a reasonable approach to the pediatric patient with EGJOO identified on HRM. Patients who remain symptomatic and have abnormal TBE with barium tablet retention may benefit from pneumatic dilation and/or botulinum toxin injection [81]. There are limited data on use of per-oral endoscopic myotomy (POEM) as a treatment of EGJOO; however, studies suggest that in patients with persistent symptoms (greater than 70 months) and prior therapy, it is safe and effective in adults [82, 83]. Given its invasive nature and permanent disruption of the LES, it is critical to have an accurate diagnosis and exclude all secondary causes of obstruction prior to engaging with surgical correction by POEM.

EGJOO as a diagnosis should also be considered in patients with post-fundoplication dysphagia. Given the paucity of data in the pediatric population, optimal management of these patients is unclear. A small case series of these patients suggests that the primary symptom of dysphagia presents approximately 2 weeks after procedure and that esophageal dilations provided no relief. However, spontaneous resolution of dysphagia was observed in 75% of patients [84].

Collagen Vascular Disorders

Among collagen vascular disorders, scleroderma is the most severe and commonly manifests in the gastrointestinal (GI) tract. Other collagen vascular disorders with esophageal manifestations are systemic lupus erythematosus (SLE), mixed connective tissue diseases (MCTDs), Sjörgen's syndrome, and rheumatoid arthritis. Scleroderma is the hardening of tissues resulting from an autoimmune response attacking the body. Systemic scleroderma (SSc) is characterized by remarkable collagen deposition in body tissue, especially the esophagus. SSc affects esophageal tissue and motility in 75–90% of adult cases [85, 86]; pediatric studies indicate much lower prevalence [87, 88]. In a multicenter

study, Foeldvari et al. reported 65% (88/135) of pediatric SSc patients presented GI tract involvement; only involvement with the skin, joints, and Raynaud's phenomenon preceded GI tract [89]. Of those 135 cases, under 50% ($n = 63$) involved the esophagus [89].

Esophageal smooth muscle becomes atrophied and replaced by fibrous tissue leading to severe motility disturbance of the distal esophagus. A study of SSc revealed that childhood onset is sometimes preceded by trauma in the area of deposition, a unique phenomenon compared to adult cases of scleroderma [88]. It is postulated that trauma releases the neuropeptide ET-1, stimulating collagen synthesis in fibroblasts [88]. In the presence of SSc, esophageal manometry reveals an incompetent LES, low-amplitude peristalsis in the distal esophagus, and a normal proximal esophagus that is made of striated muscle of the esophagus (Fig. 23.2) [85].

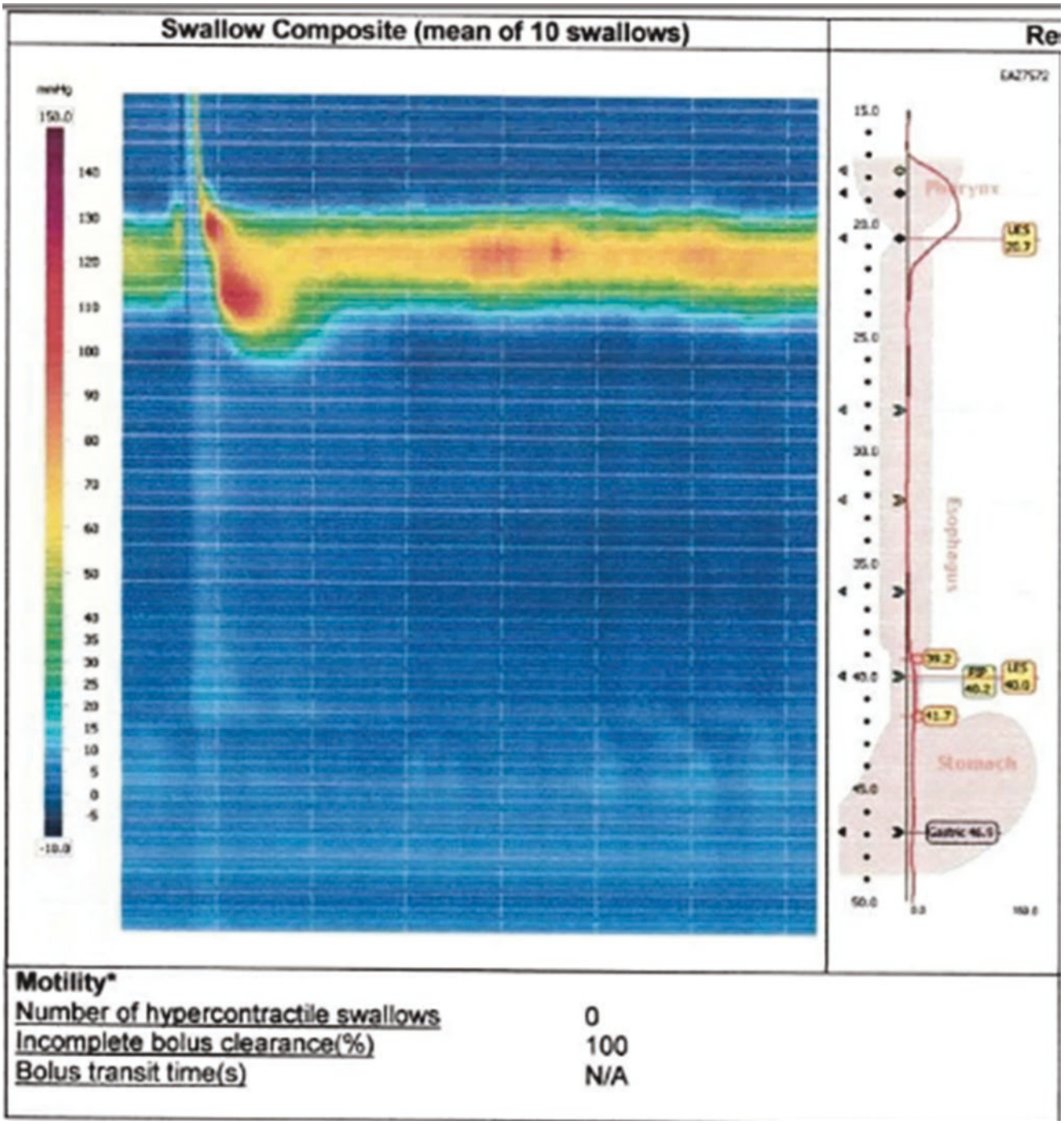

Fig. 23.2 Scleroderma

The retrograde movement of gastric contents, related to LES pressure, exposes the esophagus to acidity, which can compromise peristalsis. Frequent contact between acidic gastric contents and esophageal mucosa degrades tissue quality; esophagitis, bleeding, and strictures are other known complications. However, studies have noted that many who experience reflux secondary to SSc can be asymptomatic [85, 90]. Abnormalities in HRM, including ineffective esophageal motility (IEM) and aperistalsis, were found in 84% of asymptomatic patients with SSc [91]. In a study by Weber et al., 15 pediatric patients with scleroderma or mixed connective tissue disease underwent 24-h pH monitoring. While 85% had an elevated number of reflux events and 50% had reflux events lasting greater than 5 min, only 3 patients had clinical symptoms [90]. Aside from manometry, barium esophagram, 24-h ambulatory pH, and endoscopy are also used to diagnose the extent of esophageal disturbance secondary to SSc [85]. More recently, adult patients with SSc and symptoms of reflux and/or dysphagia have been shown to have significantly reduced EGJ distensibility on EndoFLIP when compared to healthy controls [92].

Common symptoms of SSc with esophageal involvement are dysphagia, chest pain, weight loss, food impaction, and early satiety [85, 93]. Weber et al. reported reflux events in over 60% of pediatric patients with SSc [90]. Overall, mortality for SSc with esophageal involvement is very rare; death is usually a consequence of multisystem involvement [88, 89]. Treatment of SSc primarily involves immunosuppressants (prednisone, methotrexate, mycophenolate mofetil, tumor necrosis factor-alpha, cyclophosphamide) [88, 94]. However, the suspected effect of immunosuppressants on fertility must be further evaluated in the pediatric population [95–97]. Gunawardena and McHugh suggest proton-pump inhibitors, bulking agents, nutritional supplements, and antibiotics as additional treatment options [93, 98]. More investigation into effective treatment of pediatric collagen vascular disorders with esophageal manifestation is needed.

Chronic Idiopathic Intestinal Pseudo-Obstruction

Chronic idiopathic intestinal pseudo-obstruction (CIIP) is a rare primary disorder that involves the entire gastrointestinal tract (see Chap. 24). Esophageal involvement is very common [99]. Non-idiopathic intestinal pseudo-obstruction is usually secondary to systemic, metabolic, genetic, or mitochondrial etiologies. CIIP is often diagnosed during infancy and childhood, and symptoms are usually both severe and frequent at onset. Patients with esophageal involvement present with clinical symptoms of GER, dysphagia, nausea, vomiting, and weight loss [100, 101]. Dysphagia, however, is usually a chief complaint when CIIP is secondary to another disorder.

Upper GI endoscopy, manometry, and full thickness biopsies are used to diagnose CIIP. Abnormal manometry is intermittent, and abnormalities include uncoordinated (neuropathic) or low-amplitude (myopathic) contractions with swallowing [100]; these findings are more common than aperistalsis. Decreased LES pressure is also a common clinical finding. Pharmacologic treatment of CIIP is similar to that of other esophageal motility disorders, involving antiemetics, prokinetics, and antispasmodics. Antibiotics are suggested to reduce bacterial growth, which may also benefit abdominal pain, distention, and diarrhea [100].

Hirschsprung's Disease

Lack or poor formation of the enteric nervous system defines Hirschsprung's disease (HD) (see Chap. 25). Though primarily a disease of the small and large bowel, HD is occasionally associated with abnormal esophageal motility indicated by poor peristaltic wave propagation [102]. Staiano et al. examined esophageal involvement in children with HD, in comparison to those with idiopathic megacolon and healthy controls with no esophageal or colonic diseases. Abnormalities in the amplitude and frequency of distal esophageal body contractions were significantly higher in HD patients than other groups [103]. The severity of HD in this group was unrelated to esophageal involvement. Another study evaluated if upper GI dysmotility in HD patients persists into adulthood [104]. Sixteen adult HD patients and 17 controls evaluated via antroduodenal and esophageal manometry revealed increased contractile activity of the small bowel during fasting and post-prandially in HD adults.

Caustic Ingestion

Caustic ingestion of harmful substances is a common accident among young children, especially in developing countries. Common signs and symptoms include salivation, oropharyngeal burns, vomiting, bleeding, epigastric and retrosternal pain, and malignant transformation [105, 106]. Esophageal burns, though less common than oropharyngeal, are associated with fibrosis of deep muscle tissue that impairs normal motility. Acids and alkalis produce different types of tissue damage. Esophageal motility studies report low-amplitude and non-peristaltic contractions in patients with dysphagia and structuring [107–109].

Ineffective Esophageal Motility

Ineffective motility of the esophagus has evolved from being included in an initial description of nonspecific esophageal motility disorder (NEMD) to a more precise terminology establishing it as a separate entity. The unifying feature of swallows contributing to the diagnosis of ineffective esophageal motility (IEM) is poor bolus transit in the distal esophagus. In 2001, using conventional manometry, Spechler and Castell defined IEM as having low or normal esophageal sphincter pressure, normal LES relaxation, and greater than 30% low-amplitude waves characterized by the following: wave amplitude <30 mmHg, peristalsis that does not travel the length of the esophagus, simultaneous contraction <30 mmHg, or aperistalsis [110]. Tutuian and Castell indicated in 2004 that patients with ≥50% ineffective wet swallows (<30 mmHg) are more likely to have abnormal bolus transit [111]. Blonski et al. showed that this definition was more frequently associated with esophageal symptoms (dysphagia and heartburn) and abnormal bolus transit compared to those who had only 30–49% ineffective swallows [112]. The *Chicago Classification* by HRM defines IEM as DCI <450 mmHg s cm with ≥70% ineffective swallows and/or ≥50% failed swallows [10]. IEM is the most common abnormality on esophageal manometry, with an estimated prevalence of 20–30% [113]. With the use of HRM to define IEM, the prevalence of IEM has increased. Boland et al. performed HRM on 350 adult patients referred for esophageal function testing between August 2012 and May 2013 [114]. Thirty-one percent of patients had IEM compared to 21% 10 years prior, when 350 patients had been evaluated via multichannel intraluminal impedance–esophageal manometry (MII-EM).

Patients with IEM present with various complaints. Analysis of 228 IEM patients in a study showed dysphagia in 25% of patients, cough in 15%, chest pain in 13%, heartburn in 12%, and regurgitation in 12% [115]. Among patients with dysphagia, bolus transit was defective in 89%. The presence of dysphagia with defective bolus transit in patients with severe IEM was also shown in 2008 [112]. IEM thus appears to subdivide into two groups, a more severe form that manifests with dysphagia and is associated with a more defective bolus transit and a milder form of which the clinical significance is not very clear. The association between IEM and GERD is well documented, and IEM is more prevalent in patients with more advanced reflux disease. Multiple studies showed esophageal peristaltic dysfunction was increasingly prevalent with more severe GERD presentation, from non-erosive reflux disease (NERD) to erosive esophagitis (ERD) and Barrett's esophagus [116–119]. It has not yet been determined whether IEM is a rare primary disorder or merely secondary to increased acid exposure.

Currently there are little data regarding ineffective esophageal motility (IEM) in the pediatric population. In infants with apparent life-threatening events (ALTE), prolonged spontaneous respiratory events are associated with ineffective esophageal motility characterized by frequent primary peristalsis and significant propagation failure, thus suggestive of dysfunctional regulation of swallow–respiratory junction interactions [116].

Nonspecific Esophageal Motility Disorders

Nonspecific esophageal motility disorders (NEMDs) capture those cases with irregular manometry, but not characteristic of an established disorder [1, 13, 120]. Criteria for NEMDs are ≥30% of wet swallows with non-transmitted or low-amplitude contractions or at least one of the following contraction abnormalities: triple-peaked contraction, retrograde contraction, prolonged-duration peristaltic waves (>6 s), or isolated incomplete LES relaxation (>8 mmHg) [120]. Low-amplitude contractions are thought to be the most common manometric finding [121]. NEMDs differ from achalasia in that with swallows, there are intermittent normal and abnormal peristaltic waves; complete lack of peristalsis is characteristic of achalasia. Additionally, NEMDs involve low-amplitude waves, whereas DES typically involves high-amplitude pressure waves. Despite these notably distinct symptoms, it is suggested that NEMDs may be an early disease state of achalasia and DES [121]. Naftali et al. reported a minority of patients who progressed from NEMD to achalasia or DES, noted during a repeat manometry procedure. In a retrospective study following 43 patients with NEMD over 4 years, 28 patients had repeat manometry for persistent symptoms, and, among them, 15 patients had progressed to achalasia. Almost all of them were <46 years old, suggesting that an early age of onset is predictive of disease progression [122].

Common symptoms are dysphagia, vomiting, chest and epigastric pain, and food impactions [2, 13, 26]. NEMDs are much less common than other primary esophageal motility disorders, such as achalasia and DES. In a cohort of 154 children with upper GI symptoms, 30 were not diagnosed with GER. Of those 30 patients, 43% (n = 13/30) were found to have nonspecific esophageal motility disorders (NEMDs), representing 8% of the entire cohort [123]. In addition to normal esophageal pH, many of those diagnosed demonstrated normal endoscopic appearance and esophageal histology; thus, clinical findings (i.e., food impaction) are of great significance with regard to NEMDs [123]. Palliative treatment method for NEMDs usually involves antispasmodic agents, prokinetics, antacids (where GER is present),

and/or PPIs [2, 124]. Improvement with these methods is variable; some may even improve without pharmacologic intervention [123].

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Gastric Motor Disorders

24

Neha R. Santucci and Ajay Kaul

The motor function of the gastrointestinal (GI) tract is a complex interaction of stimulus and effect. Normal function results from the coordination of various processes in response to internal and external stimuli including ingestion of food. Effective stomach filling and emptying relies on the interplay of the autonomic nervous system, neurotransmitters, enteric smooth muscle, sensory afferent nerves, and other intrinsic and extrinsic factors. Interruption of any of these components may result in dysmotility. Gastroparesis is a disorder of the stomach in which emptying of gastric contents is delayed in the absence of mechanical obstruction. It occurs in up to 4% of adults and can result in significant disability. Dumping syndrome is another symptomatic disorder related to rapid gastric emptying and may be equally debilitating.

Gastroparesis

Incidence

Gastroparesis is a motor and sensory disorder of the stomach with delayed gastric emptying in the absence of a mechanical obstruction [1]. It is one of the more common dysmotilities that occur in the gastrointestinal tract [2, 3]. Initially thought to primarily affect adults, the incidence is rising in children and adolescents and poses a huge increase in healthcare costs related to hospitalizations [2–5]. Unlike adult data, the etiology and literature are limited in the pediatric population [1]. Adult studies demonstrate that gastroparesis is common and more frequent in females and that hospitalizations related to the disorder have been increasing [6]. Studies conducted in two tertiary care centers found that 25–62% of children who underwent 4-h scintigraphy had abnormally delayed gastric emptying [7–9]. In children, gender predominance of gastroparesis seems to vary by age. In infancy, gastroparesis is more common among boys, has a similar prevalence in both genders in children, and predominates in females in adolescence [10]. Differences in etiological factors between children of various ages and between children and adults may explain these findings.

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Gastroparesis and Functional Dyspepsia

Symptoms of gastroparesis often overlap with those of functional dyspepsia (FD). Recent literature considers them to be part of a continuous broad spectrum of gastroduodenal sensorimotor dysfunction with shared upper gastrointestinal symptoms [11, 12]. Abdominal pain may be present in both disorders; however, it rarely represents the most bothersome symptom in patients with gastroparesis. Nausea is present in 29% of children with FD [13] and 77% of children with gastroparesis [7].

Abnormalities of gastric electrical and motor activity [14] may be present in both disorders, and a subset of children with FD may have delays in gastric emptying [15, 16]. The recognition of this overlap is important at the time of recommending treatment, for the understanding of the pathophysiology of both disorders, and for the identification of specific cohorts in research studies.

Etiology

The etiology in adults includes diabetes, idiopathic, and post-surgical [17, 18]. Most cases in children are post-viral or idiopathic [2]. Together, both have been associated with up to 70% of cases of gastroparesis in children [2]. A fewer number are post-surgical or related to diabetes. Surgery, metabolic conditions, and medication induced are the next most common factors implicated in children. Multiple other

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Table 24.1 Etiology of gastroparesis in children

Idiopathic
Post-infectious
CMV, EBV, rotavirus, mycoplasma, norovirus, varicella
Post-surgical
Fundoplication, vagotomy, partial gastrectomy
Other thoracic and abdominal surgeries
Metabolic
Type 1 DM, type 2 DM
Hypothyroidism, hyperthyroidism, hypopituitarism, Addison's disease, Turner's syndrome, cystic fibrosis
Dysautonomic
Amyloidosis, toxins, infection (Chagas disease, HIV), hereditary disorders, immune-mediated and autoimmune disorders, paraneoplastic syndrome
Anatomic abnormalities
Congenital diaphragmatic hernia
Esophageal and tracheoesophageal fistulae
Intestinal malrotation
Scoliosis
Immune mediated
Celiac disease, inflammatory bowel disease, cow's milk protein allergy, autoimmune neuropathy
Medication related
Anticholinergics, opioids, tricyclic antidepressants, proton-pump inhibitors, H2 receptor antagonists, antacids, sucralfate, octreotide, beta-adrenergic agonists, calcium channel blockers, levodopa
Others
Pyloric dysfunction
Ehlers–Danlos syndrome hypermobile type
Hirschsprung disease
Constipation
Rumination
Malnutrition and eating disorders
Muscular dystrophy
Critical illness
Mitochondrial disease
CNS disease
Prematurity
Caustic ingestion
Marijuana

etiological factors have been described in children of various ages (Table 24.1).

Post-infectious

In children, gastroparesis has been reported following rotavirus, Epstein–Barr virus (EBV), cytomegalovirus (CMV), norovirus, varicella, and *mycoplasma* infections [5, 19–21]. An infectious etiology is suspected frequently in the course of clinical care of a child with gastroparesis, but the infecting agent is rarely identified. Post-infectious gastroparesis is suspected when a previously healthy individual has acute onset of gastrointestinal symptoms characteristic of infectious enteritis—nausea, vomiting, diarrhea, fever, or abdominal pain. At presentation, the clinical findings of children who develop post-infectious gastroparesis can be mild or severe and identical to other children with acute gastroenteritis. However, in children with gastroparesis, the gastrointestinal symptoms persist for months to years. Long-term outcomes are excellent, with resolution of symptoms typically between 6 months and 2 years [19, 22]. Evaluation of adults with gastroparesis demonstrates abnormalities of enteric neurons and interstitial cells of Cajal (ICC), and it is hypothesized that viral infections could cause such injury. Although several types of infection can result in gastroparesis, not every infectious agent that affects the stomach is associated with delayed emptying. A study on adult patients found a lower prevalence of *Helicobacter pylori* infection in patients with gastroparesis than controls [23].

Post-surgical

Gastroparesis may follow specific surgical procedures including fundoplication, bariatric surgery, and heart or lung transplantation [24]. Although purposeful vagotomy is infrequently performed, inadvertent vagal injury may occur during the course of other upper abdominal or thoracic procedures. Gastroparesis-related symptoms following vagal injury can improve with time, possibly due to enteric nervous system adaptation or vagal nerve reinnervation [24]. Fundoplication may result in accelerated or delayed gastric emptying, underscoring the complex interplay of factors associated with surgery. Multiple pathophysiological mechanisms may result in abnormal function following surgery. Antireflux procedures may affect sensorimotor function of the proximal stomach. Motor abnormalities that have been most frequently described in patients with fundoplication include alterations in antral peristalsis and receptive relaxation [25].

Diabetes Mellitus

Diabetes mellitus is an uncommon cause of delayed gastric emptying in children. In contrast, up to 30% of adults with type 2 diabetes mellitus (T2DM) have gastroparesis [26]. Poor glucose control, vagal parasympathetic dysfunction, and depletion/dysfunction of ICC and gastric enteric neurons are postulated to alter gastric physiology in diabetics [27]. Relaxation of the fundus and gastric capacity are decreased in diabetics. Uncontrolled diabetes may cause gastric dysrhythmias; ineffective contractions of the fundus, corpus, and antrum; and pyloric hypercontractility [28–30]. Similar to adults with T2DM, children with type 1 diabetes mellitus (T1DM) may have antral hypomotility, gastroparesis, and gastric electrical dysrhythmias [31, 32]. A study comparing children with T1DM to children with chronic dyspepsia or chronic constipation (but no T1DM) identified lower serum motilin concentrations among diabetics, but found no difference in

autonomic function, gastric emptying, or total intestinal transit time [33]. Other studies found delayed gastric emptying [31, 32], autonomic dysfunction [34], and even rapid gastric emptying [35], underscoring the need to study the gastric function of T1DM patients who present with gastrointestinal symptoms to establish individual therapeutic plans.

Dysautonomia

Autonomic peripheral neuropathies may occur secondary to diabetes mellitus, primary and hereditary amyloidosis, toxins (organic solvents, vincristine), infection (Chagas disease, human immunodeficiency virus [HIV]), hereditary disorders (hereditary and sensory autonomic neuropathies, Fabry disease, Allgrove syndrome), immune-mediated and autoimmune disorders (Guillain–Barré syndrome, systemic lupus erythematosus, myasthenia gravis), and paraneoplastic syndrome [36]. Symptoms typically affect multiple organs with variable severity although upper gastrointestinal symptoms are common.

Autoimmune Neuropathy

Autoimmune gastrointestinal dysmotility presents with subacute onset of autonomic dysfunction. Clinical findings may be generalized or limited to the gastrointestinal organs and include nausea, vomiting, and/or gastroparesis. Involvement of the esophagus (including achalasia), pyloric stenosis, intestinal pseudo-obstruction, and anal spasm have been reported [37]. A case series of adults with ganglionic acetylcholine receptor antibodies found gastroparesis, constipation, anhidrosis, dry eyes and dry mouth, a neurogenic bladder, and orthostatic hypotension [38]. Although there were few patients, significant variability in disease severity and the potential for chronic duration were demonstrated. A case series screening sera of patients with autoantibodies and gastrointestinal disease identified 12 patients with delayed gastric emptying [37]. The patients had antibodies to ganglionic acetylcholine receptor, voltage-gated calcium channels *N*-type, thyroperoxidase, thyroglobulin, glutamic acid decarboxylase 65 kDa isoform, islet cell antigen 512, antineuronal nuclear autoantibody, type 1/anti-Hu, and muscle acetylcholine receptor.

Disturbances in gastrointestinal motility including delayed esophageal, gastric, and small intestinal transit, as well as delayed or accelerated colonic transit, have been described in patients with celiac disease [39, 40]. A study on adult celiac disease patients found delayed gastric emptying that normalized after 1 year of gluten-free diet (GFD) [41]. A study in children with celiac disease showed near-complete resolution of antroduodenal dysmotility after 6 months of GFD [42]. However, another study in adult patients found altered antroduodenal manometry (ADM) in the fasting and fed states even in those adherent to a GFD [43]. Persisting autonomic dysfunction, peripheral neuropathy, and antineuronal antibodies found in a series of celiac disease patients on GFD could explain these findings [44].

Gastric emptying is delayed in some patients with inflammatory bowel disease, and prolonged emptying times may be associated with disease activity through a glucagon-like-peptide 1 (GLP-1)-mediated pathway [45]. Interestingly, the location of disease activity does not necessarily correlate with altered gastric motility. Gastrointestinal neurohumoral mediators (including GLP-1 and cholecystokinin) may be altered even in distal small intestinal or colonic inflammation and associate with gastric emptying delay [46]. Further, as in treated celiac disease, gastroparesis may persist in patients even with inactive inflammatory bowel disease [47, 48].

Hypermobility or Hypermobile Ehlers–Danlos Syndrome

Gastrointestinal dysmotility has been described in patients with hypermobile Ehlers–Danlos syndrome (EDS) [49, 50]. Roughly half the patients in this study reported delayed gastric emptying. Postural orthostatic tachycardia syndrome (POTS) was a predictive factor for GI dysmotility. Underlying autonomic dysfunction may contribute to GI dysmotility. Pediatric studies have also described gastrointestinal involvement in hypermobile spectrum disorders but the exact incidence of gastroparesis in children remains unknown [51].

Central Nervous System Disorder

Children with chronic illnesses including central nervous system disorders have a high incidence of gastric dysrhythmias, gastroparesis, and abnormal antroduodenal motility [52–54]. In one study, 31/50 children had gastric dysrhythmias [52], while in another study all children had abnormal antroduodenal manometry and half of them had delayed gastric emptying of liquids [53]. Although not all children with central nervous system disorders have abnormalities of gastrointestinal motility, the possibility of gastroparesis, gastroesophageal reflux disease, feeding disorders, and constipation should always be considered.

Mitochondrial Disorder

Gastrointestinal manifestations of mitochondrial disease are varied and complex [55]. Several case series identify gastroparesis in the setting of specific mitochondrial disorders.

Eighteen of 26 children with mitochondrial disease had delayed gastric emptying with delays persisting in most despite prokinetic therapy [56]. Four patients with upper gastrointestinal symptoms consistent with gastroparesis were identified to have 3243A>G mitochondrial DNA (mtDNA) mutation in specific stomach regions [57]. This mutation is implicated in mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS). Three of the patients were further studied and found to have abnormal electrogastrography (EGG) and gastric emptying, although gold-standard scintigraphy was not used. Six children with defects in mitochondrial electron transport chain enzymes of oxidative phosphorylation (OXPHOS), but no specific mtDNA mutation, were found to have abnormal antroduodenal manometry indicative of neuropathy, and four had delayed gastric emptying [58].

Hirschsprung Disease

Although Hirschsprung disease (HD) is generally considered a disorder of the lower gastrointestinal tract, abnormalities of upper intestinal motility have been identified years after repair. Specifically, esophageal body abnormalities were found on manometry of 12 children with HD [59]. Similar findings were identified in 11 children with total colonic aganglionosis who had abnormalities in esophageal body contractions and propagation, but generally preserved upper esophageal and lower esophageal sphincter tone [60]. Antroduodenal manometry in these HD patients found a mix of abnormal propagation, distribution, or occurrence of phase III activity in the migrating motor complex (MMC).

Gastric emptying function is also affected in children with HD. HD patients have significantly longer total gastrointestinal transit times than controls even after surgical repair. In only few cases does the delay in gastrointestinal transit relate to prolonged colonic transit [61]. Patients with HD had longer gastric isotope retention than controls at 60 and 90 min, with 12/21 HD patients having >60% retention at 60 min (>2 standard deviation [SD] from mean). Although HD patients frequently reported persistent vomiting and/or abdominal distension, the symptoms did not predict gastroparesis. Similarly, the frequency of bowel movements had poor correlation with gastric emptying times. Forty percent of HD patients with normal bowel frequency had delayed gastric emptying.

Food Allergy

Infants sensitized to cow's milk (cow's milk protein allergy—CMPA) had significant gastric electrical dysrhythmias and delayed gastric emptying measured by electrical impedance tomography when compared to controls with gastroesophageal reflux [62]. A positive food challenge in children identified resultant electrogastrographic changes and mast cell degranulation in proximity to gastric nerve fibers [63]. In children with FD, increased antral mast cell density is associated with slower gastric emptying [64]. Gastrointestinal eosinophils and mast cells, in animal and human studies, are increasingly associated with alterations in gastric motor and electrical function [65].

Constipation

Many other factors are related to delays in gastric emptying. In children, constipation is often associated with upper gastrointestinal symptoms (including nausea) [66] possibly through the reflex inhibition (cologastric brake) of upper gastrointestinal motor activity. Constipated dyspeptic children have more frequent delays in gastric emptying than nonconstipated dyspeptic subjects, and their gastric emptying time improves after osmotic laxative treatment [67]. Activation of the cologastric brake may explain delays in gastric emptying associated with both rectal distension [68, 69] and voluntary suppression of defecation [70].

Other Systemic Disorders

Endocrinopathies including hypo- and hyperthyroidism, hyperparathyroidism, Addison's disease, and hypopituitarism have been associated with gastroparesis. Myopathies including myotonic dystrophy and Duchenne muscular dystrophy are associated with severely symptomatic gastroparesis [71, 72].

Critically ill patients frequently exhibit severe gastroparesis that may be exacerbated by endogenous mediators, sepsis, mechanical ventilation, and medications. Over 50% of mechanically ventilated critically ill adults have delays in gastric emptying [73], potentially increasing morbidity and mortality due to inability to administer adequate enteral nutrition. Multiple potential pathophysiologic mechanisms of intensive care unit (ICU)-associated gastroparesis have been explored including the roles of cholecystokinin, secretin, oxyntomodulin, GLP-1, GLP-2, pancreatic polypeptide, and peptide YY [74].

Medications and Ingestions

Multiple medications including anticholinergics, opioids, tricyclic antidepressants, proton-pump inhibitors, H2

receptor antagonists, alcohol, antacids, sucralfate, octreotide, beta-adrenergic agonists, calcium channel blockers, lithium, ondansetron, phenothiazines, and levodopa can lead to delayed gastric emptying [75–77]. Endocannabinoids exert multiple effects on enteric neurons that may inhibit neuronal activity, synaptic transmission, and axonal mitochondrial transport [78, 79]. Delta-9-tetrahydrocannibinol (THC) slows gastric emptying in adults suggesting putative antiemetic effects are centrally mediated rather than related to alterations in gastric motor function [80]. Ingestions of caustic substances, and marijuana have also been related to delays in gastric emptying. Although patients with caustic ingestion and chronic injury did not demonstrate symptoms of gastroparesis, studies have shown that the orocecal transit time [81] and scintigraphic gastric emptying [82] were delayed.

Psychological Disturbances

Psychological stress also has effects on electromechanical function. Experimentally induced stress has been shown to increase symptoms and inhibit normal postprandial EGG responses in some, but not all, studies [83, 84]. Stress is further shown to impair accommodation and to delay gastric emptying [85]. The stress effect on gastric emptying appears to be mediated at least in part via the corticotrophin-releasing hormone [86]. Attention hyperactivity disorder, anxiety, depression, and other behavioral comorbidities have been associated with gastroparesis in children [1, 2].

Malnutrition and Eating Disorders

Eating disorders also have a variety of potential gastrointestinal manifestations including gastroparesis [87]. Patients with anorexia nervosa have increased gastric dysrhythmias [88] and increased antral distension during meals with maximal dilation reached more quickly than controls [89]. Many case reports suggest the association of gastroparesis in anorexia [87]. Severity of malnutrition may be associated with gastroparesis in anorexia nervosa [89], although the relation of body weight to gastroparesis is unclear given contradictory data. Treatment of anorexia nervosa with refeeding may improve gastric emptying time [89, 90].

Rumination

Patients with rumination syndrome are demonstrated to have normal EGG, scintigraphic gastric emptying, and MMCs on antroduodenal manometry [91]. However, rumination syndrome is at times related to gastroparesis through "conditioned vomiting" that can occur in the setting of delayed gastric emptying [91].

Development

Intestinal development continues to occur during the third trimester of gestation, and interruption in this development, most commonly by preterm birth, may result in symptomatic disorders. Normal gastric liquid emptying, both electrical rhythm and motor activity, has been demonstrated in 32–34-week gestation infants [92, 93]. Gastric electrical activity and motor function continue to develop postnatally with enteral nutrition stimulating continued maturation of intestinal motor function [94]. Gastric electrical activity develops further in the first decade of life before achieving normal adult patterns [95].

Pathophysiology

Gastroparesis may result from multiple pathophysiological mechanisms including altered fundic receptive relaxation, decreased antral contractility, and incoordination of gastric emptying and duodenal contractions. Underlying parasympathetic dysfunction has been implicated in gastroparesis and correlated with worse upper gastrointestinal symptoms [96]. Pyloric spasm or fibrosis has been implicated in the pathophysiology of delayed gastric emptying leading to a functional gastric outlet obstruction [29, 97]. Studies in adults with delayed gastric emptying have demonstrated decreased pyloric distensibility and compliance, decreased cross-sectional area and diameter, and increased basal pyloric pressure [98–100]. Dyschalasia, which is premature contraction of the pylorus during antral peristalsis, has also been implicated [101]. Altering the pyloric dynamics may cause changes in antral contractility and gastric emptying [102].

Clinical Presentation

Signs and symptoms of gastroparesis can wax and wane over time and include bloating, nausea, early satiety, abdominal pain, vomiting, failure to thrive, and weight loss. The severity of symptoms may vary from patient to patient ranging from minimal and tolerable to severe and debilitating. While nausea (90%) and vomiting (84%) are the most predominant symptoms in adults, presentation varies in children by age, with vomiting (97%) and weight loss (31%) in infants, vomiting (73%) in children aged 1–10 years, while abdominal pain (66–75%) reported in children older than 11 years of age [1].

Diagnosis

The diagnosis of gastroparesis is determined by the demonstration of delayed gastric emptying with 4-h gastric scintigraphy, the current gold standard (Fig. 24.1). Gastric scintigraphy should be performed with a standardized meal and using normative emptying values (gastric emptying of >90% at 1 h, >60% at 2 h, and 10% at 4 h) as recommended by the Society of Nuclear Medicine and the American Neurogastroenterology and Motility Society [103]. Normative emptying values were established based on data in adults and have been adopted in pediatrics. Although no

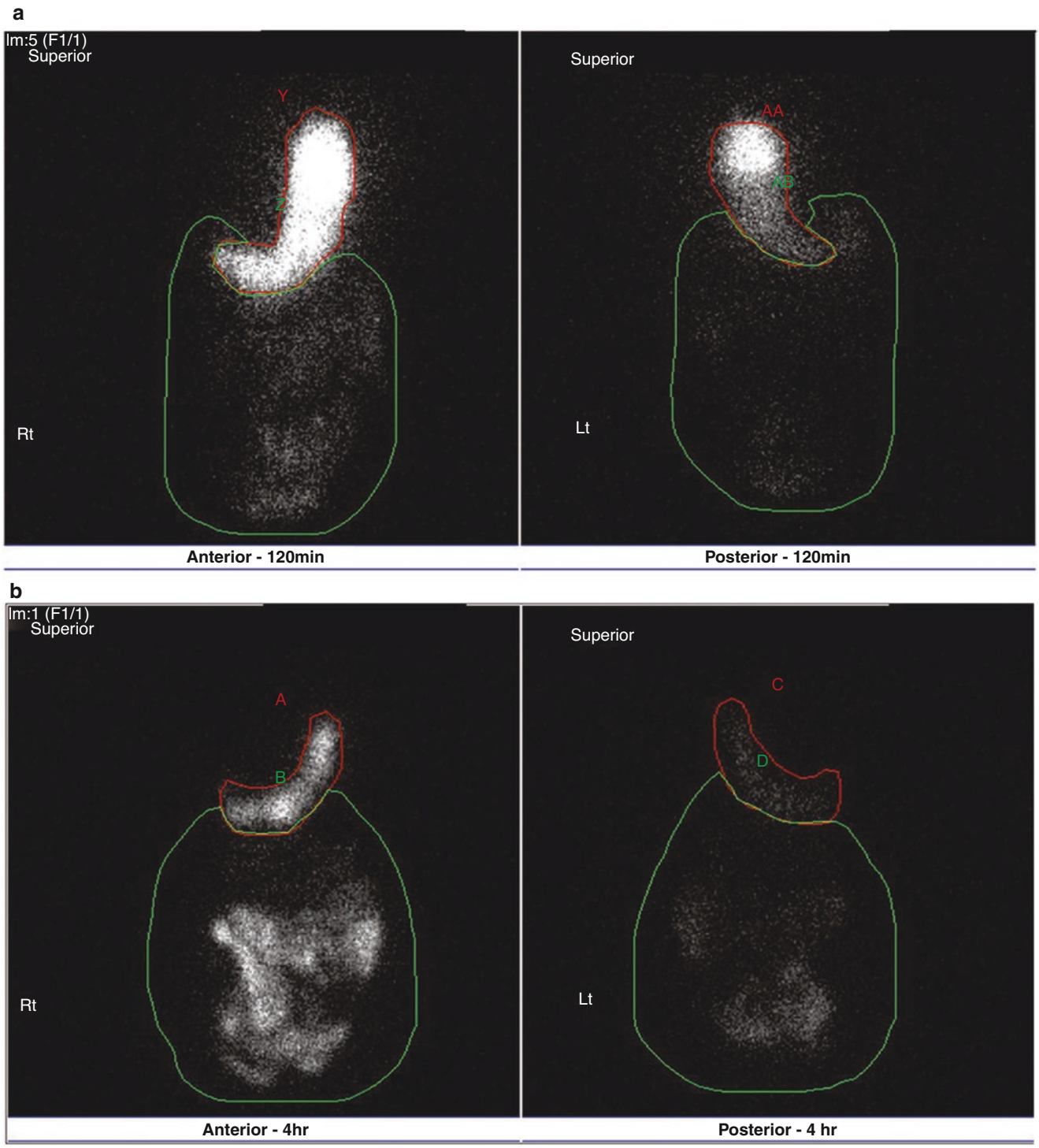

Fig. 24.1 Gastric emptying scan showing delayed gastric emptying with greater than 60% and 10% ^{99m}Tc sulfur colloid activity in the stomach at 2 h and 4 h, respectively (**a**) Delayed gastric emptying with greater than 60 % Tc 99 m sulfur colloid activity in the stomach at 2 h (**b**) Delayed gastric emptying with greater than 10 % Tc 99 m sulfur colloid activity in the stomach at 4 h

specific studies have been conducted to validate these values in children, a meta-analysis of patients of a wide age spectrum (premature neonates to adults) found no age-dependent effect on gastric emptying [104]. The importance of completing a 4-h test was demonstrated in adult and pediatric studies. A review of 1500 adult patients found frequent "false negatives" in studies of less than 4 h [105]. A pediatric study has also shown that the use of 4-h testing has a higher sensitivity than studies of shorter duration [8]. Thus, the use of 4-h testing and a normative standard meal is strongly recommended. Despite these recommendations, many centers continue to conduct studies with a wide variety of protocols and length of study. Modifications to the protocol may be justified in special circumstances. The solid meal is not suitable for exclusive enteral formula-fed patients, and neonates and young or small children are frequently not able to complete the adult-size meal [9]. The protocol may also be difficult to complete for those in whom an egg sandwich results in intolerable gastrointestinal symptoms or who are allergic to components of the meal. Alternative protocols have been developed to overcome the limitations of the solid food-based nuclear medicine testing and to study other aspects of the stomach function.

Liquid emptying studies can be used in younger children, but the results of liquid emptying cannot be automatically extrapolated with studies of gastric emptying using a solid meal. In the fed state, gastric emptying varies with food composition, including caloric content, osmolality, temperature, and the physical characteristics of the meal. As liquids do not need to be grinded prior to emptying, they have a faster emptying time than solids and follow a different emptying curve. A study in adult healthy volunteers proposed that a liquid nutrient meal can be used as an alternative to the standard solid meal. The study found that the *t*-1/2 gastric emptying of a liquid nutrient meal (Ensure Plus®) was similar to an egg sandwich meal [106]. A pediatric study has proposed normative values using liquid gastric emptying (200 mL of strawberry flavored milk and a caloric content of 112 kcal) measured by the [106] C-acetate breath test [107]. Liquid emptying times in this study were independent of age, gender, and body mass index (BMI). Variation in institutional protocols and lack of weight-based norms still remain a challenge with scintigraphic studies. The use of the isotope breath test is an attractive method to measure gastric emptying in children due to its simplicity and low risk. The spirulina breath test measures the C13 isotope that is labeled in the food consumed and has shown results comparable to scintigraphy in adults [108, 109] and children [110]. Recent studies have attempted to establish pediatric norms and describe the effects of gender, age, body mass index, and puberty with the use of spirulina breath test [111, 112].

The wireless motility capsule (WMC) is increasingly used to measure gastric emptying in children and adults. The American and European Neurogastroenterology and Motility Societies have recommended consideration of WMC testing in "the assessment of: (a) gastric emptying and regional and whole gut transit time in individuals with suspected gastroparesis, symptoms of upper GI dysmotility, or suspected alterations of GI motility in multiple regions" as well as for other indications [113, 114]. The nondigestible WMC has a distinct emptying pattern. Studies have shown that when given with a solid meal, the WMC empties from the stomach with the return of phase III MMCs after the emptying of the solid-phase meal occurs [115]. Several pediatric studies have used ultrasound to assess gastric emptying in children of different ages including preterm neonates [116, 117]. Ultrasound requires no radiation and the equipment is easily available; however, it requires high skill and is operator dependent. Therefore, different tests can be employed to study the mechanical properties of the stomach including gastric emptying. An in-depth discussion of the different methods used to study gastric emptying is provided elsewhere in this book.

Gastroduodenal motility depends on the prandial state, food composition, presence and type of inflammation, distal intestinal motor function, and both motor and autonomic neural inputs. Gastroduodenal function can be measured with a variety of tools including scintigraphic emptying tests, exhaled breath tests, gastric barostat, antroduodenal manometry (ADM), ultrasound, and electrogastrography (EGG) as well as newer studies including single-photon emission computed tomography (SPECT) and the wireless motility capsule (WMC). Each test measures related, but different, aspects of physiology including compliance, accommodation, contractility, coordination, and propagation. Evaluation by upper gastrointestinal endoscopy and biopsy has a relatively low yield in patients with gastroparesis, but may remain an important part of evaluation for other disorders [118].

A newer technology that assesses pyloric function through pyloric distensibility is EndoFLIP (Crospon Inc., Galway, Ireland). Decreased pyloric distensibility has shown to associate with delayed gastric emptying, symptoms, and quality of life in patients with gastroparesis although pediatric studies are lacking [98–100, 119].

Treatment

Treatment of gastroparesis includes a variety of pharmacologic, interventional, and complementary therapies including prokinetic agents, pyloric therapies, gastric electrical stimulation, acupuncture, and herbal substances. Importantly, symptom resolution correlates very weakly with diagnostic measures of gastric emptying including 4-h scintigraphy [120]. Response to pharmacologic treatment in general has been suboptimal with symptom resolution rates as low as

22% [10]. Male and younger children, post-viral etiology, short symptom duration, response to prokinetics, and absence of mitochondrial disorders are associated with a favorable response [10].

Dietary Modifications

Typically, oral dietary modifications are employed in the management of gastroparesis. Small, frequent meals have been advised with avoidance of high fiber- and fat-containing foods [3]. Liquid nutrients empty faster than solids and thus, may have a role in management. Post-pyloric feeding may be considered in severe refractory gastroparesis [121]. In infants, breast milk has shown to empty faster than formula milk [122]. Extensively hydrolyzed formulas accelerate gastric emptying compared to intact protein and partially hydrolyzed formulas and may be better tolerated in infants with gastric emptying problems [122–124].

Prokinetics

Prokinetic agents effective for gastroparesis include serotonergic agonists, dopaminergic antagonists, and antibiotics. Cisapride [125] and tegaserod [126] are serotonergic agonists that were found to be efficacious in the treatment of gastroparesis, but are currently not available (aside from compassionate use) in many countries across the world due to an increased risk of cardiac side effects. Metoclopramide and domperidone are dopamine antagonists with gastric prokinetic effects. However, the use of metoclopramide has declined in pediatric patients secondary to a U.S. Food and Drug Administration (FDA) warning related to the risk for tardive dyskinesia with prolonged use. It also appears less efficacious in children [127]. Domperidone does not have the same central nervous system risks, but in the USA is available only for compassionate use due to risk of cardiac dysrhythmias.

Prucalopride, a 5-HT4A receptor agonist, initially approved for chronic constipation, has shown to also improve gastric contractions and increase gastric emptying [128–130]. A small single-center, placebo-controlled, double-blind crossover trial showed improved Gastroparesis Cardinal Symptom Index (GCSI), nausea, vomiting, postprandial fullness, bloating, reflux, quality of life, and gastric emptying after four weeks of treatment with prucalopride compared to placebo [131]. Pediatric studies are lacking. Bethanechol, a muscarinic agonist, also stimulates gastric contractions [132]. Erythromycin, a macrolide antibiotic, activates motilin receptors in the stomach and small intestine, increases antral contraction amplitude and frequency, and induces phase III MMCs [133, 134]. However, erythromycin use in children produced the lowest resolution rate of gastroparesis symptoms [10] and tachyphylaxis has been reported, which can decrease its efficacy over time [135]. Azithromycin, a related macrolide antibiotic, may also be useful for treatment of gastroparesis [135]. Amoxicillin/clavulanate is another antibiotic that has been suggested to accelerate gastrointestinal motility; however, it has not been extensively studied for gastroparesis [136]. Other motilin receptor agonists [137], acyl-ghrelin agonists [138], ghrelin receptor agonists like relamorelin, as well as other novel agents [139] are being investigated for treatment of gastroparesis, but are not frequently utilized in clinical care of pediatric patients.

Gastric Accommodation

Another target for treatment is drugs that improve gastric accommodation and relieve symptoms of nausea, vomiting, early satiety, and weight loss. Cyproheptadine, a serotonin and histamine antagonist, may improve gastric accommodation. Retrospective studies have shown benefit in dyspeptic symptoms of nausea, vomiting, retching, and abdominal pain in children [140]. Although widely used in pediatrics, there are no clinical trials for gastroparesis in children. Mirtazapine is a tetracyclic antidepressant, anxiolytic, and a serotonergic antagonist. It exhibits an anti-nausea affect and improves gastric accommodation via 5-HT3 receptor blockade [141, 142]. It has shown to improve nausea, vomiting, retching, and loss of appetite in a small cohort of patients with gastroparesis [143]. Improvements have also been reported in unintentional weight loss, bloating, postprandial fullness, early satiety, and belching in patients with functional dyspepsia [144, 145]. Side effects of drowsiness and weight gain may preclude use [143], especially in teenage females, but it may be a good choice for patients exhibiting concurrent weight loss, insomnia, or anxiety. A recent retrospective study showed benefit in children with the postprandial distress subtype of functional dyspepsia and functional nausea [146].

Aprepitant is a neurokinin receptor antagonist (NK-1) that is often employed in the treatment of chemotherapy-related nausea and vomiting [147]. Neurokinin receptors have been involved in delayed gastric emptying [148]. Aprepitant has shown to increase fasting, postprandial, and accommodation gastric volumes [149]. In adults, it has reduced symptom severity for some symptoms of nausea and vomiting, and overall symptoms in adults with gastroparesis [150]. Although it has shown benefit as a prophylactic and abortive agent for pediatric cyclic vomiting syndrome through retrospective reviews [151], studies in gastroparesis are lacking.

Acotiamide, velusetrag, buspirone, and tandospirone are newer accommodation agents that may play a role in improving symptoms of gastroparesis but there are no pediatric studies [152].

Pyloric Therapies

Endoscopic pyloric botulinum toxin A injection has been used in children with gastroparesis refractory to prokinetic therapy [153] and in children with feeding disorders under 5 years of age [154]. Botulinum toxin was shown to be effective in approximately 2/3 of patients with gastroparesis; however, the effects were limited to several months' duration [153]. Similarly, symptoms improved in 2/3 of children with feeding disorders including delayed gastric emptying and there was a decreased need for post-pyloric feeding in those with enteral tubes [154]. Pyloric balloon dilation has also improved outcomes in gastroparesis in adults, likely by improving pyloric compliance [98, 155], but data in pediatrics are limited to anatomic causes (multiple). In a propensity-matched analysis, Santucci et al. reported a significant benefit with combined intra-pyloric botulinum toxin injection and pyloric balloon dilation in addition to standard care therapy compared with standard care therapy group for children with dyspepsia, especially in those with delayed gastric emptying. They noted a 78% response rate with effects lasting up to 12 months [156]. Botulinum toxin A inhibits the release of acetylcholine into the neuromuscular synaptic cleft, resulting in decreased muscle contractility. Pyloric therapies likely improve symptoms by improving pyloric distensibility and compliance and thus, altering pyloric function [98, 157, 158]. However, animal models have also suggested an analgesic effect of Botulinum toxin by reducing peripheral sensitization and afferent input to the spinal cord and thus, improving central and peripheral neuropathic pain [159].

Pyloromyotomy/Pyloroplasty

Per oral endoscopic pyloromyotomy (POP) or gastric per oral endoscopic pyloromyotomy (G-POEM) has been an upcoming modality to improve pyloric dysfunction. In this procedure, pyloromyotomy is performed endoscopically rather than surgically, where a submucosal tunnel is created to the pyloric ring [160]. It has shown to reduce symptoms, improve quality of life, and decrease health care use for patients with gastroparesis [161]. Surgical pyloroplasty has shown limited benefit in children with gastroparesis [162].

Neuromodulation

Gastric Electric Stimulation

Neuromodulation with the implanted gastric electrical stimulator (GES) has been effective for symptom reduction, especially nausea and vomiting, in a series of pediatric patients with gastroparesis and dyspepsia [163, 164] and is increasingly used for patients nonresponsive to medical therapy. Improvements in nausea, vomiting, early satiety, bloating, fullness, epigastric pain, and quality of life have been described independent of changes in gastric emptying in retrospective studies [165–167]. Some improvements were sustained at long-term follow-up over a year [165]. The mechanism of action of gastric stimulation is not completely understood. Low-frequency, high-energy stimulation is thought to entrain the gastric slow wave, increase slow-wave amplitude, and improve gastric emptying in adults with gastroparesis [168]. High-frequency, low-energy stimulation, such as that used in recent clinical trials [165], is shown to increase slow-wave propagation velocity, enhance the amplitude of postprandial slow waves [169], and lessen sensitivity to gastric distension [170], but does not improve gastric emptying rate [169].

Percutaneous Electrical Nerve Field Stimulation (PENFS)

Percutaneous electrical nerve field stimulation to the outer ear has been shown to improve abdominal pain in children with functional abdominal pain disorders including functional dyspepsia [171]. It is postulated to modulate central pain by decreasing the firing of neurons in the amygdala [172]. In a small study, PENFS showed improved abdominal pain and nausea after a waterload symptom provocation task in children with functional dyspepsia. The amount of water consumed or gastric tolerance after treatment remained unchanged. This suggests its mechanism of improving symptoms through pathways affecting visceral hyperalgesia rather than gastric accommodation [173]. The effects on gastric emptying remain unknown.

Behavioral Therapies

Behavioral therapies have not been vigorously studied in gastroparesis. Modulating the sensory input from the gut to the brain may also improve the motor output and improve symptoms as well as gastric emptying. Hypnosis has shown to improve symptoms and mild to moderate delays in gastric emptying in adults [174].

Complementary and Alternative Therapies

Alternative therapies including acupuncture additionally were found to be effective in select adult gastroparetics [175–177]. A recent systematic review highlighted improvements in dyspeptic symptoms, quality of life, gastric motility and accommodation, as well as central and autonomic functions with manual and electroacupuncture [178]. Transcutaneous electrical acustimulation has demon-

strated an increase in vagal activity, gastric slow waves, and gastric accommodation, and reduced dyspeptic symptoms in healthy individuals after a cold stress nutrient drink [179]. Thus, acupuncture shows promise but large-scale randomized controlled trials (RCTs) and pediatric studies are yet to be performed. Ginger [180, 181] and peppermint oil [182] enhance gastric emptying, but their effect on upper gastrointestinal symptoms remains unclear.

Given the interaction between the stress response, visceral hypersensitivity, and electromechanical dysfunction, treatment of stress and anxiety may have a role in the management of gastroparesis. Interventions effective in children with chronic GI symptoms, but not necessarily gastroparesis, include cognitive behavioral therapy, gut-directed hypnotherapy [4, 183], yoga [184], and biofeedback-assisted relaxation therapy (BART) [185]. An in-depth discussion of diagnostic testing and therapeutic options is provided in other chapters of this book.

Dumping Syndrome

Dumping syndrome is a disorder of postprandial gastrointestinal and vasomotor symptoms related to rapid gastric emptying. Rapid gastric emptying results in delivery of an osmotic load to the small intestine with accompanying fluid shifts, as well as nutrient delivery and subsequent disordered glucose regulation. Dumping syndrome may be idiopathic, iatrogenic, post-infectious, or related to diabetes mellitus. Classically, it was identified after surgical procedures of the upper GI tract including fundoplication in children and gastrojejunostomy, pyloroplasty, and Roux-en-Y bypass in children and adults. It is reported in up to 30% of children undergoing fundoplication [186], 35% of adults with cyclic vomiting syndrome, 13% with diabetes mellitus, and 10% with irritable bowel syndrome [187].

Dumping syndrome symptoms have "early" and "late" patterns. Early dumping begins within 30 min after a meal and may include abdominal pain/cramps, diarrhea, borborygmi, nausea, and bloating, as well as vasomotor symptoms of fatigue, flushing, palpitations, tachycardia, hypotension, lightheadedness, sweating, and syncope. Early dumping is attributable to bowel distension, gastrointestinal hormone secretion, and autonomic dysfunction [188]. Late dumping occurs 1–3 h after a meal and consists of a reactive hypoglycemia and vasomotor symptoms (including sweating, confusion, palpitations, fatigue) rather than predominant GI symptoms. Symptoms may be severe and disabling and can result in malnutrition and avoidance of eating. The two patterns of symptoms can coexist in the same patient. Many of these symptoms, particularly GI symptoms of early dumping, are also present in patients with gastroparesis, and many dumping syndrome patients may be first diagnosed with gastroparesis.

Dumping syndrome can be distinguished from gastroparesis by radionuclide scintigraphy and clinical presentation. Rapid gastric emptying with a standardized meal typically finds <35% gastric retention at 1 h in early dumping syndrome and <20% at 2 h in late dumping syndrome, although variable normative values are used. Clinical presentation remains key to diagnosis, with exclusively postprandial symptoms and the lack of history suggestive of other diseases (including carcinoid syndrome, pancreatic insufficiency, or other causes of hypoglycemic episodes). Sigstad's clinical scoring system can be utilized in adults with graded rating of symptoms [189] to aid in distinguishing from other disorders and to follow symptom course/response to therapy. The oral glucose challenge is a provocative test that can also assist in diagnosis of dumping syndrome. After a 10-h fast, 50 g glucose is ingested. Heart rate (HR) and blood pressure before, during, and 3 h after ingestion are recorded. An increase in HR >10 bpm after 30 min is indicative of dumping syndrome [190]. Associated tests of hematocrit (increase greater than 3% in first 30 min) and serum glucose (hypoglycemia 2–3 h after ingestion) can also be performed. In adults, the oral glucose challenge has sensitivity of 100% and specificity of 94%. All tests listed above are limited by lack of validation in pediatric patients, but continue to serve as useful clinical tools [190].

Treatment of dumping syndrome is typically through dietary modification. To prevent symptoms, the portion size is reduced, and frequent small meals composed of few monosaccharides and high fiber are recommended. Other dietary strategies include increasing viscosity of food with addition of uncooked cornstarch, guar gum, or pectin [191–193]. Continuous enteral feeding can be considered when initial dietary strategies are ineffective. Acarbose is an alpha-glucosidase inhibitor useful for treatment of late dumping syndrome [194]. It competitively inhibits brush-border enzymes, delaying glucose and fructose absorption and preventing significant postprandial hypoglycemia. Acarbose was shown to be effective in adults with T2DM-associated late dumping syndrome [195], as well as children with late dumping who are refractory to dietary management [196, 197]. Potential adverse effects of acarbose include diarrhea and bloating.

Octreotide has been reported to be beneficial in a systematic review of dumping syndrome patients refractory to dietary management [198]. Octreotide slows gastric emptying, inhibits insulin release, decreases enteric peptide secretion, increases intestinal absorption of water and sodium, and prevents hemodynamic changes, thereby alleviating dumping syndrome symptoms. Octreotide is typically given by subcutaneous injection three times daily, although long-acting (depot) octreotide also is effective [199, 200].

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Pediatric Intestinal Pseudo-Obstruction

25

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Introduction

The term pseudo-obstruction literally denotes obstruction in the absence of true mechanical occlusion. Intestinal pseudo-obstruction can be either acute or chronic in nature depending on the duration of obstructive symptoms (chronicity defined as symptoms' duration longer than 6 months) [1, 2]. Chronic intestinal pseudo-obstruction (CIPO) was first described in 1958 by Dudley and colleagues to report a series of 13 patients with symptoms suggestive of intestinal occlusion. These patients underwent exploratory laparotomies, which failed to identify a mechanical cause [3]. The existence of this pathological entity, in both the adult and pediatric population, was later substantiated by a number of other clinicians [4–7]. Research and clinical experience have shown considerable differences between the adult and pediatric population with intestinal pseudo-obstruction and the term pediatric intestinal pseudo-obstruction (PIPO) is now proposed to specifically characterize the condition in children.

Abnormal antegrade propulsive activity of the gastrointestinal (GI) tract, resulting from processes affecting its neurons, muscles, or interstitial cells of Cajal (ICC), is the pathophysiologic mechanism of PIPO [8]. This functional disability of the gut is responsible for a number of clinical symptoms such as abdominal distention, with or without abdominal pain, nausea, vomiting, and a reduced ability to tolerate oral and/or enteral nutrition [9]. Such symptomatology is, however, non-specific and the condition can remain undiagnosed for a long period of time during which patients may undergo multiple diagnostic investigations and often repeated surgical explorations in an effort to identify the underlying cause [9].

Although, by definition, the small intestine is always involved, any part of the GI tract can be affected in CIPO [1, 2] (Fig. 25.1). Esophageal involvement may lead to dysphagia due to impaired peristalsis, in some cases similar to that seen in achalasia [10, 11]. Involvement of the stomach results in poor feed tolerance due to gastroparesis suggested by the presence of delayed gastric emptying, while involvement of the large bowel and anorectum manifest with constipation (delayed colonic transit) and defecation disorders (sphincteric dysfunction), respectively [1].

This chapter will focus on various aspects of PIPO and will attempt to address areas of controversy by exploring the most recent advances in the overall approach and management of this clinical entity.

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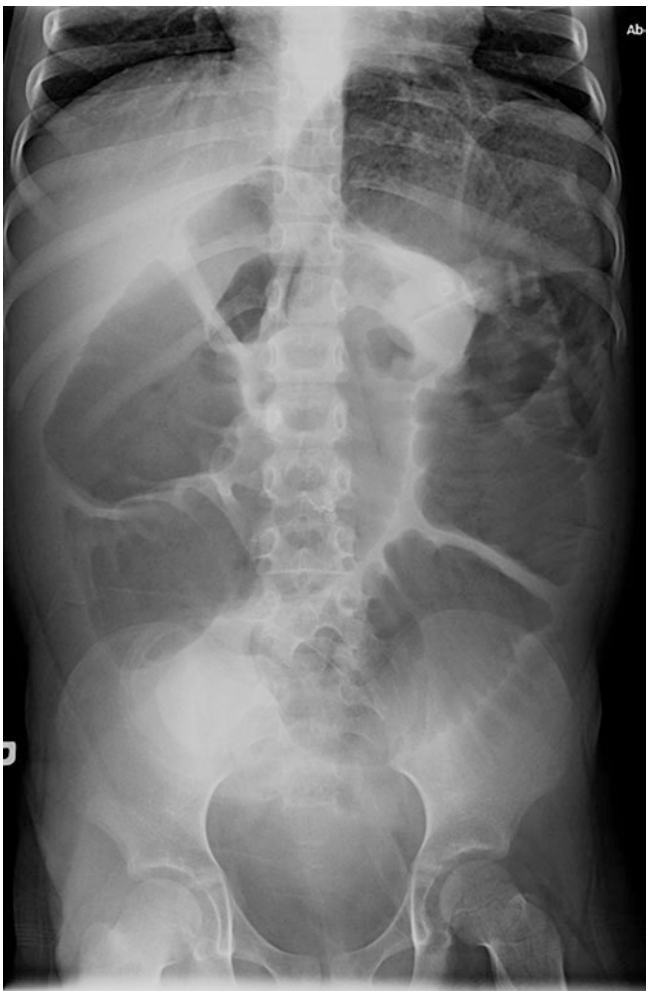

Fig. 25.1 Plain abdominal X-ray in a 7-year-old girl with PIPO. Note the enlarged and hugely dilated small bowel loops

Definition

According to an expert European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)/International expert consensus paper on the disorder [12], CIPO in children has clear distinctions from CIPO in adults with the proposal that it be designated pediatric intestinal pseudo-obstruction (PIPO) rather than CIPO and be defined as follows: "Paediatric intestinal pseudo-obstruction is a disorder characterised by the *chronic inability of the gastrointestinal tract to propel its contents mimicking mechanical obstruction, in the absence of any lesion occluding the gut (*chronic is defined as persistence for 2 months from birth or at least 6 months thereafter)." The working group has suggested that the diagnosis of PIPO requires at least two out of four of the following criteria:

1. Objective measure of small intestinal neuromuscular involvement (abnormal validated transit; manometric and/or histopathology studies).
2. Recurrent and/or persistently dilated loops of small intestine with air–fluid levels.
3. Genetic, metabolic, or other abnormalities definitively associated with intestinal pseudo-obstruction.
4. Inability to maintain adequate nutrition and/or growth on normal oral feeding (therefore needing specialized oral and/or enteral nutrition and/or parenteral nutrition support) [12].

Epidemiology

PIPO is a rare disease; scanty epidemiological data exist regarding its incidence and prevalence in both adult and pediatric populations. A survey-based study estimated that approximately 100 infants are born in the United States every year with PIPO, suggesting an incidence of approximately 1 per 40,000 live births [13, 14]. A more recent nationwide survey for pediatric PIPO performed in Japan revealed that among children younger than 15 years of age, the prevalence of PIPO was 3.7 in one million children, of whom 56.5% developed PIPO in the neonatal period [15]. In another nationwide Japanese survey, 138 cases of PIPO were identified, with an estimated prevalence of 1.0 and 0.8 cases, and incidence of 0.21 and 0.24 cases, per 100,000 males and females, respectively [16]. Although adult studies reveal that the disease is more frequent in females [17–19], a recent epidemiological study in US hospitals focusing on PIPO revealed that the incidence of inpatient admission was 29/100,000 patients, with children of male gender and of Caucasian origin being more likely to be admitted [20]. Without doubt the development of national registries is pivotal in order to precisely define the epidemiological characteristics of this orphan disease.

Classification

The classification of PIPO is still challenging. Conditions resulting in PIPO can be classified by whether they primarily affect intestinal nerves (neuropathy), smooth muscle (myopathy), or interstitial cells of Cajal (ICC) (mesenchymopathy). The above-mentioned conditions can be further subdivided into primary or secondary, congenital or acquired, and diffuse or segmental, depending on the mode of inheritance, presentation, likely etiopathogenesis, or what part of the GI tract is involved. Where classification is not possible, they are defined as idiopathic. In truth, there is a considerable overlap [1, 2].

In primary PIPO the disease is usually localized to gastrointestinal tract, whereas in secondary cases there is a systemic disorder that directly or indirectly affects GI tract motility. Notably, in some cases of primary PIPO extragastrointestinal involvement may also be part of the clinical picture; examples include disorders of the urinary tract (e.g., hollow visceral myopathy and megacystis-microcolon-intestinal hypoperistalsis syndrome), the nervous system (e.g., central, peripheral, or autonomic neuropathies), and/or mitochondria (e.g., mitochondrial neurogastrointestinal encephalomyopathy [MNGIE]) [2, 21, 22]. Approximately 50% of PIPO cases qualify as secondary PIPO, as presented in Table 25.1 (this is particularly true for adult CIPO patients, whereas in pediatrics the disease is predominantly idiopathic or due to primary causes) [23]. Based on histological findings, both primary and secondary PIPOs can be further categorized into neuropathies, myopathies, and mesenchymopathies [24–29]. Although the onset of the disease is used to label whether PIPO is congenital or acquired, in children this area needs further elucidation [2, 8, 30].

Table 25.1 Classification of chronic intestinal pseudo-obstruction

Primary
• Sporadic or familial forms of hollow visceral myopathy/neuropathy (e.g., megacystis-microcolon-intestinal hypoperistalsis syndrome) [7, 31–47]
• Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) [22, 48–50]
• Hirschsprung disease [51–53]
• Neuropathy associated with multiple endocrine neoplasia type IIB [54–56]
• Malrotation or gastroschisis [57–59]
• Neuropathy post neonatal necrotizing enterocolitis [60]
Secondary
• Conditions affecting GI smooth muscle
– Rheumatological conditions (dermatomyositis/polymyositis, scleroderma, systematic lupus erythematosus, Ehlers–Danlos syndrome) [61–73]
– Other (Duchenne's muscular dystrophy, myotonic dystrophy, amyloidosis, ceroidosis or alternatively reported as brown bowel syndrome) [74–84]
• Pathologies affecting the enteric nervous system (familial dysautonomia, primary dysfunction of the autonomic nervous system, autoimmune GI dysmotility neurofibromatosis, diabetic neuropathy, fetal alcohol syndrome, post-viral related PIPO, e.g., CMV, EBV, Varicella Zoster Virus (VZV), John Cunningham Virus (JC virus), Human Herpes Virus (HHV)-6, COVID-19) [85–104]
• Endocrinological disorders (hypothyroidism, diabetes, hypoparathyroidism, pheochromocytoma) [105–109]
• Metabolic conditions (uremia, porphyria, electrolyte imbalances, e.g., potassium, magnesium, calcium) [110–115]
• Other (celiac disease; eosinophilic gastroenteritis; Crohn's disease; radiation injury; Chagas disease; Kawasaki disease; angioedema; mitochondrial disorders; drugs, e.g., opiates, anthraquinone laxatives, calcium channel blockers, antidepressants; antineoplastic agents, e.g., vinca alkaloids; paraneoplastic, e.g., neuroblastoma; major trauma/surgery; chromosome abnormalities; Creutzfeldt-Jakob disease; Schaaf-Yang syndrome; Treacher Collins syndrome) [116–149]
Idiopathic

Etiology and Pathophysiology

The integrity of gastrointestinal sensorimotor function relies on a precise coordination between the autonomic nervous system, enteric nervous system (ENS), ICC, and smooth muscle cells. Any noxious stimulus, as depicted in Table 25.1, which affects the GI neuromusculature may lead to impaired peristalsis and the stasis of luminal contents [1]. Neurologic and metabolic disorders may affect the extrinsic GI neurons, whereas neurotropic viruses could evoke an inflammatory process insulting both the ENS and extrinsic nerve pathways [23, 98]; furthermore, evidence of enteric angiopathy and neuromuscular hypoxia has been identified in patients with mitochondrial neurogastrointestinal encephalomyopathy [150]. Paraneoplastic syndromes could also target the ENS by initiating an inflammatory process that affects the ganglia of the submucosal and myenteric plexuses, via a cellular infiltrate and production of circulating antineuronal antibodies [23, 151]. Some pathologies (e.g., muscular dystrophy) target the enteric smooth muscle fibers whereas entities such as dermatomyositis, scleroderma, Ehlers–Danlos syndrome, and radiation enteritis lead to a mixed neuromyopathic disorder [14, 152, 153]. Celiac disease, hypothyroidism, hypoparathyroidism, and pheochromocytoma could also lead to PIPO by affecting the GI neuromusculature; however, the exact mechanism is not fully defined.

Genetics

Elucidation of the genetic basis of PIPO has been somewhat disappointing but has recently improved because of the availability of genome sequencing.

Familial cases of PIPO have been historically recognized with several patterns of inheritance, reflective of the great heterogeneity of PIPO conditions. Both autosomal dominant and recessive modes of inheritance have been described for neuropathic and myopathic types of PIPO [5, 17, 18, 152, 154]. Mutations in filamin A [155], actin γ-2 [45], thymidine phosphorylase (TYMP) [156], polymerase γ (POLG1) [157], and, finally, RAD21 [158] and SGOL1 genes [159] have also been identified in recessive forms of PIPO with an associated syndromic phenotype. More recently, with the advancement in genetic testing, novel mutations (MYLK, LMOD1,

MYL9, SGOL1, MYH11, PDCL3, and ACTG2 variants) have been identified and subsequently related to the etiopathogenesis of chronic intestinal pseudo-obstruction [160–170]. Of these, the smooth muscle actin γ-2 gene (*ACTG2*) is one of the most commonly implicated genes in Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) and prenatal and neonatal myopathic PIPO.

Three patients with a syndromic phenotype of PIPO combined with Waardenburg–Shah features (pigmentary abnormalities and sensorineural deafness) and an underlying "apparently normal" enteric innervation have been demonstrated to carry de novo heterozygous mutations of SOX10 [171, 172].

Specific genetic mutations are associated to complications. Medullary thyroid carcinoma associated with MEN2b and neurogangliomatosis should be searched for by measuring serum calcitonin levels, and early prophylactic thyroidectomy may be considered [173]. In cases with cardiac involvement (SGOL1), a pacemaker is indicated since severe bradycardia may occur [159]. Of note, a recently described cohesinopathy with SGOL1 mutation in four children represents a late-onset but severe PIPO etiology associated with severe bradycardia for which three of the four patients required a pacemaker because of sinus dysfunction at the time of PIPO diagnosis [174]. Filamin A gene on chromosome X as well as thymidine phosphorylase mutations are both associated to seizures and impaired neurological development [155].

Histopathology (See Chap. 19)

The role of histopathology in the confirmation of PIPO is still controversial. Studies in adults reveal that GI histology can be normal in up to 10% of cases, although in the experience of the authors this figure is likely to be higher in children. Adequate full-thickness bowel biopsy (preferably a circumferential sleeve of at least 1–2 cm) is recommended whenever surgery is being considered [8, 30, 175]. Recent initiatives support a more standardized histological approach for the diagnosis in GI dysmotilities such as PIPO [29, 176, 177].

On the basis of histology, PIPO is classified into neuropathy, myopathy, or mesenchymopathy; mixed forms (e.g., neuromyopathy) are also recognized [29, 178–180].

Neuropathies and myopathies can be further subdivided into inflammatory and degenerative. Inflammatory neuropathies are characterized by an infiltration of T-lymphocytes and plasma cells in the myenteric plexuses (myenteric ganglionitis) and neuronal axons (axonopathy); five or more lymphocytes per ganglion are required for the diagnosis of myenteric ganglionitis [29, 181]. Interestingly, patients with lymphocytic infiltration of the myenteric plexus may also develop increased titers of antinuclear antibodies (ANNA-1/anti-Hu, anti-VGKC); the latter could result in neuronal degeneration and loss via apoptotic and autophagic mechanisms [182–185]. Infiltration of the myenteric ganglia with other cells such as eosinophils and mast cells has also been identified but their clinicopathological significance is yet to be determined [186–189].

Degenerative neuropathies are defined by a decrease in the number of intramural neurons along with changes in nerve cell bodies and axons [176, 181, 190–192]. It has been postulated that aberrant calcium signaling, mitochondrial disorders, production of free radicals, and abnormalities in the function of glial cells initiate apoptotic mechanisms that are involved in the degenerative process [176, 178, 193, 194].

Myopathies are also categorized as inflammatory and degenerative. Inflammatory myopathy, also termed leiomyositis, is characterized by infiltration of T-lymphocytes into both the circular and longitudinal enteric muscle layers and if not treated appropriately with immunosuppressive agents may lead to a severe clinical picture of PIPO [47, 195]. A distinctive presumably acquired degenerative myopathy of unknown etiology, called African degenerative leiomyopathy (ADL), has been described in African populations in southern Africa [196]. The Ret gene implicated in Hirschsprung disease appears to confer susceptibility to ADL although the exact mechanism is not known [197].

Histopathology in degenerative myopathies reveals vacuolization and fibrosis of the smooth muscle fibers [198, 199]. In the cases where the longitudinal muscle is more affected compared to the circular muscle layer, diverticula may be identified [200, 201].

Novel techniques in immunohistochemistry, for example, smooth muscle markers such as smoothelin, smooth muscle myosin heavy chain, and histone deacetylase 8, may reveal subtle histopathologic abnormalities otherwise not detectable with conventional methods [202].

Mesenchymopathies are defined by ICC abnormalities (decreased density of ICC network, intracellular abnormalities) and have been identified in PIPO patients [176, 203]. Despite the fact that adequate data exist regarding the role of ICC in the pathogenesis of diabetic gastroparesis, further research is required to elucidate their involvement in the pathogenesis of other GI dysmotilities [29].

Clinical Picture

Signs and Symptoms

The symptomatology varies according to the age at diagnosis and the part of the GI tract, which is primarily affected. Intestinal malrotation is present in approximately one-third of children with congenital PIPO (myopathic and neuropathic) [26]. Cardinal signs and symptoms of PIPO include those of obstruction namely abdominal distention (88%), vomiting (69%, which can be bilious), and constipation

Table 25.2 Clinical symptoms in children with chronic intestinal pseudo-obstruction

Study	Abdominal distension	Vomiting	Constipation	Failure to thrive	Abdominal pain	Diarrhea	Dysphagia
Faure et al. [204]: $n = 105$	100	94	70	64	46	29	9
Vargas et al. [13]: $n = 87$	73	50	51	23	NA	21	2
Granata et al. [205]: $n = 59$	59	31	27	NA	NA	26	NA
Schuffler et al. [32, 226]: $n = 30$	23	19	20	15	NA	16	NA
Heneyke et al. [25]: $n = 44$	31	40	31	NA	NA	NA	NA
Muto et al. [15]: $n = 62$	55	33	9	NA	3	2	NA
Ko et al. [227]: $n = 66$	49	29	19	NA	4	4	NA
Diamanti et al. [228]: $n = 49$	NA	41	16	NA	5	14	NA
Total[a]: $n = 502$	341	337	243	102	58	112	11

NA not available

[a] Calculations do not include total percentages due to missing/not reported data indicated as NA

(54%). Abdominal pain, failure to thrive, and diarrhea may also be part of the clinical picture (Table 25.2) [8, 9, 175].

The diagnosis of PIPO is difficult due to the variable clinical presentation and the lack of a specific diagnostic test. The diagnosis should be suspected in children presenting with signs and symptoms of intestinal obstruction without an occluding lesion. The diagnosis of PIPO should be also considered when there is persistent vomiting after a Ladd's procedure for malrotation [58], when intestinal obstruction is associated with bladder dysmotility, or when, in a full-term neonate, there is persistent or recurrent obstruction after exclusion of Hirschsprung disease and hypothyroidism. The differential diagnosis should be carefully considered because establishing a diagnosis of PIPO may be invasive, and the psychological consequences in children and their families are significant.

Dehydration (which can be severe) and malnutrition are often underdiagnosed especially given that weight can be an unreliable measure due to pooling of significant volumes of fluid (third spacing) within distended gut loops. Delayed transit of gut content can also lead to small bowel bacterial overgrowth, which can further exacerbate symptoms of diarrhea and abdominal distention [175].

Extra-intestinal signs and symptoms may as well be part of the PIPO clinical presentation, for example, recurrent urinary tract infections or neurologic abnormalities [21, 156]. Furthermore, patients may complain of symptoms indicative of an underlying disorder that accounts for secondary PIPO (e.g., proximal muscle weakness in dermatomyositis) [62].

The clinical course of PIPO is characterized by exacerbations and remissions; the former can be precipitated by various factors such as surgery, general anesthesia, infections, and emotional stress [30]. In the most severe cases, the natural course of the disease leads to significant deterioration of the intestinal function and ultimately to intestinal failure [9, 175].

Prenatal Symptoms

Although the majority of PIPO cases present in the neonatal period or early infancy, in a few cases the diagnosis is supported in utero by ultrasonographic findings of polyhydramnios, abdominal distention, and megacystis [8, 30]. Prenatal signs can be detected in about 20% of cases [25, 204]. Megacystis is the most frequently reported sign, whereas dilated bowel at this age is quite rare. This has been noted in megacystis-microcolon-intestinal hypoperistalsis syndrome in which an antenatally enlarged bladder is seen by ultrasound in 88% of cases, hydronephrosis in 53%, increased volume of amniotic fluid in 34%, and gastric distension in only 10% [205]. Although some reports have described the detection of these signs by ultrasound as early as 16 weeks, more often the abnormalities are noted much later in gestation [206]. Antenatally diagnosed non-obstructive megacystis, with neonatal urological symptoms, may precede GI symptoms of pseudo-obstruction by several months.

Clinical Presentation After Birth

Fifty percent to two-thirds of patients present within the first month of life and 80% by 1 year of age. The remainder are detected sporadically throughout the first two decades of life [13, 24, 25, 204]. The clinical presentation is dependent on the age at onset.

Neonatal-Onset Form

In the neonatal form, PIPO presents as severe abdominal distension with bilious vomiting. Although not a universal finding, the abdominal X-ray may show dilated bowel loops with air–fluid levels suggestive of an organic intestinal obstruction. In megacystis-intestinal-hypoperistalsis syndrome, an obstructed urinary system leading to an abdominal distension may be the presenting feature (Fig. 25.2), with symptoms of intestinal obstruction appearing within days to 12 months later. In order to avoid unnecessary surgery, an exploratory laparotomy should be deferred in a neonate with antenatal diagnosis of megacystis. In these neonatal cases, the air–fluid levels on X-ray may be missing. Some affected

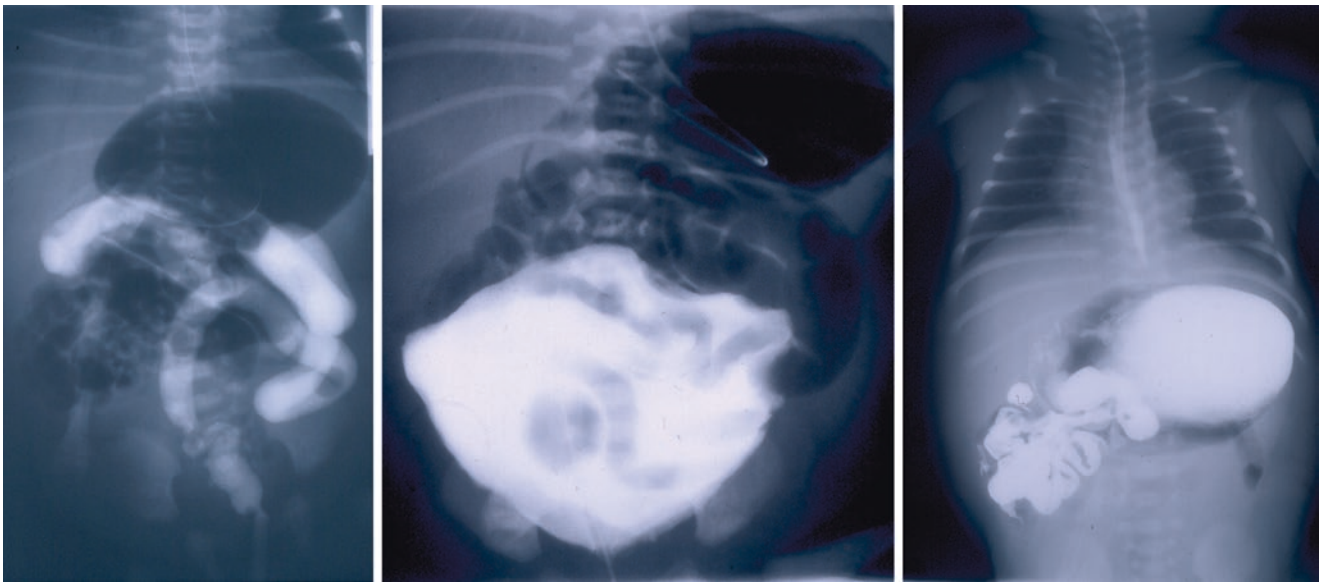

Fig. 25.2 Girl neonate with megacystis-microcolon-hypoperistalsis syndrome. Left: Colonic opacification showing small non-functional microcolon. Middle: Cystography demonstrating enlarged bladder with "footprints" of digestive loops. Right: Small bowel follow-through showing malrotation and non-functional small bowel. In neonates, despite the small bowel involvement precluding any enteral feeding, the small bowel loops may not be enlarged converse to older children in whom dilated small bowel is always present

infants may present with abdominal distension and diarrhea secondary to bacterial overgrowth.

PIPO may be mimicked by immaturity of intestinal motility in preterm infants, and thus this diagnosis should be made with caution in this group as the migrating motor complex does not appear in its mature form until a gestational age of 34–35 weeks [207, 208].

Infantile or Late-Onset Form

Major Forms

The symptoms depend on the regions of the gastrointestinal tract primarily involved. Patients present with subacute and/or recurrent episodes of gastric, intestinal, and/or colonic obstruction, necessitating frequent drainage and fluid replacement. This picture may be acute or insidious and chronic and persistent or more often intermittent. Exacerbations may be precipitated by a variety of causes including intercurrent infections, fever, vaccines, general anesthesia, and emotional stress. Diarrhea due to bacterial overgrowth is frequent and may alternate with constipation or episodes of partial obstruction. Stasis of intestinal contents is common in PIPO, and chronic dilatation leads to decompensation and elongation of the bowel, further impairing motility. When fluid and air accumulate in these decompensated loops, torsion caused by mechanical forces is possible. Dehydration (which can be severe) and malnutrition are often underdiagnosed, especially given that weight can be an unreliable measure due to pooling of significant volumes of fluid (third spacing) within distended gut loops [147]. Mechanical obstruction is normally absent in PIPO patients, but it can, however, be a complication of PIPO, especially after multiple interventions. Volvulus of the splenic flexure and colonic volvulus have been reported in numerous PIPO cases due to torsion of fluid-filled bowel loops [209–211].

Abdominal pain is often severe enough to lead to feeding difficulties resulting in malnutrition. Although esophageal involvement is frequently detected by manonetry, dysphagia is rarely reported [212]. Recurrent episodes of functional partial bowel obstruction may be very difficult to differentiate from true mechanical obstruction in the child who has undergone a prior laparotomy and who may have adhesions. A change in symptoms such as the new occurrence of abdominal pain may suggest the latter.

Urinary tract involvement occurs in 33–92% of cases, independent of the type of PIPO [204, 213–215]. Megacystis with a hypocontractile detrusor, and increased bladder capacity and compliance, is the most frequent pattern of urological abnormality (bladder adynamia). Ureterohydronephrosis is seen in 56–68% of cases but vesico-ureteral reflux occurs in less than 10% [215]. Urinary tract infections are frequent but may be asymptomatic. The renal prognosis is generally good, provided that careful, active evaluation and management of the poorly dynamic bladder are performed, to ensure adequate bladder emptying and to prevent urinary tract infection [215]. Where they are taken bladder biopsies show non-specific fibrotic changes in both neuropathic and myopathic forms of PIPO and are thus not useful for subtype classification.

Comorbidities

Malrotation is frequent, especially in neonates (up to 40% of cases) [24, 25, 204], and has been reported in an X-linked familial syndrome associating PIPO, malrotation, and pyloric non-hypertrophic stenosis (Fig. 25.3) [155, 216–218].

The physical examination should encompass a thorough neuromuscular assessment, including testing for pupillary reactions to light and accommodation and external ocular movements to help identify conditions associated with autonomic neuropathy or mitochondrial diseases. Testing for orthostatic stability should be performed in children, especially where postural dizziness, visual disturbances, and sweating abnormalities may suggest the presence of an underlying autonomic neuropathy [44].

External ophthalmoplegia associated with deafness may suggest a mitochondrial defect namely mitochondrial neurogastrointestinal encephalopathy (MNGIE). The onset of symptoms (gastrointestinal or ocular or both) generally occurs during adolescence, although very early-onset disease has been reported (5 months of age) [219]. Peripheral neuropathy and diffuse muscle weakness are the predominant manifestations, although almost all patients have indices of leukoencephalopathy on magnetic resonance imaging (MRI) of the brain [50]. Thymidine phosphorylase activity and plasma thymidine should be measured when suspecting such a diagnosis [220]. Audiological assessment is important to rule out deafness, seen in patients with a *SOX10* gene mutation [171, 172]. The dermatological examination should note signs of connective tissue disease (i.e., scleroderma, dermatomyositis, lupus), including: Raynaud's phenomenon, skin eruption, palmar erythema, telangiectasia, nodules, and scleroderma of the hands, feet, face, and forearms. Digestive symptoms may precede the skin involvement in these disorders [221].

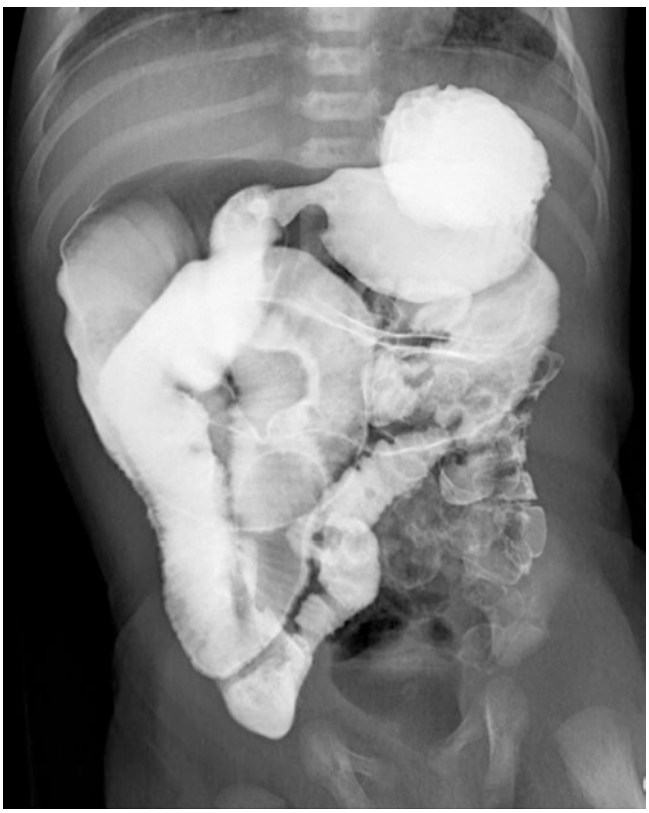

Fig. 25.3 Small bowel follow-through in a 6-month-old boy with an X-linked filamin-A mutation-related PIPO. Note the malrotation, narrowed pylorus, and enlarged bowel loops

Neural crest-derived tumors (neuroblastoma) and pheochromocytoma should be suspected and ruled out in children and infants with Chronic Intestinal Pseudo-obstruction (CIP): appropriate computed tomography (CT) imaging and ultrasound studies should be considered to exclude the presence of thoracic or abdominal tumors [222, 223].

Cardiac rhythm and function must be evaluated by electrocardiography (ECG) and echocardiography, since dysfunction of cardiac sinus node may be associated to PIPO [224] and abnormal cardiac contraction should lead one to suspect muscular diseases such as desmin myopathies [225].

Patients with suspected autoimmune GI dysmotility can present with acute or subacute (<8 weeks) onset of GI symptoms, family history of autoimmune diseases, an infectious episode preceding the onset, and extra-intestinal neurological symptoms like dysautonomia [103, 104].

Diagnosis

Chronic intestinal pseudo-obstruction should be suspected in children with early onset, chronic, recurrent, or continuous signs of intestinal obstruction especially where imaging or indeed surgery fails to reveal a mechanical obstruction of the gut (e.g., repeated "normal" exploratory laparotomies). Since the symptoms of PIPO are not specific, a careful differential diagnosis is of paramount importance.

The diagnosis of PIPO should be guided by a structured algorithm, and the ESPGHAN criteria previously described should be applied [12]. A detailed history combined with a meticulous clinical examination and laboratory tests (e.g., serum electrolytes, thyroid stimulating hormone [TSH], lactic acid, specific autoantibodies) may suggest the presence of PIPO and potentially elucidate its cause; however, the establishment of a definitive diagnosis should rely on the use of targeted investigations to: (1) exclude mechanical occlusion of the gut lumen; (2) confirm GI dysmotility, and (3) rule out treatable causes.

The diagnostic tests, which exclude luminal obstruction and confirm the presence of impaired GI motility in children, thus ruling in the diagnosis of PIPO, are discussed below.

Imaging

Since small bowel is always involved, plain abdominal radiographs demonstrate a dilated GI tract with air–fluid levels while contrast GI series can demonstrate anatomical abnormalities (e.g., malrotation, microcolon) and also exclude the presence of gut occlusive lesions [2, 175, 229]. It needs to be kept in mind that a water-soluble substance should be used instead of barium in order to prevent flocculation and inspissation of the contrast material (Figs. 25.1, 25.2, and 25.3).

Novel imaging modalities such as multidetector row helical CT and cine-MRI have been recently performed with promising results in adult series but there are currently limited data regarding their applicability and usefulness in pediatrics [230–235].

Endoscopy

Endoscopy may identify upper or lower bowel mechanical occlusion previously missed on radiology, and allows for duodenal biopsies to exclude mucosal inflammation [224]. Novel techniques (e.g., natural orifice transluminal endoscopic surgery—NOTES) may revolutionize the role of endoscopy in the diagnosis of gut motility disorders by providing the ability of full-thickness biopsy sampling in a safe and minimally invasive way [236, 237].

Motility Investigations

These studies are performed in order to assess the GI motility and to define the underlying pathophysiologic process; in pediatrics, they form the hallmark of diagnosis. The aforementioned studies include gastrointestinal manometries (esophageal, antroduodenal, colonic, anorectal; see Chaps. 10–13), scintigraphy (e.g., gastric emptying, colonic transit; see Chap. 16), electrogastrography, and radio-opaque marker studies (see Chap. 17). The usefulness of novel technologies, such as SmartPill, remains to be determined [8, 238–240].

Although in children with PIPO the involvement of GI tract may be generalized, the small intestine is always affected; thus antroduodenal manometry remains the most discerning test. It needs to be stressed though, that the optimal placement of the manometric catheter is of pivotal significance for a *lege artis* execution and precise interpretation of the this test [241]. Neuropathic cases manifest with uncoordinated contractions, which are of normal amplitude, whereas in myopathic PIPO motor patterns have normal coordination; however, the amplitude of intestinal contractions is low [212, 242, 243]. Of note, a newly proposed enhanced Antroduodenal Manometry (ADM) analysis and associated score Great Ormond Street London Antroduodenal Manometry Scoring System (GLASS score) has proven useful in order to discriminate between PIPO and non-PIPO patients and also between distinct histopathological pathologies [244]. Additionally, manometry may facilitate the dynamic assessment of potential pharmacotherapeutic options and feeding strategies (e.g., feasibility of oral or enteral feeds) as well as indicate disease prognosis [245–247]. Antroduodenal manometry features suggestive of PIPO are depicted in Table 25.3 and also described in Chap. 11.

Table 25.3 Features in antroduodenal manometry associated with PIPO

Interdigestive or fasting period
Absence of phase III
Short intervals between phase III
Abnormal phase III
Stationary
Retrograde
Non-migrating burst of contractions[a]
Sustained simultaneous cluster of contractions[b]
Low-amplitude contractions
Postprandial or fed period
Failure to switch to postprandial period
Postprandial hypomotility
Low frequency of contractions
Low amplitude of contractions
Non-migrating cluster of contractions

[a]A burst of contractions is defined as sequences of intense irregular pressure waves not satisfying the definition for phase III of MMC
[b]A cluster of contractions is defined as the presence of 3–10 pressure waves of slow frequency showing higher amplitude and duration than isolated individual contractions

In the most challenging cases, exploratory surgery (laparotomy or laparoscopic-assisted procedures) may be required to definitively exclude mechanical obstruction; however, it should be borne in mind that surgery may precipitate a pseudo-obstructive episode and may also lead to intra-abdominal adhesion formation, which in turn can further complicate future diagnostic or therapeutic procedures as well as lead to secondary mechanical obstruction. Where possible, investigations and then diagnostic/therapeutic surgery should be performed in timeline sequence and in referral centers with relevant expertise in the management of PIPO patients.

Histopathology along with both genetics and antroduodenal manometry can also be very useful in establishing or confirming the diagnosis of PIPO, highlighting the underlying pathophysiologic process and thus aiding the overall management.

Figure 25.4 summarizes the basic steps in the diagnostic evaluation of pediatric patients with suspected PIPO.

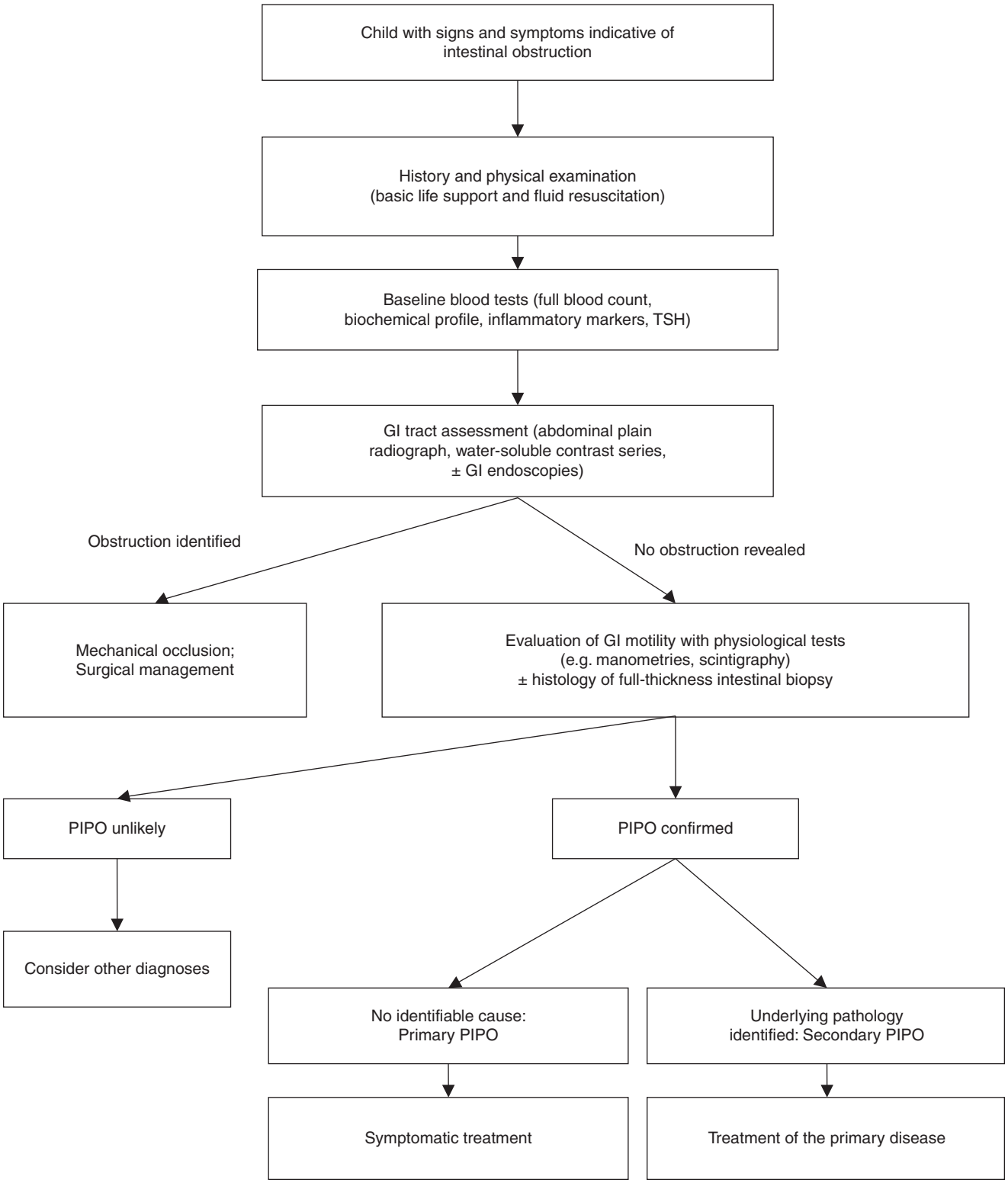

Fig. 25.4 Suggested diagnostic algorithm for pediatric intestinal pseudo-obstruction. (Modified from Rudolph CD, Hyman PE, Altschuler SM, Christensen J, Colletti RB, Cucchiara S, et al. Diagnosis and treatment of chronic intestinal pseudo-obstruction in children: report of consensus workshop. J Pediatr Gastroenterol Nutr. 1997;24(1):102–12; Thapar N, Saliakellis E, Benninga MA, Borrelli O, Curry J, Faure C, et al. Paediatric Intestinal Pseudo-obstruction: Evidence and Consensus-based Recommendations From an ESPGHAN-Led Expert Group. J Pediatr Gastroenterol Nutr. 2018 Jun;66(6):991–1019, with permission [2, 12])

Differential Diagnosis

PIPO has to be differentiated from mechanical obstruction of the GI tract; the latter is usually characterized by marked abdominal pain (in keeping with the abdominal distention), specific radiologic signs, and manometric patterns [248–250]. Acute functional obstruction (e.g., postoperative ileus), functional GI disorders (e.g., rumination syndrome), and pediatric condition falsification should be considered and appropriately investigated and managed [175, 251, 252]. Table 25.4 provides differential diagnoses of PIPO.

Table 25.4 Differential diagnosis of PIPO in children

Aerophagia
Gastroparesis
Constipation
Rumination syndrome
Cyclic vomiting syndrome
Severe irritable bowel syndrome
Hirschsprung disease
Bacterial overgrowth of various origin (lactase deficiency, disaccharidase deficiency, intestinal duplication)
Aerodigestive fistula
Fabricated induced illness (pediatric condition falsification)

Treatment

The therapeutic approach in PIPO is threefold as it aims to: (1) preserve growth and development by maintaining adequate nutritional intake; (2) preserve and even promote GI motility with combined medical and surgical interventions; and (3) treat disease-related complications or underlying pathologies in the cases of secondary PIPO.

In spite of the limited effect of the currently applied therapeutic options, refinements and evolution in nutritional, medical, and surgical strategies have considerably improved the overall PIPO management [153, 253]. Acute episodes of pseudo-obstruction are generally treated conservatively by intravenous fluid administration (patients remain nil by mouth) and decompression of the affected bowel with drainage of luminal contents via Nasogastric (NG) tube or preformed ostomies. Careful attention to fluid and electrolytes' balance is imperative.

Nutrition

The role of nutrition in PIPO is of paramount significance as it is well established that gut motility improves with optimal nutritional support and declines in the face of under- or malnutrition [8]. In the long term, approximately one-third of pediatric PIPO patients require either partial or total parenteral nutrition, another third requires a degree of intragastric or enteral feeding, whereas the remaining children are able to tolerate sufficient oral nutrition [8]. Within all of the above-mentioned groups, patients able to tolerate feeds may require some dietary modification in order to maintain enteral nutrition and avoid bezoar formation (e.g., low-residue feeds, bite and dissolvable food, restriction diets, hydrolyzed formula).

Although parenteral nutrition is life-saving, it is associated with significant risk of complications, such as central line infections and liver disease; thus, maintaining patients on maximally tolerated enteral nutrition is always strongly encouraged [30]. In the more severe PIPO cases, continuous rather than bolus feeds administered via a gastrostomy or jejunostomy may be better tolerated; the latter is particularly true in those children with impaired gastric motor function [254–256].

Medications

Pharmacotherapy in PIPO patients is mainly confined to the control of intestinal inflammation, suppression of bacterial overgrowth, and promotion of GI motility [246, 256]. In cases of suspected autoimmune GI dysmotility or proven inflammatory process confirmed on full-thickness intestinal biopsies, urgent immunosuppressive therapy with high doses of intravenous steroids, intravenous immunoglobulins, or apheresis should be considered, especially if antineuronal antibodies are detected [103, 104].

Prokinetics (e.g., metoclopramide, domperidone, erythromycin, azithromycin, octreotide, neostigmine, pyridostigmine, prucalopride) and antiemetics (e.g., promethazine, ondansetron) have been used to reduce the severity of nausea and vomiting and improve GI motor function along with enteral feed tolerance [257–263]. The use of some of these agents is limited because of their variable efficacy and unacceptable extra-intestinal side-effects (e.g., metoclopramide, neostigmine). The best studied and tested prokinetics, that is, cisapride and tegaserod, have been withdrawn from the market due to safety concerns [264]. Recent data suggest that antibiotics such as co-amoxiclav may have prokinetic effects and induce an increased number of migrating motor complexes during the fasting phase of antroduodenal manometry. The need for novel prokinetics with increased safety profile and efficacy has resulted in the development of new products (e.g., prucalopride, aprepitant, ghrelin), but there are limited data regarding their use in pediatric PIPO, further impacted on by restricted availability and licensing [265–267]. Undoubtedly, current medical regimens for PIPO are based on limited literature and/or expert opinion (e.g., combined use of octreotide and erythromycin) and are yet to be tested in future in the context of controlled trials [246, 268].

A small pilot study has recently demonstrated the safety of using fecal microbiota transplantation (FMT) in adults with CIPO, with improvement in symptoms, tolerance of oral feeding, and with no severe adverse events [269]. The utility of FMT in PIPO has not been determined.

Surgery

Surgery remains a valuable intervention on patients with PIPO as it has a multidimensional role in both the diagnostic (e.g., full-thickness biopsies) and therapeutic processes (e.g., insertion of feeding tubes, formation of decompressing ostomies such as gastrostomy, ileostomy) [256, 270, 271].

Indeed, adequate bowel decompression (e.g., gastrostomy, gastrojejunostomy, ileostomy) is crucial not only in providing symptomatic relief by reducing the frequency and the severity of pseudo-obstructive episodes but also in limiting further deterioration of the intestinal motor activity secondary to chronic distention, and in enhancing the tolerance of enteral feeding [24, 25, 256, 270, 272–275]. Long decompression enteral tubes and extensive bowel resections are approaches mainly reported in adult CIPO cohorts but remain untested in terms of practicality, efficacy, and safety in pediatrics [276–278]. Moreover, small bowel resections may lead to short gut syndrome and intestinal failure-associated liver disease [270, 279]. One additional concern is that resections of small intestine may decrease the abdominal domain required for the successful outcome of a potentially necessary future intestinal transplantation [270, 279].

Enterostomy-associated complications (e.g., ostomy prolapse) [280, 281], recurrent pancreatitis [282], diversion colitis [283], excessive fluid losses with high ileostomy output [284], and hemodynamic collapse due to cardiac dysfunction and abdominal compartment syndrome [285] have been reported in patients with chronic intestinal pseudo-obstruction. In patients with gastric and upper digestive tract involvement, gastric perforation and gastric bezoars may occur [204].

Closure of the decompressive ileostomy and restoration of the gut continuity may be attempted in carefully selected patients who have demonstrated significant and clear improvement post ileostomy formation, and have managed to wean parenteral nutrition and remain on full enteral and/or oral feeds without experiencing any troublesome symptoms for a period of at least 2 years. In the opinion of the authors, this is most likely to occur in neuropathic cases of PIPO and least in myopathies. In patients who show recovery with an ileostomy in situ, an ileo-rectal Duhamel pull-through has proven to be the most effective approach [25, 204, 278, 286].

Incidences of the enterostomy-associated complications are not insignificant in PIPO patients as these patients do have an increased rate of stomal prolapse along with a high risk of intestinal necrosis [280, 281]. A meticulously constructed ileostomy combined with careful management of the ostomy, reduces the probability of stomal prolapse thus minimizing the risk of additional intestinal resection [25, 280].

Novel surgical methods involve implantation of devices providing electrical pacing of the GI neuromusculature, but data on children are scanty and limited [287]. Significant progress has been made in regenerative medicine (see Chap. 49), especially with neural cell replacement within the bowel [288, 289]. This has not yet reached clinical trials and is hampered by poor disease characterization [290].

Small bowel transplantation still remains today the only definitive cure for PIPO. The outcomes and survival rates in experienced centers have significantly improved (up to 50% survival rate at 3 years) during the last decade owing to advances in both the surgical approach (e.g., multivisceral transplantation) and the immunosuppressive treatment [291–299] (see Chap. 51).

Natural History, Outcome, and Prognosis

Both pediatric and adult PIPO patients have a severe clinical course, characterized by repetitive relapses and remissions. Regrettably, the low index of suspicion among physicians along with the lack of well-defined diagnostic criteria and readily available facilities in performing specialized diagnostic tests (e.g., manometry), often account for repetitive unnecessary investigations and surgery as well as delayed diagnosis and thus initiation of appropriate management.

The majority of the patients complain of symptoms, which progressively worsen and impact upon the tolerance of enteral nutrition consequently increasing reliance on total parenteral nutrition [227, 228]. The latter in conjunction with disease-related adverse events (e.g., central line infections, impairment of the liver function, immunosuppression after small bowel transplantation, surgical procedures) account for high morbidity, poor quality of life, and mortality rates up to 30% [13, 25, 32, 204, 205, 226, 300–302].

Despite recent diagnostic and therapeutic advances PIPO in children remains a serious, life-threatening disease with significant impact on the well-being not only of patients themselves but also of their families [301].

Outcomes

In secondary and acquired forms of PIPO, outcome is dependent on the underlying disease responsible for the dysmotility. In cases of destruction of enteric innervation or musculature (autoimmune GI dysmotility), deterioration may occur rapidly without specific treatment [103, 104, 303].

Most often viral infection resolve spontaneously [304] but some chronic cases have been reported [305, 306].

In primary forms of PIPO, the prognosis is poor. In one series of 105 patients, two-thirds required parenteral nutrition and 41% could not be enterally fed. More than half of the patients were Total Parenteral Nutrition (TPN)-dependent for periods ranging from 2 months up to 16 years. Eleven patients (10%) received TPN for more than 10 years. Twenty-four of the 58 patients who underwent bypass surgery were able to eat normally and 20 of those eventually had their stoma closed [204]. Heneyke and colleagues reported that if TPN is required for more than 6 months, the child will probably be TPN-dependent for at least 4 years [25].

Mortality

Progress in the management of parenteral nutrition and the use of bowel decompression have modified the high mortality rate reported in historical series in neonates, for whom up to 90% of patients died before 1 year of age [59, 205]. In series published more recently, mortality varied from 4.8% (3/62 patients) [15] to 10% (10/105) [204], 25% (22/85) [24], and, in one study, just over 30% (14/44) [25]. Of these, underlying PIPO is rarely the primary cause of death except in cases with MEN2b and medullary carcinoma. In pediatric series reported to date, the high mortality rate is almost always due to iatrogenic complications. Long-term TPN-related complications, including central venous catheter-associated sepsis, liver failure, and thrombo-embolic events, as well as post-transplantation complications are the major contributing factors to mortality and morbidity in PIPO patients [24, 25, 204]. Sudden cardiac arrest has been reported in two patients with chronic intestinal pseudo-obstruction [307].

Prognostic Factors

In the large pediatric series published to date, comparison between patients requiring and those no longer requiring artificial feeding shows significant clinical differences in terms of likelihood of neonatal onset, urinary tract involvement, requirement for surgery during the course of the disease, and myopathic disorders, all features that are more frequent in cases with a poor prognosis [24, 25, 204, 227, 228]. The presence of phase III of the Migrating Motor Complex (MMC) on antroduodenal manometry has been reported by several groups to be a good prognostic indicator for tolerance of enteral feeding [212, 254], response to cisapride [245], and mortality [247]. Malrotation is also a factor associated with worse prognosis [25].

Summary

Pediatric PIPO is an enigmatic disease with poorly defined etiopathogenesis, which is reflected on the limitations encountered in both the diagnostic process and therapeutic management. Clearly, multinational initiatives are required to raise awareness, establish stringent diagnostic criteria, and evolve current therapeutic modalities.

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Hirschsprung Disease

26

Robert O. Heuckeroth

There are many excellent articles on Hirschsprung disease (HSCR) that provide detailed information about the clinical presentation, epidemiology, genetics, diagnosis, and associated medical problems [1–10]. This chapter summarizes and simplifies the complex HSCR literature. Percentages in the text and tables are estimates, since widely divergent numbers are presented in different manuscripts.

Definition

The enteric nervous system (ENS) is an integrated network of neurons and glia that controls most aspects of intestinal function. This includes intestinal motility, response to luminal and intramural stimuli, regulation of epithelial and immune cell activity, and control of blood flow [11–13]. To perform these tasks, neurons are normally distributed along the entire length of the bowel. When the ENS is absent or defective in any region of the bowel, profound problems with intestinal function occur causing significant morbidity and in some cases death.

Hirschsprung disease (HSCR), the most well-understood intestinal motility disorder, is characterized by the complete absence of enteric neurons (i.e., aganglionosis) in the myenteric and submucosal plexus of the distal bowel. In the absence of ganglion cells, the bowel tonically contracts causing functional intestinal obstruction. Many, but not all, clinical manifestations of HSCR result from tonic contraction of aganglionic bowel.

Nomenclature describing the extent of aganglionosis in HSCR is not consistent. However, most affected individuals have "short-segment" disease, where aganglionosis is restricted to the rectosigmoid region of the colon [14, 15]. "Long-segment" HSCR means that aganglionosis extends proximal to the sigmoid colon and is usually distinguished from "total colonic" aganglionosis. In a small percentage of cases, aganglionosis extends into the small bowel leading to very serious lifelong disability often requiring total parenteral nutrition (Table 26.1) [15, 16]. Although some authors have suggested that clinical presentation varies with the length of aganglionosis [17], others say that clinical symptoms are not related to the extent of disease [18]. From a practical standpoint, it is best to assume that the extent of aganglionosis and the severity and character of symptoms are unrelated.

Table 26.1 Extent of aganglionosis

Short segment	74–89%
Long segment	12–22%
Total colon	4–13%
Total colon and small bowel (partial or total)	3–5%

Clinical Presentation

HSCR is debilitating and can be fatal. Clinical presentation is highly variable and diagnosis requires a high index of suspicion (Table 26.2). Recognizing HSCR is important, since surgical management dramatically reduces disease morbidity and mortality.

In the current era, most people with HSCR are diagnosed by 12 months of age [19–23], but it remains common to diagnose HSCR in older children and HSCR has been diagnosed in adults up to 73 years of age [24]. A case report from 2021 describes a 53-year-old man in Japan with newly diagnosed HSCR [25]. He had constipation since childhood, but lacked other HSCR symptoms, highlighting the variability in symptom character and severity discussed below. HSCR needs to be considered in anyone with severe chronic constipation that began in early infancy, especially if suppositories or enemas are needed for stool passage. However, because

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Table 26.2 Presenting symptoms in HSCR

Symptom	Comment
Abdominal distension	Very common in HSCR or anatomic bowel obstruction
Bilious emesis	Common and suggests HSCR or anatomic obstruction
Constipation	Common in older children with HSCR but also in healthy toddlers and infants
Diarrhea	Foul-smelling, bloody, or "explosive" diarrhea suggests enterocolitis (HAEC)
Delayed meconium	Common in HSCR, but 50% of infants with HSCR do not have delayed meconium
Bowel perforation	Should raise concern for HSCR

constipation is common, affecting up to 35% of all children [26, 27], and HSCR is rare (1/5000 people), recognizing distinct features suggest that HSCR is important for diagnosis. Furthermore, constipation is only one feature of HSCR. Typical presentations for HSCR include:

Neonatal Intestinal Obstruction

Infants present with marked abdominal distension and bilious emesis. Distension may be severe enough to cause respiratory compromise. Obstruction may occur on the first day of life, but children may also initially have apparently normal bowel movements or "mild constipation" and then present acutely with abdominal distension and vomiting at an older age. Because HSCR requires a high index of suspicion for diagnosis, some infants are hospitalized repeatedly for episodes of presumed "gastroenteritis" that were actually a manifestation of HSCR-associated intestinal obstruction or enterocolitis. The clinical distinction is that gastroenteritis may cause severe vomiting, but does not typically cause as much abdominal distension as HSCR. Vomiting associated with infectious enteritis is also usually followed by diarrhea, whereas intestinal obstruction should be accompanied by reduced stool passage. Enterocolitis causes explosive diarrhea and marked abdominal distension (see details below). A distended abdomen occurs in 57–93% of infants with HSCR and bilious emesis occurs in 19–37% [16, 18, 28–30]. Abdominal distension and bilious emesis are also a very common presentation in premature infants with HSCR (96% and 92%, respectively). Note that since the ENS forms during the first trimester of pregnancy, incidence of HSCR is similar in term and preterm infants [31].

Neonatal Bowel Perforation

HSCR presents with bowel perforation about 5% of the time [32, 33] and HSCR causes about 10% of all neonatal bowel perforations [34]. Symptoms may not be specific and include poor feeding, emesis, abdominal distension, constipation, diarrhea, and lethargy. In two series with 55 cases reported [32, 33], only one child with perforation was more than 2 months old. Sixty-two percent of the perforations were in the cecum or ascending colon and 15% were in the appendix. Many of the children with bowel perforation had long-segment disease (34% total colonic aganglionosis, with an additional 23% having aganglionosis proximal to the splenic flexure). Since long-segment HSCR is less common than short-segment disease (Table 26.1), proximal colon perforation in a young infant should dramatically raise concern for long-segment HSCR. In 55% of reported cases, the perforation was proximal to the transition zone in ganglion cell containing bowel. In 13%, the perforation was at the transition zone. In 30%, however, the perforation occurred in aganglionic bowel distal to the transition zone.

Delayed Passage of Meconium

Delayed passage of meconium should suggest the diagnosis of HSCR, but defining HSCR risk in infants with delayed passage of meconium is challenging, because the timing of meconium passage reported for healthy infants is variable. In a study of 979 infants older than 34 week gestational age in the United States, 97% passed meconium by 24 h of life, and 99.8% passed meconium by 36 h of life [35]. Breastfeeding or bottle-feeding did not influence the timing of the first bowel movement, and multivariate analysis demonstrated that only prematurity was a significant predictor of delayed passage of meconium. A similar study in Turkey [36] also demonstrated that 724/743 (97%) passed meconium by 24 h after birth and 740/743 (99.6%) passed meconium by the time that they were 48 h. However, a smaller study in the Netherlands reported that only 56/71 (79%) of term infants passed meconium by 24 h after birth [37], and in a study of 267 healthy infants in Nigeria, only 92% passed their first bowel movement by 48 h after birth [38]. In the Nigerian study, 5% of the infants were preterm, but even if the preterm infants are excluded, the data suggest that at most 97% of the healthy full-term infants studied passed their first bowel movement by the time that they were 48 h. Excluding premature infants from the analysis is important, since prematurity predisposes to delayed passage of meconium. A study of 611 infants reported that only 57% of infants less than 29 week estimated gestational age (EGA), 66% of infants between 29 and 32 week EGA, and 80% of infants between 32 and 37 week EGA [39] passed meconium by the end of their "second calendar day" and 1% of premature infants did not pass meconium until after day of life 9.

Table 26.3 Making sense of HSCR risk for isolated delayed passage of meconium

Symptom in full term infants	Frequency in healthy infants (number used to calculate risk)	Frequency in children who have HSCR	HSCR risk if this is the only symptom
No meconium at 24 h after birth	97% (300/10,000)	1/10,000	1/300[a]
No meconium at 48 h after birth	99.8% (20/10,000)	1/10,000	1/20
No meconium at 48 h after birth	92% (800/10,000)	1/10,000	1/800

[a] *Method of calculation*: 97% means 300 out of 10,000 healthy neonates will not have passed meconium at 24 h after birth. About 1/5000 children have HSCR, but half of those children do pass meconium in the first 24 h after birth, so only 1/10,000 neonates has HSCR and presents with delayed passage of meconium. Thus, if delayed passage of meconium at 24 h after birth is the only HSCR symptom in a full-term infant, then risk of HSCR is about 1/300 instead of the usual population risk of 1/5000. Similar logic applies for the other calculated risk estimates

In children with HSCR , delayed passage of meconium is much more common than in healthy infants. Nonetheless, up to 50% of children with HSCR pass meconium by 48 h after birth [28, 40, 41], so passage of meconium within 48 h of birth does not exclude a diagnosis of HSCR. Table 26.3 defines HSCR risk based on these numbers, and highlights why it is important to consider HSCR symptoms, family history, and associated birth defects or genetic syndromes when deciding who to evaluate for HSCR.

Chronic Severe Constipation

HSCR causes constipation, but constipation unrelated to HSCR is very common (e.g., >25% of healthy children) and HSCR is rare, so constipation alone usually does not indicate HSCR (using the logic above, 1250/5000 children have constipation, so if constipation is the only symptom 1/1250 will have HSCR). "Severe" constipation and constipation beginning within the first few months of life does increase concern for HSCR and the likelihood of disease. For example, in one study, rectal biopsy was performed on all children over a year of age who were referred to a specialty center for consultation and who had constipation refractory to more than 6 months of medical management. Nineteen out of 395 biopsies demonstrated HSCR (5%), a 250-fold increased risk compared to the population prevalence of HSCR (1/5000) [42]. Constipation in isolation also appears to be an uncommon presentation of HSCR in infants. In particular, the wide range of normal bowel movement frequency in healthy infants makes it difficult to use constipation as the only indication to evaluate for HSCR. In a study of 911 healthy children in Turkey [36] between 2 and 12 months of age, mean stool frequency was once a day, but at 2 months of age, stool frequency varied from once a week to eight times per day.

Abdominal Distension Relieved by Rectal Stimulation or Enema

In children with HSCR, rectal exam or other forms of rectal stimulation may cause a sudden "explosive" release of intraluminal contents and relieve abdominal distension. Explosive release of stool and air after rectal exam is a sign of HSCR-associated enterocolitis (HAEC) [43]. This sign uncommon in other conditions and should raise concern about HSCR. Rectal exam is, however, not otherwise useful in identifying children with HSCR. In particular, "anal tone" is not a reliable indicator of disease. Occasionally anal stenosis or sacral teratoma can also be detected by rectal exam, so rectal exam can be valuable in children with intractable constipation and suspected HSCR.

Enterocolitis

Defining when children have enterocolitis presents its' own challenges (see below for symptoms), but enterocolitis is a dangerous and common presentation for HSCR. When enterocolitis occurs, children with HSCR have diarrhea instead of constipation.

Who Should Be Biopsied to Evaluate for Hirschsprung Disease?

Rectal biopsy is the "gold standard" diagnostic test for HSCR (see below). Unless another diagnosis is evident, children with the following clinical presentations *should undergo* rectal biopsy to evaluate for HSCR:

1. Neonates with significant abdominal distension, especially in combination with bilious vomiting or delayed passage of meconium, unless mechanical blockage in the bowel, is demonstrated.
2. Neonates with bowel perforation.

Also *consider* rectal biopsy for HSCR in children with:

1. Neonatal bloody diarrhea. Given the low incidence of infectious enteritis in breastfed or formula-fed neonates, bloody diarrhea in neonates is concerning for HAEC (see

below). Note, however, that many infants have small streaks of blood in the stool without diarrhea or other symptoms of HSCR, and hematochezia alone does not warrant rectal biopsy.
2. Healthy-appearing full-term infants with delayed passage of meconium even in the absence of other symptoms. Given the risks associated with untreated HSCR, I usually recommend biopsy in full term infants who do not pass meconium within 48 h of birth (Table 26.3 suggests that 1/20 will have HSCR). If meconium is first passed at 24 h after birth, rectal biopsy is much less likely to demonstrate HSCR, unless other symptoms of HSCR are present. I do not recommend biopsy for infants who pass meconium at 24 h after birth unless other signs or symptoms suggest HSCR.
3. Young children with constipation refractory to oral medication. Constipation beginning after a year of age is rarely due to HSCR. Constipation that improves dramatically with oral medication is also unlikely to be due to HSCR. The common form of functional constipation that occurs in toddlers may be challenging to treat, usually requiring complete disimpaction and daily maintenance medicine for relief of symptoms, so it can be challenging to know if toddlers are truly "refractory to oral medication." Some children with HSCR have very few symptoms within the first year of life, however, so the absence of neonatal symptoms does not exclude HSCR.

Red Flags (Conditions That Should Raise Suspicion for HSCR)

1. Constipation with episodes of abdominal distension or vomiting. Constipation does not cause vomiting, but many disorders cause both vomiting and reduced bowel movement frequency, including HSCR.
2. Growth failure. This is a common feature of untreated HSCR.
3. Trisomy 21. HSCR occurs in 1–2% of children with Down syndrome, so HSCR should be more readily suspected in children with trisomy 21 [44–46].
4. The presence of additional major anomalies also increases the likelihood of HSCR, but remember that most children with HSCR (>70%) do not have other major medical problems [22, 47, 48]. In particular, congenital anomalies of the kidney and urinary tract (CAKUT) occur in ~20% of children with HSCR and should raise suspicion of HSCR.
5. Family history of HSCR (see section "Epidemiology/Genetics Overview") may dramatically increase HSCR risk.
6. HSCR-associated genetic syndromes also increase risk (see Table 26.4 and added detail below).

Table 26.4 Selected HSCR-associated syndromes

Syndrome name	Genetic defect	Comments
MEN2A = multiple endocrine neoplasia 2A	RET mutation in codons 609, 611, 618, or 620	~2% of children with HSCR may have MEN2A RET mutations
FMTC = familial medullary thyroid carcinoma		20–30% of families with Ret 609, 611, 618, or 620 mutations have members with both FMTC and HSCR
Down syndrome	Trisomy 21	1–2% of children with trisomy 21 have HSCR
		2–10% of children with HSCR have Down's
WS4 = Waardenburg syndrome	WS4A = EDNRB	9% of children with HSCR have WS4
	WS4C = SOX10	Syndrome includes HSCR, deafness, and pigmentary abnormalities
CCHS = congenital central hypoventilation syndrome	PHOX2B	20% of children with CCHS have HSCR
		0.5–1.5% of children with HSCR have CCHS
MWS = Mowat–Wilson syndrome	ZFHX1B	60% of children with MWS have HSCR
		6% of children with HSCR have MWS
		Syndrome includes HSCR, intellectual disability, epilepsy, dysmorphic facial features, and brain and heart defects
Goldberg–Shprintzen megacolon syndrome	KIAA1279	Syndrome includes HSCR, intellectual disability, dysmorphic facial features, and brain and heart defects
CHH = cartilage–hair hypoplasia syndrome	RMRP	Syndrome includes short stature (dwarfism), other skeletal defects (short limbs), fine sparse hair, and immunodeficiency
		~9% of children with CHH have HSCR
		CHH is rare in children with HSCR

Given the diverse presenting symptoms of HSCR, it remains difficult to decide who to evaluate. The more "classic" features of HSCR that are present, the more likely the child has HSCR. Given the high morbidity and mortality in untreated HSCR, evaluation for HSCR should be performed in many children who do not end up having this disease to avoid missing this potentially life-threatening medical problem. My recent review provides additional details [8].

Diagnostic Strategies

HSCR by definition means that affected individuals do not have ganglion cells in the distal bowel. Rectal biopsy is, therefore, required to make the diagnosis and is considered the "gold standard" approach [49]. A number of other strategies for diagnosing HSCR are used, but each has problems.

Rectal Suction Biopsy

Rectal suction biopsy is a simple procedure taking only a few minutes using an instrument designed to take small pieces of the rectal mucosa (e.g., Noblett, Solo-RBT, or rbi2 instrument) to reduce the risk of bowel perforation or hemorrhage [50]. Because there are no sensory nerve endings that respond to cutting in the area of the rectum where the biopsies should be obtained, sedation and pain medicines are not required, but sedation is sometimes used in older children. Biopsies should be obtained at 2–3 cm from the dentate line (i.e., the transition between rectal and squamous mucosa), because there is a physiological submucosal hypoganglionosis in the terminal rectum. From a practical standpoint, however, some authors advocate obtaining biopsies at multiple levels (e.g., 1–3 cm from the dentate line), because precise positioning of the biopsy can be difficult. Biopsy tissue obtained is sectioned, stained, and examined by a pathologist to identify ganglion cells. There is some controversy about the optimal staining method, but hematoxylin and eosin (H&E) and acetylcholinesterase are commonly used techniques [49, 50]. Acetylcholinesterase staining might also help predict the risk of HAEC [51]. Calretinin staining might improve diagnostic accuracy [52, 53], but data are limited. A meta-analysis analyzing data from 993 patients indicated that the mean sensitivity of rectal suction biopsy for HSCR is 93%, and the mean specificity is 98% [54]. A more recent manuscript documents 935 cases of HSCR diagnosed by rectal mucosal biopsy (a total of 19,365 biopsies in 6615 children) with no false-positive or false-negative diagnoses (i.e., 100% sensitivity and specificity) [55]. Serious bleeding and bowel perforation are uncommon with rectal suction biopsy, but can occur. One series of 1340 biopsies [56] reported three bowel perforations (0.2%), one death (0.07%), and three rectal hemorrhage (0.2%) requiring blood transfusion. More recent studies also document low but nonzero rates of serious bleeding or bowel perforation (0 complication in 297 children [57], 0 complication in 88 infants [58], and two episodes of bleeding requiring transfusion (0.7%) plus one episode of rectal perforation and sepsis (0.035%) in 272 children) [59]. The most common problem with rectal suction biopsies, however, is that they are so small that 6–26% are "inadequate", requiring repeat biopsy to make a diagnosis [57, 59, 60]. The more recently introduced rbi2 biopsy instrument appears to give a lower frequency of "inadequate specimens" [58] and may give larger biopsies. It is not yet clear if there are also more complications (bleeding or bowel perforation) using the new instrument, since large cohort studies have not been published. Checking platelets, hemoglobin, and PT/PTT/INR prior to biopsy seems prudent, although I do not know of cases, where bleeding after rectal biopsy was due to coagulopathy.

Anorectal Manometry

This method tests for the rectoanal inhibition reflex (RAIR) using a small balloon attached to a tube inserted into the rectum [54]. The RAIR is reflex relaxation of the internal anal sphincter in response to rectal distension. This reflex is absent in children with HSCR. Sensitivity and specificity of anorectal manometry are 91% and 94%, respectively, but this test is not required to diagnose HSCR [54]. The equipment needed to do anorectal manometry is also expensive, and significant experience is needed to evaluate results in infants less than a year of age, so the test is not widely available. Recently developed high-resolution anorectal manometry does not appear to provide increased sensitivity or specificity for HSCR diagnosis (89% and 83%, respectively, compared to rectal suction biopsy) [61]. In fact, one study reported that 28/111 (25%) children with absent RAIR detected using high-resolution manometry were diagnosed with "internal anal sphincter achalasia" after rectal biopsies showed ENS ganglion cells, making HSCR unlikely [62].

Contrast Enema

This is an X-ray test where images are obtained as contrast is gradually infused into the colon via the anal canal to look for evidence of the distal bowel contraction that occurs in areas of aganglionosis. The region where bowel caliper changes from contracted distal aganglionic bowel and more dilated ganglion cell containing bowel is called the "transition zone". When rectum is narrower than more proximal colon, it suggests HSCR. Although contrast enema may have value in planning the surgical approach to HSCR, the radiographic and anatomic transition from aganglionic to ganglion cell containing bowel may not be in the same location. Note too that in total colonic HSCR, there is no transition zone in the colon, since the entire colon is contracted. Furthermore, the sensitivity (70%) and specificity (50–80%) are considerably lower using contrast enema for HSCR diagnosis than other methods [30, 54]. The role of contrast enema in HSCR diagnosis, therefore, remains a matter of debate, but enema is

also valuable to evaluate for other uncommon anatomic problems (e.g., stricture, sigmoid volvulus, colon cancer, and sacral teratoma).

Full-Thickness Rectal Biopsy

Deeper biopsies can be performed by a surgeon under general anesthesia if the diagnosis remains uncertain after rectal suction biopsy. This method should unambiguously identify enteric neurons if they are present. Rectal biopsy is discussed in much more detail in this excellent review [50].

Epidemiology/Genetics Overview

HSCR is a multigenic disorder, but non-genetic factors may also influence disease occurrence. As of the year 2021, rare damaging protein-altering variants had been reported in at least 35 genes in people with HSCR (*RET*, *GDNF*, *NRTN*, *ARTN*, *PSPN*, *GFRA1*, *EDNRB*, *EDN3 ECE1*, *ZFHX1B*, *SOX10*, *PHOX2B*, *KIAA1279*, *NRG1*, *ERBB2*, *SEMA3C/D*, *IHH*, *GLI1*, *GLI2*, *GLI3*, *L1CAM*, *ITGB4*, *PTK2*, *DENND3*, *NCLN*, *NUP98*, *TBATA*, *VCL*, *BACE2*, *ACSS2*, *ENO3*, *SH3PXD2A*, *UBR4*, *and TITF1 TCF4*; reviewed in Chap. 18) and there are more than 30 HSCR-associated genetic syndromes. Reduced RET kinase activity is the most commonly identified predisposing genetic risk factor for human HSCR, but most predisposing genetic variants for RET are non-coding (e.g., a common intronic SNP reduces RET expression). Copy number variants (especially trisomy 21), miRNA, and epigenetic changes are also implicated in HSCR. For more detailed reviews of molecular and cellular mechanisms that control ENS development and HSCR genetics, please see [3, 7–10, 63–65]. One valuable observation from the clinical perspective is that even when whole genome sequencing is performed, many children with HSCR do not have readily identified genetic changes that predispose to HSCR [66]. This suggests that combinations of genetic and non-genetic factors are responsible for most HSCR cases. Non-genetic risk factors for HSCR have not been defined in humans, but based on animal models, vitamin A deficiency [67], mycophenolate [68], and some medicines such as ibuprofen might increase HSCR occurrence [69].

For short-segment disease, there is an approximately 4:1 male-to-female ratio, but for total colonic aganglionosis, the male-to-female ratio is near 2:1. HSCR has been reported throughout the world in many ethnic groups. There are geographic and racial differences described in HSCR incidence, but these data are difficult to evaluate. Most reports have not been replicated over extended time periods and the difficulty in HSCR diagnosis increases uncertainty in interpreting regional data. Furthermore, it is often not possible to determine from large-scale epidemiological studies, the number of affected individuals who share mutations by common descent, so data may be skewed by families with multiple affected members such as has been described in some Mennonite communities [70]. HSCR incidence per 10,000 live births in California was reported as 1.0, 1.5, 2.1, and 2.8 for Hispanics, Caucasian–Americans, African–Americans, and Asians, respectively [71], even though these racial categories do not correlate well with most human genetic risk variants [72]. Future studies should instead discuss ethnicity, geographic origins, and ancestry instead of these racial categories. HSCR incidence was reported as 1.4 per 10,000 in Denmark, 1.8–2.1 per 10,000 in Japan [15], and 2.3 per 10,000 in British Columbia [73]. Considerably, higher rates of HSCR are reported in some small geographic areas or ethnic groups. For example, HSCR incidence is 2.9 per 10,000 in Tasmania [74], 5.6 per 10,000 for native Alaskans [75], 7.3 per 10,000 in Pohnpei State in the Federated States of Micronesia [76], and 5.6 per 10,000 in Oman [77]. In Oman, rates of consanguinity are reported to be high (75% first or second cousins), but this was not reported in other areas. The European registry (EUROCAT—European Registration of Congenital Anomalies and Twins) also describes striking differences between reporting regions, but ascertainment for HSCR is challenging, and it seems unlikely that the 31 reporting regions use the same ascertainment strategies [22]. Nonetheless, founder effects within populations, nutritional factors, differences in medicine use, or environmental toxins may account for these differences in HSCR incidence.

Recurrence Risk for HSCR in Families is High

Recurrence risk for siblings of children with HSCR is dramatically elevated compared to the general population and varies from 1:3 to 1:100 [6, 78] depending on the sex of the proband and their extent of aganglionosis. Because female sex protects against HSCR and because long-segment disease implies more serious genetic risk than short-segment disease, male siblings of females with long-segment HSCR have a 33% chance of HSCR, while new sisters have only a 9% risk. Siblings of males with long-segment HSCR have a recurrence risk of 17% and 13% in new brothers and sisters, respectively. For a male proband with short-segment HSCR, the risk of recurrence is 5% in male siblings, but only 1% in female siblings. For a female proband with short-segment disease, recurrence risk is 5% and 3% for new male and female siblings, respectively. Risk of HSCR in children whose parents have HSCR is also high. Twenty-two percent of reported familial cases include an affected parent and child [79]. These complex epidemiologic and recurrence risk data are a direct reflection of the non-Mendelian genetic underpinnings of HSCR. While these “average” data are

helpful in discussions with families, better estimates of HSCR recurrence risk might theoretically be obtained using modern molecular genetic techniques if highly penetrant gene defects were identified. From a practical perspective, I tell parents about the elevated HSCR risk in future children and about diverse HSCR presentations, so that they can alert pediatricians if any symptoms suggest HSCR. I recommend that mothers take prenatal vitamins before conception and that they avoid taking medicines or herbal supplements that are not providing clear benefit. Since ENS precursors colonize fetal bowel during the first trimester of pregnancy (weeks 3–8 of gestation) and many women first know that they are pregnant at weeks 6–7 of gestation, changes implemented after pregnancy is recognized are less likely to affect HSCR occurrence.

HSCR-Associated Medical Problems

HSCR is an isolated birth defect in ~70% of affected individuals, but ~30% of children with HSCR have additional birth defects, including the ~12% of children with HSCR who have chromosomal anomalies [22, 41, 48, 73, 80–82]. A very wide range of additional defects have been reported in children with HSCR. The most common defects are congenital heart disease, sensory neural problems (e.g., hearing loss), visual problems, CAKUT, and skeletal anomalies [83]. Many different chromosomal defects have been described in people with HSCR, but trisomy 21 is by far the most common. There are >30 genetic syndromes associated with HSCR (reviewed in [6, 84]). A few HSCR-associated syndromes are summarized in Table 26.4.

Surgical Management

Although Harald Hirschsprung first described children with the disease that now bears his name in 1886 [85], the pathophysiology of HSCR and management strategies remained unknown until the first successful surgical approach was described in 1948 [86]. There are many modifications of the original pull-through surgery, but the most common procedures today are the Swenson, Duhamel, and Suave endorectal techniques with modification of surgical approaches for total colonic HSCR [1, 18, 87]. For each of these procedures, intraoperative biopsies are obtained to determine the extent of aganglionosis. The Swenson procedure involves complete resection of the aganglionic bowel with reanastomosis of ganglion cell containing bowel to a 1–2 cm rectal cuff. In the Duhamel modification, ganglion cell containing bowel is brought through the retrorectal space and anastomosed to a segment of aganglionic rectum using a side-to-side anastomosis. In the Suave procedure as modified by Boley, the rectal mucosa and submucosa are removed and the ganglion cell containing bowel is pulled through a muscular cuff of distal aganglionic bowel and then attached within 1 cm of the anal verge. There are innumerable studies of surgical outcome, but few large-scale systematic comparisons are available [88], so it remains unclear that one procedure is better than another. Over the past two decades, there have been three major changes in surgical management. These include laparoscopic surgery, transanal surgery, and increased use of one-step surgical procedures [16, 89–92]. Systematic reviews and meta-analyses of transanal versus transabdominal surgeries suggests that the children who had transanal endorectal pull-through procedures for HSCR had shorter hospitalization, but reviews differ in conclusions about relative rates of post-operative incontinence, constipation, and enterocolitis [21, 93–95]. A comparison of single versus multistage pull-through surgery suggested that children with single-stage surgery tend to do better, but a subgroup of children who are seriously ill with HSCR may do best with multistep surgery [96]. A meta-analysis of Soave pull-through procedures suggests that children <2.5 months of age had more complications compared to children who had Soave surgery at older ages [97]. Unfortunately, many children continue to have problems after HSCR surgery (see section "Long-Term Outcome" below) and the best way to avoid these problems is not yet defined [8].

Cost for Initial Management

For children with HSCR, initial hospitalization costs average $105,000 (in 2007 dollars, Nashville Tennessee, USA; $139,000 in 2021 dollars) and the hospital stay averaged almost a month [98]. Taking into account HSCR incidence and birth rates, estimated cost for initial care of children with HSCR in the United States is at least $86 million/year (2007 dollars, $114 million in 2021 dollars). This cost estimate does not include the expense of lost work time or other expenses families encounter while caring for an ill child. Estimates also do not include the cost of ongoing care after the initial hospitalization, which in some cases may be significant, especially in children with enterocolitis. For children with aganglionosis extending into the small bowel, long-term parenteral nutrition adds dramatically to cost and disease morbidity. Finding new ways to treat or prevent HSCR remains desirable.

Enterocolitis

HAEC is common, can occur at any time before or after surgery, and is the most frequent cause of death in infants and children with HSCR [8, 99–101]. Death from HAEC occurs,

because HSCR predisposes to bacterial translocation into the bloodstream that leads to sepsis. Nonetheless, recognizing HAEC is difficult, and until recently, there was no standard clinical definition for HAEC. In 2009, a consensus of expert surgeons and gastroenterologists developed a systematic scoring system to identify children with HAEC [43]. Components of the score include "explosive" diarrhea, foul-smelling diarrhea, or bloody diarrhea. Additional components include abdominal distension, explosive discharge of gas and stool with rectal exam, reduced peripheral perfusion, lethargy, and fever. Radiographic findings include multiple air fluid levels, distended loops of bowel, sawtooth and irregular mucosal lining, pneumatosis, and rectosigmoid cutoff sign with the absence of distal air. Laboratory findings include leukocytosis and a left shift. Many of these features are also listed as presenting symptoms for HSCR, because HAEC is common in children with HSCR, especially before surgery.

The reasons that children with HSCR develop HAEC are not clear, but enterocolitis does not occur in children with "severe" functional constipation. Possible predisposing factors for HAEC in children with HSCR include residual partial bowel obstruction, defects in epithelial integrity, reduced blood flow to bowel under pressure, dysbiosis, and abnormalities in the mucosal immune system [8, 101, 102]. Partial obstruction may result from stricture or from intestinal dysmotility leading to increased intraluminal pressure and changes in gut flora [103–105]. Epithelial dysfunction may occur, because enteric neurons and glia support bowel epithelial repair and regulate fluid secretion, in addition to controlling antimicrobial peptide and mucin production [13, 63, 106–120]. Furthermore, aganglionic bowel has a "leaky" epithelial barrier that is permeable to small proteins (and perhaps larger molecules or bacteria) [121] Mechanisms, underlying these observations are complex and often involve interactions between microbes or microbial components, neurons, glia, immune systems cells, and epithelial cells [13, 122–128]. For example, diverse immune system cells respond to ENS neurotransmitters, including vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), acetylcholine, substance P, and serotonin [129]. Enteric glia modulate bowel immunity [119] by producing CXCL10 in response to gamma interferon [130], increasing NGF and NT-3 while reducing IL-18 and IL-β in response to *Bifidobacterium* [131], and by producing brain-derived neurotrophic factor, which reduces TLR4 responses to lipopolysaccharide [132]. In addition, enteric glia secrete GDNF that activates RET on group 3 innate lymphoid cells (ILC3) to induce the production of IL-22. Secreted IL-22 enhances epithelial reactivity and repair to reduce bacterial translocation and bowel inflammation [133]. IL-18 from enteric neurons reduces bacterial invasion by increasing epithelial anti-microbial peptide production [126]. Mucins that reduce microbial invasion are abnormal in HSCR [111, 115, 120, 134]. Macrophages closely interact with the ENS to impact ENS function and respond to ENS signals [13, 125, 127, 135, 136]. Bowel macrophages can reduce or promote inflammation (depending on macrophage phenotype) [137, 138], and can also break down the blood–myenteric plexus barrier, permitting inflammatory cells to damage the ENS leading to chronic dysfunction and dysmotility [139]. Finally, extrinsic innervation may impact risk of enterocolitis, since the absence of mucosal acetylcholinesterase-stained fibers in aganglionic colon predicts increased enterocolitis in human children [51]. There is much more to learn about these gut microbe–epithelial–neuron–glia–extrinsic innervation–immune cell interactions, but these emerging data provide strong support for the hypothesis that enterocolitis results in part from a compromised epithelial and immune cell barrier when the ENS is absent or defective. Some genes mutated in children with HSCR also have ENS-independent immune cell roles, suggesting that shared genetic mechanisms independently impact immune cell function. For example, RET is important for Peyer's patch formation [140] and alters activity of other immune cells [141, 142], while EDNRB is important for spleen development [143]. Collectively, dysmotility, dysbiosis, and dysregulation of immune and epithelial cell function probably explain why HSCR predisposes to HAEC.

Optimal methods to treat or prevent HAEC are not yet known. Current treatment includes bowel rest, nasogastric tube drainage, intravenous fluids, decompression of dilated bowel via rectal dilation and/or rectal irrigation with normal saline, and the use of broad-spectrum antibiotics [102]. When the child is acutely ill with HAEC and markedly distended, simple rectal exam can lead to rapid release of air and stool, restoring blood flow to the bowel. Children with HAEC often feel and act better quickly after rectal exam, rectal irrigation, or rectal tube reduces intra-abdominal pressure. This therapy may also reduce the risk of sepsis, so do not delay rectal decompression. Routine (e.g., daily) rectal irrigation [144] and long-term metronidazole for children at high risk of enterocolitis may further reduce HAEC episodes. Probiotics might reduce HAEC frequency [145], but beneficial effects are not consistently reported [146]. However, probiotics, prebiotics, and dietary effects on enterocolitis have barely been investigated. Two recent observations suggest that these therapies might be effective. First, a prospective study demonstrated that exclusive breastfeeding reduced HAEC risk by 40% in children ($n = 111$, 95% CI 0.44–0.85, $P = 0.003$) with HSCR [105]. Our study in an inbred HSCR mouse model also demonstrated a dramatic (fivefold) change in life expectancy when mouse facility and diet changed [121]. Because HAEC is potentially fatal, it is critical that families understand symptoms of enterocolitis and that plans are in place for prompt treatment should HAEC symptoms arise.

Long-Term Outcome

HSCR is a deadly disease, but outcome with modern surgical methods and improved medical management strategies is dramatically better than in the past. Nonoperative management leads to very high mortality rates (e.g., >50–80%), and reports from the 1970s describe mortality rates of 25–35% [18, 147] even with surgical treatment. HSCR death rates today remain about 2–6% despite modern therapy in large part attributable to enterocolitis [14, 15, 41, 148, 149]. Enterocolitis occurs commonly both before and after surgery for HSCR (25–45% of children) [21, 98, 150, 151]. Long-term outcome even years after surgery also remains less than ideal with only 45–89% having normal bowel function. Many individuals continue to have soiling (4–29%), constipation (3–22%), or permanent stomas (7–10%) [152–154]. Normal bowel function is even less common in children with Down syndrome (34%). Bowel function appears to improve as children get older with "normal" continence in 58% at 5–10 years after surgery, 68% at 10–15 years after surgery, and 89% at 15–20 years after surgery in one study [154]. In this analysis, however, 7% had marked limitation in their social life 5–10 years after surgery, but this problem improved as children became older.

Lessons from Mouse Models

There are many mouse models with distal bowel or total intestinal aganglionosis that mimic human HSCR [3, 63, 155–160]. This includes mice with mutations in *Ret*, *Sox10*, *Ednrb*, *Edn3*, *Ece1*, *Ezh2*, *Phox2b*, *Zfhx1b*, *Sall4*, *Hoxb5*, *Ihh*, *Itgb1*, *Pds5A*, *Pds5B*, *Pax3*, *Raldh2*, *Impdh2*, *Rara*, and *Pax3*. Recent mouse studies also suggest that excess collagen VI may underlie increased HSCR risk in Down syndrome [161]. Overexpression or inactivation of many additional genes also affect ENS structure or function without causing distal bowel aganglionosis, including *Ahr*, *Apoe*, *App*, *Ascl1*, *BMP4*, *C3ar1*, *Card11*, *Cdh2*, *Celsr3*, *Dat*, *Dcc*, *Dmd*, *Erbb2*, *Fzd3*, *Gas1*, *Gfra2*, *Gdnf*, *Gli1*, *Gli3*, *Gnaz*, *Hand2*, *Hlx1*, *Hoxa4*, *Kif26a*, *L1cam*, *Lgi4*, *Lrrk2*, *Mecp2*, *Met*, *Nedl2*, *Net*, *Nlgn3*, *Nog*, *Nos1*, *Nrtn*, *Nt3*, *Ntrk3*, *Pbx3*, *Phactr4*, *Pofut1*, *Pten*, *Raldh1*, *Raldh3*, *Rara*, *Rest*, *Sert*, *Shh*, *Smn*, *Smo*, *Snca*, *Spry2*, *Tbx3*, *Tcof1*, *Tfam*, *Tlr2*, *Tlr4*, *Tlx2*, *Tph2*, *Uchl1* (arranged alphabetically) as well as a wide array of neurotransmitters, neurotransmitter receptors, and proteins that re-uptake or degrade neurotransmitters [13]. These observations in combination with the large number of human genetic variants documented in people with HSCR [10, 66, 162–164] suggest that ongoing problems after pull-through surgery may be manifestations of ENS dysfunction that results from abnormal "wiring", abnormal ENS cell subtype ratios, or abnormal function of specific ENS cell types in regions deemed "normal" based on clinical pathology. A few mouse studies confirm that ENS is abnormal in the proximal bowel of mice with distal bowel aganglionosis [165–167], but much more detailed analyses of ENS structure and function need to be done, especially in human tissue. Finally, in some mouse models, ENS anatomy is nearly normal, but function is profoundly abnormal [168, 169], emphasizing that even sophisticated pathological methods may not provide the information needed to optimize intestinal function. Limited human data support the hypothesis that ENS in the bowel of children with HSCR bowel may not be normal even when "ganglion cells are present" [170–172]. Consistent with this hypothesis, bowel motility problems of the stomach, small bowel, and esophagus appear to be common in humans with HSCR [173–177].

The Future of Hirschsprung Disease

Outcomes for children with HSCR today are quite good, but many challenges remain. The primary problems and opportunities include:

1. *There have been major advances in our understanding of the genetic underpinnings of HSCR, but these findings are not yet routinely incorporated into clinical practice*. Furthermore, there is no consensus about what type of molecular genetic testing, if any, should be performed on children with HSCR. One reasonable argument is that all children with HSCR should be tested for RET mutations that cause MEN2A (but this is still not common practice), since people with MEN2A are at high risk for potentially preventable malignancy. As genetic testing becomes less expensive and the capacity to test for many mutations simultaneously increases, it may become practical to perform more comprehensive analysis that would provide information about the risk of other medical problems. It is important that we develop user-friendly methods to understand the type of complex genetic data that are relevant for children with HSCR.
2. *There are many HSCR-associated medical problems that may be missed if routine screening is not implemented*. One prospective study of 106 consecutive children with HSCR arranged for each child to have a renal ultrasound, cardiac ultrasound, cerebral ultrasound, as well as audiology and ophthalmology assessments [83]. Forty-six children had ophthalmologic issues (mostly refractive errors), 22 had CAKUT, 5 had congenital heart disease, 5 had hearing impairment, and 1 had corpus callosum agenesis. These rates are much higher than prior retrospective reports that did not employ systematic screening. This

suggests that routine screening for HSCR-associated anomalies makes sense, especially for problems not easily identified by history or physical exam.

3. *Enterocolitis remains a common cause of morbidity and the most common cause of mortality in children with HSCR. We need a more complete understanding of factors that predispose to HAEC and new ways to prevent this problem*. Recent studies demonstrate many complex interactions between gut microbes, enteric neurons, glia, epithelial cells, macrophages, and other hematopoietic lineage cells in the bowel wall. These interactions maintain the protective barrier that prevents bacterial translocation from the lumen while preventing excess bowel inflammation. There is undoubtedly much more to be learned about why aganglionosis predisposes to HAEC, but new mechanistic observations allow us to think creatively about novel strategies to treat or prevent HAEC. For example, how do medicines that alter acetylcholine or serotonin signaling affect epithelial or immune cell barrier function? Would strategies to increase GDNF production in enteric glia be helpful, since many factors impact GDNF synthesis [178]. Would probiotics or specialized diets be useful? Are there additional medicines that could reduce HAEC rates? Would a more systematic analysis of pathology at the time of surgery help? The underexplored emerging information about HAEC biology should lead to human clinical trials as new data define mechanisms.
4. *We need improved methods to evaluate and visualize the ENS*. Acousto-optic spectral imaging [179] and optical coherence microscopy [180] permit visualization of the ENS in mice, but the thicker human bowel wall makes it challenging to visualize the ENS without getting closer to the cells of interest. Human ENS can be visualized in vivo using confocal laser endomicroscopy and fluorescent contrast agents once the mucosa is removed or bypassed [181–183]. To take full advantage of this approach, we still need to define normal human ENS anatomy at various ages in defined bowel regions. Then, confocal laser endomicroscopy might make pull-through surgery faster and provide better data about the location of the anatomic transition zone. New imaging data should improve surgical outcomes and reduce postsurgical HAEC rates by enhancing the surgeon's ability to evaluate the density of enteric neurons in the bowel intraoperatively. To begin to address this problem, we developed a new way to make fixed bowel translucent, stain the ENS with antibodies and image via confocal microscopy [184]. Our method cannot be used intraoperatively, but generates detailed images of ENS cells over cm^2 bowel regions without sectioning, permitting three-dimensional relationships to be readily understood. By applying this method to bowel from children with and without HSCR, we hope to define anatomic features that predict good outcomes after pull-through surgery.
5. *We need to determine if there are ways to reduce HSCR occurrence rates or to reduce the extent of aganglionosis in affected individuals*. New data from model systems suggest that many environmental factors, including maternal vitamin A levels, mycophenolic acid, ibuprofen, and other medicines, might impact the likelihood that children develop HSCR [67, 68, 185]. Reports of monozygotic twins discordant for HSCR also suggest that HSCR is not a purely genetic disease [41, 48, 186, 187]. Large-scale epidemiological studies coupled with work in model systems should be pursued to identify maternal medicines, health conditions, or nutritional problems that could be modified to prevent HSCR.
6. *We need to find new ways to replace or repair the damaged ENS to rebuild the ENS when development is abnormal*. Recent exciting studies suggest that stem cell therapy might provide substantial benefit for treating ENS defects [188–192], but many obstacles need to be overcome for stem cell replacement therapy to become a practical treatment strategy. One promising approach transplants gut-derived ENS progenitors to the bowel after in vitro culture [193–195]. These cells integrate into the ENS and form functional enteric neurons and glia. Recent studies also provide a method to convert human embryonic stem cells (hESC) or induced pluripotent stem cells (iPSC) into ENS precursor-like cells. These hESC-derived cells can prevent death in a murine HSCR model after transplantation [196]. This work suggests that autologous stem cell therapy using iPSC might be an alternative to pull-through surgery for HSCR if safety concerns could be addressed (e.g., risk that transplanted cells will become neoplastic). Several other sources of cells are being tested for beneficial effects in HSCR models [188, 197]. As an alternative to stem cell therapy, 5-HT4 agonists and GDNF enemas appear to induce regeneration of the endogenous ENS and might be beneficial in specific settings [121, 198]. Manipulating gut microbes, inflammatory responses, and micronutrients also seem likely to be valuable strategies to shape ENS biology [199].

Summary

Over the past century, dramatic advances have been made in HSCR diagnosis, surgical management, developmental biology, and genetics. Ongoing studies provide new hope that we will be able to reduce HSCR incidence, prevent HAEC, replace missing enteric neurons using stem cells, regenerate

the ENS from endogenous cells, image the ENS intraoperatively, improve surgical techniques, and incorporate genetics into clinical practice.

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Motility Problems in Developmental Disorders

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Massimo Martinelli and Annamaria Staiano

Cerebral Palsy

Cerebral palsy (CP) refers to a group of chronic, non-progressive disorders of movement, posture, and tone due to central nervous system (CNS) damage before cerebral development is complete. The prevalence of CP is approximately 2 per 1000 live births. The different types of CP vary from series to series, with the spastic type being the most frequent, while periventricular leukomalacia and/or cortical/cerebral atrophy represent the main neuropathological correlates [1]. The survival of children with severe neurological disorders, such as CP, has created a major challenge for medical care. Gastrointestinal (GI) motor dysfunction, such as gastroesophageal reflux disease (GERD), dysphagia, vomiting, and chronic constipation, is known to occur frequently in children with different degrees of CNS damage. The degree of GI dysmotility seems to correlate with the degree of brain damage [2]. Swallowing disorders are common in patients affected by CP. In the study by Del Giudice and colleagues, the authors found that 30 of the 35 patients with CP presenting with dysphagia had swallowing disorders. The great majority of patients showed dysfunction of the oral phase of swallowing with abnormal formation of the alimentary bolus due to either uncoordinated movements of the tongue or it being contracted and rigid. Alternatively, they had a normal bolus but huge defects in its propulsion toward the oropharynx, due to the lack of finely coordinated movements of the tongue against the palate. Swallowing disorders have significant implications for development, nutrition, respiratory health, and GI function of this group of patients [3]. The development of dysphagia is associated with a progressive reduction of food intake and represents the main pathogenic factor for malnutrition [4]. At the same time, swallowing disorders can often cause recurrent episodes of pulmonary aspiration. For all these reasons, it is essential to diagnose these conditions as early as possible. Videofluoroscopic swallow studies are considered to be a valuable diagnostic tool for children with CP, given their ability to assess both pharyngeal motility and airway protection during swallowing. There is growing evidence that the method of feeding is an important variable in outcomes of children with more severe CP. In those patients with dysphagia, undernutrition, and associated respiratory diseases, the adoption of gastrostomy tube feeding is recommended [5, 6]. In 2017, the European Society of Gastroenterology, Hepatology, and Nutrition (ESPGHAN) released a consensus statement, which provides uniform recommendations on the proper assessment of nutritional status, diagnosis and treatment of major GI symptoms and, above all, timing and modalities of nutritional intervention and rehabilitation in children with neurological impairment [6]. The ESPGHAN panel suggested oral feeding in CP children only when it is nutritionally sufficient, safe, stress-free, and if feeding time is not prolonged [6]. The use of enteral feeding is always suggested when the total oral feeding time exceeds 3 h per day. A prospective cohort study with a follow-up of 12 months of a cohort of 57 children with NI receiving a gastrostomy showed a substantial increase in weight gain and improved health as reported by the parents and a significant reduction in feeding time with no increase in respiratory infections [7, 8]. On the basis of this evidence, when the oral feeding is not sufficient, unsafe or time-consuming, the ESPGHAN group recommended using a gastrostomy as the preferred way to provide intragastric access for long-term tube feeding in children with CP [6].

GERD is very common in patients with a severe neurologic impairment. The incidence is reported to be between 70% and 90%, depending on the different investigations used including esophageal pH studies and/or upper GI endoscopy [3, 9]. The pathogenesis of GERD in children with CP seems to relate mainly to the impaired motility of the esophagus. Del Giudice et al. demonstrated that most of the neurological patients affected by GERD showed prolonged gastric emptying and abnormal esophageal motility. The main abnormalities consisted of significantly low ampli-

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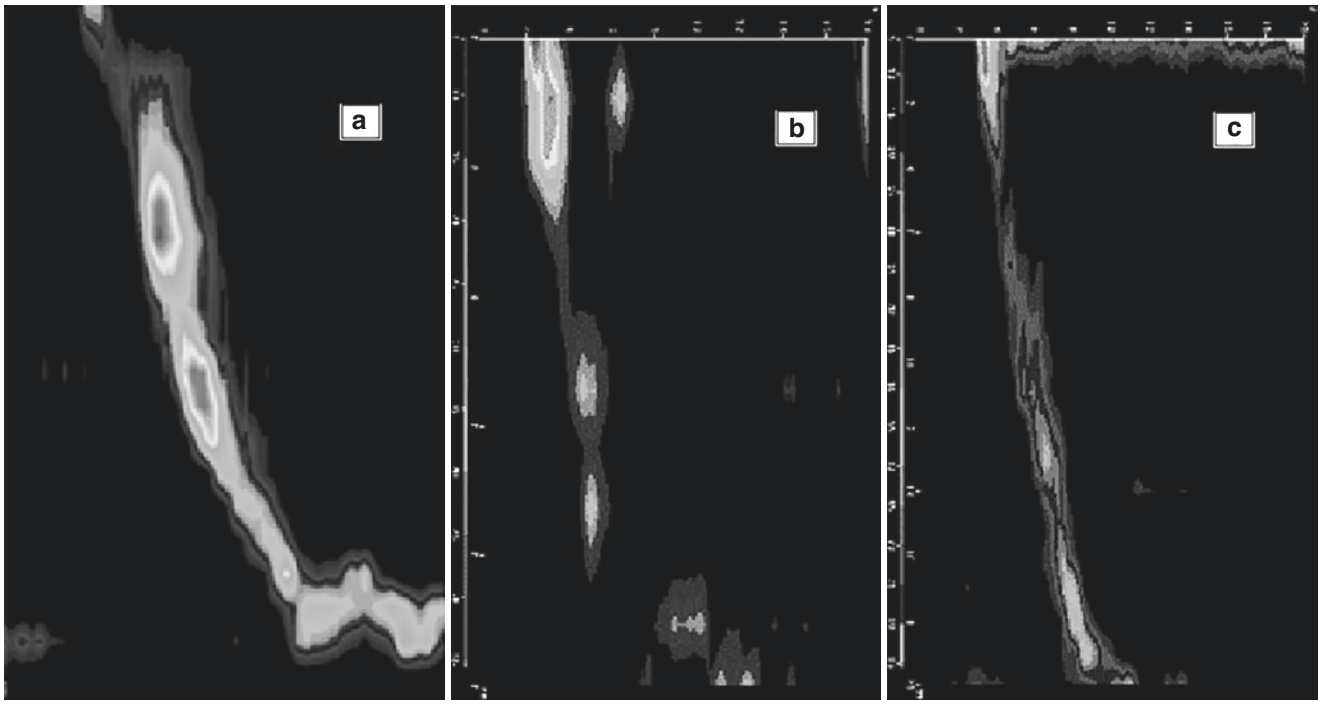

Fig. 27.1 Examples of high-resolution esophageal manometry tracings in a control subject (**a**) and in two patients (**b**, **c**) affected by cerebral palsy. Note in (**a**) a normal esophageal tracing, whereas in (**b**) hypotensive lower esophageal sphincter and low amplitude contraction. In (**c**), marked hypomotility of the smooth muscle region is visible

tudes of the lower esophageal sphincter (LES) and esophageal contraction waves and an increased number of simultaneous waves, compared to control children (Fig. 27.1) [3]. These findings, part of a more generalized dysmotility of the GI tract, together with the other conditions often present in these children, such as spasticity, prolonged adoption of supine position, scoliosis, seizures, and reduced amounts of swallowed saliva consequent to the drooling, increase the predisposition to the development of GERD and may be responsible for the high failure rate of both medical and surgical treatments in this category of patients. The correct therapeutical approach to GERD in CP patients is still controversial. Both the ESPGHAN–NASPGHAN guidelines on GERD and the ESPGHAN guidelines on the evaluation and treatment of GI and nutritional complications in children with neurological impairment recommend the use of proton pump inhibitors (PPIs) as the first-line treatment in children with CP [6, 10]. An alternative medical approach is represented by the use of an elemental diet. Miele et al. reported a lower incidence of GERD in neurologically impaired children with refractory esophagitis treated with amino acid-based formula [11]. Baclofen may be recommended to control vomiting [10]. Although, conventional medical management is less effective in neurologically impaired children, surgical intervention is associated with high operative risk given the poor physical condition of the patients. The benefit/risk ratio of antireflux surgery in patients with persistent symptoms despite optimized medical therapy is not clear. Nissen fundoplication has been associated with several complications in neurologically impaired children. In addition, postoperative morbidity rates are up to 50%, reoperation rates up to 20%, and mortality substantial [12, 13]. Recently, the advent of laparoscopic Nissen fundoplication has become the procedure of choice. Esposito and colleagues reported a 30% rate of postoperative complications and 6% rate of reoperation [14]. Nevertheless, due to the high risk of postoperative morbidity, the ESPGHAN panel does not recommend the routine use of fundoplication at the time of gastrostomy placement, but only in case of failure of optimized medical therapy [6]. Jejunal tube feeding may be considered as an alternative in those children in whom intragastric feeding is not tolerated due to a severe gastric motility disorder, or severe GERD not amenable to antireflux surgery. In these cases, jejunal access may be provided trough a nasojejunal tube, a jejunal tube introduced through a gastrostomy, or surgical transcutaneous jejunostomy [6]. The advantages of jejunostomy vs. fundoplication plus gastrostomy in terms of efficacy and complications are still unclear [6]. As a matter of fact, a recent meta-analysis demonstrated no significant differences in the rates of mortality, pneumonia, major, and minor complications [15].

Constipation represents another frequent and often undiagnosed problem in patients with CP. The prevalence of the chronic constipation varies from 25% to 75% of patients

with CP [3]. Chronic constipation is the result of prolonged colonic transit, which is secondary to the underlying gut dysmotility. Colonic transit time seems to be delayed predominantly in the left colon and rectum [16]. It has been suggested that disruption of the neural modulation of colonic motility may play a predominant role in the development of constipation in neurologic disease. This could explain why prokinetic drugs have little impact on the delayed colonic transit seen in children with brain damage. The low fiber and fluid intake as well as the frequent delay in diagnosis certainly contribute to the development and the reinforcement of constipation in neurologically impaired children. Staiano et al. demonstrated the efficacy of dietary fiber glucomannan in improving bowel frequency in children with severe brain damage, despite no measurable effects on delayed transit [17]. The current therapeutic management for constipation includes the use standard treatments as in typically developing children, unless there is a risk of aspiration of polyethylene glycol or liquid paraffin, plus increasing fluid and fiber intake as an additional strategy [6].

Down Syndrome

About 77% of neonates affected by Down syndrome (DS) present with or develop associated GI abnormalities [18, 19]. Cleves et al. reported an elevated relative risk for GI malformations (OR 67.07) in infants with DS [20]. The most frequent GI malformation associated with DS is Hirschsprung disease (HSCR); however, esophageal atresia, tracheoesophageal fistula, duodenal atresia or stenosis, and imperforate anus were all described. Some of the most common functional GI symptoms reported by DS patients are dysphagia for liquids and solids, vomiting/GER, and heartburn, as well as other esophageal dysmotility symptoms [19, 20]. Children affected by DS are at high risk of GERD and its serious complications, such as oropharyngeal aspiration and pneumonia [21]. As for other conditions with neurological impairment, such as CP, treatment of GERD in DS patients should associate optimized antisecretory therapy to behavioral measures, including feeding and positional changes [10]. Despite optimized medical therapy, some DS patients with GERD, especially patients with respiratory complications of GERD, need antireflux surgery [22]. It has been observed, however, that neurological impairment and GI disease necessitating surgery have been independently associated with poorer development outcome [23]. With regard to esophageal motor disorders, different cases of association between achalasia and DS have been described in the literature, and although achalasia remains a rare entity, it should be considered in any DS patient who presents with dysphagia [24]. Among the most common motor disorders in DS children and adults, unexplained chronic constipation is included [25]. In children with chronic constipation, it is important to exclude HSCR, observed in approximately 1 in every 200–300 DS patients [26]. Moore et al., studying a population of 408 HSCR patients, reported a prevalence of 3.2% of DS with an 85% association with other anomalies [27]. The well-described correlation between DS and HSCR indicates a possible role for chromosome 21 in the etiology of the latter. Nevertheless, the existence of trisomy 21 although seemingly increasing the risk of developing HSCR does not invariably lead to its occurrence. In the literature, several studies investigating the role of chromosome 21 as a potential candidate area for a modifying gene in HSCR exist [28], but lately, the possible role of genes mapping outside chromosome 21 (such as SOD1, ITGB2, and protein s-100 beta) is emerging [29]. In addition, well-studied has been the relationship between the major susceptibility genes associated with HSCR (RET and EDNRB) and DS. Arnold et al. [30] demonstrated that the RET enhancer polymorphism RET 19.7 at chromosome 10q11.2 is associated with HSCR in DS individuals. Interestingly, the RET19.7 T allele frequency is significantly different between individuals with DS alone (0.26 ± 0.04), HSCR alone (0.61 ± 0.04), and HSCR and DS (0.41 ± 0.04), demonstrating an association and interaction between RET and chromosome 21 gene dosage. Similarly, a novel EDNRB variant was identified in DS patients with HSCR [31]. Moreover, there appears to be a significantly higher overall incidence of preoperative enterocolitis and postoperative enterocolitis in DS with HSCR [32].

Williams Syndrome

Williams syndrome (WS), also known as Williams–Beuren syndrome, is due to a homozygous deletion of a contiguous gene on the long arm of chromosome 7 (7q11.23) [33]. The estimated prevalence of WS is 1 in 7500 live births [34]. Most individuals with WS (99%) have a 1.5 megabase deletion in 7q11.23 encompassing the elastin gene (ELN) and 25–35 other genes, all of which are detectable by fluorescent in situ hybridization (FISH) [35]. Clinical features of WS include distinctive facial anomalies; congenital heart defects, in particular supravalvular aortic stenosis; slight to severe mental retardation; herniae; growth deficiency; and infantile hypercalcemia [36]. GI symptoms such as chronic abdominal pain, feeding problems, constipation, and GERD are seen relatively frequently in children with WS [37]. Hypercalcemia may contribute to irritability, vomiting, constipation, and muscle cramps; it is more common in infancy, but may recur in adults [38].

Autism Spectrum Disorders

Autism spectrum disorders (ASD) are neurodevelopmental conditions that unfold in the first few years of life and involve significant impairments in social interaction and communication, with restriction in interests and extreme attachment to routine or to repetitive or perseverative behaviors [39]. The term includes autistic disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified [39]. Estimates of ASD in pediatric populations have dramatically increased over the past decade, and in 2016, the National Health Center for Health Statistics released its latest prevalence rate and reported a new record high, citing that ASDs could be found in as many as 1 in 36 children [40]. GI dysfunction is frequently cited among children with ASDs, and many causal and therapeutic theories of ASDs involve the GI system [41]. This includes the hypothesis that a specific GI pathology is associated with ASDs, triggered by abnormal immune function or elevated intestinal permeability. A great amount of controversy has surrounded this issue since publication in 1998 naming a new pathologic entity, "autistic enterocolitis," as responsible for developmental regression in 12 children after administration of the measles–mumps–rubella vaccine [42]. Ultimately, this research was retracted for several reasons, including questionable research practices, as found by the General Medical Council of the United Kingdom [43]. Although the presence of a unique GI pathophysiology specific to ASDs has yet to be identified, elevated risk for GI symptoms in this population remains a critical issue in pediatric settings, because this population is significantly more likely to use GI agents and experience hospitalizations related to GI disturbance. The prevalence of GI symptoms in children with ASDs is poorly understood and it is still unclear whether it is increased when compared with control subjects. Indeed, prospective well-controlled studies are unavailable. To date, prevalence has been reported with a wide range from 9% to 70% [44–47]. A recent multicenter study demonstrated that children with ASDs are over three times more likely to have parent-reported GI symptoms than the general population and almost two times more likely than the other developmental disorders [48]. The most common GI symptoms reported in children with ASDs are chronic constipation, abdominal pain with or without diarrhea, and encopresis as a consequence of constipation [41]. Other GI motility abnormalities that have been described for individuals with ASDs include GERD and abdominal bloating [41]. In children with ASDs, GI conditions can present typically or atypically as non-GI manifestations, including behavioral changes. Horvath et al. reported disturbed sleep and night-time awakening for 52% of children with ASDs who had GI symptoms (vs 7% of age-matched healthy siblings; $p < 0.001$) [44]. Children with ASDs who had reflux esophagitis exhibited unexplained irritability more frequently (43%) than those who did not (13%) [44]. Behaviors may be markers of abdominal pain or discomfort in individuals with ASDs [48, 49]. Nevertheless, a consensus report on the evaluation, diagnosis, and treatment of GI disorders in individuals with ASDs, published in 2010, concluded that the existence of a GI disturbance specifically correlated with ASDs has not been established and the pathogenetic hypothesis has not been determined [41]. Well-designed trials are, therefore, needed in order to develop evidence-based recommendations for optimal diagnostic and treatment strategies in children with ASDs. Until then, the consensus clearly reports that application and, where necessary, adaptation of conventional recommendations for the general pediatric population are relevant to children with ASDs [41].

Turner's Syndrome

Turner's syndrome (TS) affects about 1 in 2000 live born females [50]. In about 50% of cases, karyotype analysis of peripheral lymphocytes reveals the complete loss of one X chromosome (karyotype 45,X), whereas the remaining patients display a multitude of chromosomal abnormalities, including part absence of one X chromosome or mosaicism [50]. Already, in the early 1980, Chen et al. reported a high incidence of feeding difficulties in early childhood of children affected by TS, associated with regurgitation and vomiting [51]. In 1992, Mathisen and colleagues investigated ten infants affected by TS and ten control girls in order to detect oral motor dysfunction and feeding disorders [52]. Through the use of video recording of routine meals and the administration of the feeding assessment schedule, the authors clearly demonstrated that patients affected by TS presented considerable and persistent early feeding problems correlated with a characteristic range of oral-motor dysfunction [52]. Breast-feeding as well as introduction of solid foods were especially difficult for the mothers of case infants. In addition, most of the case-group mothers reported vomiting and regurgitation, suggesting that some children with TS may have some dysfunction of the lower gastro-oesophageal tract [52]. Following these findings in 1996, Staiano and colleagues evaluated upper GI motility in patients with TS in order to detect the presence of GI motor dysfunction [53]. The study population consisted of 13 girls with TS and two comparison groups: seven girls with familial short stature and eight control girls. All the subjects underwent gastric emptying study, through the use of scintigraphy. In addition, six girls with TS and eight control children also underwent oesophageal manometry [53]. The percentage of retention of solids at 60 min and 90 min was significantly greater ($p < 0.001$) in patients with TS than in control subjects and in

children with familial short stature. Five of the 13 (38%) girls with TS had a gastric emptying result at 60 min exceeding the mean and 2 SDs of the results in control children. Gastric emptying delay in TS children was independent of the body weight. Conversely, esophageal manometry did not show significant differences in TS children when compared with the control group. The authors concluded that the impaired gastric motility represented a novel GI finding of this syndrome. To the best of our knowledge, no further report of motility dysfunction in TS children has been published since.

Noonan Syndrome

Noonan syndrome (NS) is an autosomal dominant disorder characterized by short stature, typical face dysmorphology, and congenital heart defects. The incidence of NS is reported to be between 1 in 1000 and 1 in 2500 live births [54]. Severe feeding difficulties are commonly in described in NS children, although the prevalence and underlying cause are poorly understood [54]. In 1992, Sharland and colleagues reported the clinical characteristics of 151 children affected by NS. Feeding histories were obtained in 144 children. Among them, significant feeding difficulties were reported in 109 children (75.6%) [55]. In 34 patients (24%), these difficulties were defined as severe, requiring tube feeding for 2 weeks or longer. In 54 cases (38%), feeding difficulties were moderate, defined as very poor suck, with slow feeding and recurrent vomiting [55]. Following these early reports, in 1999, Shah et al. conducted a study in order to characterize GI motility in children affected by NS [56]. Twenty-five children with NS were consecutively enrolled. Poor feeding described as poor suck or refusal to drink or eat solids, and recurrent vomiting were present in 16 of 25 patients (64%). Eight of 16 infants with GI symptoms had evidence of gastro-oesophageal reflux. In seven of eight, this was demonstrated by pH study [56]. The children with the most severe symptoms were further investigated by surface electrogastrography (EGG) and antroduodenal manometry (ADM). Four of the five patients who underwent EGG had evidence of abnormal gastric myoelectrical activity. ADM showed an immature contractile activity rather than neuropathological in appearance, reminiscent of that seen in neonates of 32–35 week gestation [56].

Rett Syndrome

Rett syndrome is a neurodevelopmental disorder characterised by a period of developmental regression at approximately 6–18 months with loss of hand and communication skills, development of hand stereotypies, and impaired gait [57]. Most cases are caused by a mutation in the MECP2 gene [57]. Two recent papers clearly demonstrated in an in vitro model the importance of MECP2 in the development of enteric nervous system and GI motility clarifying some aspects of motility disorders observed in children with Rett syndrome [58, 59]. As with other neurodevelopmental conditions, disorders of GI motility such as GERD, constipation, and abdominal bloating are common [59, 60]. In 2014, a group of experts published a systematic review of the literature, in order to give some practical recommendations for the management of GI motility disorders in children with Rett syndrome [61]. GERD has been reported up to 39% of girls and women affected by Rett syndrome [62]. According to the expert panel, common indicative symptoms include vomiting, rumination, regurgitation, and respiratory signs, and unexplained weight loss [61]. The diagnostic approach should not differ from the other patients, including pH monitoring and upper GI endoscopy. With regard to treatment, the majority of the panel agreed that conservative strategies such as small frequent feeds and the use of more upright positioning in combination with pharmacological management should be adopted. PPIs are the first choice of treatment, followed by H2 receptor blockers and prokinetic agents [61]. Laparoscopic fundoplication should only be advised in case of refractory GERD. Despite the prevalence reported in up to 80% of affected girls and women in a recent US family survey, it is still unclear on how constipation should be best diagnosed and treated [62]. Diagnosis is often difficult due to the communication impairment. A stepwise plan for management was identified with a high rate of agreement from the panel members on the use of various laxative agents [61]. Abdominal bloating, as a result of aerophagia or air swallowing, has been reported in almost half of the cases in a population-based sample [63]. In some case reports, severe aerophagia has been associated with gastric perforation [64]. Treatments such as simethicone or magnesium sulphate or selective serotonin reuptake inhibitors have been suggested. There was no consensus on the use of magnesium sulphate; its use has only been supported by case reports. Where symptoms are severe, a gastrostomy may be considered [61].

Prader–Willi Syndrome

Prader–Willi syndrome (PWS) is a multisystemic genetic disease, which was first described in 1956 [65]. The incidence of PWS is 1:15,000–30,000 newborns. The syndrome is characterized by muscular hypotonia, feeding difficulties, failure to thrive, developmental delay, short stature, and hypogonadism [65]. GI motility in children with PWS has been sparsely investigated. Following case reports describing gastric rupture in PWS children [66, 67], Arentz and colleagues measured the gastric emptying in eight PWS

pediatric patients through nuclear scintigraphy after a standardized test meal [68]. In contrast with adult literature [69], the authors found a delayed gastric emptying in five out of eight (62.5%) children and concluded that this may represent a risk factor for the development of gastric rupture [68]. More recently, Kuhlmann et al. evaluated colorectal function in 21 adult PWS patients [70]. All enrolled patients underwent a whole assessment for diagnosis of constipation, including Total GI Transit Time (GITT). Eight out of 21 patients (40%) fulfilled diagnostic criteria for functional constipation. GITT was >3 days in 5/21 (24%) of PWS and none of the controls ($p = 0.04$). To the best of our knowledge, no pediatric study has evaluated the prevalence of functional constipation among PWS children.

Familial Dysautonomia

Dysautonomia is a complex primary or secondary neurological disorder that affects the sensory system and autonomic nervous system functions. Familial dysautonomia (FD), also known as Riley–Day syndrome, is an autosomal recessive disease, occurring predominantly in the Ashkenazi Jewish population with an incidence of about 1 in 1370 individuals [71]. Although FD is caused by one gene and the penetrance is always complete, there is a great deal of variation in expression. The sensory dysfunction is characterized by alterations of small fiber neuronal populations, such that FD patients have impaired sensations of temperature, pain, and vibration. The autonomic dysfunction affects multiple systems and it is characterized by cyclic manifestations of typical "dysautonomic crisis". These crises represent systemic reactions to physiologic and psychological stress; GI perturbations such as vomiting are the predominant part of the constellation of symptoms seen during an episode; other symptoms include hypertension, tachycardia, diaphoresis, personality changes, blotching of the skin, piloerection, functional ileus, and dilatation of pupils [72]. Malfunction of the GI tract is the main clinical manifestation of FD with oropharyngeal incoordination being one of the earliest symptoms in the newborn. Discoordinated swallow is found in about the 60% of patients with FD and it is often responsible for the development of severe feeding alterations, malnutrition, and recurrent aspiration, which can lead to chronic lung disease [73]. Impaired brainstem reflexes seem to underlie these abnormalities [74]. Videofluorograpic swallow study allows for visualization of bolus flow throughout the upper aero-digestive tract in real time and it is used to examine the presence and the timing of aspiration. In addition, cineradiographic swallowing studies may document the level of functional ability [75, 76]. However, the prominent GI symptom is the propensity to vomit. Recurrent vomiting can be caused by peripheral as well as central autonomic dysfunction. Vomiting can occur cyclically as a part of dysautonomic crisis or daily in response to stress of arousal. When the vomiting is associated with a constellation of symptoms, including hypertension, tachycardia, and diffuse sweating, the symptom is secondary to the autonomic crisis. The efficacy of diazepam in reducing vomiting during autonomic crisis suggests that the crisis is caused by a central phenomenon, probably developed from autonomic seizures [77]. Gastro-esophageal reflux is another common problem. Sundaram and colleagues found a prevalence of 95% of GERD in a sample study of 174 FD patients [78]. Clinical symptoms can range from regurgitation to more atypical manifestations, such as wheezing, apnoea, or iron deficiency anemia secondary to severe esophagitis. A major contributor to the development of GERD is represented by dysfunction and increased relaxation of the LES. The LES is controlled by postganglionic parasympathetic fibers within the vagus nerve and preganglionic sympathetic fibers. The parasympathetic circuits are able to control both the relaxation and the contraction of LES, while the sympathetic system exclusively evokes contraction. The pathogenesis of GERD is correlated with the reported degeneration of the sympathetic nervous system and the consequent prevalence of the parasympathetic. Thickened fluids and smaller more frequent meals represent the first steps in management. Medical management including H2-antagonists and PPIs is usually needed. However, if symptoms persist and events such as hematemesis occur, surgical intervention (fundoplication) is strongly recommended. Up to 80% of FD patients will undergo fundoplication surgery [79, 80]. The impact of the fundoplication wrap on the natural history of these patients compared with that of untreated patients has not been clarified. GERD can reoccur after the fundoplication, and up to 12% of patients who underwent the procedure will require a second surgery [81]. Esophageal dilatation and achalasia are possible recognized complications after fundoplication surgery [82, 83].

Mitochondrial Disorders

Mitochondrial disorders (MD) refer to a clinically heterogeneous group of disorders that arise as a result of dysfunction of the mitochondrial respiratory chain. They can be caused by either inherited or spontaneous mutations of nuclear (nDNA) or mitochondrial DNA (mtDNA) which lead to altered functions of the proteins or RNA molecules that normally reside in mitochondria. Defects in nDNA can be inherited from either parent, while defects in the genes of the mtDNA are maternally inherited. Mitochondria are present in virtually all cell types of human body and their damage affect especially the main energy-dependent tissues, such as brain, heart, liver, skeletal muscles, kidney and the endocrine

and respiratory systems [84]. MD primarily affect children, but adult onset is becoming more common. Many mtDNA abnormalities (>100) have been described in the literature as being associated with MD, some resulting in profound disability and premature death [84]. GI symptoms are reported in 15% of MD patients occurring usually in childhood, before the onset of more classical symptoms of MD [85]. The major MD presenting with GI symptoms are: mitochondrial neuro-GI encephalomyopathy (MNGIE) (peripheral neuropathy, ophthalmoparesis, leukoencephalopathy, muscle wasting, and cachexia) [86]; Leigh syndrome (subacute necrotizing encephalomyelopathy resulting in hypotonia, bulbar paresis, abnormal eye movements, lack of coordination of extremities, and regressive psychomotor development) [87]; Kearns–Sayre syndrome (chronic progressive external ophthalmoplegia, atypical pigmentary retinopathy, ataxia, and heart block) [88]; and MELAS syndrome (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes) [89]. MNGIE is a rare autosomal recessive disorder caused by mutations in the gene encoding thymidine phosphorylase, which lead to absolute or nearly complete loss of its catalytic activity, producing systemic accumulations of its substrates, thymidine (dThd), and deoxyuridine (dUrd) [90]. MNGIE typically presents between the first and third decades with GI symptoms as presenting feature in approximately half of the cases [91]. Nevertheless, all patients will develop GI symptoms during the course of the disease. The main symptoms attributable to GI dysmotility are: dysphagia, early satiety, nausea, vomiting, abdominal pain and cramps, borborygmi, intestinal pseudo-obstruction, and bloating. These symptoms invariably lead to weight loss, which may manifest as extreme cachexia. Although the average age at presentation is approximately 18 years, GI symptoms have been reported earlier during the first year of life, including diarrhoea at 5 months of age in one case and intussusception at 8 months in another infant [91]. Recently, a position paper on the management of MNGIE has been released by an International Network [92]. Swallowing tests, gastric emptying, and GI manometry are among the suggested diagnostic work-up to detect GI motility anomalies [92]. Different mtDNA mutations have been associated with GI disorders in MD. Recently, Horvath et al. found a new heteroplasmic mutation in the anticodon-stem of mitochondrial tRNA of a girl presenting with clinical symptoms of MNGIE-like GI dismotility and cachexia [93]. Intestinal pseudo-obstruction is an increasingly recognized clinical feature in MNGIE and may represent an important cause of chronic intestinal failure. The pathogenesis of intestinal pseudo-obstruction in MD is still unclear. Giordano et al. described the presence of smooth cells atrophy, mitochondrial proliferation, and mtDNA depletion in the muscularis propria of the small intestine in two different studies and performed in 1 and 4 patients suffering from MNGIE, respectively [94, 95]. Their pathogenetic hypothesis was that in MNGIE patients, the baseline low abundance of mtDNA molecules may predispose smooth muscle cells of the external layer of muscularis propria to the toxic effects of circulating dThd and dUrd. More recently, Zimmer et al. first reported evidence for an alteration of the interstitial cells of Cajal (ICC) network in MNGIE [96]. These findings support the hypothesis that ICC loss might be an early pathogenetic event in MNGIE-associated gut motor dysfunction before significant myopathic and/or neuropathic structural changes occur [96]. Poor feeding and vomiting are often the initial presenting symptoms in Leigh syndrome [97, 98]. Mutations in the nuclear gene encoding SURF1, a mitochondrial protein involved in cytochrome c oxidase assembly, have been noted in many patients with Leigh syndrome and GI symptoms [99]. Dysphagia is also common in patients affected by Leigh syndrome [100]. Dysphagia seems to be due to primary esophageal dysmotility, neurogenic causes, or a combination of these two factors. Fifteen percent of patients with Kearns–Sayre syndrome, an MD characterized by deletions in cytochrome c oxidase deficiency, present with swallowing difficulties and dysphagia [101]. Shaker et al. described the manometric characteristics of a cervical dysphagia in a patient with Kearns–Sayre observing absence of pharyngeal peristalsis, abnormally low upper esophageal sphincter resting pressure, and absence of proximal esophageal peristalsis [102]. Eighty percent of patients with MELAS have the same mtDNA mutation, m.3243A>G, while the remaining cases are caused by a range of other mtDNA mutations. Diagnostic criteria include a stroke-like episode occurring before 40 years, neurological disturbance characterised by seizures and/or progressive dementia, lactic acidosis, and a ragged red fibres myopathy [103]. Other neurological features include severe migraines, sensorineural hearing loss, peripheral neuropathy, and psychiatric problems, including depression. GI disturbances have been frequently reported in children affected by MELAS. Sproule et al. reported GI disturbance in 64% of a prospective cohort of 45 patients with a diagnosis of MELAS [103]. Symptoms included abdominal discomfort, vomiting, constipation, diarrhoea, gastroparesis, intestinal pseudo-obstruction, and recurrent pancreatitis [104]. Other MD are characterized by non-specific GI symptoms, including dysphagia, delayed gastric emptying, feeding difficulties, GER and/or vomiting, diarrhea, failure to thrive, and abdominal pain [105]. GI symptoms are predominantly localized in the upper GI tract. Chitkara et al. reported the cases of six children with MD who presented upper GI symptoms, such as vomiting, food aversion, GER, poor suck, and feeding intolerance [106]. Dysmotility disorders such as delayed gastric emptying and intestinal pseudo-obstruction have been shown in child and adult patients with MD [106]. Gastroparesis has been associated with various diseases and may occur as part of an MD [106, 107]. There is no consensus regarding

management of patients with gastroparesis who do not respond to simple antiemetic or prokinetic therapy. Tatekawa et al. proposed a new surgical technique in a 12-year-old girl with pyruvate dehydrogenase complex deficiency and refractory gastroparesis [108].

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Gastrointestinal Disturbances in Autism Spectrum Disorder

28

Lena Gottesman-Katz, Jonathan Miller, and Kara Gross Margolis

Introduction

Autism spectrum disorders (ASD) are complex neurobehavioral conditions that present with varying phenotypes and severities. Although specific underlying etiologies remain elusive, ASD is currently understood to be caused, at least in part, by varying genetic and environmental risk factors. In addition to the neurobehavioral manifestations that are key to an ASD diagnosis, gastrointestinal (GI) co-morbidities in children with ASD are common and often difficult to diagnose and treat. Underlying clues to their pathophysiology have been identified in studies that relate specific genetic or environmental susceptibilities to subsets of children with ASD and GI dysfunction. We provide an overview on the current understanding of GI problems in children with ASD, with focus on their prevalence, clinical presentations, potential pathophysiologies, screening tools, and treatment options.

Prevalence of Gastrointestinal Issues and Clinical Manifestations in Children with ASD

GI co-morbidities have been increasingly recognized in children with ASD. Prevalence data have shown a wide variation in studies, ranging from 9% to 91% [1]. More recent individual studies have both confirmed the high prevalence of GI disorders in the ASD population and have also highlighted the most common conditions. One study found a prevalence of 58% with the leading diagnoses being functional constipation and gastroesophageal reflux disease (GERD), found in 35% and 30% of individuals, respectively [2]. The Childhood Autism Risks from Genetics and the Environment study, the largest population-based case–control study comparing GI manifestations in children with ASD to those with neurotypical development, found that individuals with ASD were three-to-nine times more likely to exhibit GI symptoms and that constipation and diarrhea were the most prevalent diagnoses [3]. A comprehensive meta-analysis that incorporated 15 studies including 2215 children found that GI symptoms are fourfold more common in children with ASD compared to non-ASD controls [4]. Other studies have further confirmed the high prevalence of GI problems in children with ASD, with constipation, diarrhea, and abdominal pain comprising the most common complaints [5–7].

Although children with ASD develop the same GI conditions as their neurotypical peers, their presentations may be distinct. Children with ASD can have altered pain sensitivity and heightened or diminished responses to various GI stimuli [8]. This failure to predictably respond to GI sensory input is further complicated by the inability of some of these children to verbalize and localize discomfort. Consequently, seemingly unrelated behavioral concerns linked with GI discomfort have been described. For example, irritability has been associated with esophagitis [9], rigid compulsive behavior with functional constipation [10], and sleep disturbance, and/or aggressive and self-injurious behaviors with GI symptoms [10–12]. Complicating these presentations is the finding that these behaviors can also be present in the absence of GI issues [11]. These atypical presentations of GI distress can hinder the ability of medical providers to make timely and/or accurate diagnoses [8, 9, 12, 13]. Because of these associations, however, it is advisable that evaluation for GI prob-

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lems be considered for children with ASD in the setting of new-onset and/or worsening behavioral symptoms, and should occur in parallel with therapies targeted toward the observed behaviors [1, 11].

Atypical eating patterns, such as food selectivity and food refusal, are common behaviors in children with ASD and research suggests that these behaviors are often associated with GI symptoms [6, 14] and more severe ASD symptoms [15]. Food preferences in children with ASD often include processed foods as well as foods high in carbohydrates and/or sugar. These foods are often low in fiber and may exacerbate GI issues, such as constipation [16]. ASD can also be associated with a higher incidence of pica which has also been proposed to be associated with GI pain or discomfort [17, 18].

Psychiatric co-morbidities frequently accompany ASD diagnoses and may also impact GI function. For example, anxiety disorders, attention deficit hyperactive disorder, and/or oppositional defiant disorder occur in up to two-thirds of individuals with ASD having two or more comorbid conditions [19–21]. The observed correlation between stress and GI symptoms has led to interest in the study of links between ASD, psychiatric comorbidities, and GI symptomatology [22]. Specifically, an enhanced cortisol response in children with ASD was associated with GI symptoms in the lower intestinal tract [23]. Similarly, autonomic dysregulation may correlate with the presence of GI findings in children with ASD [10]. The mechanistic pathways connecting these phenotypes, scientific evidence of causality, and the initiator of dysfunction (intestinal vs. extra-intestinal), however, require further study.

In an effort to further understand the significant phenotypical heterogeneity in the ASD population and to determine whether GI problems correlate with specific co-morbidities, several studies have evaluated whether there are subsets of individuals who present with the same cluster of medical issues and GI dysfunction. A study that utilized retrospective diagnosis code analysis found that GI issues clustered with seizures [24]. Another study, using data available from two large registries, found that the highest (23%) co-occurrence of GI disturbance occurred with sleep problems, with a twofold increased risk of having both conditions [25]. Additional studies confirm this link between GI problems and sleep dysfunction [26]. Providers should thus consider evaluation for underlying GI symptoms in child with ASD and sleep and/or seizure disorders.

Overall, expert consensus is that GI problems among children with ASD are common and can have significant effects on behavioral symptom severity [1]. The many limitations of current studies, including in methodology (i.e., small sample size, retrospective design, and population biases) and potential underdiagnosis of GI issues due to atypical presentations, necessitate the requirement for large, prospective studies that include extensive clinical phenotyping [27].

Risk Factors and Suspected Pathophysiology

The current research devoted to understanding the common origins of ASD and GI tract dysfunction has thusfar largely focused on genetic contributions and environmental factors. Genetic studies have revealed hundreds of genetic variations, both inherited and de novo, that are associated with ASD [28, 29]. Several of these genetic variants have also been found to play important roles in gut development and/or function. The presence of a specific polymorphism in the promotor region of the MET tyrosine receptor kinase gene, which has been associated with ASD, has also been found with higher prevalence in those with a concurrent GI disorder [30]. Other genetic mutations found to potentially play a role in ASD and GI dysfunction include the variant Ala56 of the serotonin (5-HT) transporter gene, SERT [31]. Mice with this mutation were found to have increased 5-HT clearance, autism-like behaviors, enteric nervous system hypoplasia and GI dysfunction including increased colonic transit time (constipation) and abnormal colonic peristalsis. Mutations in the SHANK family of genes, which code for synaptic scaffolding proteins of glutamatergic neurons in the brain, have been associated with ASD and GI abnormalities in a subset of patients [32]. Accordingly, in an SHANK3 knock-out mouse model, small intestinal villi length was significantly decreased and microbiome composition differed compared to wild-type mice [33]. While this model showed no distinct phenotypic GI dysfunction, loss of intestinal barrier function and increased inflammatory cytokine levels were reported. Chromodomain helicase DNA-binding protein 8 (*CHD8*) has also been associated with ASD and GI symptoms in afflicted individuals [34]. Children with mutations in this gene typically have macrocephaly, specific dysmorphic facial features, and GI issues. In a zebrafish model with this mutation, fish developed a hypoplastic enteric nervous system and slowed GI transit. Other mutations have been significantly associated with ASD and GI dysfunction such as neuroligin mutations and the BTBR $T^{+}Itpr3^{tf}/J$ strain. A murine model of a human neuroligin-3 missense mutation showed significant alterations in intestinal function, enteric neuron quantity, and colonic microbiome composition. The BTBR $T^{+}Itpr3^{tf}/J$ strain, a widely used mouse model of ASD, harbors GI manifestations, including delayed transit time, increased intestinal permeability, and altered microbiome signatures [35, 36].

Environmental risk factors that have been studied as potential risk factors for ASD development include gut microbiota imbalance, prenatal maternal infection, maternal inflammation, and maternal obesity. The gut microbiota may

impact both brain and gut development as well as function. For example, germ-free mice and rats display decreased sociability with improved behavior following colonization with wild-type mouse microbiota [37–39]. Recently, it has been shown that transplanting gut microbiota from ASD patients into germ-free mice induces ASD-like behaviors, possibly through alternative splicing of genes associated with ASD, demonstrating a direct impact of the gut microbiota on behavior [40]. Of note, germ-free mice also display abnormalities in ENS development and function [41–43].

The effects of gut microbiota imbalance may persist past development. An important study by Luna et al. was the first to show a link between gut microbiota differences, neuroimmune abnormalities, and GI manifestations in ASD. Previous studies revealed a positive association between individuals with ASD and an upregulation of certain types of Clostridia. Luna et al. replicated this finding and additionally found that these Clostridia species were significantly correlated to specific stool and/or blood proinflammatory cytokines and neurotransmitters, including serotonin and tryptophan, that were associated with GI pain [44]. Although other clinical studies have identified differences in GI microbiota composition and diversity between neurotypical individuals with those with ASD, results have been diverse and even contradictory [45, 46]. There have been significant limitations in many of these studies, including small sample size and a lack of examination for critical confounding factors (e.g., GI motility issues, diet, and medication use). Diet is an important consideration in such studies, particularly because children with ASD often are given altered diets (e.g., casein- and/or gluten-free) or have self-imposed intake limitations. In a small study of children with ASD and GI issues, decreased levels of disaccharidases and hexose transporters were found to be associated with gut microbiota changes, but these data have not been confirmed in a larger population [47–49]. While these findings provide evidence that children with ASD may have different microbial signatures than neurotypical kids, more research is needed in larger cohorts before conclusions can be made.

Multiple studies show an association between viral or bacterial maternal infection and an increased risk of ASD in offsprings [32, 50–52]. It is suggested that maternal infection, with changes in the maternal cytokine milieu and gut microbiome, may confer ASD risk through exposure of the fetus to maternal inflammation, a process referred to as maternal immune activation (MIA). MIA has been mimicked in murine studies, whereby inflammation is induced by the injection of pregnant mice with the viral mimetic, polyinosinic:polycytidylic acid (Poly I:C) [50, 53, 54]. Supportive of the hypothesis that the gut microbiota plays a role in MIA-induced behavioral dysfunction is a study demonstrating that partial normalization of the microbiota with Bacteroides repletion in an MIA mouse model resulted in correction of the ASD phenotypes [27].

A systematic review found that excessive weight gain during pregnancy was associated with an increased risk of ASD in offspring [55]. Additional studies further support obesity as a maternal risk factor for neurodevelopmental disorders in progeny [56]. Maternal obesity impacts hormones such as leptin which directly influence inflammatory cytokines and may also impact fetal brain development [56, 57]. Another way in which maternal obesity may impact neurodevelopment is through the gut microbiota. In a study using a murine model, mice fed a high fat diet during pregnancy led to significant dysbiosis, impaired social behavior, and decreased neural plasticity in offspring [58]. Furthermore, oral treatment with *Lactobacillus reuteri* improved social behaviors in these mice, demonstrating the potential interactions between maternal diet, microbiota imbalance, and neurodevelopment.

Diagnosis and Management

Diagnostic Considerations

Making a GI diagnosis in children with ASD can be challenging given the wide range of atypical presentations, the common limitation in communicative abilities and the increased incidence of comorbidities. Pediatricians and gastroenterologists should probe for comorbid conditions, including behavioral problems, sleep disorders, and seizures, in addition to classic GI signs and symptoms. Because the interactions of these clinical phenotypes can be challenging to treat simultaneously (e.g., increased risk of constipation with many medications utilized to treat problem behaviors) and can result in polypharmacy, individuals with GI dysfunction and other comorbidities often require a team approach, including a gastroenterologist and primary pediatrician as well as a psychiatrist, neurologist, sleep specialist, and/or nutritionist, as appropriate [1].

Functional abdominal disorders, common in typically developing children, may have an even higher prevalence in children with ASD [5, 59, 60]. The Rome IV criteria, considered the gold standard for diagnosis of disorders of gut-brain interactions, often cannot be reliably used in children with ASD because many of these criteria require verbalization of subjective complaints. As a way to attempt to address this limitation, an alternative screening tool was developed that relies on caretaker assessment of signs associated with GI dysfunction and was found to be sensitive for the diagnosis of functional constipation and functional diarrhea, as well as GERD [2].

Anticipatory Guidance

Caretakers of children with ASD often present to health care providers with questions regarding the roles of gut inflammation and permeability in ASD. Though some studies have supported the notion that increased rates of intestinal epithelial permeability and/or inflammation may exist in this population, these studies are small and have often been contradictory. Thus, there is currently no definitive evidence that individuals with ASD have increased intestinal inflammation, permeability, or a brush border enzyme deficiency [61].

There has been intense interest in the role of the gut microbiota as a potential therapeutic target in children with ASD, but there remains no consistent microbial profile known to be specific to individuals with ASD [62–67]. The interest from families in the gut microbiota may come in the form of questions regarding the utility of specific diets, pre- and probiotics and/or fecal transplant. Although there is not definitive evidence from double blind, placebo-controlled trials or cross-over studies to suggest that specific diets are beneficial for children with ASD, several diets are often utilized, most commonly the gluten- and casein-free diet. [1, 68–70] Several studies have found varying benefit, but lack adequate placebo control groups or blinding of subjects to the treatment arm [70–72]. It is thus possible that some individuals with ASD will benefit from specific diets, but determination of how those individuals can be identified remains to be clarified.

There is a lack of evidence to support the use of pre- or probiotics as a treatment for ASD. Double-blind randomized, controlled trials, crossover studies and feasibility pilot studies have also shown conflicting results, underscoring the need for more rigorous, larger, prospective studies to determine whether specific subsets of children may improve [73–76]. Most recently, there has been interest in fecal microbiota transplant as a treatment for GI and behavioral symptoms in children with ASD. A small, open-label, non-placebo-controlled trial assessing the efficacy of fecal transfer in 18 children with ASD showed improvement in GI symptoms scores and behavioral scores persisting at 8 weeks and up to 2 year post-transplant [77, 78]. Although these results are exciting, a larger, randomized, placebo-controlled trial will be necessary to confirm these effects.

Management

Recommendations regarding the management of GI conditions in children with ASD remain similar to those of neurotypical children. Standardized approaches and algorithms targeted toward children with ASD remain an area of need [1]. One such algorithm was created that provided constipation management guidelines for the pediatrician with further guidance for when to provide referral to a gastroenterologist [79]. Dietary modification should be an early consideration in management. For example, diarrhea may be secondary to sugary foods and drinks with high osmotic loads; constipation can be related to low fiber intake. Clinical suspicion for other GI conditions should warrant similar diagnostic testing to what is conducted in the neurotypical population. Nonetheless, for all GI disturbances, treatment response in some patients may only be monitored through close attention to problem behaviors and seemingly unrelated presentations, as discussed above.

Providers will likely find that many children with ASD, especially those with comorbid psychiatric manifestations, will have been prescribed anxiolytics, anti-psychotics, or anti-depressants, many of which cause off-target GI side effects, especially constipation. Monitoring for behavioral and GI changes associated with psychiatric medication administration is thus vital and underscores the need for multi-disciplinary communication and close follow-up with pertinent providers.

Future Directions

As the prevalence of ASD increases, there is a greater need for further understanding of the GI disturbances that affect these children, effective tools to diagnose GI issues in this population, and novel therapeutics. As our knowledge of the pathophysiology and phenotypes of ASD improve and the specific factors linked to GI dysfunction become elucidated, this will lead to improvements in caretakers' abilities to identify and treat ASD-related GI co-morbidities. The gut microbiota may provide an avenue for therapeutic targets, but requires more study through prospective, placebo-controlled trials that incorporate well-described clinical phenotypes, diet, and other individualized traits that impact microbiota composition. Large, prospective longitudinal studies are thus necessary to provide a more complete understanding of how these different factors contribute to ASD and GI dysfunction [80].

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Part IV

Motility Disorders After Surgery and Developmental Anomalies of the Enteric Neuromuscular System Secondary to Anatomical Malformations

Esophageal Atresia

29

Usha Krishnan, Franziska Righini-Grunder, and Christophe Faure

Introduction

Esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) is the commonest congenital digestive anomaly, occurring in 1 in 2400–4500 births worldwide [1]. Since the first successful surgery in 1941, anesthetic, surgical, and neonatal care have improved tremendously and caretakers focus has shifted from achieving survival to improve short- and long-term morbidity and optimize quality of life [2]. Beside respiratory problems, motor disorders of the esophagus leading to gastroesophageal reflux (GER), esophageal strictures, eosinophilic esophagitis (EoE), feeding disorders, and dysphagia remain the most frequent clinical problems. With increased survival and potentially related to chronic acid exposure of the esophageal mucosa, Barrett's esophagus and esophageal carcinoma are also a concern [3, 4]. International recommendations on management of gastrointestinal and nutritional complications in children with EA have been recently published [5].

Gastroesophageal Reflux

After EA repair, the prevalence of GER is reported to be between 22% and 63% depending upon patients' age, EA type, and diagnostic techniques or criteria. In infants and children with isolated EA (type A), GER is reported in almost all patients [5]. GER is often associated with compications, such as esophagitis and recurrent anastomotic strictures as reported by non-controlled studies [6–8]. Respiratory complications (persistent atelectasis, aspiration pneumonia, asthma/increased airway reactivity, chronic lung disease with bronchectasis and worsened tracheomalacia, airway obstruction, and/or acute life threatening episode) may also be associated with GER [6, 8]. However, pulmonary symptoms can also be related to aspiration of mucus or food retention in the proximal pouch or distal esophagus, anastomotic stricture, congenital esophageal stenosis, aspiration during swallowing due to a co-existing laryngeal cleft, recurrent or missed fistulae, tracheal pouch, EoE, or esophageal pooling over a fundoplication.

Using impedance testing in 24 children with EA, Fröhlich et al. demonstrated an abnormal bolus index (percentage of recording time with esophageal exposure to a refluxate) in 67% of the patients [9]. Catalano et al. studied a group of 22 children with EA at a median age of 15 months with an uneventful postoperative course: reflux episodes were mainly nonacidic (76.4% of total refluxes), especially in children younger than 1 year (89.2%) [10]. Pathological acid reflux was reported in 10 of 22 patients (45%). However, in a case control study by Tong et al. which compared 35 EA patients with 35 age- and sex-matched normal controls with suspected GERD, the authors found no significant difference in the total retrograde bolus movements between the EA cohort and the control group [11]. One of the limitations of pH-impedance testing in patients with EA is that baseline impedance is lower than in control patients because of poor esophageal function and/or stasis of liquid especially in the lower esophagus [9, 11]. Therefore, a careful manual analysis, in addition to automated analysis, is essential in these patients.

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Patients with EA are at high risk of developing severe GER for several reasons: esophageal dysmotility, hiatal hernia, smaller portion of the intra-thoracic part of esophagus, vagal nerve surgical injury, and anomalies of gastric motility. A combined impedance-manometry study conducted in 10 children aged less than 3 years with non-complicated type C EA reported that transient LES relaxation was the pathophysiological mechanism in 2/3 of the reflux episodes [12]. No similar data are available in long gap (LG) EA and this finding may not apply to patients with high-tension anastomosis leading to abnormal anatomic location of the LES as well as impaired esophageal motility. Recent recommendations suggest that GER should be systematically treated with proton pump inhibitors (PPI) for prevention of peptic complications and anastomotic strictures up to the first year of life or longer, depending on persistence of GERD [5]. However, in a retrospective observational study by Donoso et al., prophylactic PPI-treatment did not reduce the rate of anastomotic stricture [13]. In addition, in a study by Stenström et al., development of anastomotic strictures in the first year after reconstruction of EA was not reduced by prolonged PPI prophylaxis (12 vs. 3 months) [14]. Similar results were found in a recent longitudinal cohort study, which compared prospective data from 73 EA patients, over 11 years systematically treated with PPI, with a historical cohort of 134 EA patients. The authors found no significant difference in the incidence of anastomotic strictures between the present cohort on systematic PPI compared with the historical cohort (44% vs. 39%), and concluded that PPI treatment does not prevent the formation of anastomotic strictures [15].

Dysphagia

Studies have reported that dysphagia is very common occurring between 21% and 84% of infants, children, and adults with EA after surgical repair [16–20]. A recent systematic review found an overall pooled estimated prevalence of 50.3% in patients older than 10 years [21]. Dysphagia is probably more prevalent than reported, because children may not recognize their symptom as abnormal and may appear better adapted to their unique situation [18]. Dysphagia should be suspected in patients with EA who present with food aversion, food impaction, difficulty in swallowing, odynophagia, choking, cough, pneumonia, alteration in eating habits, vomiting, and malnutrition. Children may have minor or occasional difficulties with swallowing, may eat slowly or drink excessive amounts of liquids with foods, or develop food impaction. Significant changes in eating habits are reported in up to 73% of patients with dysphagia (need to drink, change in diet, and last to finish meal) [18]. A study by Menzies et al., which evaluated 75 children who attended a multidisciplinary EA clinic, found that 54% of children required texture modification at their meals mainly due to parental feeding concerns. Younger children were less likely to be eating age-appropriate textures, but this improved after 5 years of age [22].

A step-by-step investigation of this symptom requires a barium swallow and an upper endoscopy with biopsies [5]. The etiology of dysphagia may include inflammatory or anatomic causes, such as peptic esophagitis, EoE [23], anastomotic stricture, congenital stenosis [24], peptic stricture, post-fundoplication obstruction, vascular anomalies [25], inlet patch, anastomotic diverticulum [17, 26], and mucosal bridge [27]. In the absence of the latter causes, esophageal dysmotility remains the most likely explanation. The guidelines state that although esophageal manometry may be useful to characterize esophageal motility patterns in EA patients with dysphagia, the impact on clinical outcome is yet to be determined [5].

Feeding Disorders

A cross-sectional study using the Montreal Children's Hospital Feeding Scale in 145 toddlers with EA/TEF found 42% of subjects having a feeding disorder with an oppositional and aversive behaviour in 89% and signs of oral hypersensitivity in 67% [28].

The evaluation of aspiration during swallowing is very important to pursue as 20–47% of children with EA have aspiration or penetration [29, 30]. If aspiration is identified, the differential must include laryngeal clefts, vocal cord paralysis, a neurologic etiology, including Chiari malformations and developmental delay in swallowing function. Studies of patients with EA suggest that 3–17% have clinically significant vocal cord paralysis, and while the incidence of laryngeal cleft in patients with EA is not known, 27% of patients with laryngeal cleft have EA [31–33].

Eosinophilic Esophagitis

Recently, an increased incidence of EoE has been described in patients with EA. The largest reported number of EoE patients was in the study by Dhaliwal et al., which reported a 17% incidence in a retrospective review of biopsies taken from 103 EA patients over a 13-year period [23]. In another prospective longitudinal cohort study performed over 12 years in 77 children with EA–TEF, the incidence was 21% [34]. This is greater than the reported incidence of EoE in the general pediatric population of 1 in 10,000 children, and 8–10% in children with suspected GER refractory to anti-reflux treatment. In the study by Dhaliwal et al., EA patients with LG had an 11.8 times relative risk of developing EoE. The higher

incidence of EoE in the EA cohort has been ascribed to a possible genetic association, impairment of esophageal mucosal barrier function by acid refluxate, prolonged use of acid suppressive medications, or esophageal motility disturbances resulting in prolonged exposure to potential allergens in the already-damaged mucosa [35]. Significant reduction in dysphagia, food bolus impactions, reflux symptoms, and strictures needing dilation post-treatment of EoE in patients with EA was reported in study by Chan et al. [36]. This symptomatic improvement significantly correlated with a decrease in esophageal eosinophilia. However, whether this symptomatic improvement was due to improved inflammation and/or motility parameters is currently not known. The current guidelines recommend that EoE be excluded in patients with EA of all ages with dysphagia, reflux symptoms, coughing, choking, or recurrent strictures refractory to PPI, before proceeding to anti-reflux surgery [3]. For diagnosis of EoE multiple esophageal biopsies, both proximal and distal to the anastomosis should be taken and management of EA patients with EoE should follow consensus recommendations for treatment of EoE in the general population [5].

Esophageal Motility

Esophageal dysmotility has been reported in almost all patients with EA, but does not correlate with symptoms of dysphagia. Esophageal motility has been assessed in children by either esophageal manometry (using water perfused [12] or high-resolution solid-state technology [18, 20, 37]), impedancemetry [38] or videofluoroscopy [39]. Although clinical symptoms do not correlate well with conventional assessment methods of motor function, such as radiology or manometry, they may correlate with bolus flow. The current state of the art of diagnosis uses high-resolution manometry combined with impedance measurements in order to characterize the interplay between esophageal motor function and bolus clearance. Esophageal symptoms due to a motility disorder generally occur as a response to increased esophageal wall tension because of bolus retention and/or increased intrabolus pressure, and measurement of these features by pressure flow analysis (PFA) method enhances the understanding of esophageal symptoms.

Upper Esophageal Sphincter (UES)

The UES function has been reported to be normal by most authors [18, 20], but incomplete relaxation has been described in newborns [40]. When evaluated by videomanometry, an inadequate coordination between pharyngeal contraction and UES relaxation was found in adults [39]. Aspiration during swallowing assessed by videofluoroscopy has been reported in 20–47% of children with EA [29, 30]. There is no study on UES in patients with EA using PFA.

Esophageal Body

Esophageal body dysfunction has been reported in nearly all patients with EA. It is found in children [12, 18, 20, 37, 40–45] and persists life long as demonstrated by adult studies [17]. Using high-resolution manometry, the patterns of esophageal dysmotility in children with EA were recently described and were reported abnormal in all patients, with three types of abnormalities observed: aperistalsis, isolated distal contractions, and pressurization (Fig. 29.1a–c) [18]. Consistently, the pattern of esophageal dysmotility has not been predictive of the presence or severity of dysphagia. Impedance coupled to high-resolution manometry allows to categorize the pattern of esophageal dysmotility and to correlate the degree of motility abnormalities with bolus transit (Fig. 29.1d). In a recent case control study by Courbette et al., high-resolution impedance manometry was performed in 16 children with EA and 13 controls using PFA. Patients with EA were subgrouped according to their motility pattern: group A with the presence of distal contraction in ≥50% of the swallows and group B with the presence of distal contractions in <50% of the swallows. Esophageal peristaltic motor patterns were abnormal in all patients with EA. Bolus transport was significantly more impaired as shown by the higher impedance ratio in EA than in controls. Impedance ratio was also higher in group B (n = 8) versus group A (n = 8). However, symptoms of dysphagia did not correlate with the PFA measures. Contractile segment impedance, a marker of mucosal integrity, was significantly lower in the EA group. Bolus transport, although severely altered in patients with EA, was also not predictive of symptoms. The presence of residual distal contractions was associated with a more efficient bolus propulsion [46].

GER-related symptoms are prominent in patients with aperistaltic esophagus [18, 37]. There are no prospective longitudinal studies of patients with EA reporting the natural history of esophageal dysmotility. Using conventional manometric technique in 101 adults, Sistonen et al. demonstrated non-propagating peristalsis with weak and simultaneous esophageal pressure waves in 80% of patients, with ineffective distal esophageal peristalsis in all. Manometric abnormalities were significantly worse in those with epithelial metaplasia [17].

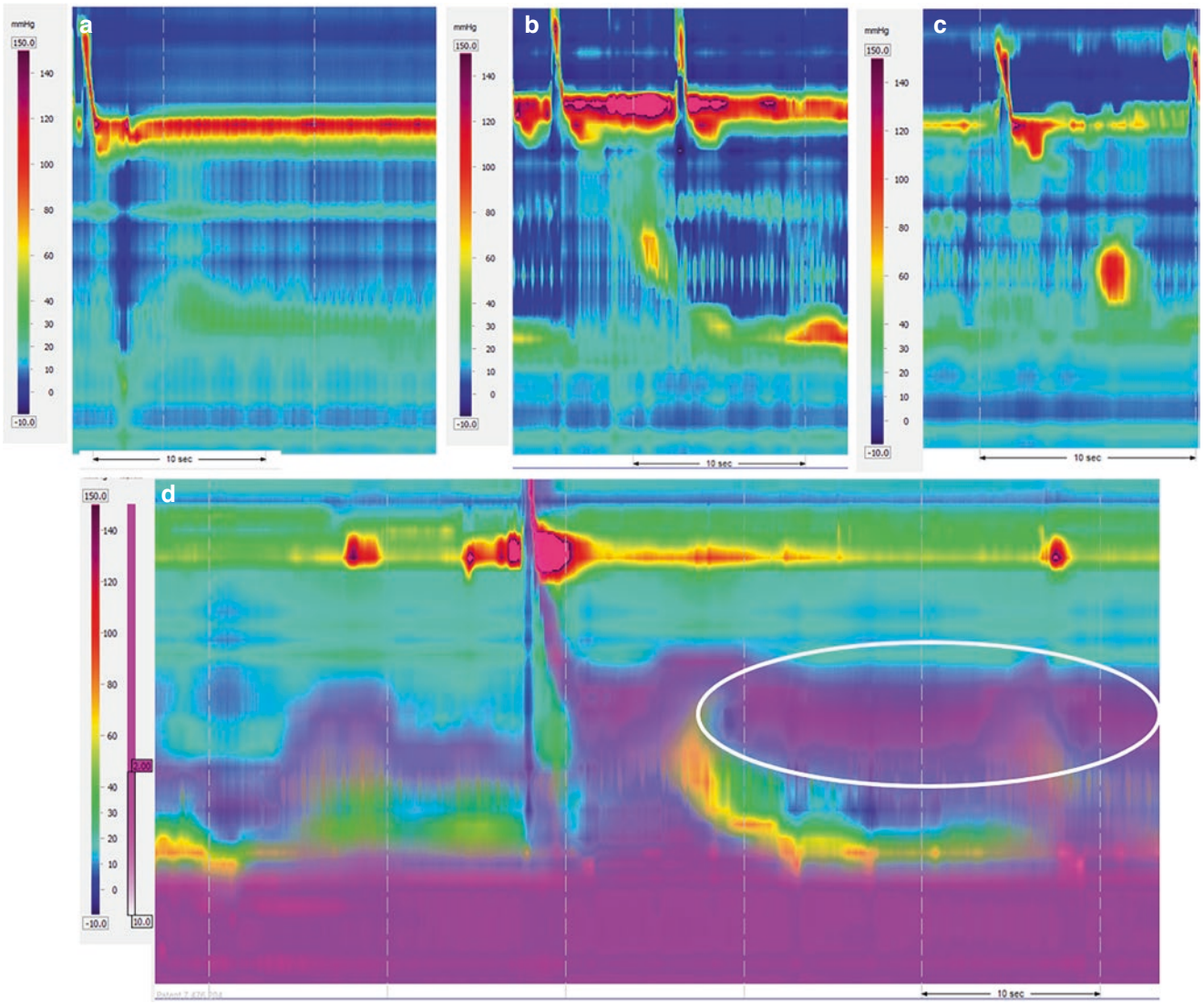

Fig. 29.1 High-resolution esophageal manometry tracings recorded in patients with esophageal atresia. Aperistalsis pattern (**a**); distal (weak) contraction pattern (**b**) and (**c**). (**d**) Shows a liquid swallow studied by high resolution/impedance in a patient with a type C esophageal atresia. Note the distal weak peristalsis with abnormal bolus clearance. The white circle depicts residual liquid (purple area) in the esophagus

Lower Esophageal Sphincter (LES)

In most studies including those using HREM, LES function is generally similar to controls [18, 20, 26, 40, 41, 47, 48]. A study conducted in children with non-complicated type C EA reported that transient LES relaxation is the pathophysiological mechanism in 2/3 of the reflux episodes [12].

The etiology of the esophageal motor disorder remains unclear. It may be caused by (1) intrinsic factors related to abnormal development of the esophageal smooth muscle and intrinsic innervation and vagus nerve or (2) operative manoeuvres and postoperative complications. Data indicating a key role of the congenital malformation are gaining strength. The key role of the abnormal development of esophageal innervation and musculature in esophageal dysmotility is supported by several lines of evidence. Romeo et al. utilized esophageal manometry in 20 newborn with EA and demonstrated motor abnormalities in the proximal (pouch) and distal esophagus prior to surgery [40]. Similarly, abnormal esophageal motility patterns have been described in children and adults with isolated TEF without atresia before surgical repair [49]. Pathological data support also the role of abnormal intrinsic and vagal innervation of the esophagus. Detailed analysis of esophageal intrinsic innervation in deceased newborns with EA showed abnormalities in the Auerbach plexus (plexus hypoplasia and abnormal interganglionic network) [50]. Other studies found hypoplasia of esophageal innervation or smooth muscle [51] in the proxi-

mal pouch [52], distal esophagus [53, 54], or in the fistula [51, 55]. Findings on adriamycin-induced EA in the fetal rat model have similarly shown an abnormal distribution of nerve tissue in the esophagus [56] and inherent abnormalities in the branching pattern of the vagus nerves [57].

On the other hand, the dysmotility may also be secondary to the dissection during surgery damaging vagal nerve and its esophageal branches [53]. However, unilateral vagotomy has no effect on peristalsis, presumably because of extensive crossover of vagal innervation within the esophageal wall [58]. Surgery may also result in an extensive mobilization and denervation of the esophagus. Shono et al. demonstrated, in two patients with pure EA studied before surgery, a coordinated peristalsis between the proximal and the distal esophagus as well as a normal LES reflex relaxation, suggesting that surgery may alter the esophageal motility [59]. However, this is not supported by experimental animal studies, where transection and anastomosis of the esophagus did not cause severe esophageal dysmotility [60].

Anti-reflux surgery with a Nissen fundoplication may worsen the symptoms of esophageal dysmotility and careful attention must be used to determine when such procedure is indicated [5]. The wrap creates a mechanical obstruction in those patients with an abnormal esophageal motility leading to a potential exacerbation of the dysphagia secondary to the combination of impaired esophageal motility and a tight wrap. Prevention of the gravity-driven esophageal clearance worsens the esophageal stasis and, in turn, it may worsen respiratory symptoms, so the decision to proceed with fundoplication for respiratory symptoms alone should be made with caution. Current guidelines suggest that surgical anti-reflux procedures may be considered if, despite maximal medical therapy, there are life-threatening or life-limiting symptoms, such as recurrent esophageal strictures, poorly controlled GERD, long-term dependence on trans-pyloric feeding, and dying spells [5].

Gastric Motility

While much is known about the abnormal oesophageal function and poor motility in EA patients, little is known about gastric function. It has been postulated that abnormalities in gastric function may contribute to high prevalence of gastrointestinal complications, such as GERD and feeding difficulties in this cohort. The etiology of the abnormal gastric function could be due to intrinsic and operative damage to the vagi as postulated by Qi et al. [57] or to an abnormal development of the myenteric plexus in the oesophagus as well as in the stomach [61]. Abnormal gastric emptying on scintigraphy has been reported by Montgomery et al. in 27% of a small cohort of EA patients [62]. Romeo et al. reported that 36% of patients with EA have delayed gastric emptying on scintigraphy and 45% abnormal gastric peristalsis on manometry [63]. Using ^{13}C-octanoate gastric-emptying breath test, Van Wijk et al. reported that 57% of a small cohort of children with EA had a gastric emptying time > 90th percentile [12, 64]. Cheng et al. were among the first to assess gastric myoelectrical activity in children with EA with electrogastrography (EGG). They found a significantly wider distribution of frequency than the controls [65]. EGG anomalies were also reported in 38% by Yagi et al. [66] and 73.3% by Bokay et al. [64].

Dumping syndrome is often unrecognized and its diagnosis delayed. In children with EA, it is most often encountered after a fundoplication or in patients with microgastria [67]. It has also been reported in patients with EA and no other predisposing factors [68]. In a recent prospective case series study by Aumar et al. which investigated 38 infants with type C EA without fundoplication, the oral glucose tolerance test showed abnormalities consistent with dumping syndrome in 29% [69].

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Anorectal Malformations

30

Célia Crétolle

Epidemiology and Embryology

Anorectal malformations (ARMs) are rare diseases (according to the European Parliament definition of rare diseases in 1999), given their prevalence in the Caucasian population varies from 1/2500 to 1/5000 live births. They comprise all anorectal tract defects and are the most frequent malformations of the perineum. The sex ratio of females:males is 1.6:1. The majority of cases are sporadic [1]. In isolated forms (without any associated malformation), no familial predisposition factor is identified [2, 3].

ARMs are "frequent rare" defects occuring between the sixth and tenth weeks of embryological development and thus cover a wide spectrum of malformations with heterogeneous functional prognosis, depending on the stage of development that they occurred and, as a consequence, the severity of the defects. They cover a wide spectrum of congenital abnormalities of the terminal portion of the hindgut which lies partially or completely outside the anal sphincter complex. In these conditions, the gastrointestinal tract ends blindly or opens ectopically onto the skin or the genitourinary tract (fistula).

In the normal embryo, the cloaca is formed around the fourth week of gestation. It consists of a common cavity into which the hindgut (rectum), the allantois (bladder), and the mesonephric ducts (Wolffian) open cranially. Caudally, the cloaca ends as the tail gut. The cloacal membrane extends vertically and anteriorly from the allantois to the tail gut. As a result of the ventral growth of the genital tubercle, the shape of the cloaca changes and the cloacal membrane swings to a horizontal position. A urorectal fold (or urogenital septum) situated between the allantois and the hindgut descents caudally until it meets the cloacal membrane. This descent results in the separation of the urogenital sinus and the rectum and in the disintegration of the cloacal membrane at that area at seventh week of gestation. The dorsal cloaca in the tail region remains fixed and will constitute the anal orifice. The muscles surrounding the anorectum develop at the same time and are composed of three parts: the external sphincter, the puborectalis muscle, and the internal sphincter. The external sphincter appears first, followed by the puborectalis muscle which appears before 10 weeks of gestation and forms a sling around the anorectum. The internal sphincter constitutes the muscular end part of the gut, grows after the rupture of the cloacal membrane, and is not well-differentiated until 10 weeks [4, 5]. In ARM animal models, an unusual shape of the cloaca, excessively shortened cloacal membrane (absent dorsal parts), and abnormal junction between the proximal hindgut and the cloaca were observed.

Even if the embryogenesis of ARM remains controversial [6], it can be schematically outlined as two different groups of defects. The high form of ARM is a defective progression of the cloaca septation that leads to a communication between the terminal digestive tract and bladder or urethra in boys, vagina or in its extreme form in girls, to a persistence of the cloaca with a single perineal fistula and a common channel for urogenital and terminal digestive tracts. The low form of ARM results from abnormal permeation of the anal membrane occuring in more advanced stages of the digestive pathway development leading to a communication of the terminal digestive tract with the perineum, anteriorly to the normal position of the anus (perineal skin or scrotum in boys, posterior vestibule, or fourchette in girls).

Whatever the precise mechanisms underlying the genesis of ARM, the malformation process, particularly in high forms, appears more global with impacts on the development of other caudal structures of the embryo. In more than half of cases, there are other associated malformations, beyond the only anorectal tract: involving the sacrum or lumbar vertebrae, conus of the spinal cord, urinary and/or genital sys-

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tems, or even more complex associations/defects occurring early in development, such as thoracic/cervical vertebral anomalies, esophageal atresia, and cardiac defects. A syndromic form is clearly identified in nearly 30% of cases (e.g., Currarino syndrome or Townes Brocks syndrome).

Classification

The French JZ. Amussat first described a proctoplasty in 1835 [7]. Different classifications have accompanied advances in understanding ARM anatomy and evolution of surgical strategies. The Melbourne classification was the reference since 1970, based on the major prognostic criteriae according to the work of Douglas F. Stephens: quality of the pubo-rectal component of levator ani, and on the level of the lower part of rectal cul-de sac. Three major forms of ARM were described: high, low, or intermediate, according to the embryology and the rectal cul-de sac level, respectively, above, below, or at the same level of the insertion of the levator ani muscles, whatever the level of the fistula [8]. This older classification is important to know to understand the older medical literature on the subject and to have an idea of the expected functional outcome: the higher the anomaly, the worse the prognosis for fecal continence due to hypotrophy of the levator ani. Schematically, ARMs without perineal fistulae are grouped under the high forms, and those with a perineal rectal opening are considered low forms.

A. Peña in the 80s introduced a classification based on the level of the rectal fistula that aims to adapt the surgical strategy and to predict the functional outcome. This classification has evolved to a consensus in 2005, after the Conference of Krickenbeck, Germany [7], where 26 international experts on congenital anomalies of the pelvic organs and perineum reviewed the recent advances and developed an international classification for ARMs. This classification, always the reference nowadays, is essentially based on the existence (or not) of a fistula and its level, separating the common forms and exceptional ones (Tables 30.1 and 30.2; the main forms of ARM are shown in Figs. 30.1, 30.2, 30.3, 30.4, and 30.5).

Table 30.1 ARM classification according to the Krickenbeck conference, 2005 [7]

"Classical" forms	Complex and unusual defects
Males	Pouch colon
Recto-perineal (cutaneous) fistula	Rectal atresia/stenosis
Recto-urethral bulbar fistula	Recto-vaginal fistula
Recto-urethral prostatic fistula	H type fistula
Recto-vesical fistula	Others: Cloacal exstrophy, posterior cloaca, associated to pre sacral mass …
Imperforated anus without fistula	
Anal stenosis	
Females	
Recto-perineal fistula	
Recto-vestibular fistula	
Cloaca with short common channel (<3 cm)	
Cloaca with long common channel (>3 cm)	
Imperforated anus without fistula	
Anal stenosis	

Table 30.2 ARM frequency (Krickenbeck conference classification, 2005) [7]

Formes	Frequency (%)
Recto-perineal (cutaneous) fistula	35–40
Recto urethral fistula (bulbar or prostatic)	20–25
Recto-vesical fistula	5
Recto-vestibular fistula	15
Cloaca	5
No fistula	5
Rare variants	5–10

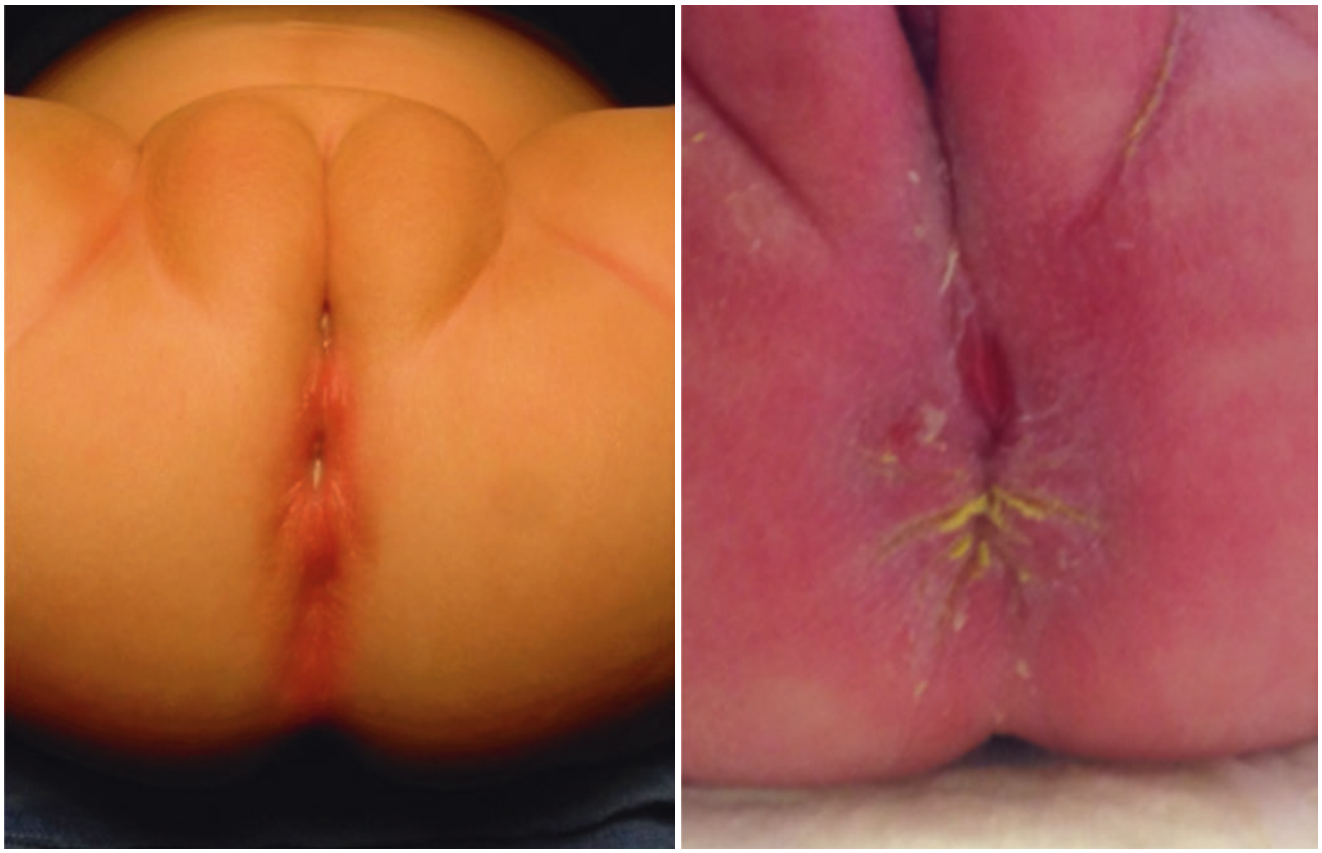

Fig. 30.1 Anterior anus (Left) is considered a normal anatomic variant and is defined as an anus anteriorly located in the perineum, fully surrounded by the sphincter muscle complex, with a normal caliber. In some cases, anterior anus is associated with a perineal groove (right), corresponding to an incomplete epidermization of the ano vulvar region

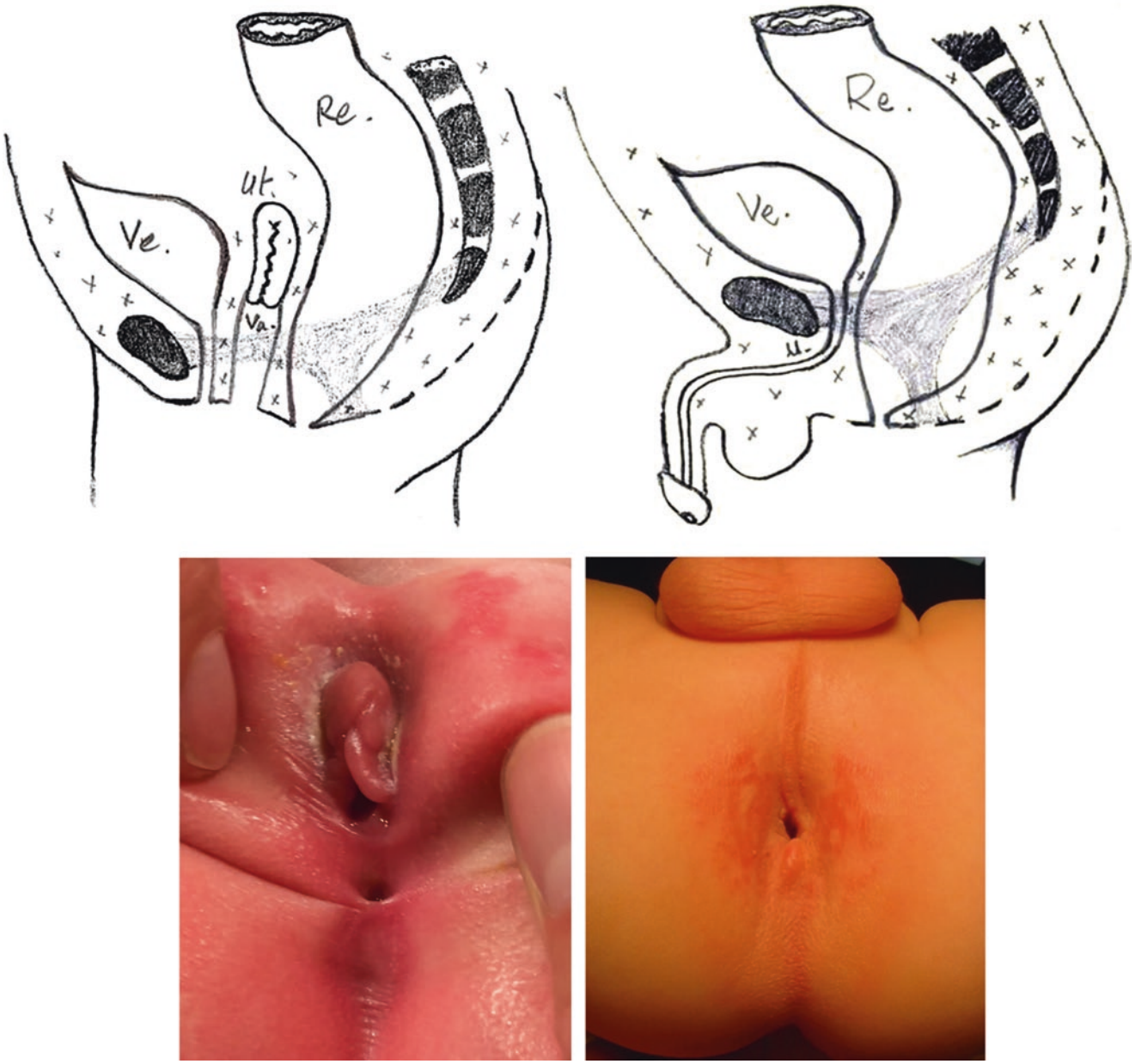

Fig. 30.2 Anterior recto-perineal fistula (Low form of ARM) (Left: in girl. Right: in boy). The perineal fistula opens in front of the lower part of the striated sphincter muscle complex normally developed

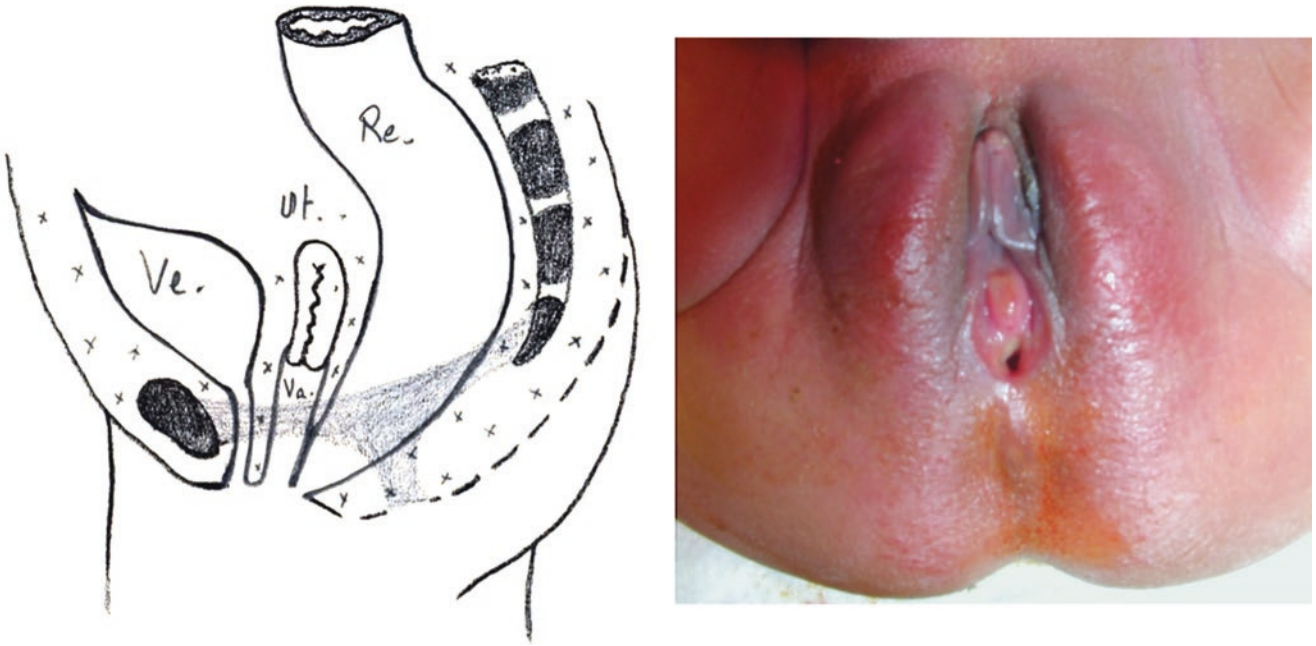

Fig. 30.3 Recto vestibular fistula (Low form of ARM). The lower part of the rectum and the posterior part of the vagina are closely joined. The striated sphincter muscle complex is well-developed

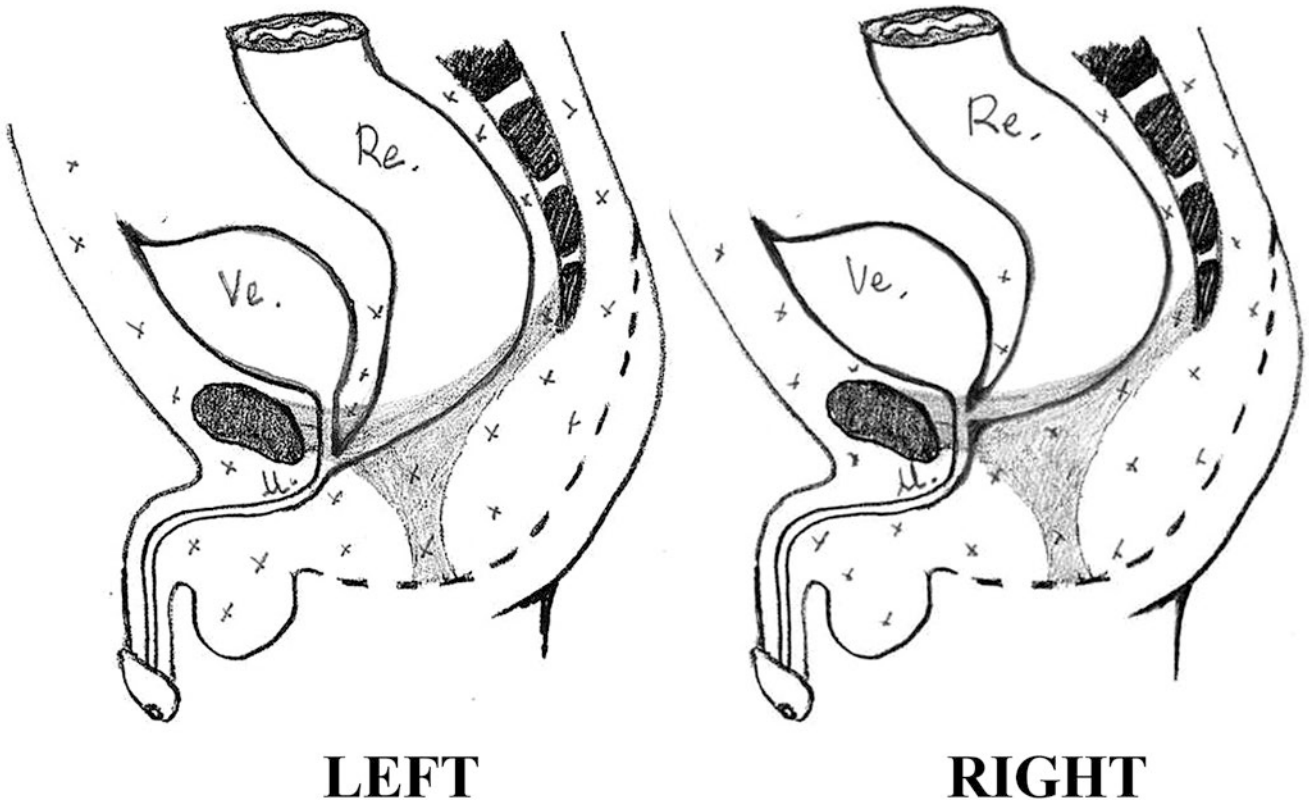

Fig. 30.4 Recto-bulbar fistula: High form of ARM in boy Left. Right: Recto-prostatic fistula. The muscular sphincter complex is present, more developed as the fistula is low

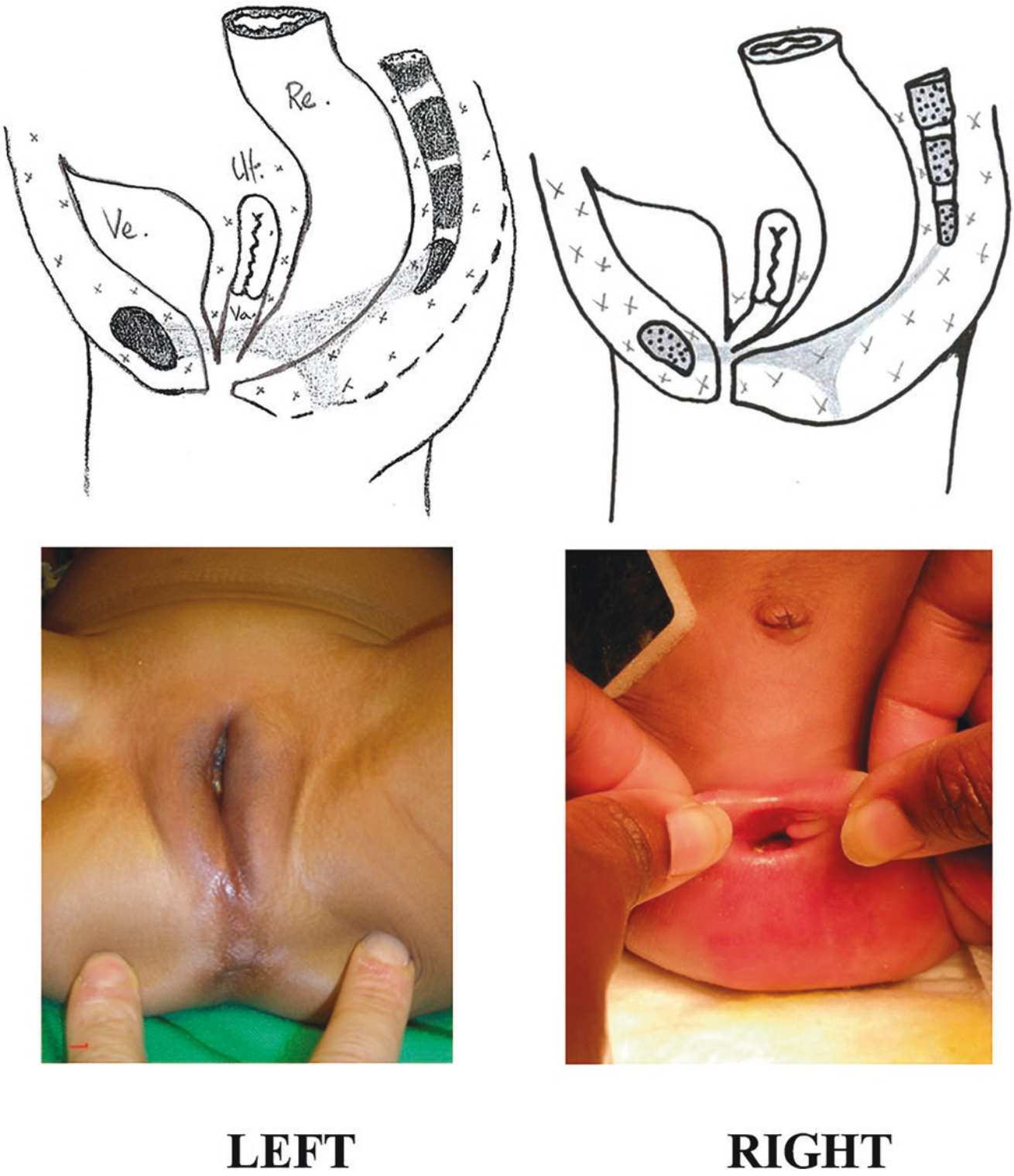

Fig. 30.5 Cloacal malformation: high form of ARM in girl. On the left, the common channel is short (<3 cm), the sacrum and the sphincter muscle complex are well-developed. On the right, the common channel is long (>3 cm), the sacrum is incomplete, and muscle complex is atrophic

Diagnosis

Clinical Examination and Neonatal Management

The diagnosis is rarely established in the antenatal period, but it is sometimes suspected if there are associated malformations (e.g., VACTERL association), enterolithiasis, or rarely intestinal distension. ARM should also be suspected in case of foetal hydrocolpos in girls, which can be observed in a cloacal malformation, especially if associated with sacral vertebrae, urogenital, or spinal cord anomalies. Exceptionally, cloacal exstrophy is suspected in case of parietal defects [9].

At birth, the diagnosis of ARM is based on clinical examination and targeted radiological assessment if the diagnosis is confirmed. A thorough physical examination is of critical importance and will often lead to the diagnosis of the ARM and any associated anomalies [10].

When inspecting the perineum, it is important to identify the presence of an ectopic anal opening, to look at the color and aspect of the skin around it, to assess the external sphincter contraction, and estimate the development of the gluteal muscles. In boys, the presence of meconium at the meatus or in the urine will automatically confirm the presence of a rectourinary fistula. In girls, a single perineal orifice establishes the diagnosis of a cloaca. In this eventuality, it is mandatory to rule out a urinary obstruction and/or hydrocolpos. In cases where there is no visible meconium on physical examination, it is important to wait 24 h before labeling the type of anomaly and planning the surgical intervention. In the meantime, the baby should receive intravenous fluids and nasogastric decompression. Associated anomalies must be ruled out by echocardiography, renal and spinal cord ultrasound, and spinal plain X-ray (front and side, including sacrum).

In females, precise perineal orifice examination is mandatory to identify a cloacal malformation with a single perineal fistula (Fig. 30.5). In this situation, the features of the vulva can determine the difference between good functional prognosis forms with a short common channel (< 3 cm) (Fig. 30.5a) from those of poorer prognosis, with a long common channel (> 3 cm) (Fig. 30.5b), where the gluteal muscles are poorly developed or absent, frequently associated with sacral and spinal anomalies.

Perineal fistula can be difficult to identify if the orifice of the fistula is narrow and located at the base of the vulvar "fourchette" (Fig. 30.2).

Conversely, the diagnosis of ARM can be missed if the anal orifice is just anterior to the normal position of the anus and, therefore, characterized as a normal anus (Fig. 30.1). Anterior anus is considered a normal anatomic variant and defines an anus anteriorly located in the perineum, fully surrounded by the sphincter muscle complex, with a normal caliber. In some cases, anterior anus is associated with a perineal groove, corresponding to an incomplete epidermization of the ano vulvar region (Fig. 30.1). Hence, the diagnosis is often delayed in these minor forms, revealed by a chronic fecal retention, generally after cessation of breastfeeding. The absence of some of the radial folds, the existence of an inter ano-vulvar perineal groove, and anterior position of the anus should alert the clinician to consider this diagnosis.

In males, in low forms of ARM, there is an anterior perineal fistula (Fig. 30.2) or skin covering the fistula with a rectal cul-de sac just below. Sometimes, the fistula does not open onto the perineum, but rather follows a subepithelial midline tract, opening somewhere along the midline perineal raphe, scrotum, or even at the base of the penis. In higher forms, the rectum is above the levator ani insertion and the fistula communicates, in most of cases, with the urinary tract, usually the prostatic urethra (Fig. 30.4a, b). The presence of meconium in the urine confirms the presence of a fistula with the urinary tract, but is not always observed when the fistula is not permeable. In this particular case, the malformation may have been suspected in the prenatal period from the presence of enterolithiasis potentially indicating the existence of a recto-urinary fistula.

Radiological Assessment

All newborns must have an expert surgical opinion if a diagnosis of ARM is suspected. Radiological assessment is mandatory to identify the type of ARM, especially the level of the fistula, and associated malformations that will influence both the course of the initial management and ultimate prognosis.

In addition to the clinical examination, 24 h after birth, if there is no evidence of meconium in urine or through a perineal fistula, the level of the rectal cul-de sac may be assessed with Wangensteen and Rice standard X-ray or invertogram (Fig. 30.6): lateral cross table film and baby in

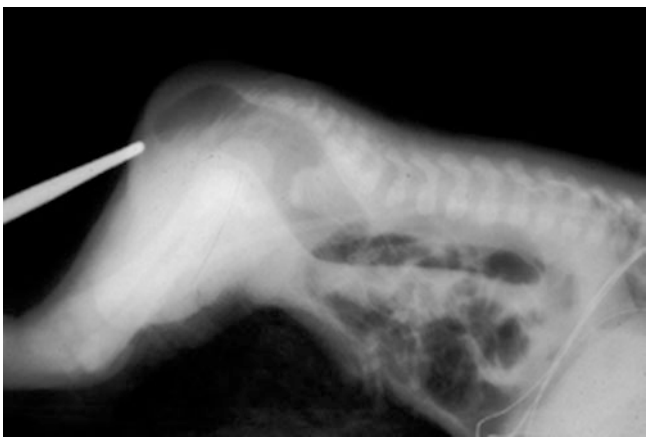

Fig. 30.6 Invertogram or Wangensteen and Rice X-Ray, lateral cross table film with the baby in prone position [5]

prone position with a marker on his bottom at the suspected site of the external sphincter. The air level is evaluated on a virtual line from pubis to coccyx, which represents the insertion level of the levator ani, but often with inaccuracies. An ultrasound of perineal soft structures can also be performed with a sensitivity of around 85% [11]. Unfortunately, the diagnosis and therapeutic decisions are often made as an emergency at birth, and it is not always possible to have this expertise. Pelvic and spinal cord MRI carry significant value, as they allow assessment of the length of the fistula, the level of the rectal cul-de sac and associated pelvic and spinal abnormalities [12], but access to this specific exam is often impossible as an emergency. A distance of >15 mm between the distal rectal cul-de sac and the perineum suggests an intermediate or high ARM [13].

The anatomical shape of the ARM is an essential element of the prognosis for faecal retention and elimination control. It is assumed that the higher the rectal cul-de sac the less developed the sphincter muscles, and potentially, their innervation is likely to be. This suggests that the competencies of muscles involved in defecation and the sensations of rectal fullness-emptying are more likely to be intact if the malformative process occurred later in anorectal embryological development.

Echocardiography must be performed in emergency, before surgery, because of the high risk of associated cardiac anomalies. Complete spine (front and side, including sacrum) and rib X-rays and spinal cord conus and urinary tract ultrasounds must also be performed to exclude other associated malformations. If spinal cord anomaly is suspected, MRI is mandatory around the age of 6 months.

Associated Malformations and Syndromic Forms

The etiology of ARM is unclear, but it is assumed to be multifactorial. In animal models and human studies, environmental and genetic factors have been identified. ARMs have been induced in mice and rats by in utero exposure to Adriamycin, etretinate, and Ethylenethiourea [14].

The recurrence risk for rectovestibular and perineal fistulae is 3–4% for full siblings and approximately 2% for first-degree relatives [15].

Associated anomalies are present in 60–75% of ARM cases [15, 16] which worsen the prognosis. Cardiovascular anomalies need to be ruled out before ARM surgical management, because, if significant, can change initial management. In order of frequency: 40% have urogenital tract anomalies (hypospadias, renal agenesis, pelvic kidney, bicornuate uterus, etc.), 40% musculoskeletal abnormalities, especially of the sacrum, 20–30% cardiac defects (atrial septal defect, ventricular septal defect, tetralogy of Fallot, transposition of great vessels, and hypoplastic left heart syndrome are also possible), at least 20% central nervous system malformations (tethered cord, filum lipoma, etc.), 18% other digestive disorders (oesophageal atresia, duodenal with or without malrotation, etc.), and 10% craniofacial anomalies [17].

Lumbosacral MRI performed systematically, confirms that the frequency of spinal cord defects has long been underestimated and reported to reach 34% in the most recent series particularly when the sacrum is abnormal [18]. Sacrovertebral anomalies are the most frequent defect of bony structures (hemivertebrae, scoliosis, and hemisacrum) and affect about a third of ARM patients [18]. Hypodevelopment of the sacrum can be quantified by the sacral ratio which is associated with the severity of the ARM and a helpful prognostic tool for continence [19].

These "associated ARMs" correspond to a clearly defined "syndromic form" in only 30% of cases, including the VACTERL association of malformations (vertebral, anal, cardiac, tracheal, esophageal, renal, and limb), MURCS (Mullerian duct, renal aplasia, and cervical–thoracic somite dysplasia) as well as sequences, such as caudal regression syndrome with truncated spinal cord to sirenomelia, Klippel Feil syndrome, and OEIS (Omphalocele, bladder Exstrophy, Imperforate anus, and abnormal Sacrum). In some syndromic forms, molecular abnormalities have been identified, with autosomal dominant or recessive mode of inheritance (Table 30.3). Some ARMs are also part of syndromes with chromosomal abnormalities, the most frequent being Down syndrome (trisomy 21) and abnormalities of chromosome 22: Cat-eye syndrome (tetrasomy 22q11) and DiGeorge syndrome (del22q11.2) (Table 30.4).

Currarino syndrome was described in 1981 as a triad, with three major clinical signs: (i) a partial sacral agenesis in 92% of cases—typically scimitar or sickle shaped sacrum

Table 30.3 Main syndromic forms of ARM from molecular origin, with gene and pattern of inheritance

Autosomal dominant (AD)	Autosomal recessive (AR)	XLR–XLD
Currarino (*MNX1*)	Johanson-Blizzard (*UBR1*)	G-Opitz (*MID1*)
Pallister-Hall (*GLI3*)	Short ribs-polydactyly (type III de Verma-Naumoff)	Lowe (*OCRL*)
Townes-Brocks (*SALL1*)	Baller-Gerold (*RECQL4*)	Heterotaxy (*ZIC3*)
Okihiro (*SALL4*)	A few Ciliopathies	FG
Ulnar-mammary (*TBX3*)	Fraser (*FRAS1*, *FREM2*)	Renpenning (*PQBP1*)
Rieger (*PITX2*)		MIDAS (*HCCS*)
Kabuki (MLL2)		Christian Sutherland-Haan
G-Opitz (*MID1*)		STAR (FAM58A)

AD autosomal dominant, *AR* autosomal recessive, *XLR/XLD* X-link recessive/X-link Dominant

Table 30.4 Main syndromic forms of ARM of chromosomal origin

Trisomy 21
Trisomy 13, del13q, r13
Trisomy 18
Cat-eye (22q11 tetrasomy)
Pallister–Killian (12p tetrasomy)
Parental unidisomy 16 (maternal)
Di George (del22q11.2)
…

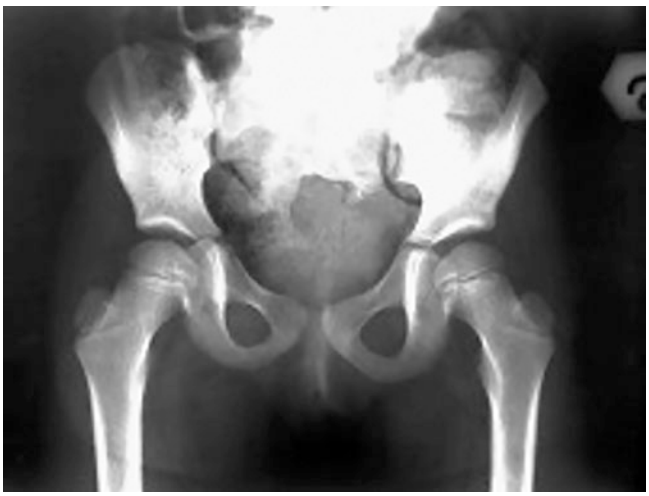

Fig. 30.7 Currarino Syndrome: typical sickle-shaped sacrum malformation

in 70% of cases (Fig. 30.7), (ii) an anorectal malformation in almost 100% of cases, corresponding to an anorectal stenosis in 88% of cases called "infundibular anus" without radial folds ("funnel" anus), and (iii) a pre-sacral tumor in 88% of cases [20, 21] (meningocele and/or a teratoma or more rarely a neurenteric cyst). Since the first description of Currarino, authors reported that associated occult spinal dysraphism is observed in 70% of cases (tethered cord syndrome and low-lying conus with filum lipoma and/or syrinx) and genital malformations in girls (Mullerian duplications) [21]. In almost half of cases, there is also frequent communication between the pre-sacral mass and meninges, exposing patients to the risk of spontaneous meningitis, favoured by faecal rectal retention. Indeed, beyond the ARM, there is, in most cases, severe slow transit constipation that remains poorly documented (probably associated with intestinal neuropathy). A heterozygous mutation of the *MNX1* gene is found in 50% of cases, with an autosomal dominant pattern of inheritance in over 80% of familial cases. The expressivity is variable with incomplete penetrance, even in the same family, which makes genetic counselling difficult. This is obviously a sequence, but, of note, a normal sacrum does not formally eliminate this syndrome, since this is described in about 5% of Currarino cases with a confirmed molecular mutation [21].

Surgical Management

Operative Management

The main goals of treatment in the neonatal period are to relieve the intestinal obstruction and recognize and treat any associated defects that may be life threatening. Relieving the intestinal obstruction can be achieved by definitive repair, anal dilation, or colostomy.

The surgical management of ARM is well-codified and depends on the anatomy of the fistula. The main goal of the definitive treatment is to anatomically reconstruct the malformation. Within the first 24 h of life, if meconium is evacuated through a perineal fistula, a primary anoplasty can be performed depending on the global status of the baby. If the baby has other life-threatening issues, is premature or must undergo another surgery, especially if congenital cardiac anomalies are associated, the fistula can be dilated and definitive surgical treatment postponed for a few weeks until the rectum is well-decompressed, to prevent megarectum development. In the latter case, if bowel movements are not normal, a colostomy is mandatory to keep the child comfortable while providing time to solve other medical and surgical problems.

Depending on the experience of the surgeon and the patient clinical status, a low form of ARM with or without perineal fistula or a vestibular fistula can be primarily repaired or initially diverted by a colostomy. Y–V proctoplasty, cutback, or posterior sagittal anorectoplasty is possible. Some surgeons will also prefer to dilate the perineal or vestibular fistula and postpone the primary repair for few weeks when the wall between the vagina and the fistula has become thicker. Low forms of ARM require frequent and prolonged follow-up because of a tendency to stool retention throughout childhood and beyond, which can, paradoxically, lead to poor control of the anal sphincter and frequent soiling [22].

If the anus is just anterior, in some cases associated with a perineal groove, surgical correction is not mandatory, because most of these patients retain normal transit as the ano-vulvar distance lengthens with growth and the unsightly appearance fades over time.

A first colostomy and delayed definitive repair at 3–4 months when weight is around 6 kg is recommended in higher forms (urethral fistula and cloaca) to better characterize the anatomy and prevent complications, such as urethral injury. In cloaca, urinary diversion and/or drainage of hydrocolpos may be necessary. A divided descending colostomy is ideal. The completely diverting colostomy provides bowel decompression as well as protection for the final repair of the malformation.

The distal colostogram represents the most accurate diagnostic study for determining the anatomy of these defects [7]. A voiding cystourethrogram is also indicated to detect vesicoureteral reflux and, when done at the same time, can help to show the position of the rectal cul-de sac compared to the

urethra if no fistula is identified on the colostogram. Urinary endoscopy under total anesthesia is also useful before the Postero-Sagittal Ano-RectoPlasty (PSARP) procedure to confirm if there is a recto-urinary fistula and its level.

Most pediatric surgeons today use the posterior sagittal approach described in 1982 by Peña and De Vries, with or without laparotomy or laparoscopy. PSARP should never be attempted without a technically adequate high-pressure distal colostogram to determine the exact position of the rectum and the fistula. Attempting the repair without this important information significantly increases the risk of nerve damage, damage to the seminal vesicles, prostate urethra, ureters, bladder neck, and bladder denervation [23]. All ARMs can be repaired by a PSARP, which will be limited to a smaller incision of 1–2 cm in the lower forms. This technique has revolutionized the surgical management of these children, because surgery preserves muscles of continence and neurovascular structures whatever is the level of rectum [24]. When the location of the rectum cul-de-sac is high, e.g., rectovesical or bladder neck fistula, or in case of cloacal malformation in girls, abdominal approach or laparoscopy is necessary [25].

Laparoscopically assisted anorectal pull-through (LAARPT) has gained popularity and offers the advantages of a good visualization of the rectal fistula and surrounding structures, accurate placement of the bowel through the anatomic midline and levator sling, and minimally invasive abdominal wound and perineal dissection [26]. With the development of minimally invasive surgery, LAARPT was described in 2000, which is now used routinely in the high forms of ARM in some centers or only in cases of high-located fistula in others [26]. Whatever the repair technique, the colostomy is usually closed 2–3 months later, followed, for some teams, with a protocol of daily anal bougienage over several months, as recommended by A. Peña. This last point remains currently controversial.

Besides these typical situations, there are more complex forms requiring the use of additional surgery on the spinal canal, e.g., Currarino syndrome, or the urogenital tract, particularly in extreme forms, such as cloacal malformation.

In all cases, even if surgery restores anatomy, the defecation processes, which involve different pelvic structures and skills, are altered. This justifies the important place of maintained post-operative supportive care to offer these patients daily fecal continence, or at least, a socially acceptable cleanliness.

Short- and Long-Term Post-Operative Considerations

Operative Complications

A colostomy is useful in higher forms to relieve the intestinal obstruction, to decompress the rectosigmoid and to assess the anatomy preoperatively [10]. It must be a double colostomy, with two separated stomas. It does, however, carry a risk of morbidity. Prolapse and stricture are the most common complications. Specific colostomy complications in ARM patients are related to the position of the colostomy: if too proximal, the rectum may not be well-decompressed and megarectosigmoid predisposes to long-term constipation and overflow incontinence. On the other hand, a colostomy too distal needs to be moved at the definitive repair to allow the rectum to reach the perineum.

Following pull-through, wound infection, dehiscence, and retraction with varying severity may occur. Deeper infection may lead to acquired rectal stenosis and/or recurrent fistula requiring reoperation and leading to long-term functional sequelae [27]. Urologic injury is a well-known complication, especially in boys [28]. The risk is decreased with PSARP if an adequate preoperative colostogram is performed [29].

With the laparoscopic approach, the surrounding structures such as bladder, ureters, vas deferens, prostate, seminal vesicles, and urethra are visualized but still at risk from trauma. Posterior urethral diverticula have more frequently been described in intermediate forms and after laparoscopic repair. Anal stenosis and rectal mucosal prolapse are commonly seen after pull-through. For many authors, it is thought that postoperative anal stricture is prevented by an adequate anal dilatation program. Contrary to what was previously thought, there seems to be no significant difference in rates of mucosal prolapse between laparoscopic and open approaches [30].

Anatomical abnormalities resulting from ARM processes are definitive. Despite the major progresses in surgery that have been made over the last decade, *ad integrum* restitution of functions to ensure continence, rectal feelings, and normal bowel movements is not possible. In addition to the possible associated sacral and spinal cord abnormalities, there are certainly intrinsic defects of perineal and intestinal innervation that may explain the persistence of poor functional results in some cases, despite a “cosmetically” satisfactory repair.

In recent years, progress in surgical techniques has allowed focus on the improvement of postoperative care by taking better account of the associated malformations. In the absence of normal continence (i.e., normal competence of muscles involved in defecation mechanisms and normal sensation of rectal fullness-emptying), the aim is to get, at least, controlled cleanliness that is consistent with a satisfactory social life. This therapeutic strategy is based on a multidisciplinary long-term management involving the digestive surgeon and urologist, neurosurgeon, orthopaedist, pediatrician, gastroenterologist, cardiologist, and nephrologist depending on associated malformations. Involvement of supportive care is fundamental, and the repeated interventions of a dietician, psychologist, social worker, and physiotherapist (after the age of 6 years) are useful. The acquisition of a controlled cleanliness based on these multidisciplinary medical and

para medical supports is essential to ensure a good functional outcome in adulthood.

Vigilance must be a priority to maintain regular bowel movements (i.e., stools: 1 per day or 1 day out of two), including with the use of oral laxatives to soften stools and rectal stimulation with multi-weekly suppositories or enemas to facilitate evacuation [31], or even daily and regular pelvic floor muscle training if perineo-sphincter muscles are competent. The management must be adapted to each case and every age (dietetic, psychology, and perineo sphincter rehabilitation). Diet plays an important role in modulating stool consistency, probably by activating digestive motility and optimizing the microbiota. In the absence of such support, patients are exposed to either a complete lack of control of stools, or severe constipation leading to the development of a mega colon and rectum, faecal retention, and overflow incontinence with multiple daily soiling, which are not socially acceptable [32].

Active patient and family involvement in treatment and monitoring is a prerequisite to move toward an optimal result. This is not always easy to obtain, because this condition affects the most intimate parts of the individual, and the care often requires parents (and the patients themselves with age) to perform invasive procedures (dilatations, enemas, etc.). It can generate psychological problems that can lead to destabilization of the familial unit. In this context, the development of therapeutic education programs should help parents and child to accept these constraints (e.g., http://hopital-necker.aphp.fr/marep/etp-a-marep/). Familiarization of parents and patient with anatomy, physiology, and self-care techniques can widely contribute to obtain socially acceptable controlled cleanliness by improving understanding of the pathology, and empower themselves toward ARM sequelae.

In most series, the assessment of long-term functional results of ARM has been carried out on patients often not receiving regular follow-up or supportive care, who develop a mega dolichocolon, chronic stool retention, and gradual degradation of bowel movements. Finally, the definition of "good or bad results" in terms of continence is variable depending on the series. Thus, results of the various studies on "faecal continence" conducted between 1985 and 2000 may vary from 10% to 90% depending on the series and surgical approaches, figures tending more toward 10–20% continence when the monitoring was extended [33]. It is interesting to note that low forms of ARM had results regarding faecal continence that did not seem better than higher forms, with 30–40% incontinence [34].

A consensus score was elaborated during the Krickenbeck conference in 2005 to better evaluate and compare results [7]. In the literature, there is a great variation in the criteria used to evaluate long-term results after repair of ARM [35]. The multiple scoring methods based on subjective parameters that have been designed to quantify the bowel function have made comparisons between studies difficult [3, 36]. The Krickenbeck outcome classification tried to solve this problem (Table 30.5). This descriptive, nonscoring method is applicable after the age of 3 years and permits uniformity in the reporting of results [2, 37–41].

Table 30.5 International classification (Krickenbeck) for postoperative results [7]

1. Voluntary bowel movements		Yes/no
	Feeling of urge	
	Capacity to verbalize	
	Hold the bowel movement	
2. Soiling		Yes/no
Grade 1	Occasionally (once or twice a week)	
Grade 2	Every day, no social problem	
Grade 3	Constant, social problem	
3. Constipation		Yes/no
Grade 1	Manageable by changes in diet	
Grade 2	Requires laxatives	
Grade 3	Resistant to diet and laxatives	

One of the most interesting studies using this score is the work reported by the German network dedicated to ARM (CURE-Net), on 123 patients with an average age of 10 years. It showed that 70% of patients reported fecal incontinence and that complete cleanliness is obtained only in 40% of patients with perineal fistula, 24% of those with vestibular fistula, 17% of those with recto-urethral fistula, and no patients with a cloaca. These results differ from those reported by the A. Peña team with continence rates of 89%, 64%, 46%, and 13–37%, respectively [42]. This difference probably relates to the "bowel management program" developed by this team that helps these children to be, if not continent, at least clean. An English study, in 2009, reported results similar to those reported by A. Peña with a "faecal continence" (i.e., voluntary bowel movements) of 70% on average [43]. However, therapeutic programs used to achieve these good results were not clearly described in this study.

During the transition to adulthood, many problems related to the ARM persist, in the digestive, urological, gynaecological, and psychological fields. During this period, there is a major risk of failure in the management and 'loss of sight', as adult specialists are not trained to the follow-up of these patients, except for a few "expert" centers. The physical, psychological, and economic impact of the daily management of incontinence leads to difficulties in social functioning, particularly in the professional life of patients. A questionnaire sent to 55 adults aged 18–56 years by the CURE-Net German team showed that 21 suffered from anal prolapse and 18 had a mega-sigmoid/mega-colon. Neoanal stenosis was present in 42% of men and 18% of women and neurogenic bladder in 32% of men and 18% women. 60% of women and 32% of men had recurrent urinary tract infec-

tions [44]. Most studies show an impairment in the quality of life compared to the control groups [24]. In contrast, we have recently reported in a cohort of 58 adult patients identified in the reference center that the level of education was higher than in the general population, but that these patients have sedentary positions of a lower level compared to their qualifications. About 80% of these patients had sexual activity, 62% of women were married compared to 32% of men. The fertility rate of 1.5 was no different from the general population [45]. In a recent meta-analysis summarizing the large literature on the subject, it appears that functional problems are more important in childhood than in adolescence, but, in contrast, psychosocial issues dominate in adolescence [46].

It is, therefore, essential not to create a break in the follow-up of these young patients, to prepare the child for adult life with their malformation sequalae, and to establish a real adolescence transition program before performing the transfer to care departments for adults. One of the priorities for a successful transfer is that the young patient and his family are in a phase of stability.

Management of Associated Malformations

Surgical untethering of the cord may improve the motor function in symptomatic patients, but it does not change the bowel or urinary function [35]. However, in some cases, it stops the worsening of urinary and digestive sphincters if it has started. Patients with tethered cord have a worse functional prognosis that is also predictable by the type of ARM and sacral defect, but there is no evidence that prophylactic surgery can change the prognosis [36]. Close clinical follow-up and urodynamic studies are recommended in patients with tethered cord [37]. Genitourinary anomalies affect one-third to half of patients [38]. Vesicoureteral reflux is the most frequent anomaly, affecting 60% [39] followed by renal agenesis and dysplasia. In males, 20% have cryptorchidism [40] and 5% have hypospadias [38]. Patients with ARM associated with partial sacral agenesis are at increased risk of bladder–sphincter dysfunction and should be assessed by urodynamic studies [41]. Gynecologic anomalies have been unrecognized in the past, but constitute a significant cause of morbidity on the long term [47]. In girls with rectovestibular fistula, 5% have a vaginal septum and 9% an absent vagina [48]. Hydrocolpos can cause a urinary obstruction or pyocolpos in the neonatal period. The absence or underdevelopment of the Mullerian structures can cause obstruction of menstrual flow at puberty [49].

Long-Term Outcomes

According to Pena's extensive series of more than a 1000 patients over two decades, 77% of patients have voluntary bowel movements by the age of 3 [33]. Half of them soil their underwear occasionally, meaning that only less than 40% are totally continent. Even though 25% are totally incontinent, a definitive repair of all the types of ARM is still recommended, because a bowel management program can be effective to treat the fecal incontinence and keep the patients clean. It is, however, important to give realistic information to parents about what to expect in the long term, since the outcome is related to the severity of the anomaly, but also relates to multidisciplinary follow up provided by the expert center. Voluntary bowel movements are possible in 90% of patients with rectal atresia/stenosis, perineal fistula, vestibular fistula, and imperforate anus without fistula. However, total continence is achieved in only half of the vestibular fistula and imperforate anus without fistula. Gender differences have also been noted with less incontinence and constipation in males than in females with perineal fistula [50]. According to this same study, perineal and vestibular fistulas had similar outcomes in girls. Regarding higher forms, voluntary bowel movements are present in 80% of patients with a short cloaca or a bulbar rectourethral fistula, but only 30% do not have fecal soiling. Prostatic rectourethral fistula and long cloaca have voluntary bowel movements in 73% and 55% of cases, but only 45% and 39% do not have fecal incontinence. Rectovesical fistula has the worst prognostic with 35% on voluntary bowel movements and no patients without soiling [33].

With the advent of the LAARPT, it became crucial to study the outcome of this technique compared to PSARP. A prospective study of 24 cases of high–intermediate ARM found no differences in sphincter thickness as assessed by echoendosonography and MRI, but the clinical score was better for LAARPT [51].

A randomized control trial (RCT) did not find a difference in clinical outcomes in the short term, but the anal resting pressure assessed by manometry was improved [52].

A systematic review and meta-analysis grouping this RCT together with six retrospective cohorts, with a total of 187 patients, found no differences in rates of defecation scores [30]. Defecation outcomes, however, were inconsistently reported, and some reports included patients younger than 3 years.

Long-Term Sequela Related to Associated Anomalies

Urinary incontinence from a neurogenic bladder is expected after repair of a cloaca, but should be rare in male except if there is associated abnormal sacrum or spine [39, 41].

A third of patients with short cloaca require intermittent catheterization and long cloaca require intermittent catheterization in 70–80% of cases [53].

Patients with cloaca are also at risk for chronic renal failure due to structural anomaly of the urinary tract, such as renal dysplasia, ectopic/solitary/duplex kidney, and ureteropelvic junction obstruction. Vesicoureteral reflux and sacral abnormality are present in many of them [54].

Fertility does not seem to be affected in low forms of ARM [55], but it is decreased in higher forms [56]. Gynecological problems are usually related to the associated defects. In males, erectile dysfunction, weak or missing erection, and retrograde ejaculations have been reported [56]. Avoidance of sexual activity may be chosen by patients because of poor bowel continence (20% of the patients with high anomalies and 13% of the patients with low anomalies) [55, 56]. Frequent orchiepididymitis are observed, particularly when recto prostatic fistula.

Methods to Improve Fecal Continence

Bowel Management Programs

Because fecal incontinence can have disastrous consequences on self-esteem and quality of life, it is ideal to establish a bowel management program before the entrance to school. This program consists of the daily administration of enemas by the parents to clean the colon. Before starting it, it is important to understand the physiopathology of fecal incontinence: overflow "pseudo-incontinence"(fecal incontinence because of fecal retention more than muscular inefficiency) and/or "true fecal incontinence" (non-retentive) [57].

The differentiation between the two is essential, because the treatment is different. "Pseudo-incontinence" is caused by constipation and is suspected in the presence of a history of stool impaction (fecaloma on physical examination or on an abdominal X-ray and dilatation of the rectosigmoid on a barium enema). Colonic motility is decreased as can be demonstrated by colonic manometry or scintigraphy. True fecal incontinence is caused by increased motility, the absence of rectal reservoir, and sphincter failure. It is suspected in cases of diarrhea, when a barium enema shows a non-dilated colon with haustrations going down into the pelvis [33]. In the first group, the treatment consists of daily suppositories, "microenemas", or large-volume enemas with eventually additives (glycerin, phosphate, or bisacodyl). The second group is easier to clean with smaller volume of saline enemas, but will also require a constipating diet and medications to decrease bowel motility (e.g., Loperamide) [10, 58].

The bowel management program is generally well-accepted by the children, but when they become adolescents, antegrade enema through an appendicostomy or a cecostomy constitute better solutions, because they allow a self-administration of the colonic irrigation. Anterograde enemas have been shown to improve quality of life of patients [59].

Surgical Alternatives

In certain very selected cases, resection of the dilated distal segment may be successful in treating constipation and fecal incontinence [60], but it can also convert a case of overflow incontinence to one of the true incontinence because of the loss of the rectal reservoir. Optimal conservative management seems to have similar bowel functional outcomes to surgical treatment [61].

Redo surgery for mislocation of the rectum can be offered in patients with good prognostic factors, but it does not necessarily lead to improved fecal continence [62, 63]. Different sphincter reconstructions have been proposed, but the long-term results are not convincing [64].

Other Alternatives

Sacral nerve stimulation (SNS) has shown promising results for children with urinary and fecal incontinence in a randomized crossover study [65]. Etiologies for incontinence were mainly of neurological origin. SNS consists of the surgical implantation of a neuromodulator in the S3 foramen. It is well-tolerated by the patients. Other groups are collecting prospective data on that therapy [66]. Biofeedback conditioning has also been used to treat fecal incontinence with limited results. It is effective when the functional and morphologic assessment pretreatment is favorable [67]. It may represent an important adjunct to a multidisciplinary behavioral treatment [68, 69].

Conclusions

ARMs are serious pathologies that have inherently high risk of permanent faecal incontinence, possibly associated with urinary and gynaecological disorders. The associated malformations can be part of complex association of malformations in more than half of cases that require treatment and special and coordinated multidisciplinary follow-up. The management should be organized in an expert center to ensure high-quality surgery and supportive care management and follow-up. Nevertheless, surgical correction is not enough, and these patients need support in the long term with, age-appropriate activities to improve their social functioning and quality of life, which remains highly impaired in the most recent studies. Disability generated by these malformations is invisible but important, because it affects a sphere "taboo" of which it is still difficult to speak in our societies. Failure of appropriate follow-up and isolation of patients are still important, and can lead to extreme situations, particularly in adulthood. This requires informing and training adult practitioners to this type of support. Patients

with ARM sequelae should be followed-up life long, hence the importance of organizing a transition to adult and therapeutic patient education program development.

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Motility Changes After Small Bowel and Colonic Surgery

31

Roberto Gomez and John E. Fortunato

Introduction

Surgery of the small intestine and colon is commonly performed in children for a variety of indications ranging from intestinal failure needing intestinal rehabilitation and transplantation to the need for decompressing venting or enteral feeding access to underlying motility disorders. Under most circumstances, non-emergent operations allow a multidisciplinary team approach between surgeons and gastroenterologists to devise a thorough preoperative diagnostic strategy. Unfortunately, abdominal catastrophes such as malrotation with volvulus often preclude the luxury of time before surgery, necessitating a strong relationship between surgeon and gastroenterologist to address the potential consequences of such an event. In both cases, the motility of the small bowel and colon remains a critical feature that often predicts the success of an operation and, most importantly, the prognosis of the patient. This chapter aims to address several of the more prevalent motility disorders observed in children after small bowel and colonic surgery.

Small Bowel Motility after Resection

Resection of short or long segments of the small bowel may be necessary for different indications, including *surgical emergencies* such as bowel ischemia or necrosis from volvulus and perforation; *congenital anomalies* such as intestinal atresia, malrotation, and gastroschisis; or *acquired etiologies* encompassing structuring Crohn's disease, ulcerative colitis, severe necrotizing enterocolitis, intestinal pseudo-obstruction, or abdominal trauma. Advances in intestinal rehabilitation postoperatively include: home TPN, lipid solutions, frequent small bowel bacterial decontamination, central line technology decreasing the number of line infections, and recently, introduction of the intestinothrophic factor, glucagon-like peptide analog, which can significantly increase intestinal absorption [1]. These advances have dramatically improved the prognosis of infants after small bowel resection. Preservation of bowel length, particularly the small intestine, is critical to ensure adequate absorption of nutrients, fluids, and electrolytes, but is contingent on circumstances, such as extent of the necrosis or ischemia. The consequences of a more extensive small bowel resection include symptoms such as frequent diarrhea, malnutrition, and bloating due to bacterial overgrowth and may result in the need for parental nutrition with its associated complications.

There are several classifications of small intestinal resections. Three categories are described, based on length of residual small bowel: short resection with 100–150-cm length remaining, large resection with 40–100 cm remaining, and massive resection with 40 cm or less remaining. In general, massive resections particularly in the context of an absent ileocecal valve are associated with inability to wean completely from parenteral nutrition [2]. The absence of ileocecal valve has been associated with increased diarrhea and small bowel bacterial overgrowth (SBBO). In addition, significant changes in absorption and motility are influenced by regions, where the intestinal resection and anastomosis are performed. There are three main groups based on location of resection and site of anastomosis: ileojejunal anastomosis with the entire colon in continuity with the small bowel, jejunocolonic anastomosis in continuity with the colon, and end-to-end anastomosis with end jejunostomy and no continuity (defunctionalized colon). [3]

While mucosal adaptation has been extensively studied, there is a paucity of data regarding changes in motility after

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small intestinal resection. A better functional outcome is associated with proximal compared to distal resection, which may be related to both the adaptive capacity and intrinsic properties of the jejunum and ileum. Adaptation involves all layers of the bowel wall, including intestinal smooth muscle. The intestinal smooth muscle is coordinated by both hormonal and neuronal components which regulate the transit of intestinal contents through the gastrointestinal tract [4]. Activation of this complex circuitry allows changes in the peristaltic reflex to modulate the intestinal motility pattern from propagative to segmenting. This is accomplished through a complex integration of signals that trigger a jejunal and ileal break mechanism in response to nutrients, most notably fats. Mediators involved in this response include peptide Y.Y., chemosensitive afferent neurons, noradrenergic nerves, myenteric serotonergic neurons, and opioid neurons [5]. Following proximal resection of small bowel, for example, it has been demonstrated that the postprandial motilin response is decreased, whereas transient increases in neurotensin and peptide Y.Y. have been noted after distal resection [6].

After intestinal loss, a combination of shorter bowel length and disruption of normal physiological mechanisms may lead to poor absorption and malnutrition. Increased contractile response and proliferative changes in intestinal smooth muscle cells may contribute to the compensatory adaptive mechanism to slow intestinal transit and improve nutrient absorption. While the cellular mechanism for this process is not well-defined, mechanisms such as epidermal growth factor receptor signaling have been shown to play a role in adaptation of the smooth muscle cellular compartment [4].

Little is known about changes in the migrating motor complex (MMC) after resection. Animal models often reveal conflicting results with a broad spectrum of motility changes depending on the extent and location of resection. In the Uchiyama animal model, after extensive distal small bowel resection, 2–4-week postoperative, there was a decreased MMC velocity and longer intervals between MMCs during fasting with slight recovery of propagation frequency after 8–13 months. After 2–4 weeks, there was also impairment of MMC migration in the jejunum distal to the anastomosis with partial recovery after 8–13 months [7, 8]. Findings such as shorter phase I duration and discoordinate clustered MMC activity have also been seen using the same model [9]. There are very limited motility studies in humans after small bowel resection [10–12]. With extensive distal resection, motility changes include shorter duration and more frequent MMCs as well as a reduction in phase II activity; however, limited ileal resection does not result in detectable manometric changes of jejunal motility [11]. The postprandial motor response is not well-defined, but appears to be shorter in patients after resection [12].

Short Bowel Syndrome Perioperative Evaluation

The goal of surgery for patients with short bowel syndrome includes: maximizing intestinal absorption, improving motility and transit of the dilated aperistaltic segments, as well as delaying intestinal transit time in some cases. Laparotomy or laparoscopy is also required in some cases to close stomas or address causes of obstruction, such as abdominal adhesions [13].

A thorough and focused evaluation must be performed to determine the best surgical option in patients with short bowel. Perioperative evaluation may include assessment of intestinal length and caliber, motility, and intestinal transit. An upper gastrointestinal series with small bowel follow, for instance, can determine bowel anatomy and identify the presence of obstruction leading to possible adhesiolysis or remodeling of an anastomosis [14]. Determination of intestinal transit can also be assessed to some extent with an upper gastrointestinal series; however, the study has several limitations. First, it does not quantitatively evaluate motility. In addition, the chemical composition of the contrast itself may alter motility giving a false impression of the intestinal transit. The authors believe that antroduodenal and colonic manometry are crucial in the study of these patients. Unfortunately, motility studies are not systematically used in patients with short bowel syndrome, especially before operative management. The preoperative value of colonic and antroduodenal manometry in differentiating peristaltic versus aperistalsic bowel segments was recently addressed by Balint, et al. (Abstract presented at NASPGHAN annual meeting 2015) [15] In this series, a normal colonic manometry was the basis for preserving continuity of the colon in a patient with short bowel syndrome. In contrast, abdominal distension and feeding intolerance with absent distal colonic motility and markedly improvement after placement of a left-sided colostomy in a patient with prior gastroschisis and short bowel syndrome (Author, non-published personal observation) (Fig. 31.1).

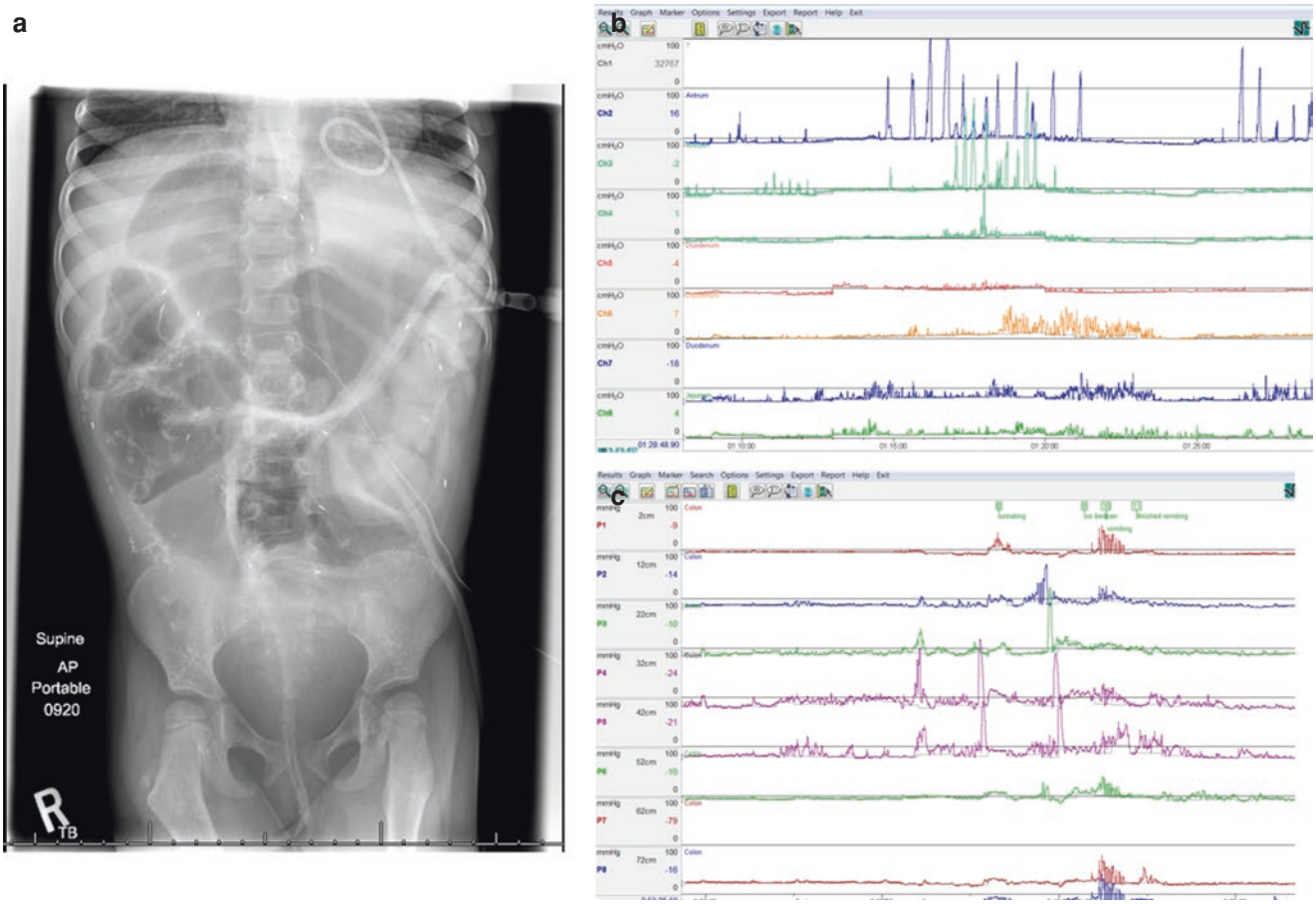

Fig. 31.1 Patient with history of gastroschisis resulting in short bowelsyndromewith persistent abdominal distension (**a**) and feeding intolerance after STEP. Antroduodenal manometry demostrated adequate small bowel motility after STEP (**b**). Absence of motility was shown in the distal colon (**c**). Subseuqent placement of a left-sided colostomy resulted in symptoms resolution and tolerance of enteral nutrition. (Courtesy of Dr. Gomez and Burns, Nemours Children's Hospital, Orlando, FL)

Short Bowel Syndrome Surgical Approaches

Procedures to Alter Intestinal Transit

Delaying the intestinal transit time has been recognized as an important mechanism in order to increase absorption and maximize contact of the nutrients in patients with short gut syndrome. Several procedures have been designed for this purpose. For example, creation of intestinal valves by placing a Teflon collar around the circumference of the bowel, or by everting the small bowel mucosa, creating a small intussusceptum can induce proximal dilatation increasing adaptation [16, 17]. Reversed antiperistalsic segments of intestine have also been proposed as an alternative for delaying intestinal transit. The reversed segment is usually short and is placed as distal as possible to prevent obstruction. This procedure has been used in adults with short bowel syndrome with 50% of patients being able to wean off total parenteral nutrition [18]. The study was based on previous findings in canine models in which the reversed segment was observed to cause retrograde peristalsis disrupting the motility of the proximal intestine [19]. Colonic interposition has also been used to delay intestinal transit time [20]. However, this study was limited by a small number of patients and lack of perioperative assessment of motility changes.

Dilation of a segment of small bowel is frequently associated with poor motility and presence of bacterial overgrowth. Therefore, increasing motility of the dilated segment has been an important aim in many types of autologous reconstructive bowel surgery. Tapering enteroplasty reduces the caliber of the bowel lumen, preserving the length, and thereby, improving peristalsis [21, 22].. The impact of this tapering on the different phases of the MMC or postprandial motility indices is not clear.

Pharmacological Approach for Motility in Short Bowel Syndrome

Advancing enteral nutrition is a key part of the treatment paradigm for the intestinal rehabilitation of patients with short gut syndrome. It is well-known that intestinal dysmotil-

ity is one of the factors that can limit feeding tolerance. Intestinal dysmotility affects intestinal transit times, leading to chronic diarrhea, malabsorption, intestinal pseudo-obstruction, and bacterial overgrowth. This often translates into perpetuation of the need of total parenteral nutrition, thereby increasing the risk of bacterial translocation sepsis and multifactorial liver disease.

Medications can be used with the goal of modulating intestinal transit time. Prokinetics medications such as Domperidone and metoclopramide (dopamine D2 receptor antagonists) have been used to facilitate enteral feedings in patients with short gut syndrome. However, Domperidone has been associated with OTc prolongation and requires an investigational new drug [23] request from the FDA for its use in the U.S [24]. Metoclopramide has a black box warning from the FDA due to concerns for tardive dyskinesia [25]. Cisapride has been withdrawn from the market because of known QTc effects and risk of arrhythmias. Cisapride was particularly effective compared with other prokinetics in improving advancement of enteral nutrition. This was recently shown in a retrospective cohort of 29 out of 61 patients with intestinal failure due to gastroschisis, necrotizing enterocolitis, intestinal atresia, and Hirschsprungs disease. Patients were not able to effectively advance enteral feedings with other prokinetic medications, such as metoclopramide or domperidone [26]. Cisapride is an 5-HT4 agonist, releasing acetylcholine from the myenteric neurons. There is a paucity of literature measuring the effect of cisapride in pediatric patients with SBS. In one study by Raphael et al., 10 patients with a mean age 30 months were studied for a period of 8 months. Six patients already had undergone intestinal lengthening procedures. Cisapride improved enteral tolerance in 7/10 patients. The improvement was not dose related, but instead related to longer duration of the therapy. Patients were closely monitored for cardiac side effects with two patients developing prolongation of the QT [27].

Antibiotics have a potential role in patients with SBS-associated dysmotility. Amoxicillin clavulanate, for example, has been studied in SBS patients with small bowel dysmotility and shown to induce MMC phase III contractions [28]. This effects appear to be due to amoxicillin modulation of the cyclic mechanical activity of the duodenal smooth muscle [29]. While it has also a role in treating SBBO, it should be used with caution due to risk of hepatotoxicity [30]. Erythromycin has been used for years to induce phase III in the stomach and duodenum and may have a role in SBS. Both Azithromycin and Erythromycin have comparable effects inducing Phase III contractions including increasing the motility index in the stomach and duodenum [31, 32]. Intragastric erythromycin also has a role in preterm infant with gastric dysmotility (not specifically short gut syndrome) to advance enteral feedings. It has been demonstrated to induce MMC phase III in preterm babies over 31-week gestational age with less effect in those less than 31-week gestation. Its safety profile is not entirely well-defined, but has been used in preterm infants with feeding intolerance with encouraging results in terms of increasing gastric emptying and decreasing intestinal transit time [33–35].

Intestinal Lengthening

Surgical procedures, including longitudinal intestinal lengthening and tailoring (Bianchi's LILT), or serial transverse enteroplasty (STEP), were designed to increase the length of the intestine and maximize absorption in patients with short bowel syndrome [36]. These procedures are usually performed after a period of intestinal adaptation and not immediately after resection. LILT isoperistaltic bowel lengthening entails longitudinal division of the bowel with isoperistaltic end-to-end anastomosis effectively doubling the length of that portion of the bowel. The STEP procedure involves the sequential linear stapling of the dilated small bowel from alternating directions perpendicular to the long axis of the intestine [37].

Both LILT and STEP have been shown to successfully result in increased caloric absorption and preserved intestinal motility [38, 39]. After LILT, there is an increased tolerance of enteral feeds, improved growth, and decreased frequency of catheter infections. Significant improvement in stool counts, intestinal transit time, D-xylose absorption, and fat absorption resulting in discontinuation of parenteral nutrition have also been observed [40, 41]. After LILT, 55–79% of the patients are able to wean from parenteral nutrition with survival rates up to 77% [42]. Limitations of the LILT procedure include its technical difficulty, involvement of at least one intestinal anastomosis, and risk to the mesenteric blood supply. It is also best performed if the bowel is symmetrically dilated. Complications such as ileal valve prolapse and recurrent small bowel dilatation have been reported after the operation [39].

STEP has become widely accepted among pediatric surgeons as it is technically easier to perform than LILT and preserves the natural mesenteric vasculature to the intestine [43]. STEP has been shown to improve weight retention, nutritional status, and intestinal absorptive capacity in an animal model. Its results are comparable to LILT with around 80% of the patients being able to wean off parenteral nutrition [42, 44]. Motility studies performed in an STEP animal model suggest that the MMC phase III is preserved after resection and anastomosis maintaining the amplitude and frequency of small bowel contractions [37]. The small bowel motility index was similar to controls. Nonspecific abnormalities observed in both groups included simultaneous or tonic contractions as well as contractions present in only

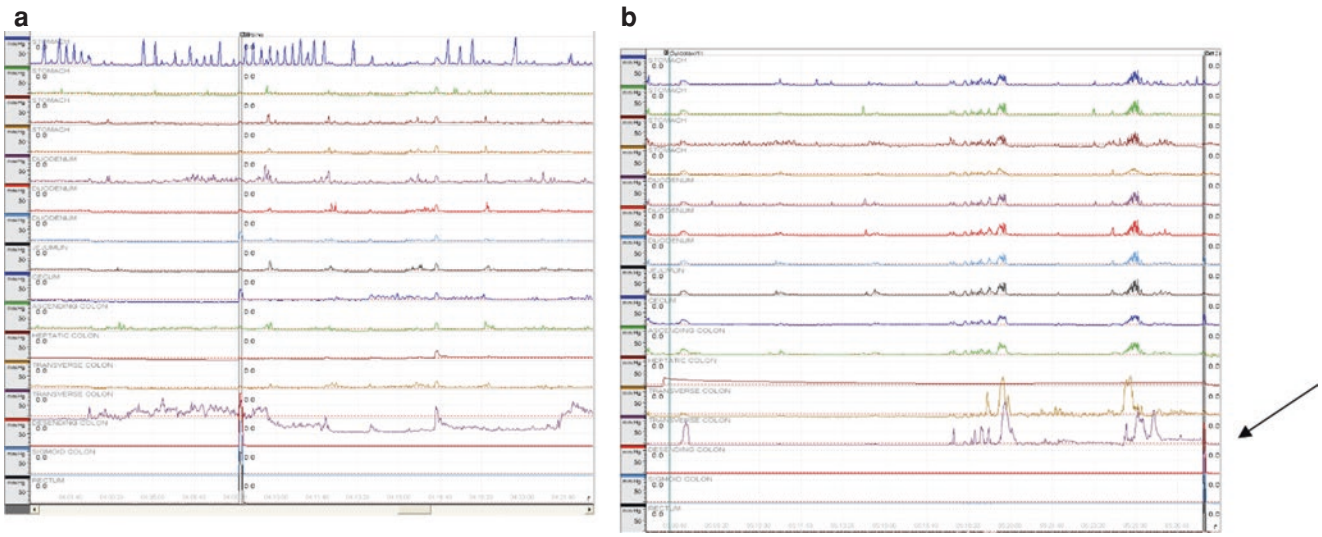

Fig. 31.2 Small bowel and colonic motility in a 4-year-old boy with a medical history of NEC, short bowel syndrome, and post-STEP procedure. (**a**) Presence of simultaneous contractions in the antrum and small bowel in the first eight channels. (**b**) HAPCs in the sigmoid after bisacodyl stimulation (arrow). (Courtesy of Dr. Di Lorenzo and Mousa, Nationwide Children's Hospital, Columbus, OH)

proximal or distal segments. The duration of phase III after octreotide was also increased in STEP animals [37]. These findings are difficult to reproduce in the clinical setting especially in patients with severe intestinal ischemia or gastroschisis and baseline abnormal motility even before STEP. After STEP, intestinal motility continues to be affected correlating with feeding intolerance and TPN dependency (Fig. 31.2). Thus, preoperative severe dysmotility is a risk factor for poor outcomes from STEP [45].

Intestinal Transplantation

Intestinal transplantation has become an increasingly accepted treatment for children with intestinal failure with 3- and 5-year survival rates of 84% and 77%, respectively, with most patients becoming independent of TPN [46]. The most frequent cause of intestinal failure is SBS defined by malabsorption, malnutrition, and growth retardation secondary to extensive loss of intestinal length or functional gut mass [47, 48]. Gastroschisis, volvulus, necrotizing enterocolitis, intestinal atresia, chronic intestinal pseudo-obstruction, and congenital enteropathy are frequent conditions associated with SBS [46].

Small bowel or multivisceral organ transplantation is often necessary for children after massive intestinal resection including those with less than 25 cm of small bowel without ileocecal valve, congenital intractable mucosal disorders, persistent hyperbilirubinemia, and diminishing venous access often associated with recurrent episodes of sepsis [49, 50]. The role of performing small bowel motility studies as a gauge to determine whether intestinal transplantation should be undertaken is unclear, but has been proposed as a potential prognostic tool [51]. Most studies have focused on the impact on intestinal motility after transplantation [52].

After intestinal transplantation, maintenance of intestinal motility with coordinated smooth muscle function and adequate absorptive capability is paramount. Animal models have confirmed that intrinsic nerves are generally preserved after transplantation [53, 54]. The consequence of extrinsic denervation from the small bowel may lead to poor functioning of the grafted intestine. In a canine model, for instance, body weight and serum albumin levels remain stable after autotransplantation. However, transplanted animals demonstrated significant defects in fat and D-xylose absorption compared to controls, possibly attributed to overgrowth in fecal flora [53]. In a similar model, dogs undergoing auto transplantation experienced rapid intestinal transit compared to short-gut animals which may suggest that adaptive responses of the transplanted intestine may be impaired by neuromuscular injury associated with denervation or ischemia [55].

Intestinal motility after small bowel transplantation has been studied in children using antroduodenal manometry. Interdigestive phase III motor activity with normal manometric characteristics was seen as early as 3-month post-transplantation in the majority of patients. However, disruption of an orderly MMC was noted across the anastomosis as well as abnormal postprandial motility, which may in part be responsible for abnormal intestinal transit and poor absorption [52]. After intestinal transplant immune-mediated dysmotility is common. Perioperative infliximab in addition to tacrolimus may decrease the inflammation that contributes to dysmotility [56, 57]. These studies emphasize how little is known about the effect of small bowel transplantation on motility and underscore the need for future prospective

research. Because a significant part of graft motility depends on the Cajal cells, particularly in the context of extrinsic denervation, inflammation of the tunica muscularis either by ischemia reperfusion or by frequent episodes of rejection or infections, often leads to poor functioning of the graft and presence of bacterial overgrowth [58]. In animal models, small bowel graft rejection is associated with decreased MMC phase III amplitude and propagation of contractions [59, 60].

Roux-en-Y Jejunostomy and Bariatric Surgery

Roux-en-Y gastrojejunostomy has been employed in both children and adults for a variety of indications, including postgastrectomy for peptic ulcer disease, as a component of bariatric surgery, and for jejunal feeding access [55]. The technique limits reflux of bile into the gastric remnant and esophagus. Common postoperative symptoms attributed to secondary dysmotility include abdominal fullness, distension, pain, nausea, and vomiting [61]. These symptoms are likely the result of interrupted slow-wave electrical conduction which occurs after transecting the jejunum resulting in shortened phase III MMC duration and abnormal motor response to meals [62]. The consequence of disruption of the enteric nervous system may include serious conditions such as ascending cholangitis due to stasis of bowel contents in the proximal limb of the roux segment, known as blind-loop syndrome [63].

It has been shown in both adults and animals that using an "uncut" Roux-en-Y technique may avoid the problems observed with jejunal transection by prolonging the phase III MMC, thereby enhancing digestive clearance. While gastrectomy is uncommon in children, there has been an increase in pediatric gastric surgery to treat obesity particularly in adolescents [64]. Both laparoscopic adjustable gastric banding and laparoscopic Roux-en-Y gastric bypass have been performed in children, but there is a paucity of data examining the effects of these operations on gut motility. Overall, there seems to be an improvement in health-related quality of life based on early studies, which may suggest limited disturbances in motility in these patients [65].

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is a developmental defect present in less than 1 of 1000 live births resulting in herniation of abdominal viscera into the chest [66, 67]. It is associated with other anatomic malformations in 30% of the patients resulting in increased mortality [68, 69]. Long-term gastrointestinal problems, most notably refractory gastroesophageal reflux disease (GERD), have been described in patients with prior CDH repair [23]. In a recent multivariate analysis, the incidence of GERD was shown to be 39% immediately after repair and 16% 12–18 years after repair. Patients with an intrathoracic stomach and patch closure of the diaphragm seemed to demonstrate the most significant reflux symptoms in the early postoperative period [70].

Reports of intestinal motility disorders in patients with CDH are limited. However, foregut dysmotility has been postulated after CDH repair as evidenced by persistent upper GI symptoms noted in association with abnormal gut fixation seen in nearly 10% of patients [71]. For example, antral hypomotility with low-amplitude and prolonged phase III contractions has been observed after CDH repair manifesting as symptoms of severe gastroesophageal reflux and delayed gastric emptying scintigraphy testing [72].

Gastroschisis

Gastroschisis is a full-thickness defect in the abdominal wall usually adjacent to the insertion of the umbilical cord with an incidence between 0.4 and 3 per 10,000 births [73]. A variable amount of intestine and abdominal organs may herniate through this defect without the protective covering of the peritoneal sac [74]. Ten percent of infants with gastroschisis develop ischemic injury to the bowel due to vascular insufficiency which may result in intestinal stenosis or atresia [73, 75]. Gastroschisis represents one of the major causes of intestinal failure often necessitating consideration of intestinal transplantation. Approximately 40% of patients with gastroschisis require parenteral nutrition by the age of 4 months and 10% by the age of 2 years [76].

Patients with gastroschisis tend to have persistent gut dysmotility with symptoms suggestive of intestinal pseudoobstruction [77]. Even after repair with adequate bowel length, these patients have evidence of profound feeding problems, increased hospitalizations, and mortality [78, 79]. Many of these patients with feeding problems may have neuropathic predominant changes based on antroduodenal manometry (author unpublished case series). Interestingly, in postnatal autopsy studies, there is no evidence of ganglion cell or generalized myenteric nervous system abnormalities to explain the motility disorders that often accompany cases of gastroschisis [80].

Motility Disorders after Repair of Malrotation and Intestinal Atresia

Malrotation is defined by the absence of midgut rotation before reentering the abdominal cavity during the 12th week of gestation [81]. By this time in embryonic development, the

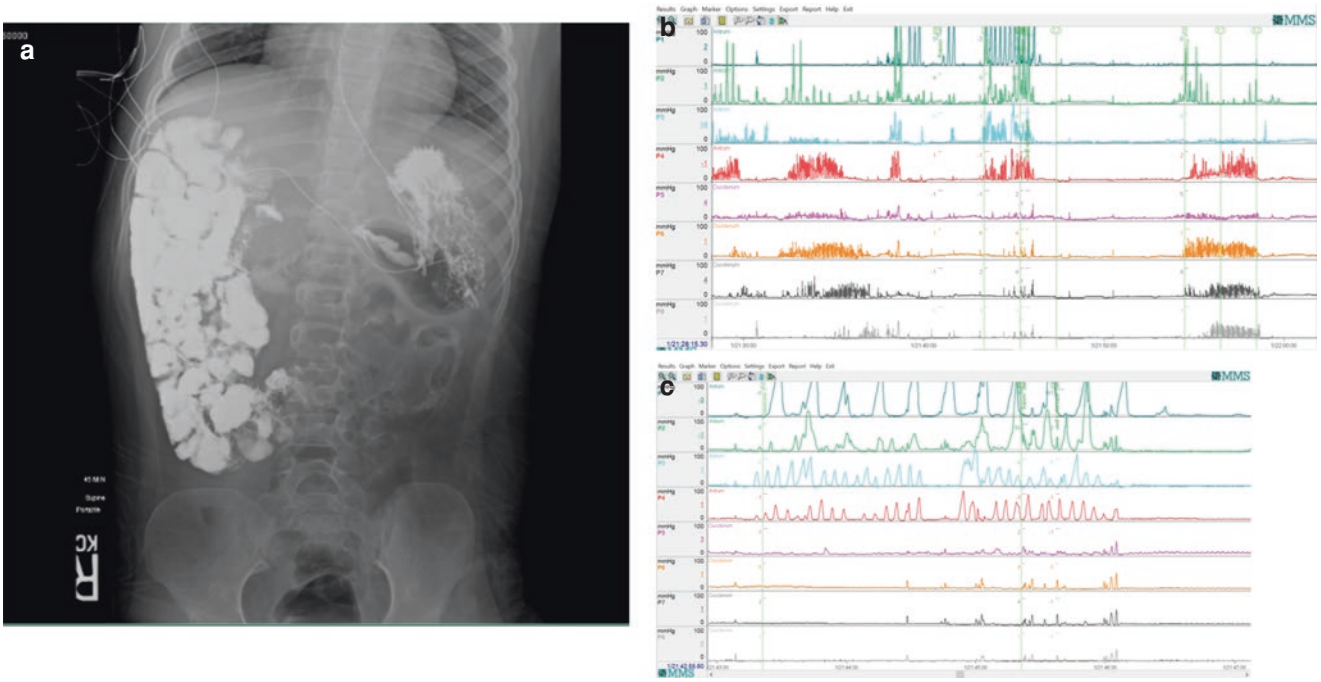

Fig. 31.3 Presence of abnormal peristalsis during antroduodenal manometry in an 8-year-old girl with malrotation and feeding intolerance, (**a**). Upper gastrointestinal series after Ladd's procedure. (**b**) Small bowel MMC slightly disorganized but preserved. (**c**). Stomach retrograde peristalsis after feedings. (Courtesy of Dr. Gomez R. Nemours Children's Hospital)

neurons forming the ENS have already migrated from the neural crest to the intestine. Surgical correction (Ladd's procedure) involves division of a fibrous stalk of peritoneal tissue attaching the cecum to the abdominal wall, known as Ladd's bands; widening the small bowel mesentery; appendectomy; and appropriate placement of the colon. Small bowel motility abnormalities including complete absence of motor activity, low-amplitude or slow-frequency contractions, and slow propagation of phase III of the MMCs have been described after performing a Ladd's procedure for these patients [82]. Retrograde peristalsis has also been observed and associated with feeding intolerance (Fig. 31.3). These manometric abnormalities have been associated in some patients with histological changes, such as distended neuronal axon hypoganglionosis or vacuolated nerve tracts in the small bowel [83].

Duodenal atresia is a congenital malformation leading to duodenal obstruction. There are several types from a fenestrated web to a complete atresia with a discontinuation of the mesentery. This condition can be associated with annular pancreas, Ladd's bands, malrotation, and preduodenal portal vein. Either a duodenostomy or duodenojejunostomy is performed for patients with duodenal atresia. Both approaches have similar outcomes in terms of growth feeding tolerance and use of prokinetic medications [84]. In some patients, there is a risk of developing blind loop syndrome resulting in abdominal pain and SBBO (Fig. 31.4).

Annular pancreas is a malformation frequently associated with Down's syndrome, Hirschsprungs disease, and other rare conditions, including presence of a pancreatic band surrounding the duodenum and producing different degrees of obstruction. Neonates often have symptoms of a gastric outlet or duodenal obstruction. Annular pancreas is most commonly seen in neonates; however, there are a few case reports of adults presenting with symptoms of gastric outlet or duodenal obstruction secondary to annular pancreas [85]. In these cases, the duodenum is frequently dilated and atonic with limited improvement in motility even after surgery.

Intestinal atresia is another frequent cause of bowel obstruction in neonates. Operative management includes resection of the atresia with primary bowel anastomosis, resection with tapering enteroplasty, temporary ostomy with intestinal resection, enterostomy with web excision, and longitudinal intestinal lengthening procedures. After surgical correction, symptoms of adhesive bowel obstruction occur in close to 25% of the patients with prolonged adynamic ileus in 9% and enterostomy prolapse in 2% [86]. Prolonged small bowel obstruction due to atresia or malrotation can lead to severe refeeding problems in the neonatal period. Cezard et al. described a form of post-obstructive enteropathy (POE) of the apparently normal small intestine segment proximal to the obstruction. POE patients showed significant abnormal peristalsis as characterized by barium and carmine transit times. Small bowel manometric recordings can varied among low amplitude, normal frequency, and propagation of the Phase III in the dilated zone with improvement of the amplitude after the intestinal tapering of the dilated small bowel [87]. In another series, there was total absence or abnormal phase III of the MMC and decreased motility index of the small intestine above the obstruction [88, 89].

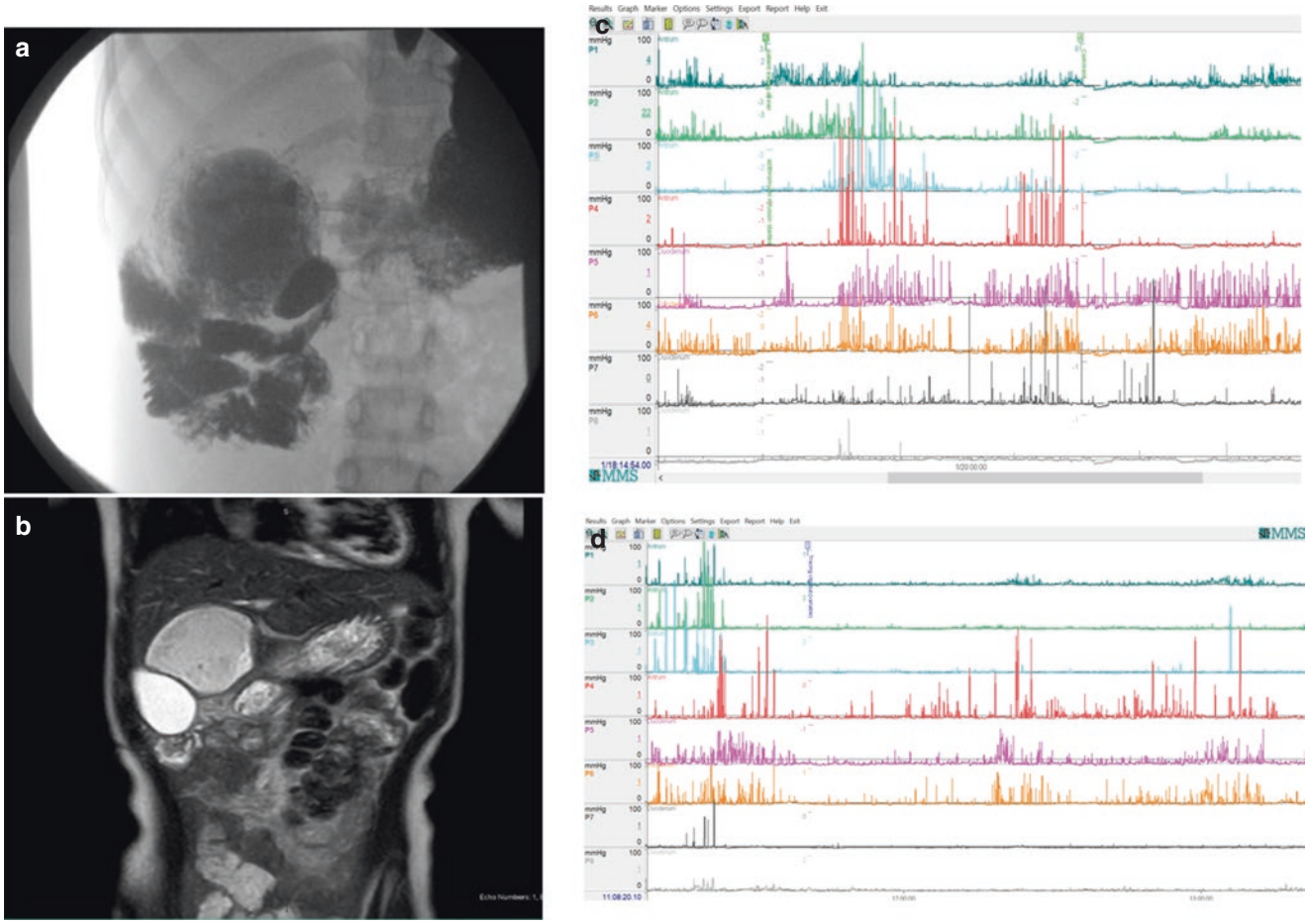

Fig. 31.4 Disorganized duodenal motility in an 8-year-old boy with annular pancreas and gastrojejunostomy (**a**, **b**). Presence of dilated duodenum with blind loop in upper gastrointestinal series and MRI enterography, respectively (**b**). (**c**) Presence of disorganized motility. (**d**) Retrograde peristalsis. (Dr. Gomez R. Nemours Children's Hospital)

Colectomy and Partial Colonic Resection

Colonic resection in children is reserved for chronic conditions, such as refractory ulcerative colitis, Crohn's colitis, familial adenomatous polyposis, severe constipation, Hirschsprung's disease, and debilitating motility disorders, such as intestinal pseudoobstruction. Small bowel and residual colonic function is contingent on the region and extent of colonic resection as well as the underlying pathology necessitating surgery. As an example, subtotal colectomy is a surgical option to treat severe cases of constipation associated with colonic dilatation. While extensive resection of colon may accomplish reduction in intestinal transit time, it may not eliminate symptoms of pain and bloating suggesting the possibility of a more generalized motor disorder of the gut [90]. Colectomy in these patients may also be associated with uncontrolled diarrhea and fecal incontinence as well as relapsing constipation [91].

The difficulties associated with subtotal colectomy may be due to the adaptive changes in the MMC resulting in increased anaerobic bacterial colonization of the small intestine [92, 93]. Partial colonic resection may alleviate some of symptoms observed after subtotal colectomy particularly if performed in conjunction with preoperative motor assessment, including Sitz markers, scintigraphy, and antroduodenal and colonic manometry [93, 94].

In patients with refractory constipation and colonic dilatation, colonic and antroduodenal manometry may be key diagnostic tests to determine the optimal surgical approach [95–97]. In a recent series by Rodriguez et al., in 555 colonic manometries, an abnormal study with partially propagated or absence high-amplitude propagating contractions (HAPCs) was predictive of surgery with higher success rates compared to medications. In patients with partially propagated HAPCs, an ACE is an appropriate consideration with partial resection in selective patients [98]. In the absence of demonstrable colonic motility, a decompressive ileostomy or proximal colostomy for several months may allow improvement in the degree of colonic dilatation with return of some degree of motor function in the distal, diverted colon [95–97].

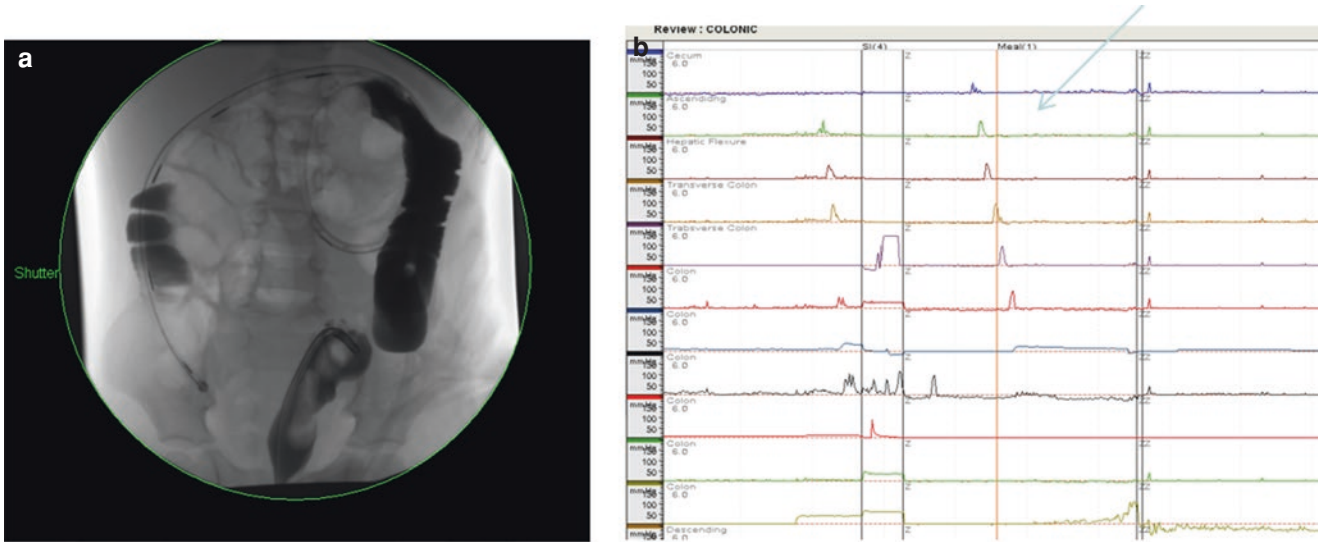

Fig. 31.5 Example of two manometry catheters placed in a retrograde fashion from a colostomy and from the anus. The left panel shows the radiology image of the two manometry catheters. The right panel shows the manometry study. There is evidence of propulsive contractions proximal to a diverting colostomy (top 8 channels in the manometry tracing) and absent motility in the distal 4 channels in the distal colonic segment (Courtesy of Dr. Gomez, Di Lorenzo, Mousa at Nationwide Children's Hospital, Columbus, OH)

Performing a subsequent colonic manometry study after a diverting ileostomy or colostomy may allow a more objective surgical decision between ostomy takedown and reanastomosis alone versus reanastomosis combined with partial resection of colon particularly in the context of adequate small bowel motility (Fig. 31.5). A permanent ileostomy may be indicated for persistently absent colonic HAPCs particularly in association with abnormal small bowel motility [95].

Summary

The need for small bowel and colonic surgery for a variety of indications is a common occurrence in children. The impact of operative manipulation and interventions on subsequent gut motility may have serious implications in terms of the functional capacity of the remaining intestine to effectively absorb nutrients without gastrointestinal symptoms. Thus, motility testing in children whether performed in the preoperative or postoperative phase of management may play a significant role in the surgical decision-making process. Future studies are needed to better discern the underlying mechanisms responsible for motility problems observed after small intestine and colonic surgery.

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Gastric Function After Fundoplication

32

Samuel Nurko

Fundoplication is one of the most common operations performed in children [1–4]. The objective of antirefux surgery is to anatomically restore the antirefux barrier and thereby reduce gastroesophageal refux episodes [5]. It is a very successful operation to control gastroesophageal reflux, but it can be associated with significant postoperative symptoms that may limit its effectiveness [2, 3, 5–10]. The problems and symptoms after fundoplication seem to cluster in two main types: (a) esophageal or (b) gastric [5, 8, 10, 11]. In this chapter, we focus mainly on describing gastric function after fundoplication and, therefore, on the later symptoms.

Effect of Surgery on Gastric Sensorimotor Function

Fundoplication reduces the volume of the stomach and uses most of the proximal stomach to create a wrap around the lower part of the esophagus that results in an increase in LES pressure and in the esophagogastric junction contractile integral of 26.3% [3–7, 9, 12, 13]. The surgery can have a major impact on gastric function, and may explain some of the post-operative symptoms that can be encountered [5–7, 10]. Theoretic causes of problems after fundoplication include impaired gastric accommodation, altered gastric emptying, and increased gastric hypersensitivity [5–7, 10]. Abnormal gastric accommodation has been suggested as the main mechanism of symptoms [6].

There have been a few studies that have evaluated gastric accommodation, sensation, and emptying in children and adults after fundoplication [5–7]. Mousa et al. [4] studied gastric compliance and gastric sensory function before and after Nissen fundoplication in children. They performed barostat studies in 13 children before surgery and repeated the test after surgery in 8. After fundoplication, patients had significantly higher minimal distending pressure values, reduced gastric compliance, and significantly higher pain scores. These indicate that gastric compliance was reduced, and presumably that lead to stimulation of visceral efferents and the heightened perception they noted. Zangen et al. [14] showed that in 12/14 children, there was a decrease in gastric volume capacity that produced retching.

Loots et al. studied 25 children before and after fundoplication with gastric emptying and esophageal manometry/impedance studies [3]. They found that peristaltic contractions were unaltered. Complete lower esophageal sphincter relaxations decreased after fundoplication (92% [76–100%] vs. 65% [29–91%], $p = 0.038$). Four (40%) patients developed postoperative dysphagia, which was transient in 2. In those patients, preoperative gastric emptying was delayed compared with patients without postoperative dysphagia, 96 min (71–104 min) versus 48 min (26–68 min), $p = 0.032$ [3], again suggesting that abnormal gastric emptying may play a role [3].

Findings of abnormal gastric accommodation have also been reported in adults [5–7]. In a case-controlled study, proximal gastric function was studied with the use of barostat in 12 adult's patients that underwent fundoplication and compared with 12 controls [15]. They found that there was no difference between groups in compliance during fasting. However, the adaptive relaxation in the fundoplication group was significantly less than that in controls after ingestion of a liquid meal [15]. They also showed that the fundal wrap is not afunctional and is still able to accommodate to pressure increments that the stomach relaxation after a meal occurs normally, but that in the patients, there was a decrease in receptive relaxation. Similar findings related to accommodation were reported by Vu et al. [16] who studied with a barostat 12 adult patients before and after Nissen fundoplication and compared the results with the findings on 12 healthy adults and 12 adults with GERD who did not undergo surgery. The sensation of fullness was increased in the postoperative patients. Again, post-Nissen patients had normal compliance, but reduced postprandial gastric accommodation

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and accelerated gastric emptying. In a recent study that compared post-fundoplication patients with dysphagia with controls groups (post-operative dysphagia and pre-fundoplication patients) showed no difference in gastric emptying, but significant alterations in gastric accommodation, as well as a correlation between post-prandial fullness and gastric accommodation [6].

Other less invasive methods that indirectly assess gastric function have also been used to study gastric function after surgery. By using single photon emission computed tomography with three dimensional analysis, Bouras et al. [17] showed that patient's post-fundoplication had a postprandial/fasting gastric volume ratio by that was lower than in healthy controls, again suggesting impaired gastric accommodation. By using the water load test, Remes-Troche et al. [18] found that asymptomatic subjects after surgery had higher scores for bloating, nausea, and abdominal pain compared to controls. They found that patients with dyspeptic symptoms after fundoplication had a significantly lower drinking capacity and higher symptoms scores than controls, including patients that were asymptomatic after fundoplication [18]. Their scores were similar than those of patients without surgery and functional dyspepsia, while the scores of asymptomatic fundoplication patients were similar than those of healthy controls [18].

Visceral hypersensitivity has been associated with abnormal gastric accommodation and hyperalgesia, and cofactors of this hypersensitivity are likely to be wall tension and the function of visceral afferents [5–7, 10].Therefore, it is possible that patients who do not develop dyspeptic symptoms after fundoplication may have a nearly normal gastric function [18].

The exact mechanism by which these changes in accommodation occur is not clear. There may be alterations in the proximal gastric wall function, and the abnormalities may be secondary to vagal dysfunction, or to the mechanical effects of the fundoplication per se [4, 6, 9, 11]. A recent meta-analysis showed that rates of adverse results involving dysphagia, gas-bloat syndrome, inability to belch, and reoperation due to severe dysphagia were significantly higher after laparoscopic Nissen as compared with Toupet fundoplication, suggesting that the type of gastric manipulation has an effect on prognosis [2]. The proximal gastric wall seems to work normally as gastric compliance, and tone and volume waves have been found to be normal [15, 16]. It is then possible that surgical manipulation itself could impair autonomic pathways affecting the gastric sensorimotor function and that changes in postprandial relaxation after reflux surgery could result from alterations in neurohormonal control [6, 7, 19]. Vagal nerve function after fundoplication has been evaluated using different methods. By using sham-feeding-stimulated pancreatic polypeptide (PP) test before and after surgery, Devault et al. [7, 19] showed that 5/12 with normal testing before the surgery developed evidence of vagal dysfunction after surgery. Interestingly, there was no correlation between PP tests and the development or worsening of symptoms after surgery. In another study that evaluated vagal function by seeing PP response to insulin-induced hypoglycemia, Vu et al. found that 11 of their 12 patients responded normally [16]. Given the information described above, it appears that the reduced gastric accommodation is probably mechanical in origin [5–7, 16].

Effects on Gastric Emptying

Patients with GERD frequently have delayed gastric emptying [5–7, 16, 20]. It has been reported that fundoplication may accelerate gastric emptying for both solids and liquids [16, 21]. More rapid gastric emptying after the creation of a fundoplication is attributed to the loss of accommodation in the stomach, thereby preventing the fundus from expanding to contain the liquid portion of the meal [5–7, 20]. An acceleration of gastric emptying after Nissen in children has not been consistently found [20]. Mousa et al. [4] found no significant change in emptying for both solids and liquids after surgery, although their patients had normal emptying before the surgery.

A fast gastric emptying after surgery can produce some of the postoperative symptoms that can be encountered [19]. Diarrhea can occur in up to 18% of patients [19], and has been correlated with rapid gastric emptying. An exaggerated fast gastric emptying for liquids may produce dumping syndrome [5–7, 19, 20]. Even though this occurrence is more frequent when a pyloroplasty has been performed, it has been shown to occur also in children and adults in which no pylroplasty was done. The pathophysiology of dumping syndrome in children is multifactorial, although it is incidence and severity appears to be proportional to the rate of emptying [22]. Fonskalrud et al. [23] described a postoperative transient dumping syndrome in 0.9% of 7467 fundoplications (0–5%), and in a prospective study of 50 pediatric patients, Samuk et al. [24] reported dumping diagnosed by testing in 30%. One of the main problems with dumping syndrome is the post-prandial hypoglycemia. The mechanisms responsible for that are not fully understood, but are thought to involve reduced post-prandial gastric relaxation and accelerated emptying, resulting in the precipitous emptying of hyperosmolar, carbohydrate-containing solutions from the stomach into the upper small bowel (3), and subsequent hyperglycemia. Although the occurrence of postprandial hyperglycemia has been blamed for the later hypoglycemia, recent studies have suggested it is most likely related to abnormal Glucagon release [7, 25].

Abnormal gastric emptying has also been postulated as one of the mechanisms for postoperative symptoms [5–7, 20]. However, most studies show that there is no association

between postoperative gastric emptying and symptoms [6, 11]. There are, however, rare cases in which there is damage to the vagus nerve and that can produce severe delays in gastric emptying [11].

Effects on Antroduodenal Motility and Gastric Myoelectrical Activity

The effect of fundoplication on antroduodenal motility has not been clearly established. No prospective studies that have measured antroduodenal motility before and after fundoplication have been reported, but studies of children and adults with postoperative problems have shown abnormal antroduodenal motility [14, 26, 27]. In one study, it was shown that 25 of 28 symptomatic children after fundoplication had abnormalities. The most common abnormality found was an absence of the migrating motor complex in 12, while 6 had postprandial hypomotility; other nonspecific abnormalities included clustered, retrograde, and tonic contractions [26]. Similar motility abnormalities have been described in adults [27].

In another study of 14 patients with food refusal after fundoplication, an abnormal antroduodenal manometry was found in nine patients, suggesting that abnormal motility after surgery does not occur in all patients with symptoms. Therefore, it is unclear if the abnormalities were present before the operation or are a result of it. Given that the abnormalities found were similar to those seen in chronic intestinal pseudo-obstruction, and that not all children with problems postoperatively have motility dysfunction, it is likely the abnormalities seen in children probably predated the operation, suggesting that those children had a more generalized gastrointestinal dysfunction, and not only gastroesophageal reflux. The presence of preoperative gastric myoelectric dysfunction has also been shown. Richards et al. measured gastric myoelectric activity before and after fundoplication with the use of surface electrogastrography in 27 children (17 neurologically impaired and 10 neurologically normal) [28]. They found abnormal gastric electrical activity before surgery in 65% of the neurologically impaired as compared with 20% of the neurologically normal group. After surgery, an abnormal myoelectrical activity developed in 6 (3 in each group), and in 4, the study deteriorated.

Relation of Postoperative Symptoms to Gastric Dysfunction

It has been reported that up to a third of patients may develop symptoms after fundoplication [4, 7, 10]. The problems and symptoms after fundoplication seem to cluster in two main types: (a) esophageal or (b) gastric [8]. Symptoms commonly seen after antireflux surgery include dysphagia, inability to belch, early satiety, bloating, dyspepsia, gas-bloat syndrome, retching, pain, feeding refusal, diarrhea, and dumping [7, 10, 14, 19].

These symptoms may be attributed to a reduction in the gastric accommodation due to the loss in the fundic volume after surgery, alterations in gastric emptying, visceral hypersensitivity, or a combination of these factors after surgery [5–7, 20]. The cause of dysphagia is multifactorial and can often be corrected with esophageal dilation and occasionally repeated surgery [3, 5–7, 20]. From the gastric symptoms, gas bloat occurs, because a compromised ability to eliminate swallowed air by belching, leading to gas accumulation and symptoms of bloating [5–8, 20]. Inability to belch is an expected outcome after fundoplication and most patients learn to compensate for this symptom [7, 20]. It is commonly assumed that an inability to vent air from the stomach by gastric belching is the cause of the gas-related symptoms that frequently occur after fundoplication [5–7, 20, 29]. However, it has also been suggested that gas-related symptoms are due to excessive air swallowing after fundoplication [30]. It has recently been described that patients who have undergone fundoplication often report that they are still able to belch in the absence of TLESRs and common cavities [5–7, 20]. Therefore, the mechanism of belching may be different after fundoplication and that belches consisted of swallowed air that has been retained in the esophagus due to failed peristalsis [29, 31]. Recently, Broeders et al. have demonstrated that in fact, most of the postoperative belching is supragastric, and not gastric, an important finding that may have therapeutic implications [5, 29]. The inability to belch gastric contents predisposes to gas bloat-syndrome. Therefore, fundoplication alters the belching pattern by reducing gastric belching (air venting from stomach) and increasing supra gastric belching (no air venting from stomach). This explains that the increase in belching experienced by some patients after fundoplication, despite the reduction in gastric belching. It can be hypothesized that the reduction in gastric belching incites patients to increase supragastric belching in a futile attempt to vent air from the stomach to reduce postoperative bloating [5–7, 20, 29].

A recent meta-analysis showed that the overall prevalence of gas-related symptoms was significantly higher after laparoscopic Nissen wen compared with laparoscopic Toupet (31.19% vs. 23.91%, RR 1.31, 95% CI [1.05, 1.65], $p = 0.02$). Inability to belch occurred in 33 of 221 (14.93%) patients following Nissen and 18 of 214 (8.41%) patients following Toupet, respectively [2]. Booth et al. reported that 18.64%/10.34% suffered from gas-bloat symptoms, 62.71%/63.79% had postprandial fullness, 74.58%/67.24% complained of flatulence, and 25.42%/31.03% experienced epigastric pain after both laparoscopic Nissen versus laparoscopic Toupet [32].

The development of retching, early satiety, diarrhea, pain, and feeding refusal is more difficult to explain [7, 14, 18, 20, 33] and is probably related to the effects that the fundoplication has on sensorimotor gastric function in the absence of a structural or mechanical obstruction [8]. Therefore, symptoms after fundoplication are most likely related to the decreased gastric postprandial relaxation, impaired distribution of intragastric food, abnormal gastric motility, visceral hyperalgesia and to the fact that the ingested material reaches and distends the distal stomach much earlier than physiologically expected [5–8, 20]. The presence of retching after fundoplication is a sign that there is excessive stimulation of the visceral afferents and that the stomach is unable to tolerate the administered volume and/or composition of feed [7, 20].

In children, Zangen et al. showed a clear relationship between a decrease in gastric volume capacity and retching in children after fundoplication [14]. In adults, Remes-Torche showed with the use of the water load test, that when comparing postoperative patients with or without symptoms, that only those patients with symptoms after fundoplication had visceral hypersensitivity or impaired gastric accommodation or both [18].

There are other factors that may predispose patients to have symptoms. The presence of a fundoplication, which both strengthen the lower esophageal sphincter and decrease transient lower esophageal sphincter relaxations [5, 9, 20, 29], may prevent venting of gas from the proximal stomach and cause increased abdominal distention, particularly when it is known that patients with gastroesophageal reflux swallow large volumes of air routinely [19]. Abnormal distensibility of the gastroesophageal junction with the use of the functional luminal imaging probe (Endoflip, See Chap. 14) has been recently described in symptomatic children with fundoplication [34]. The use of Endoflip allowed a more personalized approach of the symptomatic patient by identifying those in which the fundoplication was too tight [34].

Richards et al. found that children in which there was deteriorating gastric myoelectrical activity after surgery developed retching postoperatively [28], concluding that in children, Nissen fundoplication may be followed by a progression of gastric dysrhythmias that may be associated with retching [28]. In children, another prominent symptom after fundoplication can be food-refusal which can be secondary not only to gastric dysfunction, but also secondary to pain and behavioral issues [7, 14, 20]. Finally, anatomic failure of the fundoplication can play an important role in postoperative symptoms and should always be excluded [8, 9, 20]. Recent studies using MRI fluoroscopy have shown that it allows visualization of the normal pattern of hiatal anatomy, as well as for the demonstration of the pathologic pattern of the integrity of a fundoplication wrap and its relationship to the diaphragm [7, 9, 20]. They were able to demonstrate various patterns of fundoplication disruptions that correlated with clinical symptoms [9]. It has the advantage over barium studies that it allow the visualization not only of luminal structures, but the structural details of the esophagus and stomach itself as well as the surrounding structures [9].

Treatment

Given that the symptoms can originate from a variety of underlying problems, it is important to understand the pathophysiology of the symptoms in each patient [7, 14]. Treatment has then to be tailored accordingly, and a multidisciplinary team may be necessary [14]. Different approaches have been tried.

Modifying the feeding regimen is one of the first things that should be attempted [7]. In patients with G tubes smaller, more frequent feeds may be necessary. Continuous gastric feeds will minimize the level of afferent stimulation of the gut. At times, it may be necessary to modify the protein content as elemental diets may increase gastric emptying. Recently, the use of blenderized diets has been shown to be very effective in patients with problems [7, 35, 36]. Given that fundoplication is associated with a reduction in the frequency of transient relaxations of the lower esophageal sphincter and leads to difficulty in belching, venting of the stomach may be beneficial [7]. At times, it may be necessary to use of jejunal feedings [7, 14].

Given that abnormal gastric accommodation seems to play an important role drugs that increase gastric accommodation may be tried [5–7].

Given that $5HT_1$ receptors are involved in gastric accommodation agonists may be used. Drugs such as cyproheptadine, sumatriptan, and buspirone have been used [7, 10, 14, 18, 37]. Cyproheptadine, a drug that is widely used in pediatrics to stimulate appetite, is a well-known antagonist at multiple sites, including serotonin (5-HT2A, 5-HT2B, and 5-HT2C), histamine (H1), and muscarinic receptors, and has been shown to improve retching post-fundoplication [37]. In a retrospective review, the 14 children with retching following Nissen fundoplication showed the highest response rate (86%), with eight significantly improved and four with symptom resolution [37]. Other drugs that have been used include sumatriptan and buspirone [14, 18]. Buspirone, a serotonin subtype 1A receptor agonist, has been successfully used in adults [6, 10, 11] and was shown to be effective in a placebo controlled study [38]. The novel muscarinic receptor antagonist and cholinesterase inhibitor acotiamide have also been shown to have some effectiveness [6, 38, 39]. Mirtazapine, a 5-HT1 agonist and 5-HT2 and 5-HT3 antagonist, has been shown to be effective in patients with functional dyspepsia and concomitant weight loss, and has been successfully used in post-fundoplication patients [10].

Prokinetics may be necessary in those children with evidence of delayed gastric emptying [7]. Erythromycin has been used, but can be associated with increase pain [7]. The other prokinetics such as metoclopramide, cisparide, and domepridone have limited given their side effect profile, and lack of availability in most parts of the world [7, 10, 14]. Prucalopride, a 5HT4 receptor agonist, has recently been shown to be effective in the treatment of patients with gastroparesis and may, therefore, represent another alternative. Recent studies, however, have shown that it does not seem to modify gastric accommodation [40].

The use of botulinum toxin, an inhibitor of cholinergic neuromuscular transmission, has been shown to be useful in treating children with functional dyspepsia symptoms and feeding difficulties when applied to the pylorus [41, 42]. Limited experience has shown that it may also relieve some of the gas-bloat syndrome symptoms and retching seen postoperatively [42, 43]. Limited experience has shown that it may also relieve some of the gas-bloat syndrome symptoms and retching seen postoperatively [42], but controlled trials are necessary [10]. Recent studies have suggested that baseline pyloric distensibility obtained using Endoflip can predict response to botulinum toxin in patients with gastroparesis [44].

Techniques to decrease the visceral hypersensitivity are usually necessary. Smaller meals, use of anticholinergics and pain modulators (such as low-dose antidepressants, or gabapentin), and behavioral techniques are often necessary [7, 14]. Neuromodulators such as low-dose tricyclic antidepressant, buspirone, and mirtazapine have shown benefit in adults [10].

Summary and Conclusion

Fundoplication may have an impact on gastric sensorimotor function. Fundoplication reduces the volume of the stomach and uses most of the proximal stomach to create a wrap around the lower part of the esophagus. Studies consistently show that it may increase the rate of gastric emptying, decrease gastric accommodation, lead to impaired distribution of intragastric food with the ingested material reaching and distending the distal stomach much earlier than physiologically expected, and may also produce visceral hypersensitivity. Postoperative symptoms that may be attributed to gastric sensorimotor dysfunction after surgery include inability to belch, early satiety, bloating, dyspepsia, gas-bloat syndrome, retching, pain, feeding refusal, diarrhea, and dumping. Given that the symptoms can originate from a variety of underlying problems, it is important to understand the pathophysiology of the symptoms in each patient, to be able to tailor therapy accordingly.

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Part V

Disorders of the Gut Brain Interactions

Rome Criteria for Disorders of Gut–Brain Interaction (DGBI)

33

Samuel Nurko and Carlo Di Lorenzo

Background

Functional gastrointestinal disorders, now called disorders of gut–brain interaction (DGBIs) are common condition in children [1–5]. Although they usually represent a benign problem, parents may be concerned that the symptoms are manifestation of a serious disease, the child is often disabled and the practitioner may be focused on ordering tests that can diagnose other diseases for which medications or surgeries are needed [1, 4, 6–8]. It is now well-established that pediatric DGBIs are associated with poor quality of life [9] and can have long-term adverse outcomes, such as prolonged school absenteeism, depression, anxiety, social phobia, and somatic complaints and may persist into adulthood [1, 4, 7, 8]. One of the main challenges in dealing with DGBIs is that they have no well-established identifiable biologic biomarker [1, 10]. Thus, until recently, the diagnosis was one of exclusion after multiple tests were performed to be sure that there was "no other disease."

In an effort to provide guidance for the recognition of DGBIs in adults, in 1987, a group of experts met in Rome under the leadership of Professor Aldo Torsoli to establish symptom-based criteria to diagnose these conditions [11]. The methodology at that time was mostly based on expert opinion and consensus, because the medical literature on DGBIs was sparse at best [11]. In 1991, they published a document aimed at standardizing the evaluation and care of individuals with DGBIs [11, 12]. Initially, five committees were created based on anatomical regions: esophageal, gastroduodenal, intestinal, biliary, and anorectal [11, 12]. The reports formed the first Rome symptom-based diagnostic criteria for DGBIs in adult patients. Those initial criteria are now known as the Rome I criteria (in order to keep with the spirit of the location, where the meeting took place [11, 12], Rome numerals have since been used to label the iterations of the criteria). The criteria provided clarity and consistency to achieve a clinical diagnosis, made comparisons between groups possible, and opened the door for a new era in the study of DGBIs. Better clinical trials were developed, because it was finally possible to enroll in research studies more homogenous patient population and the development of new therapeutic agents for DGBIs ensued. As more information and research was generated, it became obvious that the Rome criteria needed to be better defined and validated and the Rome II process were developed [11, 12]. Adult gastroenterologists became enlightened that children, much like adults, suffer from DGBIs, and in 1996, a pediatric Rome Committee was formed, in order to address DGBIs in children [11, 12]. This effort was supported by the Rome foundation, and in particular by Dr. Drossman who has been instrumental in his support for the pediatric committees. The initial committee was chaired by Dr. Hyman and cochaired by Dr. Rasquin-Weber, and included Drs. Hyams, Fleisher, Milla, Staiano, and Cucchiara. The first pediatric criteria were published as part of the Rome II criteria in 1999 [13]. This was the first time that the group proposed a classification with system and symptom-based diagnostic criteria for all gastrointestinal syndromes considered to be as manifestation of disordered brain–gut function in the pediatric population [13]. The Rome II pediatric criteria were divided based on predominant symptoms: vomiting, abdominal pain, diarrhea, and defecation disorders. They also took in account the different developmental stages and emphasis was placed on the child's biopsychosocial context [13]. At the time of the publication of the criteria, there were few evidence-based data available, and the criteria were based mostly on the expertise of the individual members of the committee. The publication of the Rome II pediatric criteria marked a turning point in the field of DGBIs in children, as it spurred major validation and education efforts, as well as clinical studies

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and trials in pediatrics. Initial efforts to validate the existence of the proposed disorders were undertaken and validation questionnaires were created [14]. It soon became evident that even though the Rome II criteria represented an important beginning, they needed to be further refined, so the effort to improve them started. When the Rome III effort was born, it was decided to divide the pediatric criteria in two groups, according to the developmental stage of the patients in recognition of the importance that cognition, age, and development have on different phenotypes [15, 16]. Two pediatric committees were formed: (1) neonates and toddlers and (2) children and adolescents. The neonatal and toddler committee was chaired by Dr. Milla and cochaired by Dr. Hyman, and included Drs. Davidson, Fleisher, Benninga, and Taminiau [15]. The Child Adolescent Committee was chaired by Dr. Di Lorenzo and cochaired by Dr. Rasquin-Weber and included Drs. Forbes, Guiraldes, Hyams, Staiano, and Walker [16]. Care was taken to make sure that members of the committee were diverse in terms of geography, expertise, and gender. The division in two groups may have been somewhat arbitrary, given the overlap of some conditions (cyclic vomiting syndrome and functional constipation, for example), but it reflected the fact that the clinical expression of a DGBIs is dependent on an individual's stage of development particularly with regard to physiologic, autonomic, affective, and intellectual development [15, 16]. As the child gains the verbal skills necessary to report pain, it is then possible to diagnose pain-predominant DGBIs. In addition, the DGBIs in neonates and toddlers (particularly in the first year of life) have unique characteristics that merit separate description and approach [15]. Finally, given that the decision to seek medical care for a symptom usually arises from a caregiver's concern for the child rather than from the patient himself, effective management depends upon securing a therapeutic alliance with both the caregivers and the children, something that also needs to be individualized based on the age of child [15]. The Rome III criteria continued to greatly advance the field, and a further explosion in the published literature occurred. The criteria were better defined and validated [2, 3, 17–19]. Compared to the Rome II criteria, they were shown to be more inclusive for children with abdominal pain-related DGBIs, and defecation problems [19]. More clinical trials emerged, and the recognition of DGBIs in children improved both at the primary care and at the specialty level. International collaborative studies emerged, and the criteria were validated in different continents [4, 17, 18, 20, 21]. The biopsychosocial model was further embraced and DGBIs disorders in children crossed into well-characterized entities. For the first time, evidence-based treatments and systematic diagnostic approaches were developed [6, 22, 23]. Even though the understanding of the pathophysiology of DGBIs in children remained incomplete, significant progress had been made since Rome III. With new studies validating the criteria and with advances in neurogastroenterology and new therapies, it became necessary to consider another revision of the Rome criteria and the Rome IV committees were created. The same two age-based pediatric committees were kept. The neonate and toddler were chaired by Dr. Nurko and cochaired by Dr. Benninga. Other members of the Committee included Drs. Faure, Hyman, Schechter, and St James Roberts [24]. The Child Adolescent group was chaired by Dr. Di Lorenzo and cochaired by Dr. Hyams and the others members included Drs. Saps, Shulman, Staiano, and van Tilburg [25].

Rome IV Changes

In Rome IV, the biopsychosocial model of illness based on the complex interplay of genetic, physiological, psychological, and environmental factors is endorsed and a multidisciplinary approach to evaluation and treatment is emphasized, including psychosocial, pharmacological, and dietary interventions [1, 24, 25]. The era of diagnosing a DGBI only when every organic disease has been excluded is waning as we now have sufficient evidence to support symptom-based diagnosis for most conditions [24, 25]. In child/adolescent Rome IV, this concept has been emphasized by removing the dictum that there had to be "no evidence for organic disease" in all DGBIs definitions and replacing it with "after appropriate medical evaluation the symptoms cannot be attributed to another medical condition" [25]. This important change allows the clinician to perform selective or no testing to reach a positive diagnosis of a DGBI [25]. It is pointed out that DGBIs can coexist with other medical conditions that themselves can result in gastrointestinal symptoms (e.g., inflammatory bowel disease) [25]. New sections cover novel DGBIs (such as functional vomiting and functional nausea) and discuss new subgroups of functional dyspepsia and irritable bowel syndrome [25], as well as advances in the understanding of the neurobiology of pain [24]. Rome III "abdominal pain-related functional gastrointestinal disorders" (AP-DGBI) was been changed to functional abdominal pain disorders (FAPD) and the new term, "functional abdominal pain—not otherwise specified," was created to describe children with functional pain who do not fit a specific disorder, such as irritable bowel syndrome, functional dyspepsia, or abdominal migraine [25]. Rome IV DGBI definitions aimed at enhancing clarity for both clinicians and researchers [24]. In the Rome IV document, there are also sections on future directions, including the possibility of defining and studying new DGBIs in the future [24]. Among the novelties of Rome IV, there are also algorithms for different diagnoses of DGBIs and several clinical vignettes that use the multi-

dimensional clinical profile , a tool which aims at providing a more comprehensive understanding of the issues related to DGBIs in both adults and children and addresses the different pathophysiological mechanisms that may underlie similar phenotypes. A Rome Pediatric Book that includes all the Rome IV items related to pediatrics was also published. In addition, a Rome Foundation Pediatric Subcommittee on Clinical Trials and the European Medicines Agency was created and chaired by Dr. Saps [26, 27]. Other members of the Committee included Drs. van Tilburg, Lavigne, Miranda, Benninga, Taminiau, and Di Lorenzo. Their findings should help to develop patient-reported outcomes (PRO) and provide guidelines for the performance of clinical trials in children [28]. New epidemiologic studies using the Rome IV criteria have already been published [5].

Toward Rome V

Recent years have seen further scientific advances that have led to a better definition of the underlying pathophysiology of many of the DGBIs [29], such as an improved understanding of the role that the microbiome and diet play in DGBIs [1, 30]. In the future, the Rome criteria will undergo further transformation to make them even more clinically relevant [31], with more focus on actionable biomarkers [30] and taking into account the heterogeneous severity of the illness before initiating therapy.

Summary

We believe that the Rome criteria, although initially being considered mostly a research tool, have now crossed into the realm of clinical relevance. The goal of the criteria is to give caregivers and older patients information, reassurance, and support, and to avoid unnecessary testing. For the provider, they also allow for a positive diagnosis, better research and clinical trials, and consequently better treatment strategies.

An important question that needs to be addressed is how to prevent DGBIs from becoming chronic severe debilitating conditions and thus decrease their overall societal impact. Current evidence suggests that the primary care physician and the pediatric gastroenterologist are well-positioned to provide effective care, reassure parents, and avoid unnecessary testing [1]. However, there are still tremendous gaps in the knowledge of DGBIs and a lack of uniformity in the approach toward children with DGBIs. Given that prevention may be the best approach for children with DGBIs, there is a need for better education and opportunities to improve the management of children with DGBIs in the community. This represents the biggest challenge for the future.

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Infant Regurgitation and Pediatric Gastroesophageal Reflux Disease

34

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The European and North American Societies of Pediatriac Gastreonterology, Hepatology, and Nutrition published common guidelines on the diagnosis and management of gastroesophageal reflux (GER) and GER disease (GERD) in 2009 and 2018 [1, 2]. GER is a physiologic process of involuntary passage of gastric contents into the esophagus [1, 2]. Most reflux episodes are asymptomatic and are of short duration. GERD occurs when GER causes troublesome symptoms and/or complications, confirmed by a healthcare professional [1]. Although the definition of GERD is not age-related, adults and older children (>11–12 years) evaluate themselves when the symptoms are perceived as troublesome. In younger children (<8 years) and particularly in infants, it is the parents (or other caregivers) who interpret symptoms as being troublesome. In order to decrease the risk for misinterpretation, it is preferable if a healthcare professional confirms that the reported symptoms are a cause of discomfort and distress. However, because of the variability of reflux manifestations, there will always be a grey zone between GER and GERD influenced by the subjective interpretation of the child, parent, and healthcare professionals. Independent of the age of the patient, non-erosive reflux disease (NERD) is likely to be the most frequent presentation of GERD.

GERD is associated with an impaired quality of life, which is, especially during infancy and early childhood, mainly determined by parental perception and coping. Many infants presenting with overt regurgitation and vomiting are distressed and cry. However, crying and distress in an infant in the absence of overt regurgitation are only seldom a manifestation of GER(D). "Silent" GERD is seldom seen in infants [1, 2].

Definitions

Regurgitation, spitting-up, posseting, and spilling are synonyms and are defined as the passage of refluxed gastric contents into the pharynx and mouth, which are often expelled out of the mouth [1, 2]. Regurgitation is distinguished from vomiting by the absence of a central nervous system emetic reflex, retrograde upper intestinal contractions, nausea, and retching. Vomiting is a coordinated autonomic and voluntary motor response, causing forceful expulsion of gastric contents [1, 2]. GERD is a spectrum of a disease that can best be defined as manifestations causing esophageal or extra-esophageal troublesome symptoms or esophageal or adjacent organ injury secondary to the reflux of gastric contents into the esophagus or, beyond, into the oral cavity or airways.

Rumination is the voluntary contraction of the abdominal muscles resulting in the habitual regurgitation of recently ingested food that is subsequently spitted up or re-swallowed (see Chap. 40).

Older children and adults can also experience heartburn, which is defined as an unpleasant burning sensation rising up retrosternally from the epigastric region [3].

Prevalence

Determination of the exact prevalence of GER and GERD at any age is virtually impossible, because symptoms are not specific, not all patients seek medical help, many patients are not (fully) investigated, and auto-treatment is frequent.

Worldwide, it has been estimated that, irrespective of age, 8–33% of the population suffers from GERD, with the highest prevalence observed in Western countries and the lowest

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in East Asia [3]. Several epidemiologic studies have evaluated the frequency and evolution of infant regurgitation, which is, of course, only part of the spectrum of GER. About 25% of infants present with regurgitation that is considered sufficiently troublesome for parents to consider medical advice [4]. GER symptoms are also associated with an increase in body mass index, waist circumference, and functional constipation [5, 6]. According to data from France, the incidence of GER and GERD in children under the age of 2 years is about 12% for each, decreasing to 4.1% for GER and 3.1% for GERD, respectively, in 2–11-year-old children [7]. The prevalence of GER in 12–17-year-old children is 3.0% and GERD symptoms occur in 7.6% [7].

Our group, 20 years ago, established normal ranges for pH metry in infants that were hospitalized for 24 h for a polysomnography for sudden infant death (SID) screening [8]. At that time, GER was considered as a possible cause for pathological apnea, and it was estimated more ethical to perform the polysomnography and pH metry simultaneously than to prolong the hospitalization for a pH metry in case of the polysomnographic recording showed pathologic apneas. However, since then, pH electrodes have changed from glass to antimony or ISFET, that register different (less reflux episodes) than glass electrodes [9]. For ethical reasons, it is not possible to (re-)do pH probe or multichannel intraluminal impedance (MII) recordings in healthy asymptomatic children. GER is influenced by genetic, environmental (e.g., diet and smoking), anatomic, hormonal, and neurogenic factors.

Pathophysiology

Even today, the pathophysiology of GERD is not fully understood and it is recognized to be a multifactorial disease [10]. Amongst others, the following factors are involved: sliding hiatal hernia, low lower esophageal sphincter pressure, (inappropriate) transient lower esophageal sphincter relaxation, gastric acid pocket, obesity, delayed esophageal clearance, and gastric emptying [10]. Multiple mechanisms influence the perception of GER symptoms, such as the volume and pH of the refluxate, its proximal extent, the presence of gas in the refluxate, longitudinal muscle contraction, mucosal integrity, and peripheral and central sensitization. Reflux of duodenal contents into the esophagus caused by duodenal-GER has also been implicated [11]. Three major lines of defense limit the degree of GER and GERD: the anatomical "antireflux barrier," consisting of the LES, the diaphragmatic pinchcock and angle of His, esophageal peristalsis and clearance, and esophageal mucosal resistance [12]. In infants, non-acid reflux causes more distress than acid reflux [13]. Similarly, in adults, bile acid reflux has been associated with symptom generation, esophagitis, and Barrett's metaplasia [14]. Impaired esophageal mucosal integrity and dilated interstitial spaces have been observed in adults with GERD, irrespective of the presence of esophagitis [15]. Finally, more severe esophageal peristaltic dysfunction correlates with the degree of esophagitis [16].

Inter-individual variation of reflux perception suggests different esophageal sensitivity thresholds, which is in part determined by capsaicin levels and vanilloid receptor-1 expression [17]. Acid, temperature, and volume sensitive receptors are present in the esophageal mucosa. Esophageal sensitivity to acid decreases when esophagitis has healed. Duodenal fat increases the sensitivity to reflux. Gene expression scores may facilitate the differential diagnosis between reflux and eosinophilic esophagitis (EoE). Genes may also determine the risk for Barrett esophagitis and adenocarcinoma [18].

New information about pathophysiology is mainly restricted to adults. Acidity of the refluxate may also relate to a localized proximal gastric area called "the gastric acid pocket" that may persist even in the postprandial period when (the rest of the) stomach content is neutralized by the meal [19]. Although this entity has been fairly well-documented in adults, data in children are scarce. Delayed gastric emptying has been documented in (a proportion of) infants and children with symptomatic GER, in particular in those with neurologic disorders [12]. We could not find a relation between gastric emptying and MII/pH results in children with cystic fibrosis (CF) [20], which is analogous to findings in adults [21]. Position and sleep influence GER and gastric emptying. In the recumbent position, noxious gastric materials, rather than air, are positioned at the cardia and may more easily move into the esophagus, especially when the LES tone is decreased during sleep. Both salivation and swallowing are markedly reduced during sleep, further impairing clearance. The varying localization and characterization of mucosal afferent nerves could also play a role in the heterogeneity of symptom perception [22].

Symptoms of GERD

Reflux occurs physiologically many times per day at all ages. There is also a continuum between physiologic GER and GERD. The spectrum of GER(D) symptoms in infants and children varies with age. A relation between GERD and hiccups, chronic cough, chest pain, hoarseness, recurrent otitis media, asthma, pneumonia, bronchiectasis, apparent life-threatening event (ALTE), laryngotracheitis, sinusitis, and dental erosions have been reported, but causality or temporal association was not established in all subjects [23] (Table 34.1). The paucity of studies, small sample sizes, and varying disease definitions do not allow for firm conclusions to be drawn [23]. The laryngeal reflux finding score and laryngeal symptom index are not accurate in predicting GER in infants and children [24]. Acid reflux relates to laryngeal symptoms, but neither acid, nor proximal and weakly acidic

Table 34.1 Symptoms and signs that may be associated with gastroesophageal reflux

Symptoms
Recurrent regurgitation with/without vomiting
Weight loss or poor weight gain
Irritability in infants
Ruminative behavior
Heartburn or chest pain
Hematemesis
Dysphagia, odynophagia
Wheezing
Stridor
Cough
Hoarseness
Signs
Esophagitis
Esophageal stricture
Barrett's esophagus
Laryngeal/pharyngeal inflammation
Recurrent pneumonia
Anemia
Dental erosion
Feeding refusal
Dystonic neck posturing (Sandifer syndrome)
Apnea spells
Apparent life-threatening events (ALTE)

GER relate to laryngeal alterations [24]. There is no consistent evidence confirming the validity of medical therapy in reflux with respiratory symptoms [25]. During recent years, no further evidence has been forthcoming on these topics.

In adults, heartburn and acid regurgitation represent the typical symptoms of GERD, while symptoms—mainly arising from the ENT region—are considered atypical GER symptoms. These atypical symptoms have a low likelihood in predicting an abnormal reflux burden upon further testing [26].

Uncomplicated Regurgitation

Excessive regurgitation is one of the symptoms of GERD, but the terms regurgitation and GERD should not be interchanged [27]. While regurgitation (spilling, spitting up, and posseting) is a typical GER symptom in infants, it is unfrequent in older children and adults. About 25% of infants present with regurgitation severe enough for parents to seek medical help [1, 2, 28]. Management can often be limited to parental reassurance, e.g., by providing information on the natural evolution and adjusting feeding volume and frequency [1, 2, 27]. Regurgitation that persists after the age of 6 months strongly decreases during a 3-month follow-up with conservative treatment [29]. A prospective follow-up reported disappearance of regurgitation in all subjects before 12 months, although the prevalence of feeding refusal, duration of meals, parental feeding-related distress, and impaired quality of life observed was higher in those who presented with regurgitation (even after disappearance of symptoms) compared to those who never regurgitated [30]. Spitting during 90 days during the first 2 years of life was reported to be associated with an increased prevalence of GERD symptoms at 9 years [31]. Data on natural evolution of regurgitation and impact later in life are outdated and of poor quality according to modern standards.

Irritability or infant distress may accompany regurgitation and vomiting. However, in the absence of other warning symptoms, it is not an indication for extensive testing [1, 2]. Parental coping-capacity or anxiety will determine if a physician is contacted or not. Regurgitation is frequent in infants because of the frequent feeding, large liquid volume intake, the limited capacity of the stomach and the esophagus, the horizontal position of infants, etc. Infants ingest per kg bodyweight more than twice the volume that adults do (100–150 mL/kg/day compared to 30–50 mL/kg/day) causing more gastric distention and, as a consequence, more TLESRs.

Rumination syndrome in childhood may be underdiagnosed [32–34]. Rumination syndrome is characterized by the repeated regurgitation of material during or soon after eating with the subsequent rechewing, reswallowing, or spitting out of the regurgitated material. Rumination syndrome is classified as both a "Functional Gastroduodenal Disorder" (by the Rome Foundation's Functional Gastrointestinal Disorders: Disorders of Gut–Brain Interaction, fourth edition) and a "Feeding and Eating Disorder" (by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition). Rumination syndrome is a disorder that is often inaccurately diagnosed or missed, resulting in patients experiencing protracted symptoms and not receiving treatment for long periods [34].

Recurrent and Persistent Regurgitation/Vomiting

Although regurgitation usually causes little more than a nuisance, massive regurgitation may seldom result in caloric insufficiency and malnutrition. Poor weight gain is a crucial warning sign that necessitates clinical management (Table 34.2). These infants need a complete diagnostic workup and eventually hospitalization. There may be abnormal sucking and swallowing. These infants have no apparent malformations, and may be diagnosed as suffering "non-organic failure to thrive" ("NOFTT"), a disorder that is sometimes attributed to social/sensory deprivation, socioeconomic, or primary maternal–child problems. Poor weight gain, feeding refusal, back-arching, irritability, and sleep disturbances have been reported to be both related as well as unrelated to GERD [1, 2, 35].

Table 34.2 Warning signals requiring investigation in infants with regurgitation or vomiting

Bilious vomiting
GI bleeding
– Hematemesis
– Hematochezia
Consistently forceful vomiting
Onset of vomiting after 6 months of life
Failure to thrive
Diarrhea
Constipation
Fever
Lethargy
Hepatosplenomegaly
Bulging fontanelle
Macro/microcephaly
Seizures
Abdominal tenderness or distension
Documented or suspected genetic/metabolic syndrome

GER(D) and Cow's Milk Allergy (CMA)

Some symptoms of CMA overlap with many of GER, or may coexist or complicate GER(D) [36] (Fig. 34.1). An association between GER and cow milk "hypersensitivity" was observed in infants and children with severe GER(D) [37]. Esophageal impedance showed that the incidence of nonacid postprandial reflux was decreased after a feeding with an amino acid-based formula compared to standard cow milk-based infant formula [38]. However, this may well be as related to CMA as to more rapid gastric emptying. An extensive hydrolysate was shown to reduce esophageal acid exposure in preterm infants with feeding intolerance and reflux symptoms [39]. We showed that a non-thickened or thickened extensive hydrolysate was equally effective in infants presenting with frequent regurgitation and with a positive cow's milk challenge test [40]. In infants included

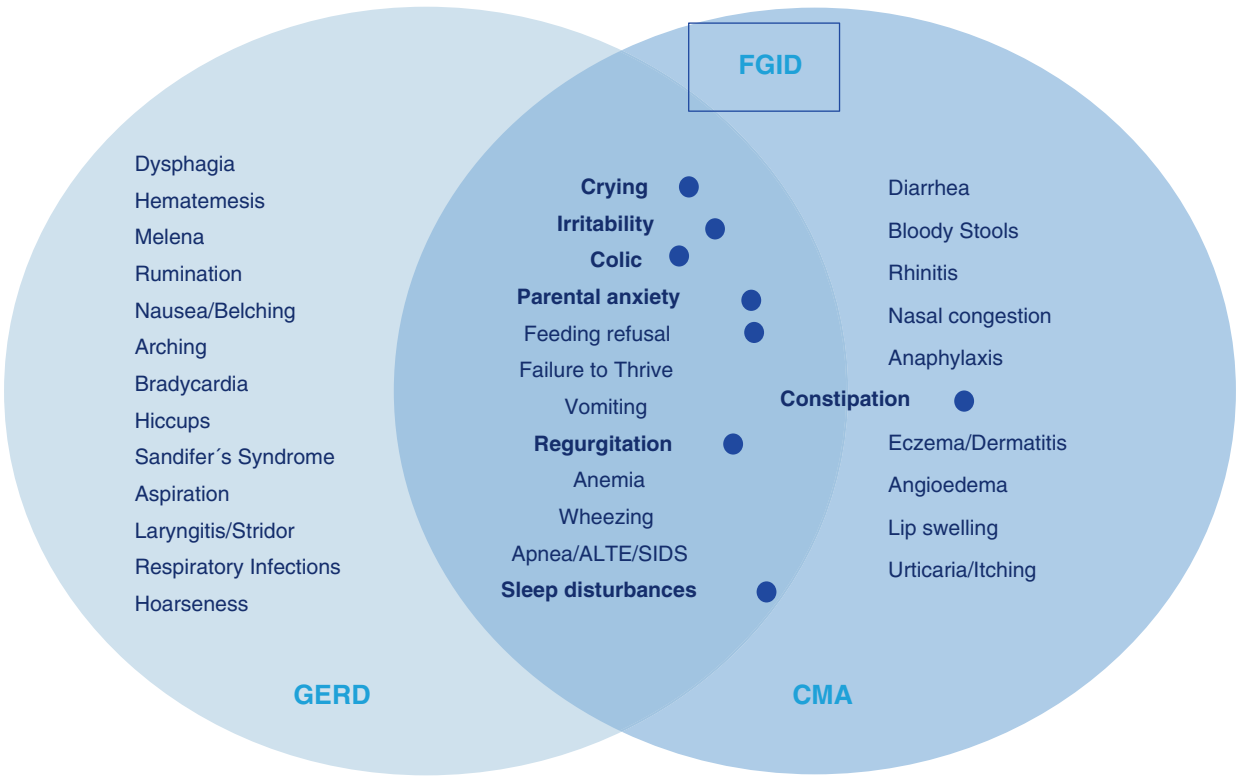

Fig. 34.1 The overlap of symptoms and signs between cow milk allergy, gastro-esophageal reflux disease and functional gastro-intetsinal disorder

in the same study but with a negative challenge test, the thickened hydrolysate was more effective in obtaining a reduction of episodes of regurgitation compared to the non-thickened hydrolysate, although the non-thickened hydrolysate resulted in a decrease of reflux symptoms as well [40]. Whether this is related to the natural evolution or to the more rapid gastric emptying needs to be further researched. However, reflux is seldom a symptom of CMA if it presents as a single manifestation [41].

GER(D) and Distressed Behavior

GERD occurs in a minority of infants who regurgitate; therefore, anti-reflux medication is not often needed [1, 2, 28]. The same amount of distress and crying may be evaluated by some parents as easily acceptable, while it will be unbearable for others. In infants, crying, irritability, sleep disturbance, and "colicky symptoms" have long been considered as heartburn equivalents. Irritability may accompany regurgitation and vomiting; however, in the absence of other warning symptoms, irritability and distress are not an indication for extensive testing or for the treatment of GERD [1, 28]. The duration of crying is not related to the duration of acid reflux measured by pH metry and a meta-analysis concluded that proton pump inhibitors do not decrease crying and distressed behavior in infants [35, 36]. Many factors, such as colic, constipation, CMA, and neurologic disorders, may cause infant irritability and GER(D) among many others.

The developing nervous system of infants seems susceptible to pain (hyper-)sensitivity when in contact with acid despite the absence of tissue damage. Some adults "learn to live with their symptoms" (only 30% of the heartburn/acid regurgitation complainers seek medical help, with 58% being satisfied with self-medication) and acquire tolerance to long-lasting symptoms [42]. In adults, "non-erosive reflux disease" ("NERD") is a generally accepted entity. It is diagnosed when abnormal acid exposure is documented by pH-monitoring in the absence of esophagitis, and is observed in half the heartburn patients with normal upper GI endoscopy [43]. Again, in adults, impaired quality of life, notably regarding pain, mental health, and social function has been demonstrated in patients with GERD regardless of the presence of esophagitis [44]. A relation between GER, GERD, and feeding refusal has not been established in infants. Likewise, there is no evidence that routine acid-suppressive therapy is effective in infants who present only with distress and irritability.

GER(D) and Heartburn

Heartburn is the predominant GER symptom in adults, occurring weekly in 8–33% and daily in 5–10% of subjects [3, 45], while the verbal child can communicate pain, descriptions of the intensity, location, and severity is considered unreliable until the age of at least 8 years, and sometimes later [27].

GERD and Esophagitis

Esophagitis is defined as visible breaks of the esophageal mucosa [1, 2]. Upper GI endoscopy can reveal a peptic stricture as a complication of GERD. Histology is recommended to rule out complications such as Barrett esophagus or other causes of esophagitis such as EoE. In adults, EoE is rarely observed when there is only pain/heartburn and no dysphagia. Differences in patient recruitment, availability of endoscopy, definition of esophagitis, and self-treatment make it virtually impossible to estimate the incidence of esophagitis at all ages. The wide acceptance of the Los Angeles classification of reflux esophagitis [46] only partly solves these issues.

Children with GER symptoms present with esophagitis in 15–62%, Barrett's esophagus in 0.1–3%, and refractory GERD requiring surgery in 6–13% [1, 2, 26]. Erosive esophagitis in 0–17-year-old children with GERD-symptoms was reported to be 12.4%, and increasing with age [47]. The median age of the group with erosive esophagitis was 12.7 ± 4.9 years, versus 10.0 ± 5.1 years in those without erosive esophagitis [47]. The incidence of erosive esophagitis was only 5.5% in those younger than 1 year [47]. Patient selection and recruitment, differences in definition of esophagitis, and availability of self-treatment, however, strongly influence these data. While the prevalence of esophagitis and Barrett's esophagus is similar in adults, erosive esophagitis is observed in 30% of adults with GERD symptoms [48].

In non-verbal infants, behaviors suggesting esophagitis include crying, irritability, sleep disturbance, and "colic." However, while the incidence of infantile colic is about 20% [49], the incidence of esophagitis at this age is only 5% [47, 48]. As a consequence, infant crying as a single presenting manifestation is not an indication for acid-reducing treatment. Infants may also appear very hungry, but become irritable and refuse to drink after their first swallow.

Odynophagia usually represents esophageal inflammation. Dysphagia may be caused by oropharyngeal dysfunction or linked to a stricture or esophagitis, both eosinophilic and reflux-

related. EoE is a chronic immune−/antigen-mediated esophageal inflammatory disease associated with esophageal dysfunction resulting from severe eosinophil-predominant inflammation. The reasons for the rise in the prevalence of EoE in recent years are still poorly understood. Atopic features, allergic symptoms, or positive allergic tests are reported in more than 90% and peripheral eosinophilia in 50% of patients, although these findings depend on patient selection. A genome-wide association study on 351 patients with EoE identified the 5q22 locus encoding TSLP and WDR36 as an EoE susceptibility locus [50]. However, environmental factors may be more relevant than genetic susceptibility [51]. At endoscopy, a pale, granular, furrowed, and occasional ringed esophageal mucosa and in more severe cases, esophageal stenosis may even appear [1, 2]. However, the esophageal mucosa may also appear visually normal, which highlights the importance of histology. The hallmark of EoE is an eosinophilic infiltrate of >15 eosinophils per high power field (HPF), whereas in reflux esophagitis, the eosinophils are in general limited to less than 5/per HPF with 85% positive response to GER treatment. Similar to reflux esophagitis, there is no specific symptom of EoE, but dysphagia for solids is often reported in older children, while symptoms in infants are more reflux-like including vomiting, regurgitation, feeding refusal, and failure to thrive [52, 53]. The longer the disease stays unrecognized, the more likely it is for the patient to have persistent or increased esophageal eosinophilic inflammation, to complain of non-resolving symptoms, and to develop fibrotic complications. Early detection depends on the recognition of initial clinical manifestations that vary from childhood to adulthood and even among patients of the same age. The overlap between GERD and EoE is well-recognized. Initially failure of PPI treatment was considered as a prerequisite to diagnose EoE [49], but this concept has changed in recent years. PPIs are now considered as an effective therapy for EoE, although the mechanism of action remains uncertain [49, 54].

GER(D) and Extra-Esophageal Manifestations

Many extra-esophageal manifestations, mostly respiratory symptoms, have been associated with GER. However, the paucity of studies, small sample sizes, and varying disease definitions and outcome measures still do not allow to draw firm conclusions on this relationship [23]. Different pathophysiologic mechanisms are involved, such as direct aspiration, vagal-mediated bronchial and laryngeal spasm, and neurally mediated inflammation.

Asthma

Chronic pulmonary hyperinflation favors many GER mechanisms. An association between asthma unresponsive to classical treatment and reflux has long been considered [23], particularly in subjects with nocturnal wheezing. In one study, in a small series of 46 children with persistent moderate asthma, 59% had an abnormal pH metry and, in them, reflux treatment resulted in a significant reduction of asthma medication [55]. In contrast, another study found PPIs ineffective in improving asthma symptoms and parameters [56]. A high prevalence of GER was reported in poorly controlled asthmatic children and showed the possible benefit of efficient GER treatment in improving asthma control [57]. The CHEST expert panelists endorsed that: (1) treatment(s) for GERD should not be used when there are no clinical features of GERD and (2) pediatric GERD guidelines should be used to guide treatment and investigations [58]. Once more, patient selection is of crucial importance, but there are currently no data that help in selecting patients in whom reflux treatment may result in a reduction of asthma medication [1, 2, 23].

Cough

GERD is not a common primary cause of chronic cough in children [58]. In children with reflux-related cough, baseline impedance levels have no role in identifying reflux-induced esophageal mucosal ultrastructural changes [59]. Reflux burden, symptom association, and rates of esophageal pathology were determined in children with intractable cough and wheezing: 5% had abnormal reflux testing (67% had an abnormal MII-pH test and 32% had abnormal esophageal biopsies) [60]. The most common MII-pH abnormality was an abnormal symptom association between cough and reflux and the most common endoscopic abnormality was reflux esophagitis. Seven percent of patients presenting only with cough were diagnosed with EoE [60]. Both acid and nonacid or weakly acid GER may precede cough in children with unexplained cough [61]. Cough may induce reflux, but cough does not induce GER [61]. In children with reflux-related cough, dilated intercellular space diameter appears to be an objective and useful marker of esophageal mucosal injury regardless of acid exposure, and its evaluation should be considered for those patients, where the diagnosis is uncertain.

ENT Manifestations

Several studies revealed the presence of pepsin in middle-ear fluid, albeit with a huge variation in incidence (14–73%) [1, 2, 62]. In addition, bile acids have been detected in middle-ear liquid, in higher concentrations than in serum [63]. The exact meaning of these findings remains unclear as there are no randomized controlled intervention trials. About one-third of children that have pepsin in their middle-ear fluid are reported to have abnormal MII-pH investigations [64]. Pepsin and pepsinogen in middle-ear effusion are probably caused by laryngo-pharyngeal reflux and may be involved in the pathogenesis of otitis media [65]. However, little is known about the esophageal reflux symptoms that these children do or do not present, the results of reflux tests in those without pepsin in the middle-ear fluid, the long-term outcome, and the impact of reflux therapy. Proof of cause and effect between extra-esophageal reflux and middle-ear inflammation is still missing [66].

GER(D) and Apnea, Brief Resolved Unexplained Event (BRUE), and SIDS

Literature can best be summarized as follows: series fail most of the time to show a temporal association between GER and pathologic apneas, BRUE (previously called apparent life-threatening events (ALTE)), and bradycardia [1, 2]. However, a relation between GER and short, physiologic apnea has been shown [67, 68]. Selected case reports or small series have been published, showing that exceptionally pathologic apnea can occur as a consequence of GER. Regarding the management of infants presenting with BRUEs, reflux continues to be implicated and children are still being discharged on acid suppression despite lack of efficacy [69]. Swallow testing remains infrequent despite its high yield [69].

GER(D) and Dental Erosions

The hypothesis that there is a widely prevalent association between dental erosion and atypical GERD has been endorsed as well as contra-indicated [70, 71]. Acid, rather than nonacid reflux, seems to have a significant role in the pathogenesis of tooth erosion [72]. Juice drinking, bulimia, and racial and genetic factors that affect dental enamel and saliva might be confounding variables that have been insufficiently considered [1, 2]. There are no long-term (intervention) follow-up studies in high-risk populations.

GER(D) and Sandifer Syndrome

Sandifer syndrome (spasmodic torsional dystonia with arching of the back and opisthotonic posturing, mainly involving the neck and back, but sparing the limbs) is an uncommon but specific manifestation of GERD [73].

GER(D) and Cystic Fibrosis

Patients with CF have a high prevalence of acid GER, even before respiratory symptoms develop [74]. GER(D) is more frequent in patients with CF than in the general population, and also more frequent than in patients with other chronic lung diseases [75]. Increased GER measured with pH metry or MII-pH recording has been reported with a range between 19% and 100% in infants and children [75]. Acid reflux is more prevalent than nonacid reflux in children with CF [76]. In CF patients, GER is also increased in patients without reflux symptoms [77]. GER is a primary phenomenon and is not secondary to cough [78]. Patients with CF and increased reflux have more severe lung disease [79]. Increased bile acids in saliva and sputum of patients suggest aspiration of duodenogastric contents [78]. The aspiration of bile acids is associated with increased airway inflammation [78].

GER in CF patients, as well as in all other patients, is mainly treated with acid suppressants, with proton pump inhibitors inducing the most effective acid suppression. However, the potential adverse effects of acid suppression need to be balanced against the benefits of the therapy. Ranitidine and PPI have been shown to improve the efficacy of the pancreatic enzymes with consequent enhancement of digestive compensation [80, 81]. PPIs are mainly initiated as treatment for classic esophageal GER symptoms, or extra-esophageal symptoms such as chronic cough and other respiratory symptoms believed to be caused by GER, or, in patients with CF, to improve the efficacy of pancreatic enzymes [75]. PPIs reduce acid GER, but do not affect nonacid GER or may even increase nonacid GER [82]. Although other literature suggests that PPIs may also reduce nonacid reflux as it reduces gastric secretion. The effects of PPIs on respiratory parameters are contradictory. Patients receiving PPIs have been reported to have a significantly smaller yearly decline of maximal expiratory flow [83]. However, others reported that patients receiving PPI showed a trend to earlier and more frequent pulmonary exacerbations [84]. Chronic PPI treatment may result in a paradoxically increased inflammatory effect in the airways [85] (side effects of PPI: see treatment).

GER(D) and Neurologic Impairment

Neurologically impaired children accumulate many risk factors for severe GERD: spasticity or hypotonicity, supine position, constipation, etc. (see Chap. 40). Diagnosis of reflux disease in these children is often difficult because of their underlying conditions. Whether this group of patients has more severe reflux disease, or has less effective defense mechanisms, or presents with more severe symptoms because of the inability to express and/or recognize symptoms at an earlier course of the condition remains open for debate. Resulting from the diagnostic uncertainties and diagnostic limitations in this group of neurologically impaired children, response to treatment, both medical and surgical, is poor compared to the neurologically normal child.

GER(D) and Other Risk Groups

Children with congenital abnormalities or after major thoracic or abdominal surgery are at risk for developing severe GERD. Children with anatomic abnormalities such as hiatal hernia, repaired esophageal atresia, and malrotation frequently have severe GERD [86]. Gastroesophageal problems in children born with esophageal atresia are common (see Chap. 40) [87]. The ESPGHAN/NASPGHAN guidelines recommend that GER be treated with acid suppression in all esophageal atresia patients in the neonatal period and during the first year of life [87]. Routine follow-up with endoscopy and pH metry in esophageal atresia patients is warranted [88]. GERD in these children is often refractory to medical treatment and requires antireflux surgery. However, the high rates of wrap failure invite close follow-up in all cases and reoperation or other measures whenever necessary [89]. Although there is abundant literature on overweight and increased GER in adults [48], data in children are scarce. There are no data in literature that preterm babies have more (severe) reflux than term born babies, although many preterm babies are treated for reflux. The role of reflux in patients with bronchopulmonary dysplasia and other chronic respiratory disorders is not clear.

GERD and Complications

Severe complications of GERD such as Barrett esophagus and esophageal adenocarcinoma are seldom in otherwise healthy children. Barrett's esophagus is a premalignant condition in which metaplastic specialized columnar epithelium with goblet cells is present in the tubular esophagus, called intestinal metaplasia. If these severe complications are found, they occur mainly in "at-risk" populations, such as esophageal atresia and neurologically impaired children. Differences in esophageal mucosal resistance and genetic factors may partially explain the diversity of lesions and symptoms. In a series including 402 children with GERD without neurological or congenital anomalies, no case of Barrett esophagus was detected [90]. In another series including 103 children with long-lasting GERD, and not previously treated with H_2 receptor antagonists (H_2RAs) or a PPI, Barrett esophagus was detected in 13%. Reflux symptoms during childhood were not different in adults without or with Barrett's esophagus [91]. There is a genetic predisposition in families in patients with Barrett's esophagus and esophageal carcinoma [1, 2].

Moreover, Barrett esophagus has a male predominance, and increases with age. Patients with short segments of columnar-lined esophagus and intestinal metaplasia have similar esophageal acid exposure but significantly higher frequency of abnormal bilirubin exposure and longer median duration of reflux symptoms than patients without intestinal metaplasia [92]. Peptic ulcer and esophageal and gastric neoplastic changes in children are extremely uncommon. In adults, a decreased prevalence of gastric cancer and peptic ulcer with an opposite increase of esophageal adenocarcinoma and GERD has been noted [93]. This has been attributed to independent factors amongst which are changes in dietary habits, such as a higher fat intake, an increased incidence of obesity, and a decreased incidence of *Helicobacter pylori* infection [93]. Among adults with long-standing and severe reflux, the odds ratios are 43.5 for esophageal adenocarcinoma and 4.4 for adenocarcinoma at the cardia [94]. It is unknown whether mild esophagitis or GER symptoms persisting from childhood are related to an increased risk for severe complications in adults.

Diagnosis

Diagnostic procedures are not discussed in detail. History is still of paramount importance, but it is obvious that history also has its limitations. Children report GER symptoms with poor reliability until the age of at least 8 or even 12 years [1, 2]. A GER questionnaire score or "response to PPI" does not accurately diagnose GERD [95]. Orenstein developed the "infant GER-questionnaire" [96], intended to allow more objective, validated, and repeatable quantification of symptoms suggestive for GERD. The I-GER was revised (the "I-GERQ-R") in 185 patients and 93 controls, resulting in an internal consistency and test–re-test reliability of over 0.85 [97]. However, Aggarwal and coworkers obtained, with the same I-GER-Q, a sensitivity of only 43% and a specificity of 79% [98]. Moreover, pH metry results were not different according to a "positive" or "negative" score of the I-GER-Q

[97]. Vandenplas and coworkers showed that no one question was found to be significantly predictive for the presence of esophagitis. The I-GERQ cutoff score failed to identify 26% of infants with GERD (according to pH metry results or presence of esophagitis) and was positive in 81% of infants with a normal esophageal histology and normal pH metry results [99]. Deal et al. developed two different questionnaires, one for infants and one for older children, and showed that the score was higher in symptomatic than in asymptomatic children [100]. In other words: the correlation between questionnaires and results of reflux investigations is poor. Barium contrast radiography, nuclear scintigraphy, and ultrasound are techniques evaluating postprandial reflux. Normal ranges have not been established for any of these procedures. There is broad consensus that barium studies are not recommended as first-line investigation to diagnose GER(D), but are indicated to detect stenosis and other anatomic or structural malformations. Modern endoscopes are so miniaturized that scoping preterm infants of less than 1000 g has become technically easy. There is a poor correlation between the severity of symptoms and the presence and absence of esophagitis in children as well as adults. In children with reflux-related cough, dilated intercellular space diameter appears to be an objective and useful marker of esophageal mucosal injury regardless of acid exposure, and its evaluation should be considered for those patients, where the diagnosis is uncertain [59]. Biopsies of duodenal, gastric, and esophageal mucosa are mandatory to exclude other diseases [1, 2]. Histology is also necessary to distinguish reflux from other types of esophagitis. Manometry does not demonstrate reflux, but is of interest to analyze pathophysiologic mechanisms causing the reflux, mainly by visualizing and measuring TLESRs, and is indicated in the diagnosis of specific motor conditions, such as achalasia [1]. Moreover, impairment of normal peristaltic function is not uncommon in GER [16]. Esophageal pH metry remains the best method to measure acid in the esophagus, but not all reflux causing symptoms is acid and not all acid reflux causes symptoms (see Chap. 40). Non-acid reflux was reported to cause more frequent distress in infants than acid reflux [13]. While the Bravo-capsule is popular in the USA, it is hardly used in other parts of the world. Although normal ranges have been established for pH metry, they are nowadays of limited value, since these are hard- and software dependent [10]. The demonstration of a time-association between GER episodes and symptoms is one of the major indications for this technique, which has in fact been poorly used for pH metry. Multiple intraluminal impedance (MII) measures electrical potential differences (see Chap. 40). As a consequence, the detection of reflux with MII is not pH dependent, but in combination with pH metry, it allows detection of acid (pH < 4.0), non-acid or weakly acid (pH 4.0–7.0), and alkaline reflux (pH > 7.0). It also measures the proximal extent of the refluxate in the esophagus. The optimal time frame to be considered as "time-association" and the optimal parameter to calculate a significant association is still debated, but in general, a 2-min interval is considered. Interestingly, pH-only episodes, reflux episodes detected with pH metry but not with MII (drop in pH without bolus movement), occur relatively frequently during the night and in infants [101]. The underlying pathophysiology remains obscure. Despite existing inter-reviewer discordance [102], a good correlation between manual and automated analyses of MII baselines was found [103]. Distal compared to proximal esophageal MII baselines was significantly lower in children with an overall positive pH-MII [104]. During the last 3–5 years, interest has focused on mean nocturnal baseline impedance (MNBI), which was shown to be lower in esophagitis, and treatment of esophagitis with PPI does increase MNBI [105]. MNBI is reported to be age dependent, which is likely to relate to the size of the esophagus [106, 107]. Moreover, since esophagitis does decrease the baseline impedance, and since reflux is defined as a decrease of impedance of >50%, severe esophagitis may have a normalizing effect on interpretation of MII tracings. If the baseline is very low, bolus reflux detection becomes more difficult and there will be fewer episodes in which the impedance decreases by >50%. MII-pH monitoring does increase the sensitivity to diagnose GERD; however, when used alone, it results in poor specificity in patients without acid-suppressive therapy or with infrequent symptoms [95]. Research in adults showed that pH-MII analysis partially enables the evaluation of esophageal clearance by the observation of an anterogradely propagating 50% decrease of impedance versus baseline following a reflux episode within a 30-s time interval, termed post-reflux swallow-induced peristaltic wave (PSPW) [108]. Still, in adults, a correlation between PSPW and esophageal hypomotility and reflux burden has been demonstrated [102]. Acid, mixed and proximal refluxes, and their duration are key factors in eliciting PSPWs [109]. The PSPW index is calculated as the ratio between PSPW and total number of reflux episodes detected by impedance monitoring. A PSPW index higher than 50% is indicative of a preserved esophageal clearance. Data on the use of the PSPW in children are lacking. Each GER investigation technique measures different aspects of reflux. Therefore, it is not unexpected that the correlation between the results of the different techniques is poor. There is no "always-best" investigation technique. Endoscopy is the only diagnostic tool to identify esophagitis: 24-h pH metry measures acid GER and MII detects all GER episodes. The Lyon consensus provides guidelines on GER diagnosis, but is only applicable to adults [26].

Treatment Options

The labeling of an otherwise healthy infant as having a "disease" increases parents' interest in unnecessarily medicating their infant [110]. The use of disease labels may promote overtreatment by causing parents to believe that ineffective medications with adverse effects are both useful and necessary [110].Therapeutic options start with reassurance, followed by nutritional management and positional adaptations, and medication (mainly acid reducing), to end with surgery. Therapeutic intervention should always be a balance between intended improvement of symptoms and risk for side effects (Table 34.3; Fig. 34.2).

Table 34.3 Schematic therapeutic approach

Phase 1	Parental reassurance. Observation. Life-style changes. Exclude overfeeding
Phase 2	Dietary treatment (decrease regurgitation)
	Thickened formula, thickening agents, extensive hydrolysates or amino acid-based formula in cow's milk allergy
	Positional treatment (°)
Phase 3	For immediate symptom relief: Alginates (some efficacy in moderate GERD); Antacids only in older children
Phase 4	Proton pump inhibitors (drug of choice in severe GERD; more safety data needed)
Phase 5	Prokinetics (although not one molecule has been shown to be effective)
	Would treat pathophysiologic mechanism of GERD
Phase 6	Laparoscopic surgery
Efficacy and safety data in infants and children for most anti-GER medication is limited	

(°): data on 40° supine sleeping position in infants are limited

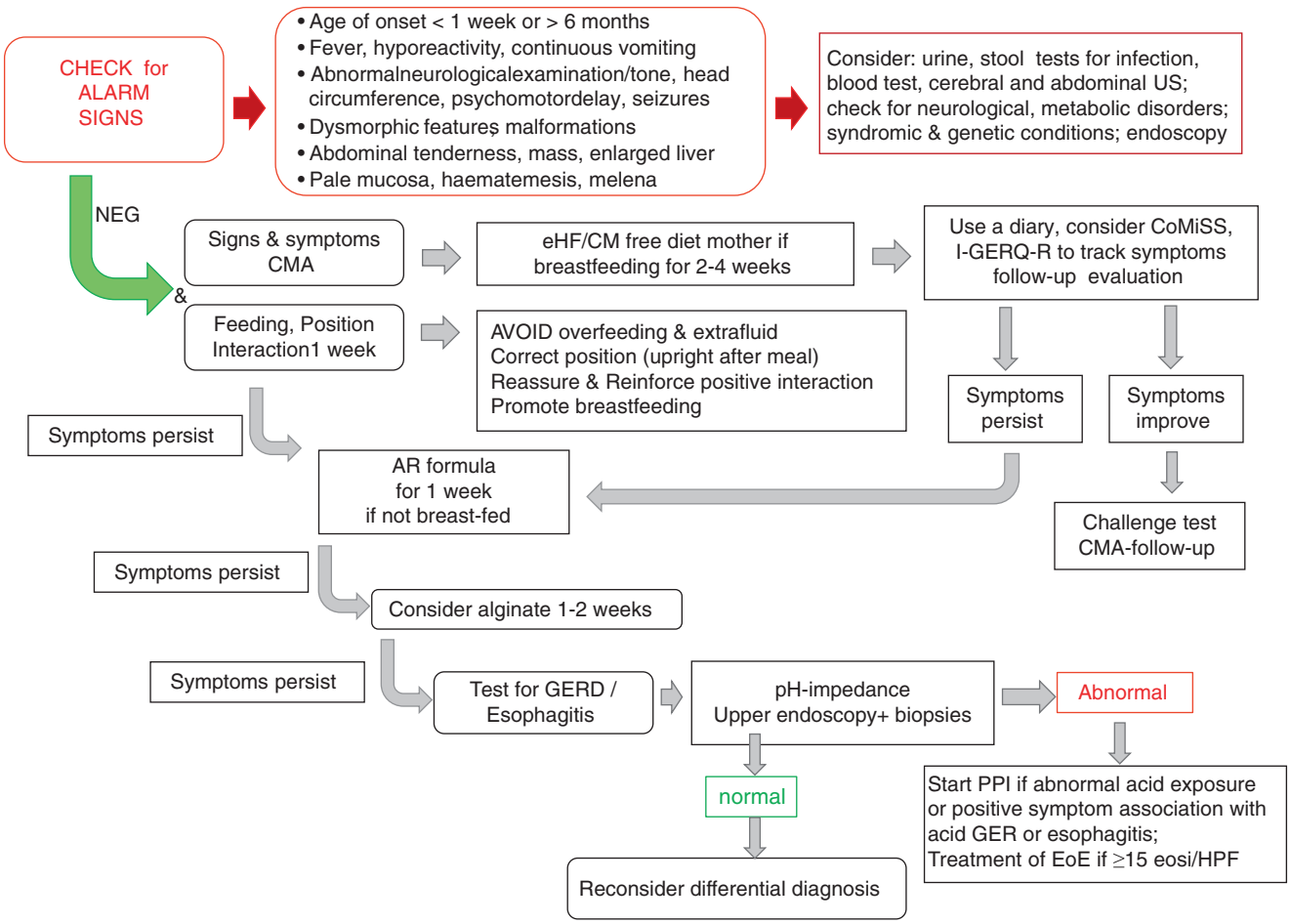

Fig. 34.2 Stepwise approach for infants with persistent (≥1 week) regurgitation and distress

Non-intervention

There are no data to suggest that early intervention during infancy would change the course of GER(D) later in life, mainly because this has not been studied. Recent accumulation of data suggests a decreased quality of life in a number of parents of infants presenting with frequent regurgitation, even if the regurgitation has disappeared [30]. Although symptoms improved in more than half of the infants with reflux esophagitis followed longitudinally for 1 year without pharmacotherapy, histology remained abnormal in all [111]. It is not known if treatment of GER during infancy changes the outcome in adults. If treatment is prescribed, not only efficacy, but also side effects of the treatment should be taken into account.

Regurgitation: Thickened Feeding

The most common reason to seek medical help for parents with young infants with reflux symptoms is frequent troublesome regurgitation and infant distress. Parental coping determines whether infant's symptoms are considered as troublesome or not. Non-pharmacologic treatment (reassurance, dietary, and positional treatment) is recommended as an appropriate first approach. Reassurance, while showing compassion for the impaired quality of life, is of importance [1, 2, 112, 113]. Data suggest that parental reports during a first consultation may be inaccurate and overestimate the incidence of regurgitation [113], similar to what is well-known regarding crying infants or infant colic. Therefore, a "prospective 3-day diary" may help in bringing reassurance. Regurgitation is not a reason to stop breastfeeding. Observation of feeding and handling of the child during and after feedings are mandatory. Many infants are overfed or fed with an inappropriate technique [1, 2].

Thickened formula or anti-regurgitation formula reduces the frequency and severity of visible infant regurgitation, and is, therefore, recommended as an enforcement tool to reassurance. The effect of thickened feeding is observed within 1 week. Commercialized thickened formula is preferred to thickening agents added to formula at home; the nutritional content of the thickening agent and its effect on osmolality has been considered in the commercialized formula [1, 2]. Cow's milk allergy may be a cause of reflux, regurgitation, and vomiting, often accompanied by distressed behavior [1, 2].

Positional Treatment

In GERD patients, TLESRs, GER, distension of proximal stomach, and gastric emptying are increased in right lateral compared to left lateral position [1, 114]. Sleeping positions to decrease regurgitation and GER are the strategy of right lateral positioning for the first postprandial hour with a position change to the left thereafter to promote gastric emptying and reduce liquid GER in the late postprandial period [114, 115]. However, there is a significantly increased risk of SID on the side compared to the supine sleeping position [116]. In preterm infants, left-side position decreases GER [117]. The results of a pilot-study with the "Multicare-AR Bed®" suggest that a special bed that nurses the infant in a 40° supine body position reduces regurgitation, acid reflux (measured with pH monitoring) and reflux-associated symptoms (evaluated with the I-GERQ) [118].

(Alginate-)Antacids and Mucosa Protectors

Alginate (−antacids) have mainly been validated in adults. The key therapeutic advantage of antacids is their rapid onset of action, within minutes. According to the NASPGHAN/ESPGHAN guidelines, there is insufficient evidence to recommend that administration of alginate [2]. However, according to a Cochrane meta-analysis, there is sufficient evidence for 2-week therapeutic trial with alginates [119]. In addition, the guidelines of the National Institute for Health and Care Excellence consider alginate as an appropriate treatment in infants with frequent regurgitation and signs of distress or irritability not improving with correct feeding and thickened formula [120]. Results showed a marginal but significant difference between an infant alginate formulation and placebo in average reflux height (being better for placebo!), and raises questions regarding any perceived clinical benefit of its use [121]. Data on compliance in infants and children (these products have a poor taste) and side effects (many antacids have a high aluminum content) are missing. In one trial in infants, the finding that magnesium alginate plus simethicone was more effective than thickened feeding needs confirmation [122]. Aluminum-free alginate-based formulations significantly reduced the number of episodes of (acid and non acid) GER detected by MII-pH impedance, as well as regurgitation, and associated symptoms in two populations of infants with persistent regurgitation and distress [123, 124]. There are different compositions of Gaviscon–alginate on the market (Table 34.4). No adverse effects were reported in the short term follow-up.

Data on the beneficial effects of monotherapy with mucosaprotectans based on hyaluronic acid and chondroitin sulphate remain scarce [125]. Extrapolation from adult data makes it unlikely that mucosaprotectors would be effective in children.

Table 34.4 Comparison of Gaviscon Infant® and Gaviscon Nourrisson®

	Gaviscon infant®	Gaviscon nourrisson®
Active ingredients	Sodium alginate; magnesium alginate [1]	Sodium alginate; sodium bicarbonate [2]
Mode of action	Physical; at the pH of the infant stomach, the alginate gels and interacts with the milk proteins and calcium ions to form softs curds, resulting in thickening of the stomach contents, thereby impeding reflux [1].	Physical; in the gastric environment an alginate gel forms. The reaction between sodium bicarbonate and gastric acidic releases carbon dioxide bubbles, which become trapped in the gel, causing it to rise and float above the gastric contents. This creates a physical barrier to reflux [2].
Form and composition	Powdered sachet; each unit dose contains 0.65 mg powder comprising 225 mg sodium alginate and 87.5 mg magnesium alginate [1].	Oral suspension; 1 mL contains 50 mg sodium alginate and 14.3 mg sodium bicarbonate [2].
Indication	Gastric regurgitation and gastro-esophageal reflux [1]	GERdisease [2]
Indicated age range	1–2 years; under 12 months with medical supervision [1]	0 months–6 years [2]
Dosing and administration	One (infants under 4.5 kg [10 lb]) or two sachets (infants over 4.5 kg [10 lb]) to be dosed part way through each feed (breast feeding) or mixed with formula feed.	1–2 mL/kg/day, to be distributed according to the number of meals. To be dosed after every feeding-bottle or meal.
	Treatment should not be administered more than six times in any 24-h period [1].	Not to be mixed with milk or food [2].
Interactions with other medicines	Not to be used with thickening agents or infant milk preparations containing a thickening agent as this could lead to over-thickening of the stomach contents [1].	Not to be used with thickening agents or infant milk preparations containing a thickening agent as this could lead to over-thickening of the stomach contents.
		A time-interval of 2 h should be considered between Gaviscon Nourrisson intake and the administration of other medicinal products [2].
Countries available	Australia, Chile, Iraq, Ireland, Honduras, Kuwait, Mauritius, Namibia, New Zealand, Oman, Panama, Philippines, Saudi Arabia, South Africa, Turkey, United Arab Emirates, United Kingdom, Vietnam	Belgium, France, Luxembourg, Morocco

Anti-Acid Medications

Ranitidine has been withdrawn from the market in many countries because of the presence of carcinogenic nitrosamines [126]. The syrup does also contain alcohol, comparable with a daily intake of a coffee spoon of wine in an infant. PPIs are the preferred option for treatment of (acid) GERD in children and adults. If the microgranules are enteric coated, the capsules can be opened and administered orally or via a feeding tube, in suspension in an acidic medium, such as fruit juice, yogurt, or apple sauce. A "home-made" liquid formulation, produced by dissolving the granula, not the microgranula, in 8.4% bicarbonate solution is an effective way to administer PPIs to infants [1, 2].The pharmacy-made liquid PPI has a limited duration of stability. It has been shown in adults and children that PPIs do not reduce the incidence of reflux episodes [82]; they only change the pH of the reflux from acid to nonacid or weakly acid. Omeprazole is approved in the USA and Europe for use in children older than 1 year of age; in the USA, lansoprazole is approved as well. Esomeprazole is approved in the USA for short-term treatment of GERD with erosive esophagitis in infants aged from 1 to 12 months [127]. In Europe, approval for esomeprazole is identical to the approval of omeprazole. Lansoprazole, omeprazole, and pantoprazole are metabolized by a genetically polymorphic enzyme, CYP2C19, absent in approximately 3% of Caucasians and 20% of Asians. Salivary secretion is decreased with omeprazole (while increased with cisapride). There is a high, and still increasing, (over-)prescription of anti-acid medication in infants [128]. PPIs are given in many neonatal intensive care units to treat clinical signs considered to be caused by GER, such as apnea, bradycardia, or feeding intolerance, despite the lack of evidence of efficacy in this population and for these symptoms [129–131]. The concept that infant irritability and sleep disturbances are manifestations of GER is largely extrapolated from adult descriptions of heartburn and sleep disturbances that improve with antacid therapy [1, 2]. PPIs have not been shown to reduce infant crying and irritability.

Although PPIs are generally well-tolerated, interest has focused on potential adverse events. Prolonged treatment of pediatric patients with PPIs has not caused cancer or significant histological abnormalities. There are different catego-

ries of adverse effects related to PPI, such as idiosyncratic reactions, drug–drug interactions, drug-induced hypergastrinemia, and drug-induced hypochlorhydria [1, 2]. Idiosyncratic reactions such as headache, diarrhea, constipation, and nausea occur in up to 12–14% of children taking PPIs [1, 2]. Acid suppression or hypochlorhydria causes abnormal gastrointestinal microbiota and small bowel bacterial overgrowth in up to 25% of all children [1, 2]. The prevalence of infectious respiratory and gastrointestinal tract infections is increased in patients on chronic PPI treatment [1]. PPIs, particularly if administered for >30 days or in a high dose, showed an association with community acquired pneumonia [132]. Hypomagnesemia is reported as a rare but severe complication [133]. Whether or not PPI are associated with an impairment of bone mineralization remains open for debate [134]. Concern about potential nephrologic adverse events, including acute kidney injury, interstitial nephritis, and chronic kidney disease, has been raised [135]. Gastric acid suppression may predispose patients to develop food allergy [100]. Anti-acid medication during pregnancy was reported to increase the risk to develop asthma in the offspring [136, 137].

Prokinetics and Other Medications

From the pathophysiologic point of view, prokinetic drugs are the most logic therapeutic approach to treat NERD in infants, since acid plays only a minor role in GERD in this age group. According to the NASPGHAN–ESPGHAN guidelines, the adverse events of prokinetics outweigh the potential benefit, since the latter was never clearly demonstrated [1, 2]. In adults, evidence for prokinetics largely predates the arrival of PPIs, while a meta-analysis did not demonstrate superior efficacy in healing esophagitis when added to PPI treatment despite possible symptomatic improvement [138]. Prucalopride has received a positive opinion from the Committee for Medicinal Products for Human Use of the European Medicines Agency on the European Marketing Authorization Application for the treatment of chronic constipation in adults, but has been withdrawn for pediatric use.

Bethanechol, a direct cholinergic agonist, is studied in a few controlled trials and has uncertain efficacy and a high incidence of side effects in children with GERD.

Baclofen, 4-amino-3-(-chlorophenyl)-butanoic acid, is a gamma-aminobutyric acid (GABA)-B receptor agonist, used to reduce spasticity in neurologically impaired patients. Baclofen was shown to reduce the number of TLSERs and acid GER during a 2 h test period and to accelerate gastric emptying [139]. Out of 53 patients (mean age 6.1 years), taking PPI once (53%) or twice daily (47%) at the time of initiation of baclofen, 35 (66%) patients experienced a significant reduction in clinical symptoms at their first follow-up visit [140]. In the remaining 18 patients, however, baclofen was stopped because of either no response (n = 15) or adverse events (n = 3) [140]. The data on baclofen are still very limited and the number of adverse events do not support widespread use.

Surgery and Therapeutic Endoscopic Procedures

Most of the literature on surgical therapy in children with GERD consists of retrospective case series in which documentation of the diagnosis of GERD and details of previous medical therapy are deficient, making it difficult to assess the indications for and responses to surgery [1, 2]. Adult series report that between 37% and 62% are taking PPI a few years after the intervention [141, 142]. Different surgical approaches do exist. In general, experience seems to be the best guidance for choosing the preferred technique. While antireflux surgery in certain groups of children may be of considerable benefit, a failure rate of up to 22% has been reported [1, 2]. Children with underlying conditions predisposing to the most severe GERD comprise a large percentage of many surgical series. Post-pyloric (jejunal) feeding has been proposed as an alternative to fundoplication in neurologically impaired children [2]. Therapeutic endoscopic procedures are rarely indicated, still considered experimental, and should only be performed in units, where there is evidence of experience.

The transoral incisionless fundoplication procedure can complement the current surgically and medically available options for children with GERD, especially in complicated patients such as those with neurological impairment [143]. Over the years, magnetic sphincter augmentation has gained in interest in adults with GERD. However, further studies are required before expanding its use beyond clinical research [144]. Surgery is indicated when symptoms are life-threatening or when a child beyond the age of 2–3 years is depending on chronic treatment with anti-acid medications.

Total esophagogastric dissociation is an operative procedure that is useful in selected children with neurologic impairment or other conditions causing life-threatening aspiration during oral feedings.

The Future

Significant changes in the diagnosis and management of GER and GERD in infants and children are not expected in the next 5 years. Epidemiologic data should bring an answer to the question if early intervention in infants with troublesome regurgitation does have an impact on later outcome.

Better insights may be accumulated on the frequency and long-term prognosis of symptoms categorized as functional gastrointestinal disorder. The initial enthusiasm about the contribution of impedance to the diagnosis of GER(D) has tempered by the lack of an effective and safe drug reducing nonacid or weakly acid reflux. Prospective trials in patients with extra-esophageal manifestations are needed to clarify the causal role of GER in these patients. Pediatric data on the role of the "gastric acid pocket" are still missing. Vonoprazan, a potassium competitive acid blocker, is in late clinical-stage development for the treatment of gastric acid-related disorders. Guidelines and recommendations are needed in high risk group of patients particularly in relation to possible increasing gastrointestinal and respiratory infections with protracted use of proton pump inhibitors.For the majority of GERD patients that are otherwise healthy, no major changes are to be expected. However, tools should be developed to better spread the news: guidelines and recommendations hardly reach primary health care.

Conclusions

The incidence of GER in healthy infants and children is unknown, since it is unethical to investigate asymptomatic children. Regurgitation is a common condition in infants and is a transient physiologic phenomenon in the vast majority of infants. GERD is a multifactorial disease, independent of age. There is a wide spectrum of symptoms and signs both for GER and GERD, which are partially age dependent. Infant regurgitation spontaneously disappears with increasing age. Regurgitation in infants is frequent cause of parental anxiety. Since "time is the cure," reassurance is the cornerstone of its management. Regurgitation or other GER symptoms are not a reason to stop breastfeeding. When breastfeeding is not possible or sufficient, thickened formula does reduce regurgitation and contributes to reassure parents. Isolated infant crying and/or distress without the presence of other symptoms is not a symptom of GERD. More in infants than in older children, there is an overlap between symptoms of EoE, cow's milk protein allergy, and GERD. Esophageal and extra-esophageal symptoms and signs caused by reflux do exist, although the evidence for causal relation between reflux and extra-esophageal manifestations is difficult to predict in an individual patient. At-risk populations, such as patients with severe neurological disorders, CF, and esophageal atresia have been identified. There is no best standard diagnostic technique. Validated questionnaires assessing GER symptoms are available, although clinical utility is more for follow-up evaluation than for the diagnosis of GERD. The best investigation to diagnose esophagitis is endoscopy with biopsies. In children with extra-esophageal reflux symptoms, pH metry and MII-pH recording are the recommended techniques. Multiple intraluminal impedance combined with pH monitoring still has limited use, because it is expensive, time consuming, and the additional information provided is mostly related to reflux symptom association. Treatment of regurgitation and moderate reflux disease should focus on reassurance, dietary and possibly also on positional treatment. Alginates may be considered when immediate symptom relief is required and in a subgroup of infants with persistent distressing regurgitation. Medical therapeutic options are mainly limited to acid-secretion reducing medications, although not all reflux symptoms and disease are caused by acid reflux. The best medical treatment of acid GERD is proton pump inhibitors. Attention is increasingly focused on potential adverse effects of these drugs, mostly related to an altered gastrointestinal microbiome because of the decreased gastric acidity. Laparoscopic surgery is recommended in patients dependent on chronic antiacid treatment and in those with severe, sometimes even life-threatening symptoms.

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Esophageal Functional Disorders

35

Rachel Rosen and Rinarani Sanghavi

Functional esophageal disorders can be classified into two groups: pain predominant and dysphagia predominant. The pain predominant disorders include non-erosive reflux disease, reflux hypersensitivity (RH) and functional heartburn (FH). The dysphagia predominant disorder is functional dysphagia. Supragastric belching (SGB) straddles both categories. These categories have been defined in adults, but categories have not been applied to children at this time, and given these new diagnoses, there are very few studies on the frequency or natural history of these disorders. Prior epidemiology studies included these diagnoses under the categories of GERD and NERD (in the case of FH and RH) or globus (in the case of functional dysphagia). However, much can be learned from examining these diagnostic categories and how their application to children may differ.

Pain-Predominant Esophageal Disorders

Definitions

The primary symptoms for pain predominant disorders in adults are heartburn, chest pain, and regurgitation and these symptoms, at least in older children, are similar. In younger children, symptoms may also include abdominal pain [1–3]. For years, these symptoms have been associated with acid suppression trials to try to alleviate symptoms and these trials have played an important role as a diagnostic test; if the symptoms respond to acid suppression, then the symptoms were triggered by acid reflux episodes. Recently, however, this use of acid suppression as a diagnostic test has been called into question because of the potential side effects of the medications and their impact on mucosal healing (i.e., medication trials prior to endoscopy heal mucosa preventing a definitive diagnosis). As a result, earlier testing rather than empiric therapy has been proposed to make definitive diagnoses and avoid unnecessary medication trials. With this early testing with endoscopy and pH/pH-impedance monitoring, however, clinicians have gained new insight into these diagnoses, including the complexities of symptom perception; not only is there an inconsistent relationship between symptoms and esophageal events but also between esophageal events and quality of life [4]. This is even more complex in pediatrics when symptom reporting is often by the patient but also by the parents/guardians. While the Rome IV criteria for adults stipulate that symptoms need to be present for at least the last 3 months with a frequency of at least twice per week, the symptom frequency needed to make a diagnosis in children is not known.

Diagnostic Testing

The mainstays for diagnostic testing are endoscopy and pH/pH-MII testing, though other tests such as high-resolution esophageal manometry are often needed to rule out masqueraders of reflux disease, such as rumination syndrome. As a first test, endoscopy is needed to rule out erosive reflux disease. However, if the endoscopy is performed, while the patient is taking acid suppression, the endoscopy may be falsely normal, so trials of medications should ideally be stopped a minimum of 8 weeks prior to endoscopy. If the endoscopy is grossly normal, primary functional diagnoses can then be considered (Table 35.1). While pediatrics relies heavily on the presence of microscopic disease to diagnose gastroesophageal reflux disease, studies in adults have shown that microscopic esophagitis is not predictive of clinical diagnosis and can be present in functional diagnoses [5, 6]. In specialized centers, pathology scoring systems that take into account microscopic inflammation have been validated

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Table 35.1 Summary of esophageal pain disorder characteristics

	Gross Esophagitis on Endoscopy	Histologic Esophagitis	Abnormal acid exposure (% time pH < 4)	Positive symptom correlation
Erosive reflux disease	+	+	+	+/–
Non-erosive reflux disease	–	+/–	+	+/–
Reflux hypersensitivity	–	+/–	–	+
Functional heartburn	–	+/–	–	–

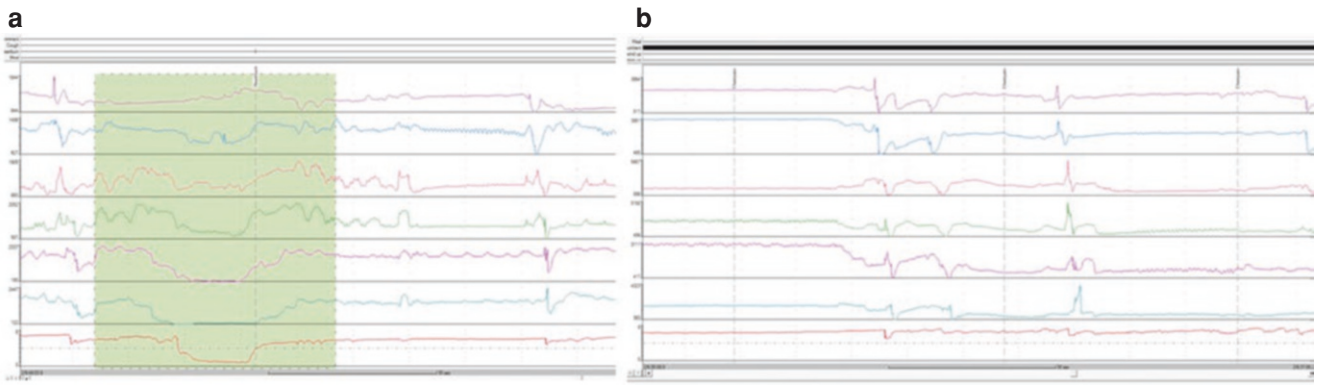

Fig. 35.1 pH-MII tracings from a patient with reflux hypersensitivity (**a**) and functional heartburn (**b**). Patients with reflux hypersensitivity have symptoms following reflux episodes (green shading). Patients with functional heartburn have no esophageal events at the time of symptoms

and shown promise in differentiating NERD from other functional diagnoses [5, 7]. One of the most studied histological component is the dilation of intracellular spaces which have been shown to be present in untreated NERD patients but absent in patients with RH and FH, though results have been conflicting depending how the patient diagnoses have been defined [6, 8]. In one pediatric study, children with non-erosive disease (which may also include FH and RH) are more likely to have microscopic esophagitis compared to controls. This pediatric study also found, likely in adult studies, that there was no difference in dilated intracellular spaces between patients with erosive disease compared to non-erosive diseases [9]. In a more recent study which phenotyped children into ERD, FH, and RH, there were no differences in the rates of esophagitis between subgroups [10]. Larger studies are needed in children to confirm these results.

After performing an endoscopy to rule out erosive disease, pH monitoring (either with pH-metry, pH-MII testing or BRAVO) is needed to further categorize patients into functional diagnoses (Table 35.1). With this additional testing, if the pH < 4 is greater than 6% over 24 h, then patients are diagnosed with NERD. If the total reflux burden is <6%, then diagnosis depend on if there is a positive symptom correlation; patients a positive symptom correlation (a symptom index >50% and/or a symptom association probability of >95%) are diagnosed with RH (Fig. 35.1a) and patients with a negative symptom correlation (a symptom index <50%, and/or a symptom association probability of <95%) are diagnosed with FH (Fig. 35.1b). Regardless of the symptom index chosen to assess symptom–reflux correlation, how the testing is conducted is critical; recent studies suggest that pH testing of known GERD or NERD patients on acid suppression results in reflux profiles identical to RH and FH, leading to an incorrect diagnosis [11]. While primary reason for performing pH-MII/pH testing is to perform symptom correlations, additional information and clues to the diagnosis can be found on pH-MII testing. For example, mean baseline impedance values (both endoscopically obtained and with calculation of the mean nocturnal baseline impedance values) may be lower in patients with NERD, particularly in the distal esophagus, compared to patients with RH or FH [12–14]. Apart from impedance baselines, pH-MII tracings can be analyzed for the presence of post-reflux swallow peristaltic waves. Adult studies suggest that the number of reflux episodes with a clearance swallow within 30 s of a reflux episode ranges from 55% to 64% in patients with functional disorders which is significantly higher than patients with GERD, suggesting that acid clearance is typically intact with functional disorders [13].

While only endoscopy and pH-MII testing is needed for diagnosis, other testing may also suggest a functional diagnosis. For example, in studies of high-resolution esophageal manometry in patients with pain-predominant symptoms, patients with NERD and RH more commonly were diagnosed with ineffective esophageal motility (IEM, defined as a distal contractile interval of <450 mm-Hg-cm-s) compared to patients with FH [15]. The presence of IEM

suggests that reflux stasis may play a role in sensory perceptions that drive this disorder. Other studies have shown that sensory testing across diagnoses shows greater visceral hypersensitivity across FH, RH, and NERD patients compared to controls [16].

Finally, functional luminal imaging probes are beginning to be used to assess for the risk of pathologic reflux in patients with erosive and nonerosive reflux disease. In adults, the presence of repetitive antegrade contractions, evidence of secondary peristalsis is associated with improved acid clearance again suggesting the importance of adequate acid clearance [17]. Interesting, there was no association between EGJ distensibility and acid clearance time, suggesting that the LES may play a less important role in pathologic reflux than motility, a finding seen in children as well [17, 18].

Triggers

Patients with NERD, FH, and RH have more anxiety and depression and more sleep dysfunction than control patients [16]. Treating the sleep disorders and the psychological comorbidities results in symptomatic improvement in reflux symptoms, suggesting that psychological comorbidities and sleep disturbances worsen pain rather than the pain triggering the psychological and sleep symptoms [19, 20]. There are no comparable studies looking at these triggers in children.

Frequently dietary interventions are recommended for symptoms of gastroesophageal reflux; alkaline, low FODMAP, gluten free, and Mediterranean diets have been proposed in adult studies to treat reflux symptoms regardless of eiology, though results are inconsistent [21–23]. The only dietary studies (dairy restriction, hypoallergenic formulas, and thickening) of gastroesophageal reflux symptoms in children have been done in infants, where there are no current functional esophageal diagnostic criteria.

Treatment

Treatment largely varies by diagnosis with the first goal to reduce triggers of symptoms (e.g., dietary interventions and lifestyle modifications). NERD and RH, whose basis is an abnormal reflux burden or a positive symptom index, are typically treated with more traditional reflux therapies, such as acid suppression and fundoplication. FH, a reflux independent diagnosis, is treated with neuromodulation. However, because NERD, RH, and FH are newly defined diagnoses, prior therapeutic trials in the literature have grouped these diagnoses together, so teasing apart the true NERD and RH response rates from FH patients is difficult. In a single adult study of placebo, omeprazole, and fluoxetine for persistent heartburn despite acid suppression and a normal endoscopy, patients, regardless of the degree of esophageal acid, did not respond more favorably to PPIs compared to placebo [24]. In the pediatric medication trials, as with adult studies, patient classification is lacking; most acid suppression trials require abnormal pH testing for entry, so patients with RH and FH are largely excluded.

Data in children are particularly limited and there are no prospective studies of acid suppression characterizing patient using the NERD/FH/RH classifications. In a study of 34 children with NERD (defined as normal endoscopy only with no additional characterization), 92% of patients experience some initial degree of symptom improvement with proton pump inhibitor therapy and 68% remained symptom free 6 months later [25]. In a study of symptomatic adolescents with a normal endoscopy, there was a 45% reduction in days with heartburn in patients taking proton pump inhibitors, but again, there was no categorization for nonerosive subtypes as the only diagnostic test was an endoscopy [26]. In the only study of pediatric patients categorized by pH-MII, Mahoney et al. found that 58% of patients with NERD, 67% of patients with acid RH, 0% of patients with nonacid RH, and 55% of patients with FH had at least some symptomatic improvement with PPI use. However, this study was limited by its small numbers and retrospective nature to assess PPI response.

Recognizing that symptom perception is a critical part of symptomatic response, the majority of therapeutic trials have focused on neuromodulator use. Tricyclic antidepressants, serotonin reuptake inhibitors and others have been trialed with varying success depending on which disorder is being treated; symptom improvement has been seen in 37–68% of adult patients [24, 27–29]. There are no equivalent studies for esophageal symptoms in children, though neuromodulator response for other functional disorders has been disappointing, particularly in the face of large placebo responses and small trial sizes compared to adult studies [30–32]. Further recognizing the importance of modulating symptom perception, hypnotherapy has been proposed for esophageal pain disorders, though there are limited data on efficacy with only a single adult study with nine patients [33].

Finally, antireflux surgery has been studied in small studies adults with nonerosive disease. In the most well-known study of 78 adults with refractory symptoms diagnosed with NERD or RH, patients were randomized to medical or surgical management. RH and NERD patients responded equally well to therapy, with surgical response better than medical response long term [34]. In a retrospective review of fundoplication outcomes in adults with RH and NERD, both patient groups had equivalent symptom control after surgery [35]. There is no equivalent pediatric study of surgical interventions. However, in a single pediatric study showing the relationship between acid burden by pH-MII testing and

quality-of-life scores, there is no relationship between reflux burden and quality of life highlighting the importance of not relying on pH-MII testing alone to make a decision about surgery [4]; surgery should be a last resort and should only be reserved for patients with clear symptom improvement with acid suppression.

Functional Dysphagia

Definition

Functional dysphagia is defined as a sensation of solid and/or liquid food lodging, sticking, or passing abnormally through the esophagus with no evidence of an inflammatory or motor explanation for symptoms. Inflammation or other mucosal lesions must be excluded by endoscopy and major motor disorders (achalasia, scleroderma, and EGJ outflow obstruction) must be excluded by high-resolution manometry. of a major esophageal motor disorder (achalasia, esophagogastric junction outflow obstruction, distal esophageal spasm, hypercontractile esophagus, and absent peristalsis). Symptoms must have been present for at least 6 months prior to the diagnosis and occur with a frequency of at least once a week for the preceding 3 months. Currently, there is no equivalent diagnostic criteria for pediatrics, though children are frequently seen with this complaint.

Diagnostic Testing

Performance of high-resolution manometry (HRM) is required to exclude major motor disorders as a cause for symptoms. In adults, HRM is the gold standard test, but assessments of bolus transit are not required. In contrast to the adult testing, pediatric centers frequently perform high-resolution manometry with impedance to correlate bolus flow with manometric findings; in pediatric patients, there are frequently more subtle motility abnormalities that result in clear bolus stasis that do not fulfill the criteria for a major motor disorder. In these cases, by adult criteria, patients would be considered as functional dysphagia, but in pediatrics, patients would have been characterized as having a minor motor disorder as an explanation for symptoms give the clear bolus stasis (Fig. 35.2). In adults undergoing HRM for the evaluation of dysphagia, 14–40% of patients had minor motor abnormalities, but because the ROME IV definitions require only an exclusion of major motor disorders, these patients would be considered functional dysphagia [36, 37]. Rates of minor motor disorders are even higher in elderly adults >70 years; 79% of patients had evidence of minor motor abnormalities [37]. The most common peristaltic abnormalities seen were weak peristalsis or large breaks in peristalsis.

Given the high rates of minor peristaltic abnormalities in patients given the diagnosis of functional dysphagia, additional studies are needed to determine: (1) are these peristaltic abnormalities associated with impaired bolus transit and (2) if these peristaltic abnormalities are corrected, do symptoms improve. If either of the two are true, then functional dysphagia may be a misnomer and patients may need to be recategorized into two groups, those with impaired peristalsis with associated impaired transit (i.e., dysmotility-triggered dysphagia) and those with normal peristalsis and transit (i.e., true functional dysphagia).

While HRM is required for diagnosis, other tests may be supportive of the diagnosis and may include a normal flip

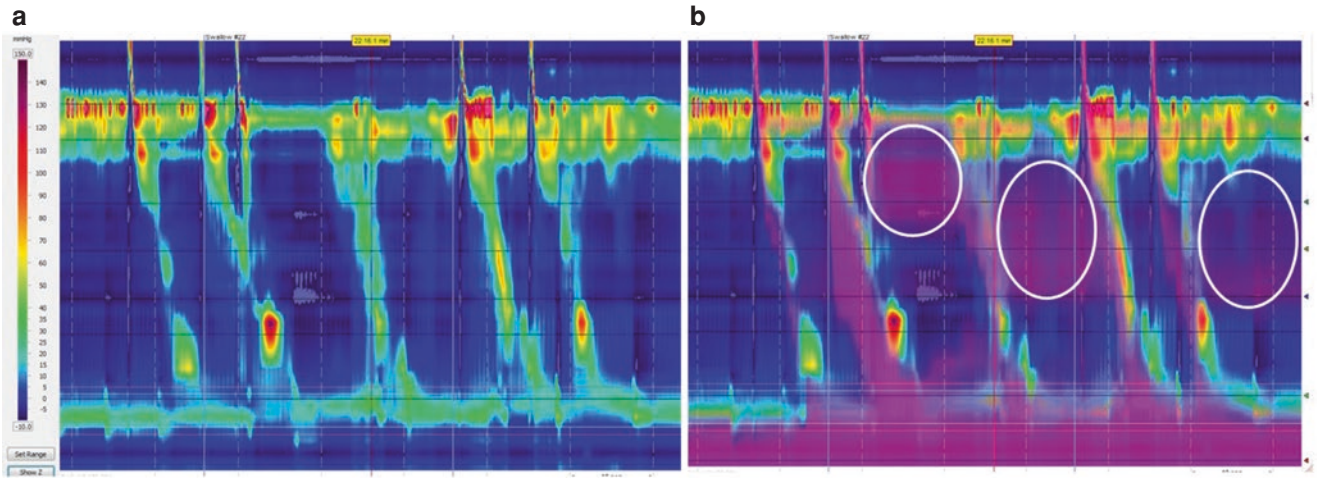

Fig. 35.2 High-resolution manometry tracing with impedance from a patient with functional dysphagia. There is visible peristalsis with normal lower esophageal sphincter relaxation (**a**). While there is evidence of peristaltic breaks, there is no primary motor disorder diagnosis, confirming the diagnosis of functional dysphagia. When bolus flow by impedance is added (**b**) to the tracing (pink shading), there is clear evidence of bolus stasis (circled areas)

defined as intact repetitive antegrade contractions and normal LES distensibility and/or a normal timed barium esophagram. Future studies will be needed to determine if these tests are sensitive enough to make a diagnosis without the need for HRM.

Treatment

There are no prospective studies of therapies for functional dysphagia, the treatment may vary depending on the manometric findings. For example, if there is evidence of breaks in peristaltic waves or waves of low amplitude resulting in bolus stasis, motility medications such as prucalopride or bethanechol may be needed [38, 39]. Other possible therapies include cognitive behavioral therapy to assist with anxiety associated with swallowing and hypnotherapy [40].

Supragastric Belching

Definition

SGB is defined by the antegrade swallowing of air into the esophagus with subsequent retrograde propulsion of air from the esophagus. Importantly, air does not ever reach the stomach. While SGB has been seen in conjunction with gastroesophageal reflux disease and IEM in adults, it is commonly seen in aerophagia in children [41]. The incidence of SGB in adults is approximately 3.4% of patients referred for symptoms and is seen in 2.7% of children undergoing pH-MII testing [42, 43]. While belching is the most common symptom, other symptoms present may include dysphagia, pain, heartburn and bloating [44]. In children with concomitant aerophagia, patients may also present with abdominal distension.

Diagnostic Testing

The diagnosis is made using either pH-MII testing (Fig. 35.3b) or HRIM (Fig. 35.4). Air is seen entering the esophagus and immediately getting expelled again from the esophagus. In a study of adults with SGB, episodes were characterized by aboral diaphragm movement, increased LES pressure, decreased esophageal body pressure, UES relaxation, and air expulsion with pressurization of the esophagus and/or stomach [45]. Unfortunately, inter-rater reliability between esophagologists for diagnosis is suboptimal, suggesting that additional biomarkers for diagnosis may be needed [46]. Other contributing factors may be IEM (seen in 44% of patients with SGB) and GERD (seen in 41% of patients with SGB) in adults [42]. In the single pediatric study, none of the patients with SGB had pathologic acid exposure and the patterns by pH-MII can differential SGB from gas reflux events (Fig. 35.3a) [43]. As with other functional diagnosis, there is significant overlap in esophageal functional diagnoses; RH, SGB, and rumination frequently coexist with the hallmark of all three being a high symptom correlation [47].

Treatment

The mainstay of treatment includes reduction of comorbidities (such as pathologic reflux) with acid suppression and interventions for behavioral triggers using cognitive behavioral therapy. Several adult studies have shown that cognitive behavioral therapy and diaphragmatic breathing exercises reduced the number of SGB (and, by extension, the number of acid reflux episodes) and this effectiveness persisted for up to 12 months after the intervention [48, 49].

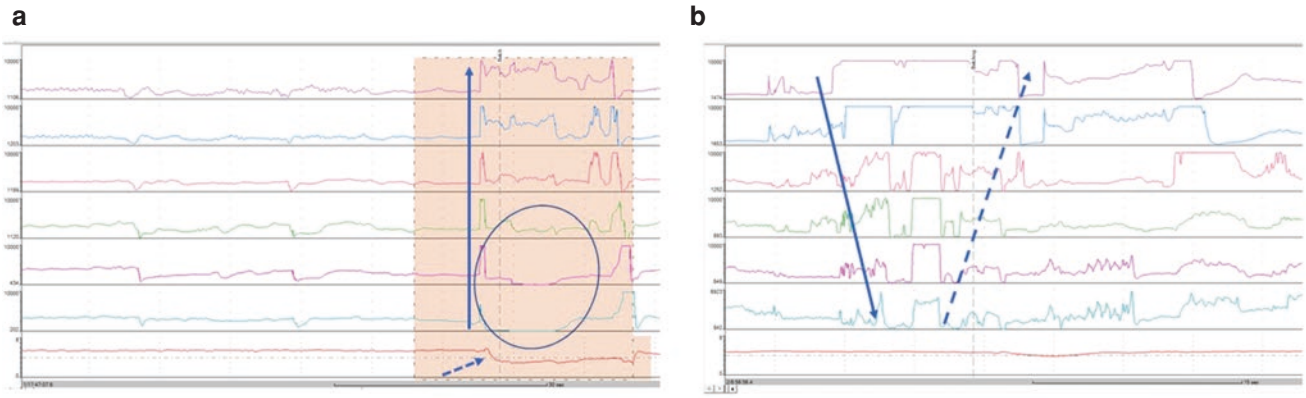

Fig. 35.3 Examples of belching types. pH-MII tracings show [1]: gas reflux emanating from the stomach (**a**) with simultaneous high amplitude peaks (solid blue arrow) followed by a drop in pH (dashed blue arrow) and a liquid reflux episode (circle) and (**b**) supragastric belching with air entering from the upper esophagus (solid arrow) and exiting (dashed arrow) forming a triangle shaped gas pattern

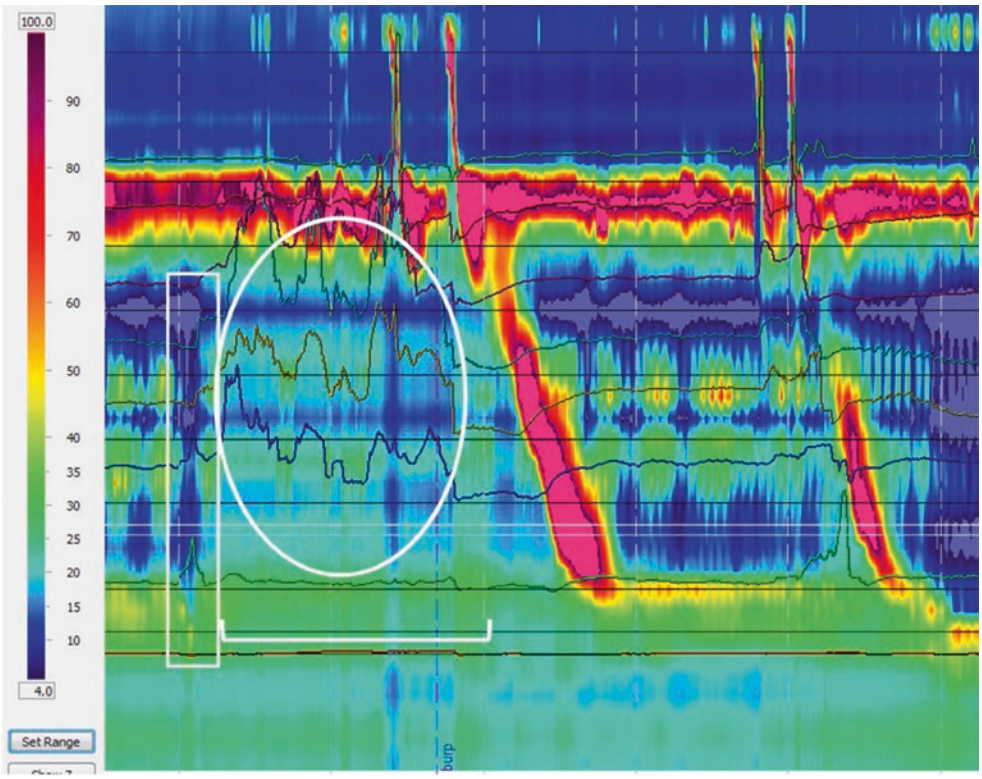

Fig. 35.4 Supragastric belching by manometry. The white box highlights the drop in esophageal pressures resulting from a drop in the diaphragm seen at the bottom of the box. There is air drawn into the esophagus (circle) seen by impedance waves followed by a belch. Note that there is no relaxation of the lower esophageal sphincter (bracket) highlighting the supragastric nature of the belch

From a medication perspective, acid reflux therapies have been tried, although symptoms are often refractory to proton pump inhibitors, triggering additional testing which yields the diagnosis [44, 47]. In a study of baclofen to treat rumination and SGB, rumination episodes improved, but there was no change in the number of SGB episodes, highlighting the different mechanisms behind the two disorders [50]; rumination begins below the diaphragm and LES, but SGB largely occurs above the LES. Despite a growing number of a therapeutic studies in adults, there are no therapeutic medication trials in children.

Summary

While functional esophageal disorders are well-defined in adults and therapeutic trials are targeted against these disorders, pediatric data both for diagnosis and treatment of these disorders are lacking. As a first step, pediatric-specific diagnostic criteria are needed to define the scope of these disorders in children. Then, critical prospective outcome studies must be conducted using well-defined patient populations and placebo-controlled studies to determine which therapies are most efficacious in children.

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Functional Gastrointestinal Disorders in Infants and Toddlers

36

Silvia Salvatore and Yvan Vandenplas

Introduction

Functional gastrointestinal disorders (FGIDs) are common conditions in the first months of life all over the world. According to the Rome IV classification, FGIDs in infants and toddlers include regurgitation, infantile colic, functional constipation, infant dyschezia, cyclic vomiting syndrome (CVS), rumination, and functional diarrhea [1]. By definition, FGIDs do not present underlying organic diseases, anatomical, or biochemical abnormalities. In the vast majority of subjects, FGIDs are transient phenomena with natural resolution after a few weeks or months. Despite being benign conditions, FGIDs have been associated with reduced duration of breastfeeding [2], frequent changes of formulas [3], short- and long-term behavioral, nutritional, gastrointestinal and sleeping problems, disturbed parent–child interaction, anxiety and distress, risk of infantile abuse, overuse and misuse of medications, and high utilization of healthcare resources [4–9].

Epidemiology

FGIDs affect 25% up to 77% of infants worldwide [6, 10–15] and many infants develop more than one disorder [10–15]. Regurgitation and colic are the most common FGID in the first months of life, while constipation is more frequent after 6 months. Infant dyschezia, CVS, rumination, and functional diarrhea are reported in less than 10% of infants [4, 6].

A recent multicenter Italian prospective study assessed the incidence of FGIDs from birth to 1 year of age in a cohort of 934 infants among whom 1/3 were preterm babies, 1/3 had received postnatal antibiotics, and 40% were born from cesarean section [13]. The cumulative incidence of FGIDs was 76.9%, 47% of infants had infant colic, 40% regurgitation, 32% infant dyschezia, 27% functional constipation, 3.6% functional diarrhea, and 60% had more than one FGID [13, 14]. Recently, among 2383 Turkish infants referred to outpatient clinics because of any symptom, 35% were diagnosed as having at least one FGID: 19% had colic, 13% regurgitation, 10% dyschezia, and 25% of affected subjects reported ≥2 FGIDs [15].

The exact incidence of FGIDs between 1 and 3 years of age is less clear, because most of the studies are limited to infants. While functional regurgitation, infant colic, and dyschezia are much more common in the first 4 months of life and progressively disappear during the following months, constipation, cyclic vomiting, and functional diarrhea affect more frequently toddlers [16]. Functional constipation is the most frequent reported FGIDs after 1 year of age. Based on subgroup analysis of American and European population, the incidence of constipation increased from 3% to 4.7% in the first months of life to 9.4–29% in subjects 1–3 years, functional diarrhea increased from 2.4% to 0.6–6.4%, and cyclic vomiting went from 0% to 1.5–10% [16–18]. A multicenter cross-sectional study investigated FGIDs in 1183 Colombian infants and young children (0–48 months of age). Four hundred eighty children (40.5%) were diagnosed with at least one FGID according to the Rome III diagnostic criteria (median age 12 months). In this population, functional constipation was the most commonly diagnosed disorder both in infants (0–12 months of age) and toddlers (age 13–48 months) being reported in 16.1% and 26.8% of subjects [19]. In contrast, cumulative data from three South American countries reported colic and functional dyschezia as the most common FGIDs in infants with a prevalence of 23% and 15%, respectively [20]. In Chinese infants and young children, FGIDs occurred in 27.3% out of 2604 total subjects: the most common disorder was infant regurgitation (33.9%) among the 0–6 months and functional constipation (7.0%) among the 1–4-year-old children [21].

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Pathogenesis

Many different factors contribute to the development of FGIDs and may coexist in the same subject. Genetic predisposition, preterm birth, postnatal antibiotics, neonatal gastric suction, trauma, stress, gut immaturity, fermentation, dismotility, hormones, visceral hyperalgesia, dysbiosis, overfeeding, allergy, parental anxiety, altered care-giver, and infant coping have all been associated with FGIDs in infants and toddlers [1, 5–8, 11–18, 22–24]. A cross-sectional study suggested that children were significantly more likely to have FGIDs when their parent experienced a functional GI disorder (35.4% vs. 23.0%) [25].

An Italian survey assessing FGIDs in 2879 infants reported an increased prevalence of regurgitation in low birth weight infants and of diarrhea in preterm newborns [10]. Noteworthy, in another Italian study, FGIDs occurred more frequently in preterm (p = 0.0001) and post-term (p = 0.010) compared to full term infants [13]. Multivariate analysis showed that prematurity and neonatal use of antibiotic were significantly associated with at least one FGID (aRR = 1.2; p = 0.001) [13]. An increased risk of FGIDs was also found for extremely low birth weight, small and large for gestational age neonates [14]. Being small for gestational age was significantly associated with infantile colic [14]. In a large Danish birth cohort, neonates with birth weight below 2000 grams and born before 32 weeks of gestation had a high risk of colic (OR = 1.7; CI: 1.3; 2.2 and OR = 1.6; CI 1.1; 2.4) [26].

Prenatal and early life events, inflammation, infection, and antibiotic exposure may influence immune and microbiota development, sensory-motor system, and pain perception predisposing to FGIDs [27–29]. Food allergy has been advocated to be a predisposing factor for FGIDs because of related gut inflammation, altered permeability, dysbiosis, dismotility, and induction of visceral hyperalgesia [30]. However, cow's milk allergy (CMA) and FGIDs may simply coexist in the same infant due to the high incidence of both conditions in the first months of life. Data supporting the pathogenic role of allergy in the development of FGIDs are limited. Moreover, the diagnosis of CMA in infants is hampered by the lack of specific symptoms and accurate biomarkers and by the limited number of patients submitted to food challenge. Gastrointestinal manifestations may be overlapping and response to elimination diet and to challenge may occur independent from immune mechanisms [30].

Dietary factors (i.e., insufficient fibers and liquid intake) and family predisposition are associated with functional constipation [31], while intake of sorbitol, fruit juices, and sugary beverages may cause excessive fermentation and lead to functional diarrhea [1, 32].

A number of studies have reported a different microbiota in infants with colic, compared to healthy controls, with reduced bacterial diversity, decreased Lactobacilli and Bifidobacteria, and increased proteobacteria and species producing gas and gut inflammation [33–36].

Among Colombian infants and toddlers, the prevalence of FGID was significantly associated to being the only child in the family or the first-born child, or having divorced or separated parents [19]. A risk factor analysis of a Chinese group of infants and young children with FGIDs showed a higher prevalence of infantile colic in high level of maternal education and low birth weight, of infantile regurgitation in males, in infants living in a rural area, being exclusively breast fed at least for 4 months or starting formula in the first month of life. In contrast, a lower prevalence of functional constipation was found in infants who were vaginally delivered [21].

Psychosocial variables may also impact occurrence, perception, and persistence of FGIDs. Postpartum maternal depressive symptoms and insecure mother–child-bonding have been associated with infant colic [37]. However, parental tiredness, distress and depression, disturbed behaviour, insecure mother–child bonding, suboptimal family relationship, and interaction may also be caused by FGIDs and may contribute to perpetuate or amplify parental and infant's problems in a vicious cycle [5]. Indeed, both infants and toddlers with FGIDs may present long-term health problems, with higher frequency of gastrointestinal symptoms during childhood and adult life, hospital admission, medical visits, behaviour, emotional and cognitive disturbances, migraine, sleep problems, and lower quality of life compared to controls [5, 17, 22, 24, 31, 38–42]. However, no evidence exists that an early or specific treatment of FGIDs reduces the risk of subsequent disorders.

Infant Regurgitation

Pathogenic mechanisms, clinical manifestations, and specific management of regurgitation and gastroesophageal reflux will not be herein discussed as they are addressed elsewhere in the book.

Infant Colic

According to Rome IV criteria [1], infant colic is typical of infants <5 months of age and is characterized by the presence of recurrent and prolonged periods of inconsolable crying, fussing or irritability that occur without obvious cause. Infant colic is more frequent in the late afternoon and the infant appears distressed, with a red face and lower limbs

flexed in absence of other alarm signs [1]. Dismotility, dysbiosis, low-grade gut inflammation, hypersensitivity, altered peripheral, and central processing of visceral stimuli, abnormal parental and infant coping, and stress contribute to the clinical manifestations, but the triggering factor for each individual subject is difficult to recognize [33]. A few studies have proposed that colic may be related to reduced lactase activity [43, 44], but administration of exogenous lactase provided no benefit in many infants [43].

Constipation

Functional constipation must include 1 month of at least two of the following: fewer than three defecations per week, history of excessive stool retention or of painful or hard bowel movements or of large-diameter stools or the presence of a large fecal mass in the rectum [1]. Abdominal pain, irritability, crying, decreased appetite, and/or early satiety are often accompanying symptoms of constipation. Their disappearance after passing stools and with resolution of constipation confirms the absence of any underlying disease [45]. In order to help describing the stool consistency and identifying hard stools in infants and toddlers, a new stool scale [the Brussels Infants and Toddlers Stool Scale (BITSS)] has been developed [46].

Functional constipation in breast fed infants is uncommon because of the peculiar composition of the human milk, the presence of palmitic acid in the Sn-2 position of triacylglicerols, resistant to lipase, the richness of oligosaccharides and lactose, the concentration of magnesium, the balanced calcium/phosphorus ratio, and other possible additional factors. In formula, fed infants with constipation hard stools may be related to insufficient fluid intake, incorrect preparation of the formula, and the possible presence of palmitic acid in the Sn-1 and Sn-3 positions of triacylglicerols easily attacked and displaced by lipase forming calcium soaps. Constipation often occurs when breast milk is switched to infant formula or after the introduction of complementary feeding. In toddlers, the onset of constipation may be related to the elimination of the diaper or the beginning of kindergarten. Incorrect toilet training in young children is also a risk factor for the onset and persistence of constipation, because children may start stool withholding, leading to hard large diameter stools, pain during defecation and infrequent evacuation in a vicious circle [47]. Association between overweight and obesity has been reported in some studies but not confirmed in others [48].

In infants and toddlers with persistent constipation and signs of allergy, inflammatory cytokines released by activated mucosal T-cells, eosinophils, and mast-cells and the migration of mast cells in close proximity to the end-nerve fibers may be responsible for the motility alteration [30, 49].

Dyschezia

Infant dyschezia is a functional disorder defined as at least 10 min of straining and crying before successful or unsuccessful passage of soft stools in an infant <9 months of age [1]. Dyschezia usually resolves spontaneously in few weeks and should be distinguished from functional constipation. Infants with dyschezia have not yet developed the coordination between increased abdominal pressure and pelvic floor and anal sphincter relaxation making them unable to easily pass stools. Parents often misinterpret this difficulty in evacuation as equivalent to constipation requiring laxatives that have no role in this condition. Although data regarding prevalence and natural history of infant dyschezia are limited, it does not appear to predispose to constipation later in infancy [50].

Functional Diarrhea

Diarrhea is common in the first years of life, but it is usually acute, or, if chronic, more frequently caused by dietary protein allergy, celiac disease and infections [51]. Functional diarrhea is uncommonly reported both in infants and toddlers all over the world [13–18, 21, 25]. Although the precise pathophysiology remains to be elucidated, evidence suggests that functional diarrhea may be the result of a gut motility disorder, modulated by dietary factors [32]. Previously denominated as non-specific chronic diarrhea, it has been associated with juice consumption, high intake of sorbitol or of high fructose to glucose ratio and low fat intake producing carbohydrate excessive fermentation and osmotic diarrhea [52–54]. Other suggested that mechanism is aberrant migrant motor complex after feeding [32]. Despite having loose stools, infant and toddler with functional diarrhea have normal growth as long as the caloric intake is adequate. The affected child appears healthy and has no pain passing stools, which should not contain blood. Functional diarrhea often resolves before school age, and for this reason was earlier called toddler's diarrhea [55].

Rumination

Rumination syndrome is characterized by the repeated regurgitation in the oral cavity of recently ingested food with subsequent rechewing and reswallowing [1, 56, 57]. If emesis occurs, it is effortless and not preceded by nausea or retching. Despite being frequently reported in mentally disabled subjects, rumination may occur in patients of all ages and cognitive abilities [56, 57]. Rumination syndrome is classified as both FGIDs and a Feeding and Eating Disorder [56], but is often under-recognized in infants and toddlers.

Pathophysiology is still incompletely understood, but involves a rise in intra-gastric pressure, generated by a voluntary or unintentional contraction of the abdominal wall musculature, during a time of low pressure in the lower esophageal sphincter, causing retrograde movement of gastric contents into the esophagus and the mouth. A typical history can be sufficient to make the diagnosis in infants and toddlers. Esophageal (high-resolution) manometry/impedance is useful to distinguish rumination syndrome from other belching/regurgitation disorders in older children and adults. Recognition of rumination is important to prevent unnecessary testing and to avoid complications, such as weight loss, electrolyte disturbances, dental damage, and relational disturbances [56, 57].

Cyclic Vomiting

CVS is characterized by recurrent individual-stereotyped episodes of incoercible vomiting, lasting hours or days and return to baseline health between attacks [1, 58, 59]. Episodes of vomiting usually occur at regular, cyclic intervals, and most often have onset late at night or early in the morning. Diagnostic criteria for CVS have been proposed by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) [58], Rome IV foundation [1], and ICH-D3 [59] with the main differences related to the number of episodes of vomiting required to fulfill the definition and the absence of nausea in the Rome criteria for infants and toddlers. NASPGHAN identifies CVS when ≥5 attacks in any interval or ≥3 attacks in 6 months of intense nausea and ≥4 episodes per ≥1 h of vomiting, not attributed to another disorder, lasting 1 h to 10 days and occurring at least 1 week apart [58]. Rome IV criteria for CVS in neonate and toddlers require ≥2 periods of unremitting paroxysmal vomiting with or without retching, lasting hours to days within a 6-month period [1]. ICHD-3 criteria include ≥5 episodes of intense nausea and vomiting ≥4 times per h, lasting at least 1 h and up to 10 days [59]. The rationale behind this decision of the Rome IV working group was the possibility to make an early diagnosis of CVS in young children [1]. In this age group, CVS is not frequently reported (ranging from 0% to 10% of the population investigated) and possibly underdiagnosed [16–19, 60].

The pathogenesis of CVS is complex and likely multifactorial with different triggers in individual subjects. Recent evidence suggests involvement of genetic factors, aberrant brain–gut or hypothalamic–pituitary–adrenal axis, mitochondrial diseases, gastrointestinal motility disorders, and calcium channel abnormalities [60]. CVS must be distinguished by several disorders that present chronic or recurrent vomiting recently grouped in the acronym "URGENTIME": URologic, Gastrointestinal, Endocrine, Neurologic disorders, Toxins/medications, (recurrent) Infections, and Metabolic diseases [60]. CVS impairs quality of life because of acute attacks, multiple visits and hospitalization mostly for dehydration, and frequent school missing [61]. In most children (50–70%), CVS resolves in late childhood or early adolescence, but may evolve into migraine headaches later in life in familiar predisposed individuals [60].

Treatment

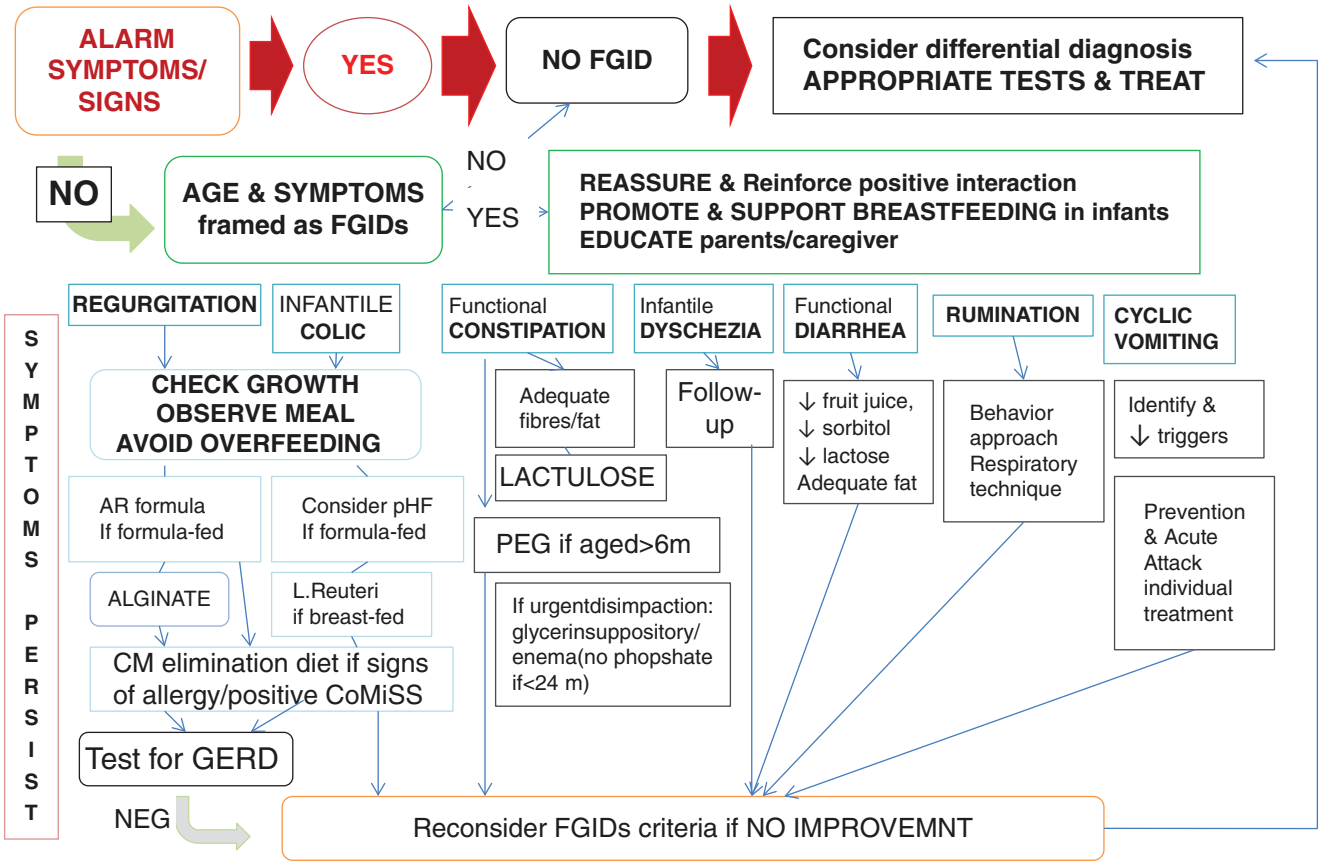
All guidelines and consensus of experts recommend parental reassurance and education as the first, and, if effective, only intervention needed for FGIDs [1, 4, 5, 7] (Fig. 36.1). Only for constipation and CVS a pharmacological treatment is often needed [1, 4, 45, 58–60].

Parental/Care-Giver Reassurance

The absence of alarm symptoms or signs in medical history, physical examination, and growth chart (Table 36.1) is the main pillar of parental/caregiver reassurance [1, 4, 5, 7]. Direct observation of a meal and of parental interaction is important to detect signs of organic disease or altered relationship between infants and parents or caregivers [5]. In particular, parental depression or excessive anxiety should be recognized to provide appropriate support and counseling [1, 5].

Education

Parents should be informed of the natural evolution of the individual FGID and factors that may contribute to their infant's symptoms [1, 5, 7] (Fig. 36.1). In particular, it should be explained that crying, colic, and repeated episodes of regurgitation soon after feeding occur very frequently in the first months of life in healthy infants and in more than 90% of subjects the symptoms spontaneously and progressively disappear [6, 10]. Specific assessment tool (such as the Face, Legs, Activity, Cry, and Consolability pain scale) can be useful to identify and recognize pain expression and for parents and health care providers to monitor infants [62]. Similarly, growth charts should be used to plot anthropometric measures and to demonstrate normal weight gain or overfeeding. Information about appropriate age-related food intake, infant position during and after feeding, and sleeping time should also be provided [5]. The BITSS has been developed to better describe stool pattern in infants and toddlers and may guide parents to recognize normal and abnormal stool consistency [46]. A digital tool has also been recently proposed [63]. It should also be explained that dyschezia differs from



Modified from [78]. See text for more details. Legend: FGID=functional gastointestinal disorder; pHF= partial hydolyzed formula; AR = anti-rigurgitaion/ thickened formula; CM= cow'smilk; PEG = polyethylene glycol; CoMiSS= Cow'sMilk Symptom Score; GERD = gastroesophageal reflux disease

Fig. 3.1 Algorithm for the management of regurgitation

Table 36.1 Warning symptoms and alarm signs for conditions other than FGIDs

Warning symptoms in history	Alarm signs on physical examination
Onset of symptoms in the first week of life	Poor reactivity, lethargy or excessive irritability
Delayed passage of meconium	Abnormal vital signs, dyspnea
Regurgitation or colic starting after 6 months or lasting into the second year of life	Abnormal head circumference, bulging Fontanelle
Bilious vomiting or hematemesis	Hypotonic or hypertonic infant/ toddler, absent or abnormal reflex
Bloody diarrhea	Psychomotor delay
Poor feeding, weight loss or suboptimal growth	Abdominal distention, enlarged liver or spleen, abdominal mass, abnormal anal or sacral region
Seizures or persistent irritability or hyporeactivity	Cyanosis, jaundice, pallor, multiple or large bruising, petechiae
Recurrent fever or infections	Fever or signs of infection
Recent trauma	Failure to thrive

constipation and relates to a physiologic learning curve of defecation mechanism and relaxation of anal sphincter and does not require any investigation or treatment [1, 5, 45].

A 3–7-day structured diary assessing food intake, episodes of regurgitation, crying time, stool pattern, and respiratory signs can be helpful to clarify the occurrence, duration, and characteristic of symptoms and to show possible improvement after reassurance or intervention. Finally, parents should be educated on warning symptoms and signs (Table 36.1), such as incoercible or bilious or bloody vomiting, persistent inconsolable crying or irritability or hyporeactivity, feeding refusal, poor growth, weight loss, presence of blood or pale or black stools, fever, cyanosis, and jaundice which need health care referral and appropriate investigations. Hospitalization of the infant may also be useful in selected cases to observe symptoms progression, parental–child interaction and behavior and, eventually, to stop the vicious circle of parental anxiety and/or sleep disturbances.

Nutrition and Diet

Nutritional advice is also considered a key factor in the management of FGID in infants and toddlers (Fig. 36.1). It should include a direct observation of a meal, the evaluation

of frequency, volume and caloric intake, parental instructions to avoid overfeeding and excessive fluid intake, and how to properly prepare milk formula in non-breastfed infants [5]. Breastfeeding should always be encouraged and promoted, while smoking should be discouraged for parental and infant health benefits.

Breastfed Infants

All benefits of breastfeeding should be emphasized, and mothers should be encouraged to never stop breastfeeding because of FGIDs [5, 7].

Mothers should be informed on the importance of a well-balanced and healthy diet consisting of all essential macro- and micronutrient and adequate caloric intake. Maternal caffeine consumption can be assessed in subjects with irritability or colic and sleep disturbances, because caffeine passes into breast milk and has a long half-life in the first month of life [64]. In infants with regurgitation, colic and excessive growth, overfeeding should be avoided by reducing frequency and duration of feeding time. In case of signs of allergy or in persistent and severe FGIDs, not improving with reassurance, education, and appropriate feeding frequency, a 2–4-week maternal cow's milk free diet could be considered. In infants with poor growth and insufficient maternal milk, donor human milk if available or infant formula should be offered as infant's supplementation. Breastfed infants generally have softer stools than formula fed infants and report less frequently constipation (1% vs. 10%) [65] and colic [66]. Several emotional and psycho-social factors, beyond nutritional components, could be responsible for the presence, persistence, and severity or resolution of FGIDs in breastfed infants [67, 68]. Hence, the efficacy of specific maternal dietary intervention has a significant risk of bias and cannot be assessed by blind controlled trials.

Formula Fed Infants

In infants with FGIDs, the correct formula preparation and daily intake should be checked. In infants with copious or frequent regurgitation, a thickened commercial formula may halve the daily episodes, with no significant difference between thickening agents (mostly corn, rice or carob) in terms of efficacy and safety [69, 70]. If a thickening agent is added to a standard formula, attention should be paid to avoid excessive amount of thickener and viscosity and to preserve normal caloric intake and a balanced composition of the formula. A number of different infant formulas with partial or extensive hydrolyzed proteins, reduced lactose, modified fat content, and supplemented with specific prebiotics and/or probiotics have been reported to reduce crying, colic, and regurgitation in selected infants [5, 7, 68, 71–76]. However, the presence of multiple components makes unclear which one is the responsible for the clinical improvement in an individual subject. Moreover, most studies had small sample size, limited follow-up, heterogeneity in terms of population recruited, formulas used and outcome measures, and risk of bias [68]. Similarly, no clear evidence of benefit exists on the use of lactase. Due to the above limitations and available evidence, a recent Cochrane review was unable to recommend any intervention for infantile colic [68]. Noteworthy, whey and hydrolyzed proteins may improve symptoms by accelerating gastric emptying compared to casein and intact proteins. In addition, rice- or soy-based formulas or with extensive hydrolyzed proteins may treat underlying CMA masquerading as FGIDs. The discrimination between FGIDs and CMA in infants is still challenging particularly in infants with negative allergy tests [77]. In infants with persistent regurgitation, crying, colic, or vomiting associated with poor growth or other signs of CMA, a 2–4-week trial with extensively hydrolyzed formulas has been proposed [5, 7, 77, 78]. In order to help clinicians to identify symptoms related to cow's milk protein and infants who can benefit from cow's milk elimination diet, an awareness tool has been proposed [79]. The Cow's Milk-related Symptom Score (CoMiSS®) is based on a clinical questionnaire, with combined quantification of episodes of regurgitation, crying time, skin and respiratory manifestation, and characteristics of stools [79]. A few studies showed a good predictive value of response to hydrolyzed formulas and a significant difference of the score between symptomatic and healthy infants [80–82]. An oral challenge should be scheduled in all infants who underwent an elimination diet both to confirm diagnosis of CMA or the acquisition of tolerance and avoidance of unnecessary protracted diet. Correct treatment and clinical follow-up of infants with CMA are also important to assess and eventually reduce the risk of development of FGIDs later in life [30, 83–86].

Softer stools and increase of Bifidobacteria have been produced by a combination of beta-palmitate and a special mix of fructo- and galactooligosaccharides [5, 7, 45]. Other dietary changes (increase of fibers, formula enriched with magnesium) have been suggested for infant and toddlers with constipation [87, 88], although the benefits are significantly lower them the ones reported with laxatives [45]. Extensively hydrolyzed formulas may also resolve some resistant cases of constipation due to underlying CMA. However, it is not recommended to start CM free diet in all constipated infants and toddlers [45].

Probiotics

Currently, there is no enough evidence to recommend any specific strain of probiotics to reduce regurgitation, vomiting, rumination, cyclic vomiting, infant dyschezia, and constipation or functional diarrhoea in infants and toddlers [1, 5, 7, 68, 89–92]. Conversely, different studies, systematic

reviews, and meta-analysis have demonstrated a significant mean reduction of daily crying time (−56 min), after 3 weeks of supplementation at a dose of 1×10^8 CFU, with a specific strain of Lactobacillus reuteri (DSM 17938) in breast fed infants [93–98]. Data showed a double probability to reduce crying time of at least a 50% in the intervention group compared to the control infants [97–99]. This beneficial clinical effect is consistent with modulation of gut microbiota, increase of regulatory T-cells, and reduced inflammation, as shown by a decreased RORγ/FOXP3 ratio and fecal calprotectin [100]. According to a network meta-analysis, Lactobacillus reuteri DSM 17938 and diet are the only evidence-based interventions that can be considered in infants with severe persistent colics [95]. No recommendation can be made on other strains of probiotics and on formula-fed infants [5, 7, 68, 89–92, 97–99].

The same probiotic strain of L. reuteri was shown to significantly reduce crying time and regurgitation episodes in a large cohort of Italian formula or breastfed infants supplemented since birth [101]. A recent Cochrane review analysed six randomized controlled trials comparing the preventative effect of probiotics (Lactobacillus reuteri DSM 17938 or Bifidobacterium breve) to placebo. While a significant reduction of crying time at 3 months of age was found in the group receiving probiotics, benefit for formula fed infants and on properly defined infantile colic still needs to be demonstrated [102].

Infantile Dyschezia

No diet modification or other treatment is indicated for infants with dyschezia [1, 5, 7, 45].

Functional Diarrhea

Adequate intake of fat and fiber and avoidance of sorbitol and fruit juices are usually sufficient to resolve functional diarrhea in both infants and toddlers [1, 5, 52–54].

Medications

There is no evidence of benefit of pain-relieving agents, simethicone, prokinetic drugs, or acid suppressive agents in FGID in infants and toddlers [1, 4, 7, 103]. Pharmacological treatment should be reserved to selected individuals with constipation and cyclic vomiting [1, 4, 45, 58–60] (Fig. 36.1). However, proton pump inhibitors are often empirically started and misused for regurgitation, crying, colic, and rumination [4, 104]. Acid secretion inhibitors are not recommended in FGIDs in infants and toddlers because of lack of efficacy and increased adverse effects, such as respiratory and gastrointestinal infections, dysbiosis, headache, and possible increased risk of fractures and allergy [4, 5, 77, 104]. In infants with frequent regurgitation associated with colic, not improving with reassurance, education, and dietary advice, alginate may be considered to reduce symptoms in both breast and formula fed infants [4, 77, 105].

Constipation in Infants and Toddlers

In case of constipation persisting after education and nutritional advice (adequate intake of fluid and fibers), the use of laxatives such as lactulose or polyethylene glycol (in infants older than 6 months) is recommended [45]. Occasional glycerin suppository or enema (not containing phosphate if aged less than 2 years) is indicated when disimpaction is needed [4, 5, 7, 45]. Milk of magnesia, lactulose, and polyethylene glycol is safe and effective. Polyethylene glycol (or macrogol), with or without electrolytes, is currently indicated as first choice treatment both for fecal disimpaction (1–1.5 g/kg/day) and maintenance (0.4 g/kg/day) because of high efficacy and safety [45]. This substance creates an intestinal osmotic gradient with retention of fluid in the stools that become softer and less difficult to pass [45]. The treatment is often needed for months to obtain resolution of symptoms. In case of persistent constipation with adequate dosage and compliance, other diagnoses should be considered. Other stimulants, mineral oil, and enemas containing phosphate should be used with caution in young subjects [45].

Cyclic Vomiting

Management of CVS includes prevention and treatment of attacks that should be individually tailored [58–60]. Cyproheptadine, pizotifen, amitriptyline, propranolol, and erythromycin can be considered to reduce the frequency of severe episodes. Rehydration, acid suppressive drugs, lorazepam, anxiolytic, and sedative agents are indicated during acute attacks [58–60].

Rumination

The mainstay of treatment for rumination syndrome is explanation of the disorder, behavioral changes, use of diaphragm, and abdominal breathing during the postprandial period and other habit reversal techniques that compete with the urge to regurgitate. This intervention is often effective but unpractical in young ages. To date, controlled trials in the treatment rumination syndrome are lacking. Rumination is often misdiagnosed as reflux disease, and proton pump inhibitors are frequently started. A number of case studies reported a positive effect of chewing gum, which led to a reduction of the number of rumination events in young children and adolescents [57].

Herbal, Complementary, and Alternative Medicine

A few studies reported a reduction of colic in infants with different fennel preparations [95, 106]. Psyllium fibers have been reported to improve constipation [106]. However, data on herbal remedies for FGIDs are scarce and conflicting and published studies have been considered of low quality [95, 99, 103, 106]. Efficacy, dosage, duration, and safety in infants and toddlers still need to be demonstrated [106]. Similarly, the role of acupuncture and manual therapy in the treatment of FGIDs is controversial and, particularly in infants and toddlers, the risk of bias is high, and the strength of evidence is low and inconclusive [5, 95, 106–112].

Conclusions

FGIDs are commonly reported in infants and young children all over the world. Exclusion of alarm symptoms and signs, parental reassure, and education are the essential steps in the management of any FGID. Breastfeeding should always be promoted, supported, and continued even in severe FGIDs. In formula-fed infants, the switch from a standard to a different formula should be motivated by distressing symptoms and should consider infant's age, the natural evolution of the disorder, the contributing factors, the components of the formula, the evidence of efficacy, and the cost–benefit ratio. A cow's milk free diet can be justified in persistent FGIDs and may have a beneficial effect by reducing underlying inflammation and improving motility. Probiotics are not helpful in most FGIDs, but use of *Lactobacillus reuteri* DSM17938 has been associated with reduction of crying time in breastfed infants. A short trial with alginate can be considered in infants with frequent copious regurgitation. Other pharmacological treatments should be reserved to infants and toddlers with constipation and cyclic vomiting.

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Abdominal Pain-Related Functional Gastrointestinal Disorder and Disorders of Brain–Gut Interactions

37

Liz Febo-Rodriguez and Miguel Saps

Introduction

Chronic abdominal pain accounts for approximately 5% of childhood visits in the general practice and 50% of referrals to pediatric gastroenterologists [1, 2]. Fifty-two percent of new referrals to the pediatric gastroenterology clinic meet criteria for one or more functional gastrointestinal disorders (currently named disorders of brain–gut interaction), and 31% meet criteria for two or more functional gastrointestinal disorders [3]. Diagnostic studies in these children show an organic cause as the etiology in only around 5% of the cases [4]. Most of the children who seek medical advice for chronic abdominal pain are actually suffering from functional abdominal pain (FAP) disorders (**FAPDs**) [5]. FAPDs, as defined by the Rome IV criteria, have an overall prevalence that ranges between 25% and 29% in children [6, 7]. These include functional dyspepsia (**FD**), irritable bowel syndrome (**IBS**), abdominal migraine (**AM**), and FAP–not otherwise specified (**FAP–NOS**) [8]. Multiple etiologies contribute to the development of these disorders, including genetic predisposition and sensitizing psychosocial and medical events (such as early use of antibiotics), which lead to the disruption of the brain–gut–microbiota axis and development of core disturbances characteristic to FAPDs [8]. Early life events, such as cow's milk protein hypersensitivity, pyloric stenosis, gastrointestinal infections, and Henoch–Schonlein purpura, have also been shown to predispose children to FAPDs [9]. These core disturbances include visceral hypersensitivity (with or without motor disturbances) and central hypervigilance [8]. Given the complex interactions that lead to FAPDs, treatment for FAPDs needs to be individualized.

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Diagnosis

Since there are no biochemical markers or structural abnormalities used to diagnose FAPDs, it is based on a thorough history and medical examination. John Apley, a British pediatrician, was the first to establish diagnostic criteria for children with abdominal pain. The Apley criteria for this disorder that he named "recurrent abdominal pain syndrome of childhood" was defined as "at least three episodes of abdominal pain, severe enough to affect their activities over a period longer than 3 months" [10]. Years later in 1999, it was found that 51% of children with recurrent abdominal pain could be classified as having IBS using adult criteria. As a result, the Rome committee issued for first time a pediatric diagnostic criteria (Rome II criteria) that were soon adopted as diagnostic and research tools [11, 12]. The Rome criteria provide symptom-based guidelines by which children are diagnosed with FAPDs [13]. The Rome II criteria had some limitations, including the requirement of persistence of symptoms for over 3 months before diagnosis, which was later thought to be excessive, low diagnostic agreement among gastroenterologists, and limited agreement between physician diagnosis and parent-reported symptoms [10, 14, 15]. Thus, in 2006, the Rome III criteria were introduced. These criteria were more inclusive, as children with recurrent abdominal pain were more likely to be classified as having one or more of the listed abdominal pain-predominant functional gastrointestinal disorders; however, there was still a low agreement among gastroenterologists [16, 17].

Rome III criteria were eventually replaced with Rome IV criteria, summarizing years of research related to FAPDs [13]. These criteria provide new insights and more precise classifications for physicians and researchers [6]. Changes in the new criteria included the substitution of the term "abdominal pain related functional gastrointestinal disorders" for "FAPDs" and adding the new term "functional abdominal pain not otherwise specified" (FAP–NOS) to describe children who do not fit a specific disorder [5]. In addition, further

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subgroups of IBS (constipation, diarrhea, mixed, and unsubtyped) and FD (postprandial distress syndrome and epigastric pain syndrome) were identified [5].

Pathophysiology

Visceral Hyperalgesia

Visceral hypersensitivity is based on the strong association between the enteric nervous system and the central nervous system and their common embryonic origin [2]. Multiple factors predispose individuals to visceral hypersensitivity, including genetic, environmental, psychosocial (early stressors in life), and diet. These factors can alter the brain–gut axis communication by altering descending inhibitory control, impairing stress response, and/or sensitizing primary sensory neurons and central spinal neurons [2]. This then leads to abnormal secretion of excitatory neurotransmitters, such as serotonin, which can result in changes in the central nervous system and trigger symptoms, such as headache, abdominal pain, and discomfort [2, 10]. Brain imaging in adults has shown that patients with IBS have connectivity abnormalities, including lower fractional anisotropy in thalamic regions, basal ganglia, and sensory/motor association regions [18]. These patients also had reduced mean diffusivity within the globus pallidus and higher mean diffusivity in the thalamus, internal capsule, and corona radiata [18]. Given these data, neuromodulation therapies that can alter central pathways are being increasingly used to treat disorders of brain–gut interaction [19].

Early life events are known to be associated with the development of visceral hyperalgesia (cow's milk protein hypersensitivity, pyloric stenosis, umbilical hernia repair, and Henoch–Schönlein purpura) [9, 10]. Rat models have shown that exposure to nociceptive somatic stimuli in the early neonatal period predisposes to visceral hyperalgesia, suggesting that disruption of the nervous system during its early development can alter the brain–gut axis, resulting in FAPDs [10, 20].

Visceral sensitivity has been studied in children with IBS. Van Ginkel et al. showed that children diagnosed with IBS per Rome II criteria had a significantly decreased threshold for abdominal pain secondary to rectal balloon distension compared with healthy controls and those with FAP diagnosed per Rome II criteria [4]. In this study, children with IBS lacked a rectal contractile response after a meal when compared to children with FAP and healthy volunteers [4]. In another study, Crandall et al. measured pain symptoms after colonoscopy in children with functional gastrointestinal disorders (19 IBS, 1 FAP) and inflammatory bowel disease (15 Crohn, 5 ulcerative colitis). He found that children with functional gastrointestinal disorders had greater baseline pain scores and longer duration of pain post procedure [21]. These results argue for the presence of visceral hypersensitivity and motor abnormalities in children with IBS.

Carbone et al. used high-resolution manometry to measure intragastric pressure in children and found that the intragastric pressure drop during meal ingestion in healthy and dyspeptic children was similar [22]. The authors suggest that increased sensitivity may be the reason why children with FD have decreased nutrient tolerance [22].

Altered Gastrointestinal Motility

Patients with FAPDs may present abnormal gastrointestinal motility, leading to diarrhea, constipation, nausea, bloating, and distention [10]. As with visceral hypersensitivity, it is thought that early life events and psychological factors (e.g., abuse, hospitalizations) can lead to alterations in the gut microbiota that result in altered gastrointestinal motility, including abnormal gastric myoelectrical activity, poor antral motility and gastric emptying, and abnormal gastric accommodation [10]. In fact, multiple studies by Devanarayana et al. demonstrated that gastric emptying rate and antral motility parameters were significantly impaired in patients with Rome III criteria of FAP, FD, and IBS [23–25]. In addition, gastric emptying was found to negatively correlate with the severity of symptoms [23, 24]. In another study led by Hoffman and Tack, children with FD were found to have slower gastric emptying than obese children (89.7 ± 54.8 min vs. 72.5 ± 26.0 min, $p = 0.05$) using the octanoic acid breath test [26]. These findings argue in favor of a role for gastrointestinal motility disturbances in patients with FAPDs.

A study in 17 children showed that gastric emptying and antral motility parameters were significantly lower in children with AM, with a significant correlation found between symptoms and gastric motility. These results suggest that gastric motility might have a role in the pathogenesis of AM [27].

Gastric accommodation to a meal consists of relaxation of the proximal stomach without a concomitant increase in intragastric pressure [28, 29]. Inappropriate gastric accommodation is the most common documented abnormality in adult patients with FD, estimated at around 40% [30, 31]. Hoffman et al. assessed fundic accommodation in children with FD using the gastric barostat and found that 69% had inappropriate fundic accommodation [32]. Di Lorenzo also used the barostat in a pediatric population to measure visceral perception and found that the sites of visceral hyperalgesia varied with the symptom phenotype. While children with IBS had hyperalgesia in the rectum, children with recurrent abdominal pain had hyperalgesia of the stomach [33]. Given the invasiveness of the test few studies evaluating the

use of the gastric barostat in children are available [32]. Two-dimensional ultrasound imaging of the antrum in children with FD has shown enlargement of the antral area, likely related to either inappropriate gastric accommodation or low antral tone [34]. Olafsdottir et al. showed that in children with recurrent abdominal pain, two-dimensional ultrasound revealed a smaller sagittal area and a higher emptying fraction of the proximal stomach 10 min after meal ingestion when compared to controls, likely due to inappropriate gastric accommodation [35].

It is also possible that children with FAPDs have abnormal gastric myoelectrical activity given that muscular activity of the stomach is preceded by gastric electrical activity [10]. A study using electrogastrography found increased gastric electrical abnormalities in children with recurrent unexplained upper gastrointestinal symptoms [36]. Further studies assessing these relationships are warranted.

Gut Microbiota

The gut microbiome is recognized as a key player in the pathogenesis of FAPDs. The microbiome is composed of approximately 10^{13}–10^{14} microorganisms with 500–1000 different species [37]. Under non-stressful, normal circumstances, intestinal bacteria maintain a homeostatic relationship with the host mucosa [38]. However, alterations to this balance ("dysbiosis") can lead to enhanced intestinal permeability, mucosal immune activation, altered gut motility, and visceral hypersensitivity [38]. Possible causes of dysbiosis in IBS include enteric infections, such as common bacterial causes of traveler's diarrhea and the use of antibiotics [39].

Psychological Factors

Children with FAPDs report a greater number of stressful experiences in the months prior to pain onset [40]. Common stress examples in children include failing an exam, separating from a best friend, loss of a parent's job, and/or moving to a new place [10]. Abuse also predisposes to FAPDs, with one study showing that abdominal pain-predominant functional gastrointestinal disorders were significantly higher in children who were abused sexually (34%), emotionally (25%), and physically (20%) when compared to those who were not abused [41]. In addition, children with FAPDs are more likely to receive a diagnosis of a psychiatric disorder, including depression and anxiety [42]. Adult studies have shown that stress induces chronic overactivity or underactivity of adaptive systems, including the hypothalamic–pituitary–adrenal axis, autonomic nervous system, metabolic, and immune systems, which affects bodily function and behavior [43]. Thus, it is probable that stressful, adverse events in early life can result in long-lasting alterations in the brain–gut axis, leading to the development of FAPDs.

Children with chronic abdominal pain have also been shown to be less confident of their ability to change or adapt to stress [44]. In addition, mothers of children who suffer from FAP were significantly more likely to have a lifetime history of IBS [odds ratio (OR), 3.9; 95% confidence interval (CI), 1.5–10.3], anxiety (OR, 4.8; 95% CI 2.2–10.6), depressive (OR, 4.9; 95% CI 2.2–11.0), and somatoform (OR, 16.1; 95% CI 2.0–129.8) disorders when compared to mothers of controls [45]. Thus, how a child and family deal with stressors may be one of the key factors in chronic abdominal pain.

Altered Intestinal Permeability

The intestinal barrier includes surface mucus, epithelial layer, and immune defense [46]. Epithelial permeability can result from increased paracellular transport, apoptosis, or transcellular permeability [46]. Growing evidence indicates that increased intestinal permeability plays a role in FAPDs. Several entities are known to cause altered gut permeability, including infection, genetic predisposition, and stress [47]. Individuals with post-infective IBS have shown an elevated excretion ratio of urinary lactulose: mannitol (measures small intestinal permeability) 4 months to 4 years after an initial Campylobacter enteritis [48]. Stress seems to stimulate T lymphocytes via mast cells, which results in inflammatory cytokine production and increases colonic permeability [49].

Gut permeability has also been found to be significantly increased in patients with AM when compared to healthy controls [2]. A study by Bentley et al. found that children with AM excreted more mannitol (12%) and cellobiose (0.25%) when compared to controls (mannitol 9%, cellobiose 0.15%) [50].

Epidemiology

Prevalence

The worldwide prevalence of FAPDs in children is 13.5%, with comparable rates across the continents [51]. Among FAPDs, FD-postprandial distress syndrome seems to be the most common disorder (7.2%) in children >4 years of age [6].

Sex

A meta-analysis reviewing FAPDs in children aged 4–18 years of age found that girls had a significant higher proportion of FAPDS when compared with boys (15.9% vs.

11.5%, pooled OR 1.5, 95% CI 1.3–1.7, $p < 0.01$) [51]. A cross-sectional study in children found that FAP–NOS was more prevalent in females (4.2%) than in male subjects (1.8%, $p = 0.04$) [6]. However, FD–epigastric pain syndrome was more prevalent in males than females subjects (0.9% males vs. 0% females, $p = 0.04$) [6]. In this study, no other differences were found by sex, race, or ethnicity with regard to FAPDs [6].

Age

A meta-analysis reviewing FAPDs in children aged 4–18 found no significant difference for their prevalence in children <12 years of age compared to children ≥12 years (12.4% vs. 13.8%, pooled OR 0.9, 95% CI 0.5–1.4, $p = 0.62$) [51]. A recent study by Robin BS et al. found that 24.7% of infants and toddlers met criteria for at least one functional GI disorder, while 25% of children and adolescents >4 years of age qualified for at least one functional GI disorder using Rome IV criteria [6].

Socio-Economic Status

Studies did not find an association between socio-economic status and prevalence of FAPDs.

Quality of Life

Quality of life is frequently affected in children suffering from FAPDs. One study found lower quality-of-life scores in children with functional GI disorders (median = 71.69, range 0–100) when compared to toddlers without a functional GI disorder (median = 87.6, range 0–100) ($n = 1129$ children ages 2–18 years of age) [6]. In another study, Shelby et al. followed 332 pediatric patients (ages 8–17 years of age) with FAP and 147 healthy subjects prospectively until young adulthood [52]. Children with FAP were more likely to have lifetime anxiety disorders compared to control group (51.2% vs. 20.4%), with an OR for any lifetime anxiety disorder of 4.59 times greater for patients with FAP (CI 2.83–7.43; $p < 0.001$) [52]. In addition, children with FAP was found to be significantly more depressed at some point during their lifetime (40.1% vs. 16.3% control), with an OR for any lifetime depressive disorder of 2.62 times greater when compared to the control group (CI = 1.56–4.40; $p < 0.001$) [52]. Thus, it is important to monitor children with FAPDs for psychiatric conditions as they have a higher risk of developing them.

Children and adolescents with a functional GI disorder are known to miss more school that those without. Within the functional group, school absences averaged 11.8 ± 15.2 days/year (vs. those without, 7.1 ± 10.9 days/year, $p < 0.001$) [3].

Health Care Visits and Costs

Children with chronic abdominal pain are likely to have emergency room visits, hospitalizations, and expensive laboratory and imaging services [2, 4]. However, organic etiologies are found in only 5% of these patients. In a large cross-sectional study by Robin el at., children who met Rome IV criteria for a functional GI disorder had higher school and day care absences when compared to those without a functional GI disorder [6]. In this same study, children with functional GI disorders were found to have significantly more medical visits in the past 6 months because of GI problems (mean = 0.92) versus children who did not have a disorder (mean = 0.19). In addition, hospital stays were also significantly higher in children with functional GI disorders (mean = 0.49) versus those who did not (mean = 0.08).

FAPD Subtypes

Functional Dyspepsia

FD is a common but heterogeneous upper GI disorder that causes recurrent and/or intermittent epigastric symptoms [53]. Numerous mechanisms have been implicated in its pathogenesis, including visceral hypersensitivity, delayed gastric emptying, psychosocial factors, dysfunction of the central nervous system, lifestyle factors, duodenal eosinophilia, and impaired fundic accommodation [53–57]. Impaired gastric accommodation is the most common documented abnormality in adult patients with FD, estimated at around 40% [30, 31]. FD can be further subdivided into epigastric pain syndrome and postprandial distress syndrome; however, these two syndromes can overlap in clinical practice [58]. Postprandial distress syndrome is characterized by symptoms that are triggered by a meal, including postprandial fullness and early satiety [53]. Impaired gastric accommodation is thought to play a role in the postprandial distress syndrome group [53].

FD is a common condition in children, with an estimated prevalence between 3% and 27% [59]. A recent cross-sectional study found the prevalence of FD–post prandial distress syndrome to be 7.2% and of FD–epigastric pain syndrome to be 0.4% [6]. Table 37.1 summarizes the Rome

Table 37.1 Rome IV diagnostic criteria for FD

Must include one or more of the following bothersome symptoms at least 4 days per month:
1. Postprandial fullness
2. Early satiation
3. Epigastric pain or burning not associated with defecation
4. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition
Criteria fulfilled for at least 2 months before diagnosis. Within functional dyspepsia, the following subtypes are now adopted:
1. Postprandial distress syndrome includes bothersome postprandial fullness or early satiation that prevents finishing a regular meal. Supportive features include upper abdominal bloating, postprandial nausea, or excessive belching
2. Epigastric pain syndrome, which includes all of the following: Bothersome (severe enough to interfere with normal activities) pain or burning localized to the epigastrium. The pain is not generalized or localized to other abdominal or chest regions and is not relieved by defecation or passage of flatus. Supportive criteria can include a) burning quality of the pain but without a retrosternal component and b) the pain commonly induced or relieved by ingestion of a meal but may occur while fasting
Criteria fulfilled for at least 2 months before diagnosis

IV criteria used to diagnose FD. Treatments for FD should be aimed to one or more of the main mechanisms: gastric emptying, gastric accommodation, and visceral pain sensation [60].

Irritable Bowel Syndrome

IBS is a multifactorial disease thought to arise from dysregulated brain–gut signaling, resulting in visceral hyperalgesia and altered bowel habits [19]. It has a prevalence of around 2.8% in children in the United States [61]. IBS can be further subdivided into categories depending on the predominant stool pattern: IBS with constipation (**IBS-C**), IBS with diarrhea (**IBS-D**), and unspecified IBS (**IBS-U**) [13]. A prospective hospital-based study in Italy found that IBS-C has the highest prevalence (45%) followed by IBS-U and IBS with mixed bowel habits (29%) and IBS-D (26%) [62]. IBS-C is significantly higher in girls, while IBS-D was found to be more frequent in boys [62]. Longitudinal studies in children have shown that at least 40% of children aged 4–16 years of age with IBS are still symptomatic 2 years after diagnosis [63]. Children with IBS tend to have a lower pain threshold and altered contractile response to a meal [4]. Table 37.2 summarizes the Rome IV criteria used to diagnose IBS.

Explaining the diagnosis and reassuring the patient have shown to be therapeutic [64]. Pharmacologic management of IBS is determined by the specific prevalent subtype. Of note, most of the available drugs target the bowel rather than the central pain pathways involved in pain amplification [19].

Table 37.2 Rome IV diagnostic criteria for IBS

Must include all of the following:
1. Abdominal pain at least 4 days per month associated with one or more of the following:
(a) Related to defecation
(b) A change in frequency of stool
(c) A change in form (appearance) of stool
2. In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome)
3. After appropriate evaluation, the symptoms cannot be filly explained by another medical condition
Criteria fulfilled for at least 2 months before diagnosis

Table 37.3 Rome IV diagnostic criteria for AM

Must include all of the following occurring at least twice:
1. Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting 1 h or more (should be the most severe and distressing symptom)
2. Episodes are separated by weeks to months
3. The pain is incapacitating and interferes with normal activities
4. Stereotypical pattern and symptoms in the individual patient
5. The pain is associated with two or more of the following:
(a) Anorexia
(b) Nausea
(c) Vomiting
(d) Headache
(e) Photophobia
(f) Pallor
6. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition
Criteria fulfilled for at least 6 months before diagnosis

Abdominal Migraines

AM, first described in 1921 by Buchanan and Brams, are episodic syndromes that present with intermittent abdominal pain severe enough to interfere with normal day activities [65, 66]. It presents mainly in children between the ages of 3–10 years of age, with peak incidence at 7 years, and is more prevalent in girls [2, 67]. Children with AM frequently report similar triggers (i.e., stress, bright light, poor sleep, travel, and prolonged fasting), associated symptoms (i.e., anorexia and nausea), and relieving factors (i.e., rest and sleep) as children with classic migraine [13]. These patients are usually symptom free during the interim and have a benign physical exam [65]. It is likely that AM, classic migraine, and even cyclic vomiting syndrome share pathophysiologic mechanisms, including being episodic, self-limited, and stereotypical, with symptom-free intervals between attacks [13]. Table 37.3 summarizes the Rome IV criteria used to diagnose AM.

There is no development of neurological or developmental deficits associated with AM and with many believing that AM does not continue until adulthood [65]. One study with 54 children with AM found that it resolved in 31 cases (61%) [68]. However, some AM in childhood can evolve into migraine headaches in adulthood [2]. In a small study, Roberts et al. found that using pediatric Rome III AM criteria, 10/13 adults with suspected AM met the criteria [69]. Larger, prospective studies on whether children with AM continue to have this disorder until adulthood are warranted.

Functional Abdominal Pain–Not Otherwise Specified

FAP–NOS was developed to replace the terms FAP and FAPD*s* previously used in the Rome III criteria. The prevalence of FAP–NOS in school-aged children in the United Sates is 1.2%, while a study in Germany found that it was approximately 2% [13, 70, 71]. Reported symptoms tend to be nonspecific and usually do not require laboratory or radiologic investigation [13]. A limited workup is often done for parental reassurance [13]. Table 37.4 summarizes the Rome IV criteria used to diagnose FAP–NOS.

Table 37.4 Rome IV diagnostic criteria for FAP-NOS

Must be fulfilled for at least 4 times per month and include all of the following:
1. Episodic or continuous abdominal pain that does not occur solely during physiologic events (e.g., eating, menses)
2. Insufficient criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migraine
3. After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition
Criteria fulfilled for at least 2 months before diagnosis

Clinical Evaluation of Non-episodic FAPDs

As mentioned previously, it is important for the physician to develop a positive therapeutic relationship with the patient and family during the first visit. Expectations as far as management and treatment outcomes should be discussed. The Bristol Stool Scale can be used to assess the nature of the stools [5].

The role of a diagnostic work-up, including labs and esophagogastroduodenoscopy (**EGD**) in pediatric FAPDs remains unclear. These patients tend to undergo extensive workup, with mostly minimal to no yield. The average cost per patient is around $6104 (range $1052–$20,994) [72]. A study evaluating the charts of children >4 years of age diagnosed with abdominal pain showed that complete blood cell count was the most commonly done investigation (92%), followed by a comprehensive metabolic panel (83%), with electrolytes abnormal in only one patient (sodium: 132 mEq/L, n = 122) [72]. In this same study, elevated inflammatory markers and celiac antibodies led to changes in in management in only five cases [72].

Unfortunately, most studies assessing the use of EGD in children with abdominal pain have had multiple limitations, including a small sample size, bias, and lack of standardization [73]. In a prospective study, Thakkar et al. showed that 38% of children (n = 109) undergoing EGD for chronic abdominal pain had diagnostic findings, with gastroesophageal reflux and eosinophilic esophagitis being the most common [74]. In another study by Thakkar et al. in children with suspected gastroparesis undergoing EGD, albeit retrospective, EGD was diagnostic in 38.1% of children (n = 1191), with reflux esophagitis being the most common (23%) [75]. However, a descriptive study by Dhroove et al. demonstrated that 34% of children had EGD with only 9.7% having abnor-

Table 37.5 Potential alarm features in children with chronic abdominal pain

Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease
Persistent right upper or right lower quadrant pain
Dysphagia
Odynophagia
Persistent vomiting
Gastrointestinal bleeding loss
Nocturnal diarrhea
Arthritis
Perirectal disease
Involuntary weight loss
Deceleration of linear growth
Delayed puberty
Unexplained fever

mal findings (Helicobacter pylori, chemical gastritis, and esophagitis), and 17.2% had colonoscopy with only 9.5% having abnormal findings (rare fork crypts and lymphoid hyperplasia) [72].

The Rome IV pediatric committee does not believe that there is compelling evidence to require an EGD in order to make a diagnosis of FAPDs, but does understand that physician practice patterns and social considerations may affect the decision to do one [13]. In addition, there are "red flags" that suggest further diagnostic work up should be done (Table 37.5) [13].

In cases of IBS-D, depending on the history and physical examination, the patient might warrant a workup to rule infectious causes, celiac disease, carbohydrate malabsorption, and inflammatory bowel disease [13]. The presence of alarm symptoms (see Table 37.5) requires additional work up.

Clinical Evaluation of Episodic FAPDs

The prevalence of AM increased after Rome II criteria was replaced with Rome III criteria, likely because the latter was more inclusive and less specific [13]. The Rome committee believed Rome II criteria was a better representation of AM prevalence, and thus Rome IV criteria made some additional changes, including consistency with cyclic vomiting syndrome diagnostic criteria and stressing that the primary symptom should be abdominal pain [13].

Children tend to present with well-defined symptoms including episodes of midline abdominal pain that interfere with normal activities and last for prolonged periods, pallor, headache, anorexia, nausea, and vomiting [76]. Episodes of pain can last from 2 to 72 h and are often described as dull or sore, not colicky [67]. Pallor can be accompanied by dark circles under the child's eye [67]. Auras can sometimes precede the attacks, involving visual disturbance, flashing lights, slurred speech, numbness, and/or tingling in distal extremities [67]. Often, there is a strong family history of migraines [2].

Diseases that present with severe episodic symptoms, such as intermittent small bowel or urologic obstruction, recurrent pancreatitis, biliary tract disease, familial Mediterranean fever, metabolic disorders, and psychiatric disorders should be ruled out [13]. However, in the absence of red flags (listed on Table 37.5), it does not seem beneficial to obtain further testing as the cause of this pain, such as pH impedance probe, EGD, or abdominal ultrasound.

Treatments for Non-episodic FAPDs

It is important to comment that most trials in children with FAPDs have joined all the disorders together, thus limiting generalizability. Treatment for AM is discussed separately (see treatments section under AM).

Prokinetic Agents

Prokinetic agents have been trialed for FD. A placebo-controlled trial using *domperidone* by Karunanayake et al. was able to show overall improvement (74% domperidone vs. 50% placebo; $p = 0.013$), decreased severity of abdominal pain (54% vs. 25%; $p = 0.008$), and overall improvement at 6 month follow-up (88% vs. 66%; $p = 0.009$) [77]. Domperidone is not approved by the US Food and Drug Administration. The European Medicine Agency has a black box warning for its use in children due to its potential for serious health risks, including cardiac arrhythmias, cardiac arrest, and sudden death [60].

Buspirone

Buspirone is a non-selective serotonin 5-HT_{1A} receptor agonist which inhibits the tone of the proximal stomach and delays gastric emptying rate in a dose-dependent manner [78]. Buspirone has been shown to be superior to placebo in alleviating early satiation, postprandial fullness, and upper abdominal bloating in patients with FD [79]. Buspirone has been trialed in children and adolescents with anxiety, proving to be generally safe and well-tolerated at doses up to 30 mg BID [80]. No studies have been done to assess its use for inappropriate gastric accommodation in children.

Neurokinin 1 Receptor Antagonist

Aprepitant, a neurokinin 1 receptor antagonist used to treat chemotherapy-induced nausea and vomiting and children, was shown to be effective for both acute and prophylactic management of pediatric cyclical vomiting syndrome in a retrospective study [81]. Further larger randomized controlled studies are needed.

Ondansetron

Ondansetron, a 5-hydroxytriptamine 3 receptor antagonist, was shown to improve stool consistency in adult patients with IBS-D in randomized placebo-controlled trials. Ondansetron is commonly used to treat nausea and vomiting in children; however, studies assessing its efficacy in treating IBS in pediatrics are warranted [60, 82].

Eluxadoline

Eluxadoline, a mixed opioid receptor agonist and antagonist, is currently in a phase 2, randomized, double-blind, placebo-controlled study in pediatric patients (ages 12–17 years of age) with IBS-D (NCT03339128). Two large adult studies showed that this drug was safe and efficacious in adults with IBS-D, resulting in improved stool consistency and abdominal pain [83, 84].

Lubiprostone

Lubiprostone, a chloride channel activator, and linaclotide, an agonist for guanylyl cyclase, are secretagogues used in the treatment of IBS-C. Lubiprostone is currently approved in the United States in adults for treatment of chronic idiopathic constipation, opioid-induced constipation, and IBS-C in women. A lubiprostone open label trial in children 17 years or younger (n = 109) found spontaneous bowel movement frequency significantly increased at week 1 when compared to baseline (3.1 vs. 1.5, $p < 0.0001$) [85]. The greatest improvement in spontaneous bowel movement frequency at week 1 was observed with lubiprostone 24 μg BID (3.8 vs. 1.6, $p < 0.0001$) [85]. Common adverse events related to the drug included abdominal pain and nausea [85]. However, a double-blind randomized controlled study found no difference in spontaneous bowel movement frequency between 12 μg of lubiprostone, 24 μg of lubiprostone, and placebo ($p = 0.1609$) [86]. Subgroup analysis showed greater responses in patients aged 10–17 years (17% vs. 10%; $p = 0.0681$), females aged 10–17 years (19% vs. 9%; $p = 0.0542$), and improvement in the symptoms of pain, straining, and stool consistency ($p = 0.045$, $p = 0.017$, $p = 0.0501$, respectively) [86]. Further studies assessing the use of lubiprostone in children are warranted.

Guanylate Cyclase-c Agonists

Linaclotide and plecanatide, both guanylate cyclase-c agonists are approved for the use of chronic idiopathic constipation and IBS-C in adults [87]. Studies have shown both drugs to be efficacious and tolerable in the treatment of these conditions [87]. Linaclotide at different doses (18, 36, 72, 145, and 290 μg) is currently being studied in children with IBS-C aged 7–17 years of age (NCT02559817). Plecanatide is currently being studied in children 6–18 years of age with IBS-C (NCT03596905).

Oral Serum Bovine-Derived Immunoglobulin

Oral serum bovine-derived immunoglobulin (**SBI**) modulates junctional regulatory proteins in the gut, and it is believed that it could help relieve symptoms of IBS by decreasing inflammation in the gut tight junctions [60]. A randomized, double-blind, placebo controlled, pilot study in 15 children aged 8–18 years of age with IBS-D (nine SBI, six placebo) demonstrated that 10 g of SBI significantly improved abdominal pain and stool form by 3 weeks ($p = 0.02$ and $p = 0.05$, respectively) [88]. In addition, their scores for pain, discomfort when eating, diarrhea, worry about stomach aches, and communication improved significantly in the SBI group (all $p < 0.05$) [88]. Larger studies are warranted.

Fecal Microbiota Transplantation

Fecal microbiota transplantation (**FMT**) from healthy donors to patients with IBS was found to reduce IBS symptoms at 3 months after administration in an adult randomized, double-blind, placebo-controlled study (own feces) [89]. Caution is required when using FMT to treat IBS given adverse effects; thus, one should consider FMT for patients with moderate-to-severe refractory IBS without systemic disease, immune deficiencies, severe illness, and treatments with immune-modulating medications [90]. No studies are available in children.

Antidepressants

Antidepressants, specifically tricyclic antidepressants and selective serotonin reuptake inhibitors, are commonly used

to treat FAPDs given their effect on the brain–gut axis through central and peripheral mechanisms [5]. Amitriptyline it is believed to have central and/or peripheral analgestc properties that can increment pain thresholds [5]. A randomized controlled study by Saps et al. in children with abdominal pain showed amitriptyline was no better than placebo in the treatment of abdominal pain-predominant functional gastrointestinal disorders [91]. However, both amitriptyline and placebo were able to significantly decrease pain (pain vs. placebo), highlighting the importance of considering the "placebo effect" when evaluating these patients [91].

Citalopram is a selective serotonin reuptake inhibitor that is sometimes used for the treament of patients with pain-related functional gastrointestinal disorders [92]. Although an open-label study found it beneficial, a randomized, placebo-controlled trial found no significant difference between placebo and citalopram in terms of pain improvement in children [92, 93]. Side effects included drowsiness and dry mouth. Further studies are needed.

Antispasmodics

Peppermint oil is known to relax the lower esophageal sphincter and relieve symptoms of dyspepsia [94]. A meta-analysis conducted in adults with IBS evaluated five double-blind, placebo-controlled, randomized, controlled trials using peppermint oil as treatment for IBS [95]. It showed a significant global improvement of IBS-symptoms in patients treated with peppermint oil versus placebo [95]. Asgarshirazi et al. compared peppermint oil with placebo and a symbiotic Lactol in a three-arm randomized control trial in children functional gastrointestinal disorders based on the Rome III criteria (n = 88) [96]. They showed that patients in the peppermint group had significant improvement in pain duration, frequency, and severity [96]. However, this trial had a high dropout rate (38% in placebo, 15% in intervention group), and the placebo was different in preparation and dose timing compared to the intervention drug [96]. Another randomized controlled trial in children with IBS (n = 42) by Kline et al. observed 75% of children receiving peppermint oil had reduced pain associated with IBS [94]. They also report that daily diaries completed by children showed significantly lower mean pain severity in the peppermint oil group [94]. Larger, randomized controlled studies in pediatrics are needed to further confirm the use of peppermint oil in children.

Drotraverine hydrochloride was studied in one double blind, randomized, placebo-controlled trial in children between the ages of 4–12 years of age with recurrent abdominal pain (n = 132) [97]. This study resulted in a reduction in number of episodes of abdominal pain [mean (SD) number of episodes 10.3 (14) vs. 21.6 (32.4); p = 0.01] and lesser school absence [mean (SD) number of school days missed 0.25 (0.85) vs. 0.71 (1.59); p = 0.05] in the drotraverine group (vs. placebo) [97]. No results were available as far as pain severity.

Mebeverine is another antispasmodic trialed in children aged 6–18 years of age with FAP (n = 87) in a randomized, placebo-controlled trial [98]. There was no significant difference between the treatment versus placebo group [98]. Drotaverine and mebeverine are not available in the USA. There are no studies to confirm the efficacy of antispasmodics that are commonly avalaible in the USA, such as hyoscyamine and dicyclomine.

Antihistamines

Cyproheptadine is an antihistamine that is commonly used to treat FAPDs. As mentioned previously, it is used as prophylactic therapy for AM. Not many studies randomized trials exist in the pediatric population assessing its use for FAPDs despite its popularity. A double-blind randomized placebo-controlled trial led by Sadeghian et al. resulted in improvement in the intensity and frequency in abdominal pain among children treated with cyproheptadine when compared to placebo (n = 29) [99]. Unfortunately, this study is limited by its small size and non-validated measurement tools. Further studies assessing the use of cyproheptadine are warranted.

Electrical Stimulation

Modulating central pain pathways and consequently visceral hypersensitivity by the use of percutaneous electrical field stimulation (**PENFS**) (Neuro-Stim, Innovative Health Solutions, IN, USA) has been studied in randomized clinical trials. A randomized, sham-controlled trial in adolescents aged 11–18 years who met Rome III criteria for abdominal pain-related functional gastrointestinal disorders found that Neuro-Stim had sustained efficacy for abdominal pain [100]. Patients who received electrical stimulation (n = 57) had greater reduction in worst pain after 3 weeks of treatment (median score 5.0; sham: 7.0) with sustained effect at follow-up (median follow-up 9.2 weeks) [100]. Side effects were minimal, including ear discomfort, adhesive allergy, and syncope due to needle phobia. No serious adverse events were reported.

A recent randomized, double-blind trial in adolescents with IBS observed improvement in abdominal pain in those who received the PENFS (vs. sham) [19]. Fifty-nine percent of adolescents with IBS who received PENFS (n = 27) were observed to have significant reductions of 30% or more in abdominal pain versus 26% in the sham group (n = 23) [19]. Patients who received PENFS had a composite pain median

score of 7.5 versus 14.4 for the sham group [19]. As a result of these studies, data are now supporting the use of auricular neurostimulation for abdominal pain in adolescents with IBS. This led to approval of the auricular PENFS device by the FDA in adolescents with IBS [101].

Probiotics

Probiotics are live micro-organisms that can provide beneficial health effects on their host when administered in adequate amounts [5]. The thought behind the use of probiotics is that they can restore the altered microbiota, prevent the overgrowth of pathogenic bacteria, and maintain the integrity of the gut mucosa [5]. A randomized study in children with FAPDs found that treatment with the probiotic *Lactobacillus GG* improved pain symptom [102]. Of note, this study had a wide CI around the result, thus results should be interpreted with caution.

A Cochrane study published in 2017 evaluated seven studies (n = 722 children) and found that children treated with probiotics were more likely to experience improvement in pain at zero to 3 months after receiving probiotics when compared to placebo (OR 1.63, 95% CI 1.07–2.47), with an estimated number needed to treat of eight [103]. Children with IBS were more likely to experience improvement in pain zero to 3 months after commencing probiotics (vs. placebo; OR 3.01, 95% CI 1.77–5.13; 4 studies; 344 children) [103]. However, given the heterogenicity of the selected trials and low number of participants, these studies were considered low to moderate quality using GRADE [103]. Given these findings, it would not be unreasonable to use probiotics as part of the treatment for pediatric patients with FAPDs. Larger studies assessing long-term effects, dosage, and optimal strain are needed.

Food

Most children are able to pinpoint certain foods that trigger their symptoms. The most commonly identified foods are spicy food, cow's milk, and pizza [5].

Fiber

Typically, changes in lifestyle and diet are recommended as initial therapy to children who present with FAPDs. Increase in water and fiber intake is usually the most common recommended dietary changes [104]. Fiber is ingested from vegetables, fruits, and whole grains, thus can sometimes be sub optimally consumed by children [104]. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition published guidelines in 2014 stating that there is no evidence supporting the use of fiber for treatment of functional constipation in children, and recommended giving the "normal" amount for age [105]. In addition, The Rome IV criteria does not mention using fiber as treatment for FAPDs, specifically IBS-C [13]. A Cochrane study assessing the use of fiber in children with abdominal pain found that those treated with fiber did not experience an improvement in pain at 0–3 month postintervention (OR 1.83, 95% CI 0.92–3.65; 2 studies; 136 children) nor a reduction in pain intensity (SMD −1.24, 95% CI −3.41–0.94; 2 studies; 135 children) when compared with placebo [103]. At this time, there is not enough evidence to recommend the use of higher doses of fiber for the treatment of constipation.

Psyllium is an insoluble fiber that can improve abdominal pain and/or symptoms related to bowel movements in adults with IBS [106]. A recent randomized, double-blind trial assessing the efficacy of psyllium fiber for treating abdominal pain and stool pattern in children with IBS showed that those in the psyllium group (vs. placebo) had a greater reduction in the mean number of pain episodes (8.2 ± 1.2 after receiving psyllium vs. mean reduction of 4.1 ± 1.3 after receiving placebo; p = 0.03) [106]. There was no difference between groups regarding stool patterns. Thus, psyllium could be considered for treatment of abdominal pain related to IBS; however, further studies are needed.

Low FODMAP Diet

Around 93% of children with IBS report food intolerances [107]. Fermentable carbohydrates such as lactose and fructose may be difficult to absorb and have been identified as the cause of symptoms in children with chronic abdominal pain [108]. Low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet, which lowers the consumption of fermentable carbohydrates, has been shown to decrease overall gastrointestinal symptoms in adults with IBS [109]. A randomized placebo-controlled study by Chumpitazi et al. showed that fructans, a commonly ingested FODMAP carbohydrate unable to be hydrolyzed by human enzymes, worsened abdominal pain, bloating, and flatulence (n = 23, all $p < 0.05$) [110]. Another double blind, randomized trial evaluating the efficacy of a low FODMAP diet in children with IBS (n = 33) showed that children on this diet (vs. a typical American childhood diet) had less abdominal pain (1.1 ± 0.2 (SEM) episodes/day vs. 1.7 ± 0.4, $p < 0.05$) [108]. A more recent randomized study in children with IBS according to the Rome IV criteria (n = 60) also resulted in less pain in the FODMAP diet group (vs. standard diet) [111]. Thus, low FODMAPS diet seem to have a role in improving GI symptoms that accompany IBS. Unfortunately, adherence to the FODMAP diet can be difficult and long-term use can result in nutritional deficiencies.

Psychological Interventions

Cognitive behavioral therapy, hypnotherapy (including guided imagery), yoga, and written self-disclosure have been used to treat recurrent abdominal pain in children. Cognitive behavioral therapy teaches coping, distraction, and relaxation techniques [5]. A Cochrane review found that cognitive behavioral therapy, when compared to control, had evidence of treatment success postintervention (OR 5.67, 95% CI 1.18 to 27.32; $Z = 2.16$; $p = 0.03$; 4 studies; 175 children; very low-quality evidence) but no evidence of treatment success at medium-term or long-term follow-up [112].

Hypnotherapy is believed to have some influence on gastrointestinal motility and central nervous system. During this session, the therapist guides the child to respond to suggestions for changes in experiences, sensations, and emotions [5]. Faymonville et al. showed that hypnosis caused a significant activation of a right-sided extrastriate area and the anterior cingulate cortex, shown by positron emission tomography [113]. This area was shown to be related to pain perception. Compared to control, hypnotherapy had evidence of greater treatment success postintervention (OR 6.78, 95% CI 2.41–19.07; $Z = 3.63$; $p = 0.0003$; 4 studies; 146 children; low-quality evidence), reduction in pain intensity (SMD −1.01, 95% CI −1.41 to −0.61; $Z = 4.97$; $p < 0.00001$; 4 studies; 146 children; low-quality evidence), and reduction in pain frequency (SMD −1.28, 95% CI −1.84 to −0.72; $Z = 4.48$; $p < 0.00001$; 4 studies; 146 children; low-quality evidence) [112].

Yoga aims to reduce anxiety, improve body tone, and improve feelings by practicing daily breathing and meditation along with physical poses [5]. Written self-disclosure on the other hand, encompasses a short session during which the patient writes down their thoughts and feelings about something distressing [5]. Neither yoga therapy nor written-self disclosure therapy were found to be effective, although there were only three randomized trials evaluating yoga in children with IBS or FAPDs and one evaluating written-self disclosure in children with recurrent abdominal pain [112]. Thus, studies are needed to assess these therapies and their efficacy in the treatment of FAPDs.

Distraction can also be a powerful tool in diminishing anxiety. A study by Walker et al. looked to assess the impact of parent attention and distraction on symptom complaints by children with and without FAP [114]. Children with abdominal pain ($n = 104$) and well children ($n = 119$) underwent a water load symptom provocation test used to induce visceral discomfort. Their parents were randomly assigned to one of three conditions: attention, distraction, or no instruction. Symptom complaint in the attention group by both groups of children almost doubled, whereas they were reduced by half in the distraction group. Thus, parent's responses to children's complaints can significantly heighten or soften these complaints.

Non-steroidal Anti-Inflammatory Agents

A Cochrane review published in 2017 assessing the use of non-steroidal anti-inflammatory drugs in chronic non-cancer pain children and adolescents aged 2–17 years of age found no evidence from randomized controlled trials to suggest these drugs are effective in treating chronic non-cancer pain in this population [115]. Another Cochrane review published in 2017 assessing the use of paracetamol (acetaminophen) in the same population found no studies eligible for inclusion and thus concluded that there is no evidence to support or refute the use of paracetamol [116]. At this time there is no evidence to support the use of non-steroidal anti-inflammatory drugs or acetaminophen in this population.

Placebo

Placebo treatment has been shown to significantly influence symptoms. A recent non-deceptive, non-concealed open placebo study by Nurko and Saps in children aged 10–21 years of age with functional gastrointestinal disorders showed placebo treatment demonstrated global improvement and lower pain scores compared to baseline (vs. control, all $p < 0.05$, $n = 30$) [117]. Something to keep in mind is that a 'true placebo-effect' can be influenced by a good physician–patient relationship, which improves treatment outcomes in patients [5].

Alternative Medications

STW 5

STW 5, also known as Iberogast® (Steigerwald Arzneimittelwerk GmbH, Darmstadt, Germany) contains nine plant extracts and has been shown to improve symptoms in FAPDs [118]. Vinson and Radke conducted a prospective, non-interventional study with STW 5 in 980 children aged 3–14 years of age with functional gastrointestinal diseases [119]. Symptom score was reduced from 16.1 ± 18.9 score points to 3.8 ± 4.2 score points, with 38.6% of children reporting complete relief and absence of symptoms [119]. Tolerability was judged as excellent or good for 95% of children [119]. STW 5 is generally well-tolerated and has not been found to have adverse central nervous or cardiac events that have been reported for prokinetics [120]. STW 5 so far offers an effective, and safe, treatment option for children. Larger randomized studies are warranted.

Treatments for Episodic FAPDs

The first approach to management should be on prevention of attacks. It is imperative to provide reassurance and give a clear diagnosis and explanation of the condition to the patient and family. Conservative treatment includes exercise, healthy diet, and normalization of sleep cycle. Triggers should be identified and avoided as much as possible. If emotional triggers are factors that contribute to the development of AM, biofeedback and counseling might offer some benefit. Biofeedback therapy appears to be effective in children and adolescents with both episodic and chronic headaches (58% response rate overall); however, studies assessing biofeedback therapy in AM are lacking [121].

Treatments for AM can be divided into two categories: abortive treatments and preventative treatments. For an acute episode, resting in a dark, quiet room has shown to resolve a majority of acute AM episodes [65]. Ibuprofen 10 mg/kg showed in two small randomized, blinded, placebo-controlled studies (Hämäläinen et al., n = 88, mean age: 10.7 years; Lewis et al., n = 84, mean age 9 years) to be more effective than placebo in improving migraine headache pain in 2 h [122, 123]. These studies, however, were considered low quality due to imprecision [124].

Prophylactic treatment is indicated when the frequency of incapacitating attacks is >1 attack per month or when the duration of the attach lasts a long time, usually >24 h) [66]. In children under 12 years of age, *triptans*, which are serotonin receptor agonists, have shown to be superior than placebo in improving pain related to migraine headaches [125–127]. Intranasal sumatriptan 10–20 mg improved abdominal pain related to AM in two pediatric cases reported by Kakisaka et al. [128]. Of note, overuse should be avoided as it can cause a rebound in symptoms. Its use should be cautioned in patients with high blood pressure.

Propranolol is a beta-blocker commonly used to treat migraine headaches in children [129]. A retrospective study in 53 children with a diagnosis of AM found 18 (75%) had an excellent response, 2 (8%) had a fair response, and 4 (17%) had no response [129]. This same study also reviewed *cyproheptadine*, an antihistamine drug that is also commonly used to treat cyclic vomiting syndrome. They observed four (33%) had an excellent response, six (50%) had a fair response, and two (17%) had no response [129]. Of the four children that did not respond to propranolol, two responded to cyproheptadine. There was no statistically significant difference between treatment propranolol and cyproheptadine.

Given the close relationship between migraines and cyclic vomiting syndrome, *amitriptyline* can also be considered as prophylactic therapy for children with AMs. Amitriptyline has been shown to be efficacious as preventative for some children with cyclic vomiting syndrome. A single-blinded randomized clinical trial comparing amitriptyline with cyproheptadine for prophylactic therapy of cyclic vomiting syndrome found that in the amitriptyline group, 66% of patients reported 100% remission (n = 32) (vs. 50% in the cyproheptadine group, p = 0.2, n = 32) [130]. A more recent study by Powers et al. did not show that amitriptyline was better than placebo with regard to reducing the number of headaches related to migraines [131]. Thus, data for the use of amitriptyline for AM in children is lacking.

Pizotifen, a serotonin receptor antagonist, was superior than placebo in children with regard to days of abdominal pain present (pizotifen mean: 4–29; placebo mean: 12–50; p = 0.005), index of severity (pizotifen mean: 7–29; placebo mean: 23–50; p = 0.005), and index of misery (pizotifen mean: 25–43; placebo mean: 81–50; p = 0.007) [132]. Unfortunately, this was a small trial (n = 14); however, authors argue that the beneficial effects of pizotifen were so striking clinically and statistically that it would have been unethical to study further patients with placebo [132]. No other trials assessing the use of pizotifen in children with AM have been published.

Flunarizine, a non-selective calcium channel-blocking agent (not available in the USA), decreased the frequency of attacks (flunarizine: 0.2–1/month, mean: 0.49/month; before flunarizine: 0.4–2/month, mean: 0.8/month) and duration of attacks (flunarizine: 4–48 h, mean: 14 h; before flunarizine: 3–36 h, mean: 7.4 h) in a small, non-randomized trial in children with AM (n = 10, mean age: 6 years) [66]. Overall, it is well-tolerated with minimal adverse effects [66]. Thus larger, randomized placebo-controlled studies are needed to assess the long-term efficacy of this medication.

Valproic acid increases brain gamma aminobutyric acid neurotransmitter by blocking reuptake, inhibiting enzymes that usually break it down, and increasing release from nerve terminals [133]. In migraine headaches, it is believed that an increase in activity of excitatory amino acids that synthesize GABA are involved in their development. Valproic acid, by inhibiting these excitatory amino acids, could potentially inhibit migraines [133]. A two-patient case report (ages: 12 years, 17 years) showed valproic acid IV resolved pain episodes related to AM. Randomized, placebo-controlled trials are needed [133].

Dihydroergotamine is an ergot alkaloid that acts as an agonist to serotonin receptors, causing vasoconstriction of the intracranial blood vessels [134, 135]. It acts as both an antiemetic and proemetic. An IV formulation was used in six children (ages 13–19 years of age), mostly female, presenting with abdominal pain at a large children's hospital [134]. Five of them reported improvement or resolution of symptoms after administration of dihydroergotamine. Side effect included nausea during the infusion, but otherwise no significant complications [134]. Some argue that dihydroergotamine should be considered in patients in which aggressive

Table 37.6 Available treatments for AM

Abortive treatment	Dose
Rest in dark, quiet room	N/A
Ibuprofen, PO	10 mg/kg
Sumatriptan, IN	10–20 mg
Preventative treatment	
Propranolol TID	10–20 mg BID or TID
Cyproheptadine PO (syrup)	0.25–0.5 mg/kg
Amitriptyline PO	Titrate to 1.0–1.5 mg/kg/qhs
Pizotifen PO	0.25 mg BID-TID
Flunarizine PO	7.5 mg/day
Valproic acid (sodium valproate), IV	500 mg TID
*can be given to patients during an acute attack that have not responded to conventional therapies	
Dihydroergotamine IV	1 mg q8h, with reduction to 0.5 mg per dose in younger children or those weighing <25 kg [135]

outpatient treatment is not working. Contraindications include allergy to the medication and electrocardiogram abnormalities [134].

An adult study assessing *IgG-based elimination diet* in subjects with migraines and concomitant IBS ($n = 21$) showed that food elimination based on IgG antibodies, compared to their usual diets, reduced migraine attacks (4.8 vs. 2.7; $p < 0.001$), maximum attack duration (2.6 vs. 1.4 days; $p < 0.001$), mean attack duration (1.8 vs. 1.1 days; $p < 0.01$), maximum attack severity (visual analog scale 8.5 vs. visual analog scale 6.6; $p < 0.001$), and number of attacks with acute medication (4.0 vs. 1.9; $p < 0.001$) [136].

See Table 37.6 for a summary of the available treatments for AM. Unfortunately, data for many of the treatments used for AMs has been extrapolated from research related to childhood migraine headache or adults with migraine headaches. Further studies specifically tailored for childhood AM are needed.

Conclusions

FAPDs represent a difficult to manage entity in children. The extrapolation of adult data and lack of pediatric-specific data represents a limitation to treatment options. The medical, social, and economic impact of FAPDs is rising, affecting not only the child but the child's family. As Lu and Saps state, "Despite all we have learned during the past 4 decades, it is hard to argue that we are truly making progress."[137] Given what we know now as plausible early causes of FAPDs (disruption of the gut microbiota, early life events that lead to hyperalgesia such as cow's milk protein), maybe we should shift our focus toward prevention and try to better understand the epidemiology and pathophysiology of FAPDs [138].

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Cyclic Vomiting Syndrome, Abdominal Migraine, and Chronic Nausea

38

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Definition

In both children and adults, the hallmark CVS symptoms described by Samuel Gee in 1882 remain applicable today and include stereotypical, severe episodes of vomiting punctuating symptom-free periods, or baseline health [1] . Earlier clinical diagnosis of CVS has been facilitated by specific consensus diagnostic recommendations formulated by the NASPGHAN (2008) and Rome IV (2016) criteria (Table 38.1), the former being quantitatively more rigorous, i.e., requiring 3–5 versus 2 total episodes [2, 3] (Table 38.2). Abdominal migraine manifests by paroxysmal episodes of intense abdominal pain and supporting features as specified in the Rome IV criteria [3] (Table 38.3). There is common confusion over the nomenclature as the older CVS classification was "abdominal migraine" (still used by neurologists) and the newer term especially since the 1990s is "cyclic vomiting syndrome" or "cyclical vomiting syndrome" (UK). Today, the predominant and most consistent symptom during episodes defines the illness, i.e., abdominal pain is termed abdominal migraine, and conversely vomiting is denoted CVS. However, as can be seen from the diagnostic criteria, there is considerable clinical overlap because ~50% of those diagnosed with abdominal migraine also vomit, and 80% of those with CVS also have abdominal pain. CVS and abdominal migraine are similarly classified in the International Classification of Headache Disorders (2013) [4].

Table 38.1 Functional nausea and vomiting disorders (pediatric Rome IV criteria)

Cyclic vomiting syndrome
Functional nausea
Functional vomiting
Rumination syndrome
Aerophagia

Table 38.2 NASPGHAN and Rome IV diagnostic criteria for cyclic vomiting syndrome [2, 3]

NASPGHAN
1. At least five attacks in any interval or a minimum of three attacks during a 6-month period
2. Episodic attacks of intense nausea and vomiting lasting 1 h to 10 days and occurring at least 1 week apart
3. Stereotypical pattern and symptoms in the individual patient.
4. Vomiting during attacks occurs at least 4 times/hr. for at least 1 h
5. Return to baseline health between episodes
6. Not attributed to another disorder
Rome IV
1. Two or more periods of intense unremitting nausea and paroxysmal vomiting, lasting hrs to days within a 6-month period
2. Episodes are stereotypical in each patient
3. Episodes separated by weeks to months with return to baseline health between episodes
4. Symptoms not attributed to another medical condition

All respective criteria must be met to meet consensus definitions for both NASPGHAN, Rome III and Rome IV (see Benninga et al.: http://www.ncbi.nlm.nih.gov/pubmed/27144631 Or [if!supportLists]2-[endif] Hyams et al.: http://www.ncbi.nlm.nih.gov/pubmed/27144632)

Table 38.3 Rome IV diagnostic criteria for abdominal migraine [3]

Rome IV
1. Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting 1 h or more (should be the most severe and distressing symptom)
2. Episodes separated by weeks to months
3. Incapacitating pain interfering with normal activities
4. Stereotypical pattern and symptoms in the individual patient
5. Pain associated with ≥ 2 of following: Anorexia, nausea, vomiting, headache, photophobia, pallor
6. Symptoms not attributed to another medical condition

Criteria must be fulfilled for at least 6 months before diagnosis

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Epidemiology

Although CVS was originally perceived as a pediatric disorder, the past two decades have witnessed a dramatic rise in diagnosed adults. The continuum between CVS and migraine was suggested by Whitney in 1898 and corroborated by other authors including us in 1998 [5, 6]. In a cross-sectional school survey in Scotland, Abu-Arafeh described a developmental progression from CVS to abdominal migraine and migraine headaches, median ages 5, 9, and 11 years with prevalence rates of 1.9%, 4%, and 11%, respectively [7]. This suggests a natural history that begins with CVS and ends with migraines. Although some experience all three phases, the largest group trades CVS for migraines by age 10. We estimate 75% will develop migraine headaches by age 18 years (Li, unpublished data).

The previous lack of a specific ICD 9 code rendered it difficult to establish the true prevalence of CVS. However, ICD 10 now includes a specific code (G43.A0) for CVS [8]. Typical misdiagnoses, including gastroenteritis, gastroesophageal reflux, food poisoning, and eating disorders, often delay accurate diagnosis by a median 2.5 years [9, 10]. At our GI clinic, CVS was second only to gastroesophageal reflux as a cause of recurrent vomiting [11]. Two school-based surveys estimated the frequency to be 2% in Scottish and Turkish children [7, 12], and the incidence of new cases of CVS was reported to be 3.15 per 100,000 children per year in Irish children. Similar prevalence data were recently documented in adult CVS in a U.S. population-based survey [13]. In our series, the average age of onset of CVS is 4.8 years with predominance in girls over boys (57:43). Similar data were replicated in a large study from Iran [10].

Two large, population-based surveys (Europe and US) found abdominal migraine among the most common DGBI with a prevalence of 7.8% and 9.2%, respectively [14, 15]. However, similar studies of Latin American and Japanese children found a much lower prevalence of abdominal migraine (1% and 0.19% respectively) as well as of CVS (0.3%) [16, 17].

Impact on QOL

CVS has a significant deleterious impact on the quality of life in affected children. Although well in between episodes approximately 90% of the time, 58% of affected children require intravenous fluids during at least one episode and average 10 visits to the emergency department in one self-reported cohort. School-age children miss an average of 24 days of school per year [7, 18]. Medical morbidity is reflected by the high average annualized cost of management of $17,000 in 1998 that includes doctor visits, emergency department visits, inpatient hospitalizations, missed work by parents, and biochemical, radiographic, and endoscopic testing [19]. In adults, a nationwide database study showed that CVS hospitalizations incurred $400 million over a 2-year period (2010–11) [20].

A growing number of comorbid conditions such as anxiety and postural tachycardia syndrome (POTS) also contribute to functional disability. We have documented lower global quality of life scores than in healthy controls and those with functional GI disorders (irritable bowel syndrome) and equivalent to that of organic GI diseases (e.g., inflammatory bowel disease, gastritis, fatty liver disease) [21]. Nearly half (47% overall, 59% of school age children) of CVS sufferers meet criteria for an anxiety disorder and we found that anxiety was the prime predictor of impaired quality of life, even more than the quantitative severity of episodes [22].

Pathophysiology

In the absence of a defined etiopathogenesis, CVS remains classified as an idiopathic disorder. Investigations support the contributory roles of mitochondrial DNA (mtDNA) mutations and dysfunction, heightened hypothalamic–pituitary–adrenal (HPA) axis activation, polymorphisms of the cannabinoid receptor type 1 and μ-opioid receptor genes (adult CVS), and autonomic nervous system (ANS) dysfunction. CVS is a functional brain–gut disorder perhaps mediated through altered brainstem modulation of effector signals.

Mitochondrial Dysfunction

In two series, a striking maternal inheritance pattern was recognized for migraines in 64% and 54% of probands with CVS [23, 24]. Evidence of mitochondrial dysfunction was first provided using NMR spectroscopy to establish decreased ATP production in peripheral muscle in migraineurs [25]. This mitochondrial pathogenesis gained substantial support following the identification of two tandem mtDNA polymorphisms, 16,519T and 3010A with impressive odds ratios of 17 and 15 in CVS and migraine in haplotype H, respectively [26]. Because the mutations are found in the control region rather than the enzyme sequence, the structure to function relationship is unclear. However, elevated lactates, ketones, and Krebs cycle intermediates during attacks are consistent with mitochondrial dysfunction. In addition, small therapeutic trials show some effects of mitochondrial supplements coenzyme Q10, L-carnitine, and riboflavin in the treatment of both migraines and CVS [27–30].

These two mtDNA mutations are also found in depression, chronic fatigue, and irritable bowel syndrome and may link these clinical comorbidities together to a common mitochondrial susceptibility factor [31]. Similarly, the mitochondrial mutation (m.3243A > G) is found at high prevalence in patients with migraine headaches [32]. Although not confirmed, migraine is considered at threshold disease that is activated by a brain-related trigger, resulting in a depolarization wave and neuronal hyperexcitability [33, 34]. Both CVS and migraine disorders share similar periodicity and triggers, suggesting neuronal excitation as part of the symptom cascade [34].

HPA Axis Activation

Stressors, both psychological (excitement, panic) and physical (infection, lack of sleep), are common triggers of attacks of CVS. Activation of the HPA axis during episodes of CVS was first described by Wolfe, Adler, and later Sato, manifested by elevated levels of adrenocorticotropic hormone (ACTH), antidiuretic hormone (ADH), cortisol, catecholamines, and prostaglandin E2 and intraepisodic hypertension [35–37]. Attenuation of CVS symptoms occurred after use of high-dose dexamethasone by Wolfe and Adler and indomethacin and clonidine by Sato et al. [38].

The role of corticotropin-releasing factor (CRF) as a brain–gut neuroendocrine mediator of foregut motility has been extensively described in animals by Taché et al. [39]. In response to stressors, released CRF from the hypothalamus stimulates inhibitory motor neurons in the dorsal motor nucleus of the vagus and causes delayed gastric emptying, independent of downstream effects of ACTH and cortisol secretion. In animals, psychological (water avoidance) and physical (cytokine IL-1β) stressors can impair foregut motility. Ongoing investigation of the pathophysiologic role of CRF in CVS may open a potential therapeutic avenue using CRF antagonists. Also, tricyclic antidepressants, which inhibit the promoter activity of the CRF gene, are the most efficacious agents in treating CVS. Gene sequencing data found that a significant number of pediatric CVS sufferers carry a mutation in a stress-sensitive calcium channel (RYR2 gene) influencing the autonomic nervous system [40]. Although speculative, these data may support involvement of stress-induced calcium release in neuronal mitochondria, which in turn may result in autonomic dysregulation.

Autonomic Dysfunction

Most of the prominent symptoms of CVS are expressed through the ANS. The peripheral vasoconstriction, hypersalivation, diaphoresis, tachycardia, and listlessness are in fact prominent manifestations of nausea that persist throughout the episode typically unrelieved by evacuation of the stomach. Although sharing many similar features such as intense nausea, lethargy, and pallor, patients with abdominal migraines and migraine headaches generally do not display the intense autonomic features of CVS (diaphoresis, salivation, etc.) [41].

Autonomic dysfunction in the form of POTS was reported in 47% of children with CVS in a small study [42]. In this cohort, treatment of POTS appeared to help reduce the frequency of CVS episodes. We found an overall POTS prevalence of 19% in our CVS patients, and when limiting the cohort to adolescents >11 years in whom POTS is known to be more common, the rate was 31%. Formal investigation of the ANS function in both children and adults with CVS reveals a fairly consistent pattern of heightened sympathetic tone and normal parasympathetic tone even during their wellness phase [43–46]. This imbalance is also described in migraines and other functional gastrointestinal disorders [47]. Further, emerging data on the natural history of CVS suggest that a large subset trade the episodic vomiting for chronic symptoms consistent with autonomic dysfunction in adolescence (Gosalves-Tejada, unpublished data). A small study linked acute stress-induced anxiety to altered heart rate variability in pediatric CVS, suggesting that anxiety and altered ANS reactivity may be linked to triggers of episodes [44].

A Model

How these pathophysiologic pathways fit together in a comprehensive model to explain CVS and migraine diatheses remains to be delineated. A recent study in adults noted decreased sensorimotor functional brain connectivity in both CVS and migraine patients, suggesting a common mechanism. Neuronal hyperexcitability, possibly linked to mitochondrial mutations and impaired cellular energy production, coupled with a lower threshold to trigger activity in specific cortical and subcortical brain regions during times of stress/higher energy demands is a plausible model. If the production cannot meet the heightened demands, autonomic neurons may be the target because of their high intrinsic energy demands. CRF may be the initiating signal triggered by psychological or physical stressors that relay altered brain to gut messages, allowing the emetic motor program to feed forward uncontrollably [48]. The brain areas modulating brain-to-peripheral ANS signals such as the emetic motor program are mediated by the vagus. Therapeutics that target these pathways via vagal neuromodulation are emerging and showing promise for treating CVS (Kovacic, unpublished data).

Stress sensitivity, periodicity, and vulnerability to environmental or internal changes are strong features of CVS and

migraine disorders. Long-term, the neural circuits processing emotional arousal may be more permanently altered in allostatic fashion and render the patient increasingly vulnerable to triggers This model of neurogenic disorders with hyperexcitabiliy reinforces the importance of mind-body interventions and may explain the efficacy of centrally targeted therapies in CVS and abdominal migraine [49].

Clinical Patterns

CVS and abdominal migraines have a distinctive on–off temporal symptom pattern that serves as an essential criterion for diagnosis. CVS is distinguished by the "on" pattern of discrete, recurrent, and singularly severe episodes of vomiting that are stereotypical within the individual as to time of onset (usually early morning), duration (hours or days), and symptomatology (pallor, listlessness). Abdominal migraine shares this symptom pattern, but abdominal pain rather than emesis is the most troublesome or disabling feature. The "off" pattern is week- or month-long intervals when the child resumes completely normal or baseline health (e.g., if there is other chronic disease), although 5–12% may have interepisodic symptoms of nausea and mild vomiting [9]. This particular persistent interictal pattern has been labeled 'coalescent' CVS, although the daily nausea and vomiting is usually less severe than that during the CVS episodes themselves. In our recent series of the natural history of CVS, 40% of children were found to develop autonomic dysfunction in concert with progression to chronic nausea during adolescence (Gosalvez-Tejada, unpublished data). This further reinforces the concept of a chronically altered autonomic state that over time changes its phenotypic expression.

During the episodes, the most common symptoms are listlessness (93%) and pallor (91%), and others include low grade fever or hypothermia, intermittent flushing, diaphoresis, nausea, drooling, diarrhea, and hypertension specific to the Sato variant. Although found in significantly higher frequency than in patients with other GI disorders, fewer than half have classic migraine features of headache, photophobia, and phonophobia.

The duration of episodes – including prodromal, emetic, and recover phases – generally ranges from hours to days with a median duration of 27 h. The largest pediatric study to date ($n = 214$) documented a mean episode duration of 48 h [50]. A study of Iranian CVS children found a mean duration of 4.3 days [10]. Episodes can last as long as 7–10 days, but are generally self-limited. Half of patients have "cyclic" intervals most commonly 4 weeks, predictable within a week, and half have "sporadic," unpredictable attacks. The most common time of onset is early morning (2–4 a.m.) or upon awakening (6–8 a.m.) in 42%. Many have a remarkably rapid onset (1.5 h) and denouement (6 h) from the last emesis to the point of being able to eat and be playful. The 67% with a prodrome experience pallor, diaphoresis, abdominal pain, and headache before the onset of vomiting, but rarely the visual disturbances of a migraine aura.

The vomiting in CVS is uniquely rapid fire and peaks at a median frequency of six times an hour and 15 times per episode. Even when the stomach is emptied, deep guttural retching may continue at the same frequency. The vomiting is typically forceful and may contain bile, mucus, and occasionally blood, the latter usually the result of prolapse gastropathy. The intense nausea differs from that in gastroenteritis or bowel obstruction in that it persists even after complete evacuation of gastric contents as if independent of gastric feedback, presumably centrally driven. In fact, many adolescents describe it as the most distressing symptom, only relieved during sleep. Due to the unrelenting nausea, during episodes, these children appear much more debilitated when compared to those with gastroenteritis, often curled into a fetal position, listless, and withdrawn to the point of being unable to walk or interact. Anorexia, nausea, midline abdominal pain, and retching are the most common gastrointestinal symptoms.

Certain unusual behaviors can be observed during CVS episodes that can raise questions about an underlying psychiatric disorder. There are children who drink compulsively and then vomit and describe that this maneuver dilutes the bitter bile and aids in its evacuation. Others take prolonged, scalding hot showers or baths until the hot water supply is exhausted. In adults and adolescents with CVS, this unique symptom is also associated with chronic, high-dose marijuana use and termed "cannabinoid hyperemesis syndrome " [51]. Nearly all turn their rooms into a darkened cave in order to avoid lights and sounds that trigger more nausea. Many are hyperesthetic to motion, odor, taste, and even parental touch and attempt to shut out the external environmental stimuli that often trigger additional nausea and vomiting.

Various recurring stressors are recognized to precipitate CVS episodes in 76% of patients. These include psychological (44%), infectious (31%), and physical triggers [9]. The psychological stress is more often of an excitatory nature such as holidays, birthdays, outings, and vacations. Episodes may be triggered by various infections including upper respiratory infections, sinusitis, strep throat, and influenza. Dietary triggers may include aged-cheese, chocolate, monosodium glutamate, and fluctuating caffeine intake (23%). Lack of sleep from excess physical exhaustion from travel, sports, sleepovers or a sleep disorder (24%), and menses (catamenial CVS—22% of post-menarchal girls) are also common inciting events. Environmental triggers include changes in barometric pressures during incoming weather fronts. One subgroup with a precisely timed interval every 60 days (predictable within a week) with no identifiable triggers is especially refractory to therapy.

Comorbidities

The evolving clinical picture of CVS has included an increasing number of associated comorbidities. In one series, 25% had coexistent neurological findings of developmental delay, seizures, hypotonia, and skeletal myopathy as well as cognitive and cranial nerve dysfunction [52]. These children were found to have an earlier age of onset for CVS, higher prevalence of dysautonomic (neurovascular dystrophy) and constitutional (growth retardation). Other common comorbidities in non-neurologically impaired children include anxiety (47%) and depression (14%) [53], irritable bowel syndrome (67%) [35], GERD (39%), colonic dysmotility (20%) [54], limited stamina or chronic fatigue (52%), sleep disturbance (onset or maintenance) (48%), POTS (19%), and complex regional pain syndrome (12%) [55]. These attendant comorbidities that occur during the well phase also contribute to the poor quality of life and have to be treated concomitantly to help restore the child to functionality.

Subgroups

There appear to be subphenotypes of CVS, some of which overlap and may be present in the same patient. The 83% that are migraine-related (positive family or personal history) tend to have significantly less severe episodes that are more responsive to antimigraine therapy [50]. It now appears that the majority has a matrilineal inheritance pattern (for migraine and other functional disorders) and may have mtDNA single nucleotide polymorphisms and mitochondrial dysfunction [24]. Many appear to have predominantly sympathetic overtone and comorbid POTS in whom treatment of POTS helps reduce frequency of vomiting episodes. The Sato variant is associated with hypertension during episodes and an endocrine profile of heightened HPA axis activation. Those with long-interval, calendar-timed episodes every 60+ days apart appear particularly difficult to treat. Boles has described a group with neurodevelopmental deficits in whom CVS begins early in life [52]. There are post-menarcheal girls with catamenial CVS who often respond to low-estrogen birth control pills or ablation of menses with progesterone.

A group of predominantly young adult males (>270 case reports) who use large amounts of recreational or medical marijuana over several years may in fact trigger CVS symptoms that have been labeled as cannabis-induced hyperemesis (CHS). However, it is more likely cannabis-triggered CVS [51, 56]. Several series document termination of bouts of emesis after cessation of chronic use of marijuana. Another case series and a large, anonymous survey of CVS indicate that marijuana users experience reduction in nausea and anxiety, raising the possibility that marijuana may have a biphasic effect and explain these contrary findings. That is, long-term high-dose usage may aggravate symptoms in some, whereas intermittent low-dose use may mitigate them in others [57]. The overlap between CVS and CHS is important to recognize as patients who present with vomiting and admit to any level of marijuana use may be inappropriately labeled as having CHS and being cannabis abusers and consequently not receive established CVS therapies.

Evaluation

At present, there are no specific tests to diagnose CVS or abdominal migraine, and the diagnosis rests primarily upon fulfilling clinical criteria [2, 3]. The first step requires differentiating a cyclic or sporadic pattern (high intensity, low frequency) of vomiting from a chronic vomiting (low intensity, high frequency, e.g., daily), one in which upper GI tract disorders predominate [11]. Approximately 90% of children who fulfill the NASPGHAN consensus criteria (Table 38.2) are ultimately found to have CVS [2, 11]. Most of the testing in undiagnosed children who present with recurrent vomiting is directed toward identifying underlying gastrointestinal, neurologic, renal, metabolic, and endocrine causes that can be discovered in the remaining 10%. The challenge to the clinician is to determine which and how much testing should be performed, as the traditional "shotgun" approach is invasive, time-consuming, and not found to be cost-effective [58].

The NASPGHAN Consensus Statement (2008) guidelines recommend against extensive initial evaluation and instead recommend an initial upper gastrointestinal series to exclude malrotation and anatomic obstructions and a basic metabolic profile (electrolytes, glucose, BUN, creatinine) [2]. Further testing beyond that should be based upon specific warning signs (Table 38.4). In those who present with bilious vomiting and abdominal tenderness, abdominal

Table 38.4 Evaluation of cyclic vomiting

• Patient meets consensus criteria for CVS UGI series to evaluate for malrotation + serum electrolytes, BUN, creatinine, and no warning signs or findings to suggest an organic disorder → trial of empiric therapy to treat CVS
If warning signs are present:
• Severe abdominal pain, bilious, and/or hematemesis → liver and pancreatic serum chemistries, abdominal ultrasound (or CT or MRI), esophagogastroduodenoscopy
• Fasting, high-protein meal, intercurrent illness precipitating episodes of vomiting → serum and urine metabolic evaluation (lactate, ammonia, carnitine profile, amino acids, and organic acids) *prior to treatment during episode and metabolic consult*
• Abnormal neurological findings (altered mental status, papilledema) → brain MRI, neurology consult

imaging should be performed to exclude hydronephrosis, pancreatitis, and cholecystitis. In those in whom episodes are triggered by intercurrent illnesses, fasting, or high-protein meals, screening should be performed for urea cycle, fatty acid oxidation, disorders of organic and amino acid metabolism, and mitochondrial disorders. This screening has a better diagnostic yield in the early part of an episode of CVS before intravenous glucose and fluids are administered. Those presenting with abnormal neurological findings including altered mental status, papilledema, ataxia, or seizure should have a neurological evaluation and brain MRI considered. Presentation of CVS under the age of 2 should also prompt further metabolic or neurological testing [2].

Treatment

Management of CVS is multifaceted and challenging. The goals of treatment are to reduce the frequency and severity of episodes, reduce school absenteeism and enhance functionality, improve quality of life, and establish a protocol for rescue therapy in home and in hospital. Treatment of nausea and vomiting, abdominal pain, and dehydration during acute episodes requires a protocol for use at home, emergency departments, and hospital wards. Lifestyle modifications, similar to those in migraines, during the well phase can help prevent episodes and are discussed below. For those with more frequent or severe episodes (e.g., more than once a month), prophylactic therapy taken daily to prevent the next episode is warranted. In some with less frequent or severe episodes, abortive therapy taken only during the prodrome or at the onset of the episode is recommended. The use of mitochondrial supplements to treat suspected underlying mitochondrial dysfunction is gaining evidence and acceptance.

At present, there are only two controlled therapeutic trials comparing amitriptyline to topiramate and amitriptyline to cyproheptadine, [59, 60] both conducted in Iran. One challenge is the high placebo response in CVS that renders all open label results difficult to interpret definitively. For example, in a formal randomized controlled trial of IV ondansetron during acute episodes, we were thwarted by an impressive 90% reduction in rate of episodes upon enrollment even without prophylactic therapy (Li, unpublished data). The 2008 NASPGHAN Consensus Statement therapeutic recommendations are based upon results from case series and expert opinion of the task force [2]. The main recommendations include first-line prophylactic use of cyproheptadine and amitriptyline in children under age 5 years and 5 years or older, respectively, with propranolol as the second line. Sumatriptan was recommended as an abortive agent for those >12 years. For rescue therapy during acute episodes, IV rehydration with high-dose antiemetic ondansetron (0.3–0.4 mg/kg/dose) and sedation from diphenhydramine or lorazepam was recommended.

Rescue Approach

The rescue therapies are used when the vomiting is well-established in an episode and fails to respond to abortive strategies. A recent study corroborates the clinical observation that delayed initiation of rescue therapy may result in worse outcomes [61]. Delayed presentation to the Emergency Department (ED) and delayed administration of antiemetic – even by as little as 1 h – were significantly associated with hospitalization from the ED [61, 62]. This study highlights not only the need for a written treatment protocol for the ED, but also its rapid implementation after initial triage. The goals are then to correct fluid and electrolyte deficits and render the child more comfortable through antiemetic therapy, analgesics for severe pain, and sedation for relief from unrelenting nausea and vomiting. The NASPGHAN recommendation is for an IV bolus of saline for rapid correction of fluid deficits and 10% dextrose 0.45 normal saline at 1.5× maintenance rates to provide sufficient cellular energy to terminate ketosis [2]. Poor response to IV therapy and progressive lethargy should prompt evaluation for hyponatremia from high ADH levels and inappropriate water retention [37]. One may have to reduce IV rates and increase Na^+ content in the face of hyponatremia and diminished urine output resulting from elevated antidiuretic hormone release, especially in the Sato-variant CVS. Ondansetron ($5HT_3$ antagonist) has been the most widely used antiemetic given safely at higher than standard doses (0.3 mg/kg/dose) and supported by a recent systematic review of rescue therapy [23, 63]. The NK-1 antagonist fosprepitant can be highly effective when administered as one IV dose and is supported by efficacy in pediatric CVS in its oral form [64]. Diphenhydramine, lorazepam, or chlorpromazine combined with diphenhydramine are used for sedation as this may be the only means of providing relief from the unrelenting nausea and pain (Table 38.5). Typical migraine agent analgesics such as ketorolac can be used to manage severe abdominal or headache pain. Opioids should be avoided due to concerns for dependence with recurrent use and exacerbation seen in migraineurs.

Table 38.5 Abortive and rescue pharmacotherapy

Antimigraine
Sumatriptan 20 mg intranasal at episode onset and may repeat once or 25 mg po once vs. *3–6 mg s.c. once SE: Chest and neck burning, coronary vasospasm, headache*
Alternatives: Rizatriptan, Zolmitriptan, Frovatriptan (longer half life)
Antiemetic
Ondansetron 0.3 mg/kg per dose (≤12 mg) q 4–6 h iv/po/rectal/topical. SE: Headache, drowsiness, dry mouth
Alternatives: Granisetron
Aprepitant 3 day regimen: 125, 80, 80 mg one q.d. prior to anticipated episode
Fosaprepitant 150 mg IV x1(>12 years);4 mg/kg x1 (2–11 years)
Sedative
Lorazepam 0.05–0.1 mg/kg per dose q 6 h iv/po: Useful adjunct to ondansetron. SE: Sedation, respiratory depression
Chlorpromazine 0.5–1 mg/kg per dose q 6 h iv/po. SE: Drowsiness, hypotension, seizures
Diphenhydramine 1.25 mg/kg per dose q 6 h iv/po: Useful adjunct to chlorpromazine. SE: Hypotension, sedation, dizziness
Analgesic
Ketorolac 0.5–1 mg/kg per dose q 6 h iv/po. SE: Gastrointestinal bleeding, dyspepsia

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Lifestyle Modifications

Lifestyle modifications are used during the interictal phase of CVS when the child is not in an episode in order to avoid exposure to known and potential precipitants of episodes. The lack of sleep resulting from disturbed sleep patterns, sleepovers, or travel is often cited as trigger of episodes. Good sleep hygiene (e.g., turning off all phones, computers, music, TV) with a regimented sleep time can help reduce the frequency of episodes. Providing at higher than maintenance fluid intake is widely used to treat migraines and POTS. Providing energy sources before strenuous activity, preferably of low glycemic index and high-protein sources, may prevent an energy deficit. Routine exercise can help reverse the deconditioned state. Finally, avoiding identified triggers specific to the individual (e.g., lack of sleep, dietary monosodium glutamate) may help reduce the frequency of episodes. In some, extending sleep by modifying the school start time past 9:00 am has reduced the frequency of episodes. Fleisher reported that consultation, education, and reassurance ("good doctor effect," perhaps relieving anxiety) alone reduced the frequency of episodes in 70% of patients without beginning prophylactic therapy [54].

Prophylactic Therapy

Prophylactic therapy is administered during the interictal period in order to prevent subsequent episodes. The NASPGHAN consensus recommendations for the initial treatment were for cyproheptadine for the younger (<5 years) and amitriptyline for the older children and adolescents (≥5 years) [2] (Table 38.6). Despite its pharmacokinetics, cyproheptadine (0.25–0.5 mg/kg) appears to be effective given as a single nighttime dose, rather than in two or three divided doses [65]. Amitriptyline causes side effects in 50%, the most common being morning sedation (like a hangover), and is stopped by the patient in 21% [66]. Beginning at a low dosage of 0.2–0.3 mg/kg at bedtime and titrating in 10 mg increments every week (unless too sedated) to the target dose of 1.0–1.5 mg/kg allows the child to adapt to the side effects. Switching to other tricyclic antidepressants (TCA) such as nortriptyline and desipramine may circumvent intolerable side effects. An EKG for QTc interval is recommended before starting amitriptyline and after reaching the target dose to monitor for prolonged QTc interval [67]. Impaired drug metabolism in those with CYP2D6 and CYP2C19 deficiency promotes TCA toxicity at low doses. Conversely, rapid metabolizers may require higher than usual TCA dosing guided by therapeutic blood levels [68]. Propranolol is

Table 38.6 Prophylactic pharmacotherapy

Antimigraine
Amitriptyline start and 0.2–0.3 mg/kg and advance to 1–1.5 mg/kg/day q.h.s.: Monitor EKG QTc interval prior to starting. First choice ≥5 years old. Side effects: Sedation, anticholinergic
Propranolol 0.25–1 mg/kg/day divided b.i.d or t.i.d: Monitor resting heart rate. SE: Hypotension, bradycardia, fatigue
Cyproheptadine 0.25–0.5 mg/kg/day divided b.i.d. or q.h.s.: First choice <5 years old. SE: Sedation, weight gain, anticholinergic
Alternatives: *Nortriptyline*, *desipramine*, *doxepin*
Anticonvulsants
Topiramate titrate to 1.5–2.0 mg/kg/day divided b.i.d.
Alternatives: *Gabapentin*, *levetiracetam*, *zonisamide*, *valproate*, *carbamazepine*
NK-1 receptor antagonist
Aprepitant 125 mg PO twice weekly (>60 kg); 80 mg (40–60 kg); 40 mg (<40 kg)
Mitochondrial supplements
L-*Carnitine* 50–100 mg/kg ≤ 2 g/day divided b.i.d. SE: Diarrhea, fishy body odor
Coenzyme Q_{10} 10 mg/kg/divided b.i.d. ≤600 mg/day
Riboflavin 10 mg/kg/day divided b.i.d. ≤400 mg/day

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second line and can be monitored for efficacy and toxicity by an expected drop in pulse rate of 15–20 beats per minute and drop below 55 bpm, respectively. A large prospective study reported high efficacy of the prokinetic erythromycin for 7 days in conjunction with propranolol compared to propranolol alone in preventing episodes (90% vs. 77%, respectively) [69]. Retrospective data on the NK-1 receptor antagonist aprepitant show promising results for this agent both prophylactically (twice weekly) and as an abortive agent if given during prodrome [64].

If standard prophylactic therapy fails, anticonvulsants and Ca^{2+}-channel antagonists have been used. Retrospective data document efficacy of topiramate (1–2 mg/kg/day) and phenobarbital (2–3 mg/kg), with topiramate also showing efficacy in migraine [70, 71]. Unfortunately, both these drugs are associated with side effects of cognitive dysfunction. Another retrospective study in children with CVS also found topiramate effective in 81% vs. 59% of those treated with propranolol [59]. One randomized trial in pediatric CVS (n = 70) found short-term efficacy of amitriptyline (1 mg/kg/d) in 68% compared to topiramate (1–2 mg/kg/d) in 39% of patients [72]. The tetracyclic antidepressant mirtazapine was found effective in a case series of children with CVS with comorbid anxiety and depression [73]. Mirtazapine may concomitantly facilitate sleep and improve appetite. Others have demonstrated efficacy of zonisamide and levetiracetam in a case series of adults with migraine headaches and cyclic vomiting syndrome [74]. Another group of agents includes Ca^{2+}-channel antagonists with the main side effect of hypotension.

The rationale for use of mitochondrial supplements as adjunctive prophylactic therapy in CVS is based upon evidence in migraines in adults, smaller studies in pediatric CVS as well as the findings of mitochondrial DNA mutations [27, 75–77]. In some children, the comorbid chronic fatigue and limited exercise stamina may respond to these supplements. The dose and duration of therapy for CVS has not been established.

Treatment by Subgroup

Treatment may be selected by clinical subgroup. Children with so-called migraine-related CVS with a positive family history or migraines themselves are much more likely to respond to antimigraine agents such as cyproheptadine, amitriptyline, and propranolol (79% vs. 36%) than those children without a migraine connection [50]. Post-menarcheal girls with catamenial CVS often respond to low-estrogen birth control pills (Loestrin, Lo/Ovral, Alesse, Seasonale) or Depo-Provera. Sato-variant CVS associated with intra-episode hypertension have been treated with tricyclic antidepressants in the US and valproic acid in Japan [27].

Abortive Therapy

Abortive therapy is administered during the prodrome or at the beginning of the vomiting episode in the hope of stopping it. The most specific abortive therapy are the antimigraine triptans. The nasal (sumatriptan or zolmitriptan) or subcutaneous (sumatriptan) forms appear more effective than oral forms that cannot effectively reach the duodenum due to repeated vomiting (Table 38.5) [2, 78–80]. The triptans appear to be either fully effective or not at all, and more effective if administered early during the prodrome and if the duration of episodes is less than 24 h (Li, unpublished data). They may also be effective in the absence of a migraine history [79].

In a few children, ondansetron given alone aborts episodes in progress. Although the oral forms may not reach to duodenum, ondansetron can be reformulated by individual pharmacies into a rectal suppository or topical forms. Although not established, we use the same dose as the oral form. The NK1 antagonist aprepitant is often highly effective if given orally during the prodrome or prior to the anticipated vomiting during calendar-timed CVS episodes. A retrospective study documented high efficacy of aprepitant 3-day regimen in children with CVS (Table 38.5) [64].

Approach to the Refractory or Disabled Patient

In tertiary and quaternary referral settings, a sizeable number of children with CVS do not respond to the therapies outlined above. There are several approaches we have used in such patients. The first is to reinvestigate the possibility of a specific precipitating factor(s) or previously missed organic etiology that can be addressed. In our experience the most common is a family- or school-related psychological stressor or intense anxiety in the child that leads to academic disability (school absenteeism) and requires a psychologist for diagnosis and treatment. If the child or adolescent cannot be progressively reintegrated into school, a referral to an intensive rehabilitation program may be required to restore functionality. A few have been diagnosed with intractable chronic sinusitis that fails to respond to standard antibiotic and decongestant therapy and requires otolaryngological intervention. Others progress from CVS to chronic daily nausea and vomiting during adolescence which has been termed ‘coalescent nausea’. In these, a high index of suspicion for progression to dysautonomia is warranted (see section on functional nausea). Continued escalation of therapy targeted towards CVS may be detrimental in these adolescents. Most important is to reconsider the diagnosis of CVS and whether there is a missed underlying organic cause. Identified surgical diagnoses found upon retesting in episodic vomiting

include volvulus from malrotation, acute hydronephrosis, and subtentorial tumors (e.g., Chiari malformation). For example, it may be prudent to obtain an abdominal ultrasound *during* the episode to determine if acute hydronephrosis was missed during a screening ultrasound when not in an episode.

If no specific trigger or cause can be identified and prophylactic monotherapy fails to reduce the frequency and severity of episodes, combination therapy has been anecdotally successful. Amitriptyline can be combined with propranolol or topiramate, in children refractory to single agents.

In children with prolonged episodes >5 days who continue to have severe and debilitating nausea and vomiting despite therapy, induced sleep may be the only rescue option. In fact, 72% of the children in our series report sleep as the harbinger of the end of the episode. We have observed that induced sleep will sometimes end the episode, seemingly as if the "vomiting center" in the brainstem has "shut down and rebooted" back to baseline in the off position. The consensus recommendation is either intravenous diphenhydramine, lorazepam, or chlorpromazine with diphenhydramine [2].

Chronic Nausea

Chronic, functional nausea is a more recently appreciated entity in children that was included in the 2016 pediatric Rome IV criteria [3]. It is defined as predominantly bothersome nausea that is generally not associated with meals or vomiting (Table 38.7). Functional nausea also has been recognized to occur in conjunction with other pain-predominant functional GI disorders [81, 82]. Multiple studies indicate a high number of multisystem comorbidities along with psychosocial disability [82–84]. This points to a multitude of underlying mechanisms, and to date, there are no physiologic studies or effective interventions for this complex patient population [84].

Table 38.7 Rome IV diagnostic criteria for functional nausea

Rome IV
1. Bothersome nausea as the predominant symptom, occurring ≥2/week, and generally not related to meals
2. Not consistently associated with vomiting
3. Symptoms not attributed to another medical condition

All criteria must be fulfilled for at least 2 months before diagnosis

Pathophysiology

The mechanisms of functional nausea are unknown but likely multifactorial, traversing foregut motor and sensory disturbances, autonomic imbalance, and CNS pathways. There is strong evidence that all emetic signals, whether from GI irritants, upper GI tract motor disturbances, circulating toxins, or stress, converge in the brainstem nucleus tractus solitarius (NTS) [85]. These pathways involve both sympathetic and parasympathetic afferents and transmit noxious signals from the GI tract to the NTS and area postrema [86]. However, nausea is more than a subemetic brainstem response. In motion-induced nausea, functional brain imaging demonstrates sustained activation of broad networks including interoceptive, limbic, somatosensory, and cognitive areas [87]. Several studies of motion-induced nausea show increased activation in anterior insula, also in association with a greater sympathetic response and autonomic modulation [88–90]. Some of the involved structures are associated with processing of stress, emotions, and fear conditioning. The bidirectional input between higher cortical networks and NTS may explain how nausea, stress, and emetic signals influence autonomic nervous system function. Altered autonomic balance found in children with functional nausea may explain many of the comorbid symptoms linking chronic nausea to abdominal pain, dysautonomia, CVS, and migraines as well as anxiety [44, 91].

Clinical Features

When nausea is the predominant symptom and occurs in isolation, the term primary functional nausea has been applied [92]. However, when nausea co-occurs with other functional GI disorders (in up to 50%) [81] and when it is not the predominant symptom, it has been termed secondary nausea [92]. Although the latter group has also been found to have significant social disability and lower school functioning, primary nausea tends to be the more severe and debilitating [81, 92]. This may be due to the added number of multisystem comorbid symptoms which may give clue to the underlying cause [82]. There are several emerging comorbid associations with primary functional nausea, in particular strong autonomic complaints and an association with CVS and migraines [82, 92]. Our prospective data suggest that symptoms such as dizziness (81%), sleep problems (73%), and impaired concentration (68%) are more common in adolescents with pri-

mary complaints of nausea than in those with secondary nausea [82]. In a retrospective study, primary nausea sufferers had a high prevalence of POTS (63%) and CVS (27%) [92].

Autonomic disorders are frequently associated with chronic, refractory nausea, particularly in adolescent females [91]. Descriptive studies of children with autonomic disorders such as POTS report a high prevalence of nausea and vomiting (50–70%) [93, 94]. One study correlated functional nausea with autonomic dysfunction based on tilt table testing and reduced heart rate variability [91].

Having a personal or family history of migraines appears to correlate with chronic nausea. Retrospective data document a high prevalence of migraines in children with chronic nausea (62%) and their families (71%) [92]. A study of adult migraine patients found that half had frequent nausea, which served as a predictor of progression to chronic migraines [95].

Children who complain of postprandial nausea, early satiety, fullness, and meal-related abdominal pain may have underlying gastric sensorimotor disturbances. As these patients may suffer from constant nausea that is not just postprandial, they may be difficult to distinguish clinically from those with delayed gastric emptying. Functional dyspepsia is a similar, pain-associated functional gastrointestinal disorder that may be difficult to separate from gastroparesis and functional nausea [3]. To complicate these overlaps, patients with dysautonomia often have symptoms suggestive of a upper gastrointestinal motility disturbances [96, 97]. Unfortunately, data are very limited, particularly in children, and confounded by inadequate tests to accurately assess stomach motor function [98].

Anxiety and stress also appear common in adolescents with chronic nausea. A large prospective study of children with functional abdominal pain found that those with concurrent nausea had significantly more somatic symptoms, depression, low self-esteem, disability, and stress [99]. Rigorous clinical studies are needed to more clearly define the complex associations between nausea, autonomic imbalance, anxiety, and other functional complaints.

The characterization of functional nausea in children is challenging for several reasons. There may a developmental progression of several interrelated disorders such as CVS, motion sickness, and functional nausea in children peak at ages 5, 9–10, and 12–14 years, respectively. As noted, autonomic dysfunction also typically peaks in adolescent years and may be under-recognized entity. Our study of the natural history of children with CVS shows that 40% develop symptoms and testing consistent with autonomic dysfunction in adolescence (Gonsalves,-Tejada, unpublished).

Evaluation

Given the multitude of disorders, drugs, and chronic medical conditions that may elicit nausea, careful consideration of underlying conditions is necessary. However, retrospective data suggest low yield of extensive diagnostic workup in a patient with typical symptoms of functional nausea and absence of red flags [92]. It is also important to recognize that nausea is a subjective symptom that overlaps with and may be misinterpreted as other functional complaints such as abdominal pain. Concurrent anxiety may also contribute to the severity of the nausea expression as children have differing behavioral coping mechanisms. The nausea experience may be difficult for younger children to articulate, separate, and quantify, which complicates the assessment.

Treatment

There are no clinical trials and much scarcity of directed therapy for functional nausea [100]. Empiric therapy with TCAs and cyproheptadine as used for related conditions such as functional dyspepsia and CVS or extrapolated from adult data is common practice [101, 102]. Other migraine agents and anticonvulsants such as topiramate or valproic acid may be effective in refractory cases. Mirtazapine at a nighttime dose of 7.5–15 mg (max 30 mg) may be effective based on adult data. Although literature is very limited in children, this agent also has some established efficacy for gastroparesis and cyclic vomiting syndrome [71, 103]. If gastroparesis is suspected, a short trial of a prokinetic such as erythromycin or metoclopramide may be warranted.

Antiemetics such as ondansetron, promethazine, or aprepitant can be tried at times of severe nausea, but are typically ineffective for the chronic nausea. A combination of antihistamine (dicyclomine) and B6 vitamin (pyridoxine) is approved in the U.S. for morning nausea of pregnancy. When administered at night, this combination can be effective in some adolescents with functional nausea and comorbid insomnia. If comorbid symptoms suggest autonomic dysfunction (e.g., POTS), high fluid intake, salt supplementation (4–8 g daily), and daily exercise should be advised. The addition of fludrocortisone at low doses (0.05–0.1 mg daily) may be effective for nausea in conjunction with orthostatic complaints [104]. Finally, alternative options such as iberogast, ginger, peppermint as well as acupuncture, auricular neurostimulation, and relaxation strategies may be useful supplements to pharmacotherapy.

Summary

CVS is a disabling disorder of recurrent, episodic emesis that often has substantial negative impact on the quality of life of patients and their families. Although CVS is now well-described in both children and adults, management is often challenging and associated with substantial health care utilization [20]. CVS shares many features with migraine disorders such as abdominal migraine in regard to closely

overlapping symptoms, pathophysiology, and management. Functional nausea is a poorly characterized entity sharing many similar features. Although the precise pathophysiology of these disorders remains undefined, there is growing evidence of involvement of aberrant signaling in HPA axis, higher cortical centers, endocannabinoid, and autonomic nervous systems. Unfortunately, there is lack of robust treatment trials and hence therapies remain empiric. Further research into pathophysiology, natural history, and treatment options is warranted.

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Aerophagia

39

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Aerophagia is a functional gastrointestinal disorder in children that can range from mere nuisance to a debilitating condition with significant impact on quality of life. The pathophysiology of this condition is incompletely understood and may involve both excessive air swallowing and decreased ability to belch. Aerophagia is a clinical diagnosis based on symptoms-based diagnostic criteria proposed by the Rome IV Child-Adolescent Committee. Phenotypic variability and symptom overlap with other organic diseases make the diagnosis and management of aerophagia in children a challenge. Treatment is based on severity of symptoms that range from education and reassurance in mild disease to behavioral therapy, psychotherapy, and benzodiazepines in severe disease.

Epidemiology

The worldwide prevalence of aerophagia ranges between 0.5% and 7.5% [1]. In a nationwide survey in the USA, the prevalence of functional gastrointestinal disorders (FGIDs) in children between 0 and 18 years of age was 23.1% of which 4.3% met Rome III criteria for aerophagia [2]. Similarly, a study done in the USA reported aerophagia in 2.4% out of 243 African American school-age children visiting a general pediatric clinic for annual school physicals [3]. Among children presenting for an initial evaluation at a gastroenterology clinic and who received a diagnosis of a FGID, aerophagia was found in 1.1% of children aged 4–9 years and 1.4% of 10–18 years old [4]. In aggregate, these data suggest that although aerophagia is not as common as other FGIDs such as functional constipation or irritable bowel syndrome, nevertheless it is likely to be encountered fairly frequently in busy pediatric gastroenterology practices.

In the past, this condition was thought to occur mostly in individuals with neurological disease, developmental delay, and gastric surgery, but several studies have reported aerophagia in children with normal cognition [5–7]. Furthermore, there is growing evidence that supports the association between aerophagia and psychosocial stressors. In a cross-sectional survey in eight randomly selected schools in four provinces in Sri Lanka, the investigators reported that a higher percentage of affected children were found to be exposed to stressful events when compared with controls [6]. In fewer than one-fifth of the children the symptoms were severe enough to interfere with daily activities. The same authors also reported that when compared to controls, adolescents with aerophagia had significantly more adverse life events including physical and emotional abuse [1]. These children had abnormal personality traits, increased somatization, and overall lower HRQoL scores [1]. Similarly, a recent cross-sectional survey in Indonesia revealed a significant association between aerophagia and psychosocial stressors such as death of a close family member and parental separation, divorce, or remarriage [8]. The high prevalence of anxiety and stress in children with aerophagia may explain why treatment with benzodiazepines may be helpful in some cases.

Pathophysiology

In normality, there is a certain amount of air that enters the stomach with each swallow [9]. Air is normally present throughout the lumen of the gut from the mouth to the rectum and swallowed air is the prevailing source of gastric gas, because the relative sterile nature of the stomach does not allow gas production from bacterial fermentation. The stomach protects itself from excessive distention either through belching (a form of "gas reflux") or by expelling air distally

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through the pylorus. When air swallowing is excessive, gas fills the gastrointestinal tract, resulting in excessive belching, abdominal distention, flatus, and abdominal pain, presumably as a consequence of luminal distention. The mechanism of "excessive" air entry into the intestinal tract is not entirely clear. The swallowing rate for normal adults is approximately 818 (range 524–1064) per 24 h with more frequent swallowing during the day and less at night [10]. Hwang et al. observed by laryngoscopy and fluoroscopy that "pathologic aerophagia" was the result of involuntary paroxysmal cricopharyngeal sphincter openings of the esophagus, like a myoclonus, and that these openings were followed by air swallowing [11]. However, the presence of increased frequency or volume of air swallowing in children with aerophagia has not been convincingly demonstrated yet. Certainly, there is a population of children who swallow excessively, whether volitionally or not, and in so doing increase intragastric and intra-intestinal air resulting in the symptoms of aerophagia. Silva et al. observed that gum chewing after yogurt ingestion increased air swallowing in patients with belching when compared to the control group [12].

Some patients with aerophagia also have excessive belching. Belching occurs through the same mechanism as gastroesophageal reflux, namely transient lower esophageal sphincter relaxation. When excessive air is ingested, there is distention of the gastric fundus, a known trigger for the relaxation of the lower esophageal sphincter, causing increased frequency of air expulsion [13, 14]. In some patients, the belching may not represent expelled intragastric air, but rather elimination of air that accumulates in the esophagus above the stomach ("supragastric belching") [15, 16]. The latter group of patients, who present with symptoms limited to frequent eructation, does not truly belong to the category of aerophagia even though they present with a similar phenotype [17].

Finally, there is a subgroup of children who seem unable to belch and in those patients symptoms of aerophagia may actually be related to inability to expel even a physiologic amount of swallowed air. This is a clinical scenario akin to patients who develop symptoms of "gas bloat" after a fundoplication, which has impaired their ability to belch and/or vomit [18].

Diagnosis

There is no single diagnostic test that can be used to conclusively diagnose aerophagia. A detailed history and physical examination in conjunction with symptom-based diagnostic criteria are the mainstay of diagnosis. Extensive testing or diagnostic workup are not necessary to establish the diagnosis of aerophagia. Reported symptoms include abdominal distention, pain, bloating, belching, and excessive passage of flatus [5, 19]. The diagnosis may be easy in the presence of the typical signs and symptoms of air swallowing which may be visible and often audible, accompanied by excessive belching and flatus. Patients commonly report abdominal distention and bloating. The abdomen is typically flat in the morning and becomes progressively more distended throughout the day. The abdominal distension then improves during the night by absorption of gas and the passage of flatus. In infants, there may be a history of nursing from an empty bottle, or prolonged sucking on a pacifier. In older children, large amounts of air can be swallowed by drinking excessive amounts of carbonated beverages. The Rome IV Child-Adolescent Committee established symptoms-based diagnostic criteria for aerophagia in children [20] (Table 39.1).

The differential diagnosis of aerophagia is fairly broad and involves other entities which present with abdominal distension. When excessive air swallowing is either not recognized by the medical provider or denied by the parents, the child may be suspected of having gastroparesis or other more generalized motility disorders, such as pediatric intestinal pseudo-obstruction. These are conditions which may also present with increasing amount of abdominal distension throughout the day. Bacterial overgrowth, malabsorption (particularly celiac disease and mucosal disaccharidases deficiency), tracheoesophageal fistula, and constipation are other fairly common etiologies of abdominal distension and excessive flatus in children. As patients with aerophagia are usually otherwise healthy with normal growth and development, extensive testing to rule out several other diseases is rarely necessary.

When radiological studies are obtained (Fig. 39.1a, b), there is usually evidence of a dilated stomach and small and large bowel full of air in the absence of air fluid levels and other signs of bowel obstruction. At times, the radiographic findings may mimic ileus or a mechanical obstruction, thus unnecessary surgical intervention may be considered but should be avoided [19]. The excessive amount of intraluminal gas is especially obvious when the studies are obtained in the evening, at the apex of the abdominal distension. The esophageal "air sign," defined as an abnormal air shadow on the proximal esophagus adjacent to the trachea on a full-

Table 39.1 Rome IV diagnostic criteria for aerophagia

Diagnostic criteria[a] must include all of the following:
1. Excessive air swallowing
2. Abdominal distention due to intraluminal air which increases during the day
3. Repetitive belching and/or increased flatus
4. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

[a]Criteria fulfilled for at least 2 months prior to diagnosis

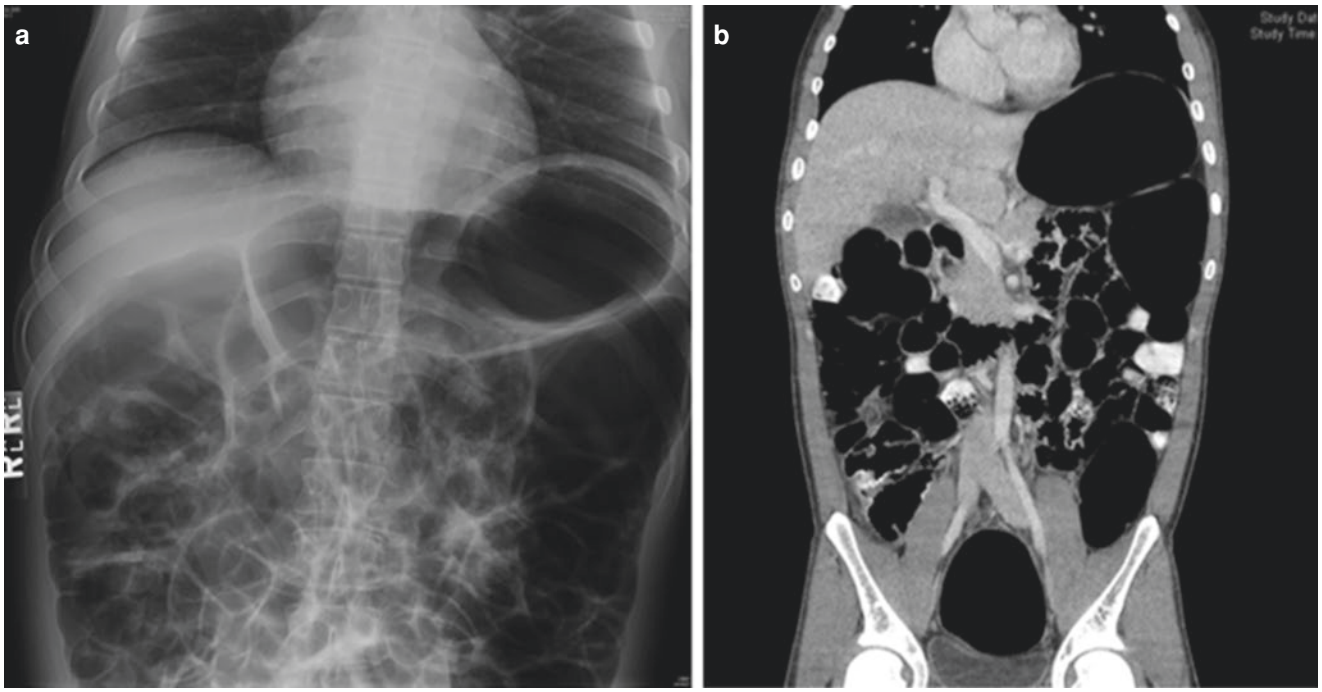

Fig. 39.1 Plain radiograph (**a**) and computerized axial tomography (**b**) of the abdomen showing gaseous distension of the stomach, small and large bowel in two children with aerophagia

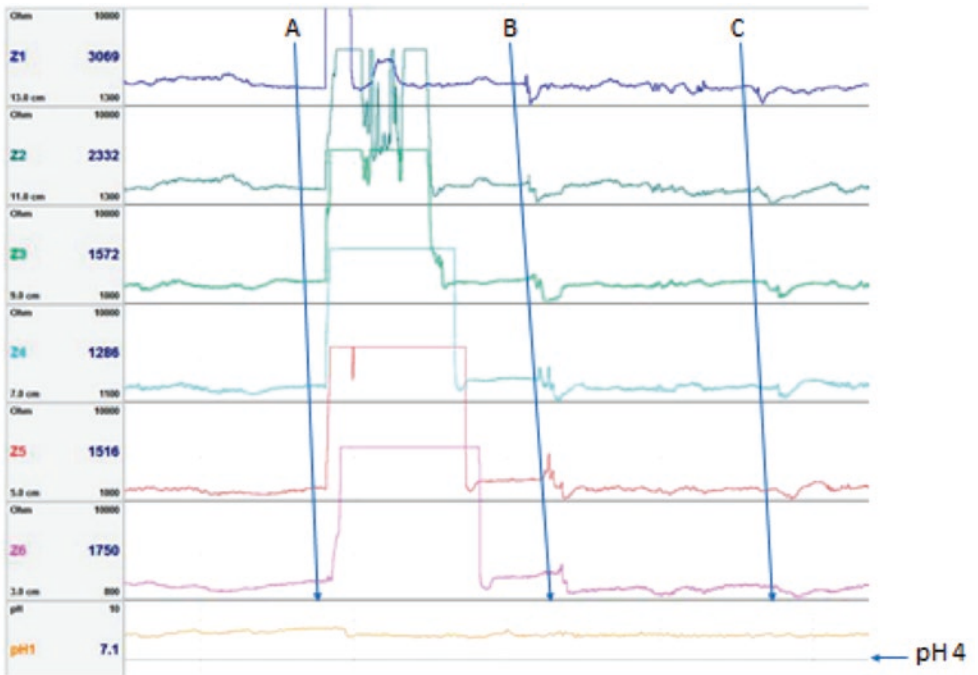

Fig. 39.2 The figure depicts three different types of swallows: (**a**) air swallow, (**b**) mixed swallow, (**c**) wet swallow

inflated chest radiograph, has been reported in the majority of children with aerophagia in one study [21], but its specificity for this condition has not been evaluated. Multichannel intraesophageal impedance is able to differentiate air from wet swallows (Fig. 39.2) because air conducts current poorly and thus it has a high impedance, leading to a dramatic increase in baseline. Impedance can be used to diagnose aerophagia by detecting an increased frequency of air swallows and may also be used to diagnose gastric and supragastric belching in children [22, 23].

Treatment

The management of aerophagia needs to be tailored based on the severity of symptoms generated. Although generally felt to be a benign condition, aerophagia has been associated with development of gastric necrosis and perforation [24], colonic volvulus [25], and colonic perforation [26]. Most commonly, children with aerophagia are brought to the attention of care providers with complaints of noisy swallowing, excessive belching, or abdominal distention. Once a diagnosis of aerophagia has been made, education about what generates the symptoms and effective reassurance that no serious underlying disease is present are the most often employed measures and may represent the most effective intervention [5]. Understanding the mechanisms underlying the excessive air swallows may be very reassuring for the parents and the child. Elimination of gum chewing and carbonated beverages and avoidance of drinking from a straw can be helpful [27]. Smoking cessation is recommended for adolescents and young adults who smoke as it increases air swallowing [19]. When the air swallowing is visible and/or audible during the clinic visit, the clinician can help the child and the caretakers become aware of air swallows so that the behavior is minimized. Keeping the mouth wide open after completion of a meal may minimize air swallow, as it is almost impossible to swallow with an open mouth. When patients with excessive belching are not aware that they are being observed or when they are distracted, the incidence of belching is significantly reduced [28]. These findings underline the importance of psychological factors and provide rationale for behavioral therapy. Patients may also work with a speech therapist to specifically decrease the behavior of excessive air swallowing [19]. Hypnosis has been suggested as a mode of therapy in a case report [29]. When primary psychological disorders, especially an anxiety disorder, are present, they should be treated [28]. Different behavioral and mechanical techniques, incorporating biofeedback, have been tried to promote self-awareness of swallowing and limit its frequency, although only in small trials and rarely with children, [30, 31]. Pharmacologic therapy has a limited role in the treatment of children with aerophagia due to the lack of thorough understanding of the pathophysiology of this condition and the potential side effects of the medications that have been tried. Benzodiazepines have been employed on the basis that the emotional state may impact swallowing rates and due to their efficacy in the treatment of myoclonus. There have been two reports in which clonazepam was shown to be effective in children with aerophagia with and without mental retardation [11, 32]. Baclofen is a muscle relaxant used to treat spasticity and movement disorders. It has been shown to improve symptoms of rumination and supragastric belching [33] and may have a role in the treatment of aerophagia. In the most severe cases, nasogastric decompression, a venting gastrostomy [34], or even laparoscopic gastropexy [35], esophagogastric separation, and abdominal esophagostomy via jejunal interposition may be justified [36].

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Rumination Syndrome

40

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Rumination syndrome, classified as effortless regurgitation of ingested food or fluids shortly after intake, often occurs in childhood or adolescence. It is a functional gastrointestinal disorder that has existed for a long time but remains largely underdiagnosed and misunderstood. It is differentiated from other types of functional vomiting based on the timing of occurrence and presentation of the vomiting. It is important to note that there is also an infantile version of rumination that occurs mostly in those with neurocognitive and developmental disorders (e.g., intellectual disability and autism spectrum disorder) which is separate from rumination syndrome that we discuss here that occurs typically after infancy and in those who are neurodevelopmentally typical.

There is much confusion over rumination syndrome in regard to it being a medical versus a psychological diagnosis. Rumination is often misrepresented to families as an eating disorder, being caused by anxiety, or needing psychiatric care to treat. This typically leads to families being more resistant to the diagnosis when they do not feel their or their child's symptoms fit that particular description. Indeed, rumination is a neurophysical issue that does require behavioral treatment to address, but not behavioral in the sense that it requires treatment of anxiety or an eating disorder. Rather, the behavioral component is meant to target the brain-gut disconnection that occurs in rumination syndrome. We discuss both the underlying physiological mechanisms and behavioral treatment of rumination syndrome at length in this chapter.

Further compounding the misdiagnosis and confusion, there is not necessarily clear testing that can always "prove" a diagnosis of rumination syndrome. Many patients with rumination undergo extensive and costly medical testing which returns as normal, yet they still have gastrointestinal symptoms. It is common for patients to have symptoms for prolonged periods of time before even hearing of a possible rumination diagnosis. This is perhaps also related to lack of awareness of the diagnosis or even discomfort in providing a label of rumination syndrome by some providers.

Our aim in this chapter is to explain rumination syndrome, including the epidemiology, pathophysiology of the illness, in efforts to increase understanding and dispel myths associated with rumination. We then review the process of diagnosis and the role of testing if and when necessary. Finally, we review both medical and behavioral treatments of rumination syndrome.

Epidemiology

Rumination syndrome has historically been considered as having a low prevalence and being more common in girls [1]. The low prevalence may, however, be due to the insufficient recognition by health care providers. This insufficient recognition of rumination syndrome as a diagnostic entity continues to undermine efforts to understand its prevalence. Further complicating estimates, the symptoms of rumination syndrome overlap with symptoms of more readily recognized conditions such as motility disorders or eating disorders [2–6]. A school study in Sri Lanka used a self-administered questionnaire given to 2163 children between the age of 10 and 16 years and found symptoms consistent with rumination syndrome in 5% of individuals, with equal prevalence between boys and girls [7]. It is unclear how many of these children had true rumination syndrome versus GERD, a much more common condition at this age.

Patients with rumination syndrome often have a long journey to a diagnosis. They end up visiting multiple providers and undergoing numerous evaluation over a course of several years [3, 8]. The multiple medical evaluations and diagnostic tests are distressing, costly, and may uncover

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incidental findings making the final diagnosis of rumination syndrome even more difficult to accept [9]. In one sample of adolescents, onset of rumination symptoms occurred around age 13 years, with the diagnosis of rumination syndrome ultimately given approximately 2 years later [3].

The onset of rumination symptoms is often preceded by physical or psychological stressors, and a substantial portion of these patients continue to have associated physical illnesses or concomitant psychological disorders [3, 8].

Pathophysiology

The reason for onset of rumination is not always clear and also remains somewhat misunderstood. There are many reports suggesting rumination syndrome is caused by anxiety or significant traumatic events. While this can be true, we have learned that this is not the case for a majority of patients who develop rumination syndrome. In many cases, rumination syndrome seems to be brought on by some illness, whether viral or physical, that leads to sensitivity of the nerves within the enteric nervous system and initiates the process of rumination. The initial illness often resolves and rumination symptoms begin (or remain if vomiting was part of the initial illness) and are maintained over time as a physiologically programmed response to intake of food or fluids. Such illnesses can be gastrointestinal viruses, but can also include other illnesses independent of the GI tract more specifically (e.g., upper respiratory illness, mononucleousis). The exact mechanism behind this process remains unknown. In many instances of rumination, there is no clear inciting trigger for onset of illness.

Gastric motor and sensory abnormalities have been reported in rumination syndrome. Barostat and manometric studies have demonstrated gastric hypersensitivity with more frequent episodes of lower esophageal sphincter relaxation in response to gastric distension. Some individuals have impaired postprandial gastric accommodation [10]. A mild degree of gastroparesis may be found in approximately 40% of adolescents with rumination, although emptying studies are difficult to interpret in individuals who continuously regurgitate during the test [3]. It is also possible for patients to present with both rumination and gastroparesis following an infectious illness. These patients may clinically present with emesis soon after oral intake and hours post-consumption. A poorly accommodating fundus and an impaired antral pump may lead to postprandial distress that is relieved by expulsion of the food just ingested. As such, the behavior of regurgitating gastric contents serves to relieve epigastric discomfort and becomes a conditioned response to the ingestion of food or fluid.

Upon ingestion of food (or even in anticipation of ingestion of food), a sequence of behaviors has been generated, including contraction of the abdominal wall, opening of the lower and upper esophageal sphincter, and subsequent expulsion of food [11]. Rumination based on high-resolution esophageal manometry is classified as primary and secondary subtypes. In the primary subtype, the R wave is followed by bolus movement into the esophagus and in the secondary subtype the onset of bolus movement into the esophagus occurs prior to the R wave. Supragastric belch, another phenomenon, is defined by the presence of an upward movement of the diaphragm simultaneously creating a subatmospheric pressure in the esophageal body and relaxation of the UES. Primary rumination is more common in children and it is further categorized into three types based on the timing of LES relaxation in relationship to the timing of the R wave. It is hoped that the ability to differentiate one type from the other will further define our therapeutic approaches [12]. Rumination consisting of a supragastric belch, is often associated with air swallowing, immediately followed by a rumination event [13]. It is unclear yet whether these different mechanisms may direct different treatment strategies or if they are associated with different prognosis.

Clinical Presentation

Rumination syndrome is rather distinct from other types of vomiting, given the manner and timing in which it occurs. Rumination occurs during or shortly after oral intake and appears in an effortless manner. There is typically minimal gagging, heaving, or retching associated with the vomiting. It is typically small volumes at a time, occurring numerous times in a row. It is often controllable, such that an individual can hold the regurgitant in their mouth and either re-swallow or maintain until they get to a place where they can spit it out. Some patients with rumination will automatically re-swallow what comes up, while others choose to spit out regurgitant. Rumination is one of the only types of vomiting that occurs directly in concert with oral intake and appears in an effortless fashion, making the pattern of vomiting easier to distinguish from other gastrointestinal vomiting (e.g., functional vomiting, cyclical vomiting, gastroparesis).

It is also fairly common for patients to have more frequent belching along with rumination, as well as globus sensation from repeated regurgitation and re-swallowing.

Although rumination has a clear pattern that is easily distinguished from other types of vomiting, it must be acknowledged that there are differing presentations of rumination. For example, some patients will have more forceful vomiting which is often related to taking in larger quantities of food or drink at a time at a rather fast pace. Other patients will report that their regurgitation does not begin until an hour or so after intake, which is often triggered by drinking something

much later after a meal that results in regurgitation of the liquid mixed with remaining food from the previous meal.

Further, there are some atypical presentations of rumination syndrome. Some patients have a cyclical variation of rumination in which they will have effortless regurgitation of food shortly after meals for a few days to a few weeks at a time with symptoms remitting on their own and returning at later points. This is not the same as cyclic vomiting, given the pattern and description of the vomiting itself. There are also known cases of patients having significant coughing or hiccupping that is brought on by eating and seems to trigger subsequent regurgitation. These cases respond to the same medical and behavioral treatment with rumination that fits the more classical presentation.

Diagnosis

The diagnosis of rumination syndrome is clinical in nature [6] and should include gathering history and progression of symptoms (Table 40.1). Getting patients to describe their vomiting, including what is it like, when does it occur, and how often it occurs can easily guide a rumination diagnosis.

In addition to clinical history, watching a patient eat or drink to observe the subsequent process of rumination can be very helpful in confirming a diagnosis of rumination syndrome. Although the vomiting will not look identical in all patients, the general effortless nature of regurgitation that occurs shortly after intake of food or fluids is rather unmistakable from other types of vomiting. Patients and families often find relief in providers observing a patient's pattern of vomiting and using this to confirm a rumination diagnosis.

Antroduodenal (AD) and high-resolution esophageal manometries are not always necessary to make the diagnosis, but either one of them can play an important role in confirming the diagnosis and convincing families or patients who are not yet confident of the diagnosis of rumination syndrome. Manometry may also be used to rule out the presence of an underlying motility disorder, a common fear among families of patients with this disorder. In patients with rumination syndrome, antroduodenal manometry shows essentially normal fasting and postprandial motor patterns [6, 14]. Esophageal manometry is also expected to show normal upper esophageal sphincter, lower esophageal sphincter, and esophageal body peristalsis with swallows. The characteristic manometric abnormality captured on manometry studies is a synchronous increase in pressure across both gastric and duodenal recording sites when the rumination occurs. These simultaneous pressurizations are called R waves and are thought to represent the effect of an intragastric or intra-abdominal pressure increase generated by the contraction of the skeletal abdominal muscles. High-resolution esophageal manometry has some advantages over AD manometry. These include catheter placement without sedation, testing time of less than an hour compared to more than 6 h for an AD, differentiating between the different subtypes, presence of a supragastric belching, and cost (Fig. 40.1). AD manometry is preferred if there are concerns of gastrointestinal dysmotility. Interestingly, in a laboratory setting with constant attention being paid to their symptoms, some adolescents with rumination are able to eat the test meal during the manometry study with minimal or no symptoms (Fig. 40.2).

Impedance-manometry monitoring allows distinction between rumination from GERD and supragastric belching. During rumination, esophageal liquid retrograde flow is driven by an early rise in intragastric pressure preceding the peak pressure observed during straining [15]. It has been suggested that the diagnosis of rumination syndrome can be made when reflux events extending to the proximal esophagus are associated with an abdominal pressure increase of >30 mmHg, because such increase is usually not seen in patients with GERD. The impedance study will also confirm the characteristic absence of nighttime reflux events in patients with rumination syndrome.

Regardless of the role of testing in making a diagnosis, when providing a diagnosis of rumination syndrome to a patient and family, it is very important to be confident in providing this diagnosis. Suggesting that rumination "may be what is going on" will not inspire confidence in the diagnosis and often leads patients to be questioning of diagnostic accuracy. Instead, saying you are confident a patient has rumination syndrome, explaining how their symptoms fit with the diagnostic criteria and emphasizing the need for behavioral treatment to address symptoms, allows patients to fully agree with the diagnosis and be open to and active participants in treatment.

Table 40.1 Rome IV criteria for adolescent rumination syndrome

Diagnostic criteria[a] must include all of the following
1. Repeated regurgitation and rechewing or expulsion of food that:
(a) Begins soon after ingestion of a meal
(b) Does not occur during sleep
2. Not preceded by retching
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition. An eating disorder must be ruled out

For more information, see Benninga et al.: http://www.ncbi.nlm.nih.gov/pubmed/27144631 Or Hyams et al.: http://www.ncbi.nlm.nih.gov/pubmed/27144632

[a] Criteria fulfilled for at least 2 months prior to diagnosis

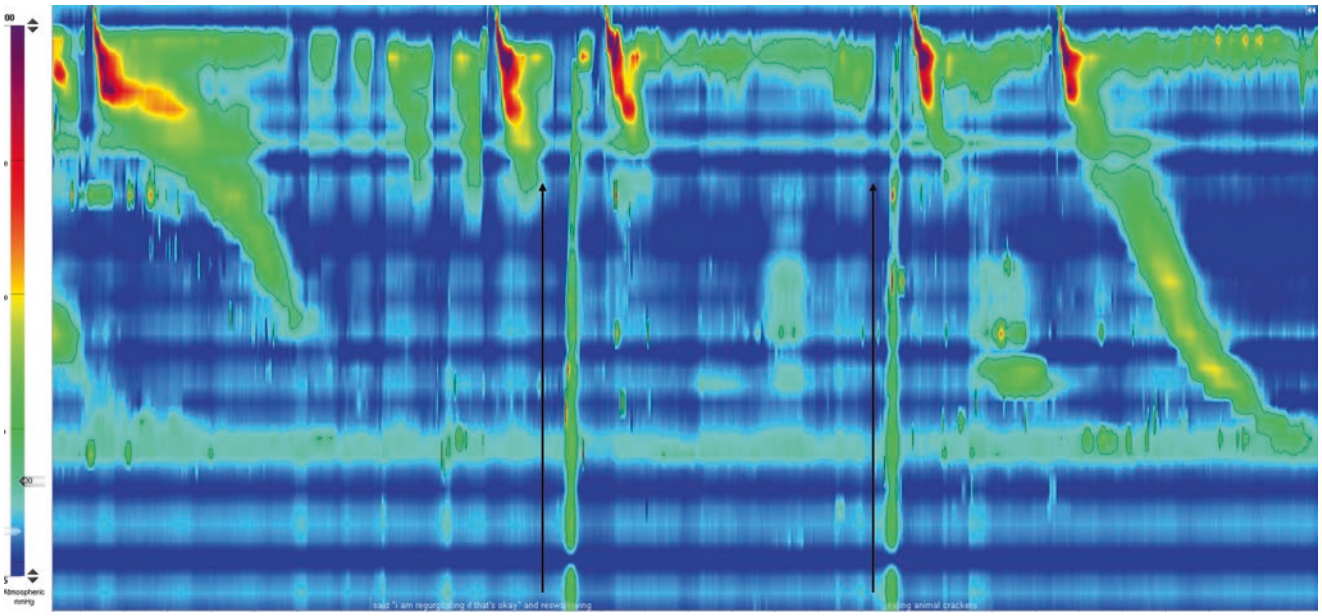

Fig. 40.1 An example of a high-resolution esophageal manometry tracing from a male patient with rumination syndrome. The simultaneous increase in pressure as indicated with the arrows is consistent with R waves that are pathognomonic for rumination syndrome

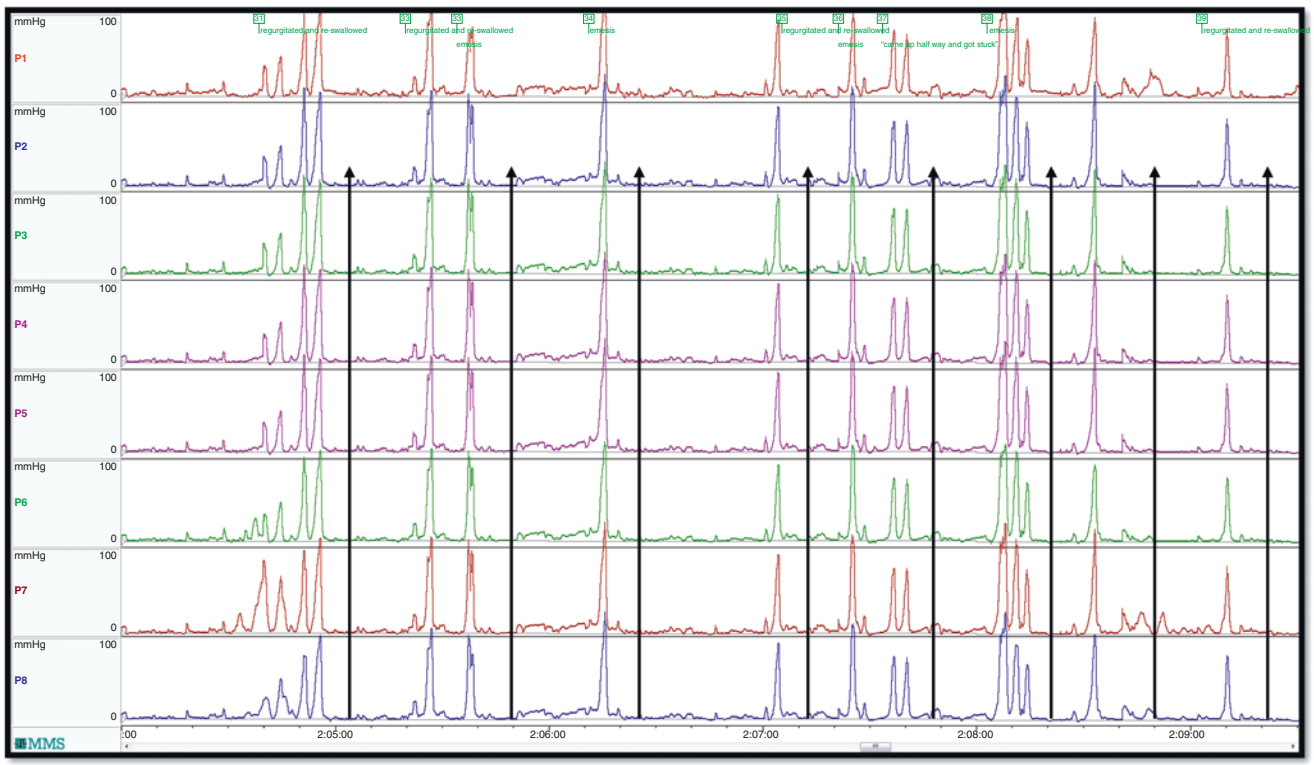

Fig. 40.2 An example of an antroduodenal manometry tracing from a female patient with rumination syndrome. The arrows mark simultaneous increase in pressure picked up by all recording sites in the esophagus and stomach. These simultaneous increase in pressure is consistent with R waves and happens at the same time of effortless regurgitations of gastric content

Medical Treatment of Rumination

There is one medication, baclofen, that has been shown to be effective in reducing rumination regurgitation episodes in adults [16]. Baclofen is an agonist of the γ-aminobutyric acid B receptor, which decreases transient lower esophageal sphincter relaxations, increases sphincter pressure, and decreases swallowing rate. In our retrospective review of children under 18, nearly half experienced improvement with decreased rumination episodes after baclofen treatment [17].

Many patients with rumination have comorbid medical symptoms or conditions. It is common for those with rumination to have symptoms of disorders of gut-brain interactions such as abdominal pain, nausea, constipation, bloating, fatigue, and dizziness, along with other medical illnesses. It is important that these symptoms are medically managed to optimize behavioral treatment for rumination. For example, patients with severe nausea, particularly that increases with oral intake, often benefit from antinausea medications, allowing ease of eating during rumination meal practices. Patients with significant constipation should be started on medications guaranting effective and regular stool evacuation, as constipation is known to worsen upper GI symptoms, including regurgitation [18].

In addition to use of medication for comorbid symptoms, patients with rumination may lose a significant amount of weight and become malnourished and/or dehydrated [19]. These patients may require inpatient or outpatient care to address these concerns including initiation of enteral feeding to stabilize their weight and hydration. Naso-jejunal or gastro-jejunal feeding tubes are preferred, as feeding into the stomach using a naso-gastric or gastric tubes often results in rumination of the formula. In the rare case in which jejunal feeding is not tolerated, parenteral nutrition may be required. Patients may also develop a superior mesenteric artery (SMA) syndrome due to significant weight loss complicating their course. It is therefore paramount that both the patient's weight and hydration are maintained prior to engaging in behavioral therapy.

Behavioral Treatment of Rumination

Although medical intervention is often helpful and/or necessary in managing rumination, rumination syndrome treatment is largely behavioral in that patients are taught a number of behavioral skills or strategies to counteract the physical process of rumination. Although the body has developed an unconscious physiological process that maintains rumination over time, the conscious use of behaviors that are incompatible with the physical nature of rumination (i.e., abdominal muscle tightening and pressure, stomach contractions, and expulsion of gastric contents) is what works best to learn to control and in some cases reduce or even eliminate rumination symptoms. Given that the approach is to use behavioral responses to inhibit the process of rumination, the treatment itself is very similar to habit reversal therapy used for tic disorders [11, 20–23].

Education and Reassurance

Providing patients with a clear diagnosis and explanation of the physiological nature of rumination syndrome is the first step to treatment. Given challenges with descriptions of different types of rumination and/or causes of rumination (as noted earlier in this chapter), many patients and families are resistant to the diagnosis of rumination syndrome until they are provided with adequate education around diagnosis and physical mechanisms that maintain the illness. Patients and families must agree with the diagnosis to fully invest in the treatment.

It is often the case that learning the diagnosis alone can provide significant reassurance to patients and families [1, 13, 24]. It is imperative that this discussion be done with confidence in the diagnosis and emphasis on the point that no further medical workup is needed to confirm the diagnosis of rumination. With this discussion, families are finally able to recognize that there is no structural or organic cause for their symptoms, while still providing an explanation for their symptoms, and provides clear direction for treatment.

When providing the diagnosis of rumination syndrome, education must include a description of the physiological process of rumination within the body. The description generally includes information to patients that rumination is driven by hypersensitivity of the nerves in the stomach that is triggered with intake of food and fluids, causing the abdominal wall muscles to contract and apply pressure to the stomach with eventual contraction of the stomach and subsequent regurgitation of gastric contents [25]. Without the physiological explanation for how rumination occurs, patients will struggle to understand how strategies such as re-swallowing regurgitation and diaphragmatic breathing can help to address their symptoms. This then allows patients to become accepting of and mentally prepared and motivated for behavioral treatment of rumination syndrome.

Education also often needs to include discussion around other comorbid symptoms. This includes other physical symptoms that are both GI (e.g., nausea, abdominal pain, constipation) and non-GI related (e.g., dizziness, headaches, fatigue) that are often present in those with rumination syndrome, but not explained fully by that diagnosis. It also includes discussion on psychological comorbidities, such as anxiety, depression, or disordered eating.

Behavioral Strategies

The necessary behavioral steps for managing rumination include: using diaphragmatic breathing to prevent regurgitation, re-swallowing regurgitation, slowing pace of eating, and eating smaller amounts at a time. Each of these components will be discussed below.

Diaphragmatic Breathing

Diaphragmatic breathing is arguably the most well-known behavioral strategy associated with rumination treatment [11, 13]. The mechanism of action behind this technique is that diaphragmatic breathing effectively stretches out and relaxes the abdominal wall muscles, relieving epigastric pressure, and thereby preventing or reducing the likelihood of contraction of the stomach and transient relaxation of the lower esophageal sphincter. Without the pressure of abdominal wall muscles on the stomach, contractions do not occur in such a manner to lead to gastric contents leaving the stomach (e.g., regurgitation). In addition, during diaphragmatic breathing, the diaphragm is raised above the stomach and applies slight pressure in the area of the GE junction, resulting in decreased transient relaxation of the lower esophageal sphincter and further preventing contents from leaving the stomach. As such, diaphragmatic breathing is an action that is incompatible with or that prevents rumination from occurring when done correctly and at the proper times [22, 23, 26].

It is important to explain to patients the mechanism of action behind diaphragmatic breathing for them to understand and buy-in to use the strategy. Explaining to patients that rumination occurs due to abdominal muscles tightening and causing the stomach to contract allows them to understand how diaphragmatic breathing effectively relaxes or prevents tightening of abdominal wall muscles which prevents stomach contractions. Patients who understand this process are much more likely to fully engage in use of diaphragmatic breathing when instructed.

Patients are instructed to engage in 5–10 diaphragmatic breaths at a slow but comfortable pace immediately before and after eating. These points of breathing are meant to relax any preexisting muscle tension or eliminate muscle tension that may already be building while the individual is looking at and preparing to eat food. Patients are also instructed to use diaphragmatic breathing any time they feel epigastric or chest pressure, increased nausea or abdominal pain, or anything they identify as a warning sign that regurgitation is soon to occur. In these instances, patients should notice a decrease in the pressure or warning sign as they use diaphragmatic breathing to prevent regurgitation. Finally, any time a patient is re-swallowing their regurgitation, that must be followed by diaphragmatic breathing to prevent recurrent regurgitation.

Re-swallowing Regurgitation

Some patients automatically re-swallow their regurgitation while others always spit out what comes up. An integral part of rumination therapy is to get patients to re-swallow what comes up. This helps the nerves of the stomach to return to interpreting food and fluids as needing to stay in the stomach and be digested, rather than being expelled. It also helps maintain oral nutrition and hydration, thereby preventing need for enteral feeding.

As noted above, many patients are able to feel increased abdominal pressure prior to regurgitation or can at least feel regurgitation as it moves up the esophagus [8, 25, 26]. In these cases, patients are encouraged to swallow their saliva with these sensations, as this will effectively return regurgitation to the stomach prior to it entering their mouth. However, patients are still encouraged to re-swallow regurgitation even if it has entered their mouth. Each of these acts of re-swallowing is to be immediately followed by diaphragmatic breathing to relax abdominal wall muscles and prevent further regurgitation. Without diaphragmatic breathing after re-swallowing, gastric contents tend to continue to come up in a serial fashion with subsequent regurgitations at times being larger volume and more forceful, thus harder to control and re-swallow.

Many patients learn quickly how to re-swallow regurgitation prior to it entering their mouth or swallow saliva to prevent regurgitation even into the esophagus. For many patients, once they begin consistently re-swallowing their regurgitation, the frequency of regurgitation will decrease overall.

Food Amount and Selection

In order for patients to be successful with re-swallowing regurgitation and diaphragmatic breathing to control their rumination, they must start by eating and drinking very small amounts at a time [27]. The exact amount varies from patient to patient based on what they seem to be able to tolerate. It is recommended to start with single bites at a time, even single pieces of food at a time (e.g., single cheerio). This very small amount allows patients to practice each skill in a step-wise fashion with an amount small enough that the majority could easily tolerate. Starting small and gradually increasing amounts as tolerated helps patients to build confidence in their ability to keep food down and manage their rumination, while also helping to reset the neuromuscular process of rumination.

At first, it can also be beneficial to separate liquids and solids. Many patients find that one or the other tends to be harder to keep down, but the combination of both can be particularly problematic. As such, many patients benefit from eating solid foods with no or only small volumes of fluid (i.e., 1–2 oz) with solids. Liquids are encouraged to be consumed slowly between meals. This approach prevents gastric overload of both solids and liquids and continues to allow easier re-swallowing of what comes up.

Many patients with rumination will also identify certain foods that come up much more frequently than others. While certain foods tend to be mentioned more than others, such as acidic or spicy foods, raw fruits and vegetables, and ice cream, these items tend to be very unpredictable and individual-specific. It is encouraged that during initial phases of treatment, patients avoid any foods that are more challenging for them to keep down to make learning the skill and managing rumination easier. Once they have mastered control of their rumination, they can gradually work to re-integrate more challenging foods into their diets starting with small amounts at a time and gradually increasing as tolerated.

For patients with feeding tubes during behavioral treatment, enteral feedings can be reduced as they are able to keep down oral food and fluids [19]. Some patients benefit from a reduction of formula at the onset of treatment to promote appetite.

In addition to food selection and amount, it is important for patients to learn to take their time with eating. Patients are encouraged to aim for 15–20 min to complete a meal, typically slightly less for smaller snacks. When meals are consumed very quickly, particularly with large bites and minimal chewing, regurgitation tends to worsen as a result.

Distraction

Although not a primary mechanism of action in rumination treatment, distraction during and after meals can be helpful for some patients. Those who tend to worry or overthink about if or when regurgitation will occur tend to struggle with increased regurgitation as a result of stress-induced muscle tension. Distraction can come in many forms, but must not interfere with eating and must not be so distracting that patients fail to engage in the behavioral strategies necessary to control rumination. Suggested strategies for distraction during meals often include simple meal time conversation, question and answer trivia, riddles, or other oral games appropriate for use at the table. After meals, any activity that is not overly physical such that it would induce rumination (i.e., strenuous physical activity, motions that result in abdominal compression) or overly distracting to prevent skill use for managing regurgitation is encouraged.

Comorbid Conditions

Many patients with rumination have comorbid condition(s) that need to be treated either prior to engaging in or simultaneous with rumination treatment. As mentioned earlier in medical treatment of rumination, it is common for patients with rumination to have other GI symptoms or functional GI disorders, or even other medical conditions (e.g., chronic headache, POTS). Much of the time, such other symptoms or conditions need to be adequately managed prior to engaging in rumination treatment. For example, if a patient has significant abdominal pain that prevents them from eating, it is unlikely they will be successful in rumination treatment that requires frequent oral intake unless their pain is better managed to allow them to eat orally.

Psychologically, it is common to see anxiety, depression, general stressors, and decreased quality of life associated with rumination syndrome [3, 8, 28]. Anxiety can be general and/or specific to rumination, with patients developing fear of vomiting or fear of eating due to not wanting to vomit. These conditions are rarely the cause of rumination, but often do exacerbate symptoms, making it necessary to have such conditions controlled well enough for patients to fully participate in rumination treatment [8].

There is also a small subset of patients with rumination who have comorbid eating disorders, such as anorexia and bulimia. If a patient has anorexia, they are unlikely to be compliant with frequent meals and the requirement of re-swallowing regurgitation. For a patient who has bulimia and rumination, self-induced vomiting that is ongoing while trying to address involuntary regurgitation prevents the behavioral treatment from working as the stomach is constantly provided with mixed messages. Binge eating disorder would also interfere with rumination treatment given the focus on small, controlled meals to prevent overloading the stomach which causes or exacerbates regurgitation. As such, comorbid eating disorders must be addressed before a patient can engage in rumination treatment.

Also of note, patients must be fully in agreement with a rumination diagnosis and motivated for treatment prior to participation. Patients who are not willing to engage in any of the strategies noted above on a consistent basis are not likely to do well in treatment and should return to treatment at a later time when they are fully committed to using strategies as instructed on a regular basis to manage their rumination.

Outcomes

Patients and families often desire outcomes of rumination treatment to be complete resolution of symptoms. While this is possible for some patients, it is not always the case. It is

important to emphasize to patients that the goal is to help them learn how to control their rumination to learn how to eat and keep their food down. For many, this does come along with significant decrease in frequency of regurgitation if not complete resolution of symptoms. There is no scientific or data-driven means of predicting which patients may have full remission versus those who simply learn to control their symptoms. Given significant individual variation in frequency of and impairment related to rumination, there is no uniform method of quantifying success of rumination treatment. Despite this, we do know that the majority of patients who engage in behavioral rumination treatment have improvement in their rumination symptoms [29].

Limited data exist on long-term, sustained improvements in pediatric patients with rumination syndrome who undergo behavioral rumination treatment. The one available study shows that at about 1 year post-inpatient behavioral rumination treatment, the majority of patients reported symptomatic and quality of life improvements that were sustained following behavioral treatment [29]. This same study did also show that over half of the patients indicated a period of recurrence or worsening of symptoms after behavioral treatment, often triggered by viral illness.

Conclusion

Rumination syndrome, or the effortless regurgitation of food or drink shortly after eating, is one of many functional gastrointestinal disorders. It should be considered a diagnosis based on clinical history, and medical testing should be reserved for cases when a diagnosis of rumination cannot clearly be made due to other red flags or incongruent symptoms. Diagnoses must be made in a timely and confident manner and discussed with families in way that allows them to agree with the diagnosis. When families believe rumination fits their child's symptoms, they will then be accepting behavioral treatment; however, this still requires significant education to help families understand why behavioral treatment is helpful for a physical illness. Patients who do engage fully in behavioral treatment tend to have significant improvement if not remission of symptoms that is largely sustainable long-term.

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Functional Constipation in Children

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Functional constipation is a common gastrointestinal disorder in children, accounting for 3–10% of general pediatric outpatient visits and up to 25% of visits to pediatric gastroenterologists worldwide [1]. Symptoms include hard, large, infrequent, and painful bowel movements, often accompanied by abdominal pain and fecal incontinence in toilet-trained children. In approximately 95% of children with constipation, no underlying organic disease can be identified and these children suffer from functional constipation (FC) [1]. The prevalence of FC ranges between 0.7% and 29.6% with a pooled prevalence of 9.5% and occurs more often in girls than in boys (ratio: 2.1:1) [1]. Three subtypes of FC are recognized: normal transit constipation, slow transit constipation, and outlet obstruction [2]. The diagnosis of FC is based on the pediatric diagnostic Rome IV criteria for functional gastrointestinal disorders (Table 41.1) [3].

Table 41.1 Rome IV criteria for functional constipation

Rome IV criteria	Must include 1 month of at least 2 of the following in infants up to 4 years of age:	Must include 2 or more of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of irritable bowel syndrome:
	1. 2 or fewer defecations per week	1. 2 or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years
	2. History of excessive stool retention	2. At least 1 episode of fecal incontinence per week
	3. History of painful or hard bowel movements	3. History of retentive posturing or excessive volitional stool retention
	4. History of large-diameter stools	4. History of painful or hard bowel movements
	5. Presence of a large fecal mass in the rectum	5. Presence of a large fecal mass in the rectum
	In toilet-trained children, the following additional criteria may be used:	6. History of large diameter stools that can obstruct the toilet
	6. At least 1 episode/week of incontinence after the acquisition of toileting skills	After appropriate evaluation, the symptoms cannot be fully explained by another medical condition
	7. History of large-diameter stools that may obstruct the toilet	

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Physiology

Meconium Passage and Defecation Frequency

In more than 99% of healthy term neonates, the first meconium is evacuated within the first 48 h of life [3, 4]. Delayed passage of the first meconium beyond the first 48 h of life is suggestive of an organic defecation disorder (e.g., Hirschsprung's disease or anorectal malformations). During the first months of life, the defecation frequency may vary from child to child and is influenced by the feeding method; breastfed children have a higher defecation frequency and softer stools than formula-fed infants [4–6]. In the first weeks of life, the defecation frequency is around 3–4 stools a day and this frequency gradually decreases over time until it is approximately once a day in children at the age of 2–4 years [4, 7–12]. This stabilization of the defecation frequency is correlated with maturation of the gut microbiota composition [13]. In older children, defecation usually occurs either daily or every other day [8, 10, 12, 14, 15].

Defecation Dynamics

The physiological dynamics of defecation are complex and rely on several intricate processes involving the autonomic and somatic nervous system, the pelvic floor muscles, and the internal and external anal sphincters. In the colon, feces are propelled by propagating colonic contractions. Several different colonic motor patterns have been described [16, 17], but the most well-recognized propagating motor patterns are high-amplitude propagating contractions (HAPCs) and low-amplitude propagating contractions (LAPCs). HAPCs typically occur upon awakening, following meals, and can be induced by bisacodyl or other colonic irritants [18]. HAPCs can be fully propagating, when they reach the sigmoid colon, partially propagating when they stop at the level of the splenic flexure or at the descending colon and absent when there are no HAPCs observed in the entire colon and can be classified as normal or abnormal based on the morphology of pressure waves within the contraction sequence (Fig. 41.1) [16]. LAPCs occur considerably more often during the day than at night and increase in frequency upon wakening and following meals, much like the HAPCs. Differences were found between children with slow-transit constipation and healthy controls in the mean number of ascending, transverse, and descending LAPCs [16, 19]. Besides these HAPC and LAPC patterns, other motility patterns have been described in children with functional constipation. These children lack a normal postprandial increase in retrograde propagating motor patterns. Moreover, during the preprandial phase, children with constipation show greater numbers of antegrade propagating long single motor patterns [20]. However, the clinical significance of these findings is still unclear. Normally, anterograde colonic movements lead to filling of the rectum, which induces a relaxation of the internal anal sphincter, allowing feces to travel further down the anal canal; this reflex is known as the recto-anal inhibitory reflex (RAIR). Subsequently, sensory stimuli caused by rectal distention and by the contact between fecal material and the mucosa of the proximal part of the anal canal result in an urge to defecate. At this point, voluntary contraction of the external anal sphincter can postpone defecation, by moving the fecal load back, higher up in the anal canal and rectum, until the place and time are appropriate for defection. When defecation is initiated, voluntary relaxation of the external anal sphincter and the pelvic floor musculature (i.e., the puborectalis muscle and musculus levator ani) allows for an easy defecation process. In young children, this can be promoted by proper support of the feet when sitting on the toilet and by a relaxed posture. Then, by gently increasing the intra-abdominal pressure, stools can be expelled from the rectum.

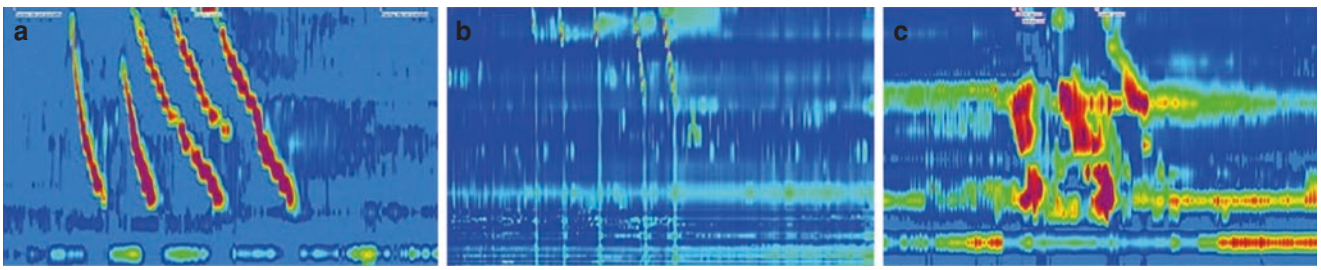

Fig. 41.1 Normally and abnormally propagating high-amplitude propagating contractions (HAPCs) have been identified by high-resolution manometry in children. (**a**) In normal HAPCs, the amplitude is >75 mmHg and the contractions propagate distally to the rectosigmoid junction. The anal sphincter relaxes concurrently to the HAPC. (**b**) In abnormally propagating HAPCs, the contractions do not propagate beyond the transverse colon. (**c**) An abnormal configuration of HAPCs with multipeaked waveforms and prolonged duration. This configuration has been associated with histological evidence of colonic neuropathy [19]. Reproduced with permission under the terms of the Creative Commons CC BY from Corsetti, M., et al. (2019). First translational consensus on terminology and definitions of colonic motility in animals and humans studied by manometric and other techniques. Nature Reviews Gastroenterology & Hepatology, 16(9), 559–579

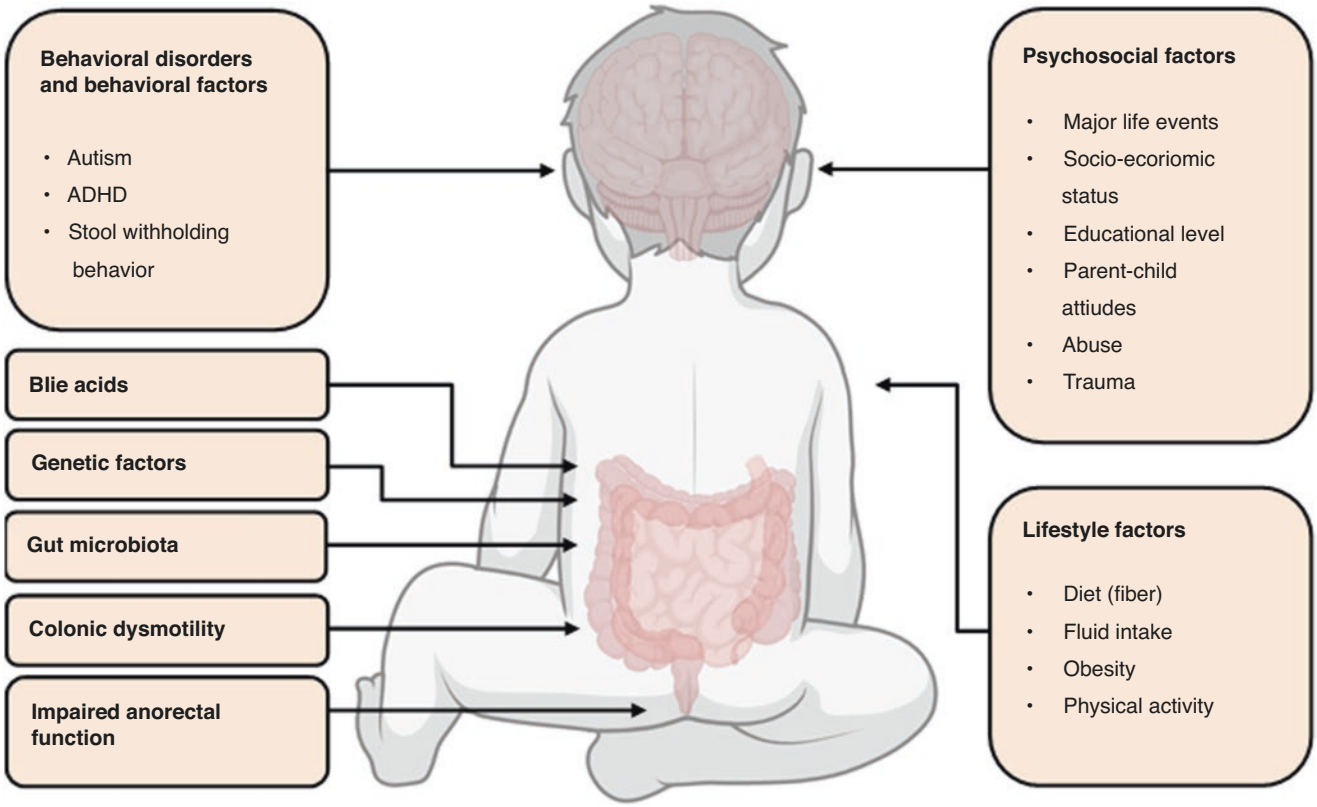

Fig. 41.2 Pathophysiological factors involved in functional constipation in children

Pathophysiology

The pathophysiology of FC is incompletely understood; multiple factors are likely to play a role in its pathogenesis and may affect different phases of the physiological defecation dynamics (Fig. 41.2).

Age of Manifestation

FC occurs in children of all ages, but there are three phases in life when children seem to be more prone to developing constipation: (1) in infancy, concomitant with changes in feeding (e.g., change from breastfeeding to formula-feeding, introduction of solid foods); (2) around the time of toilet training; and (3) in school children who avoid going to the toilet at other places than home [21]. This suggests that both dietary and behavioral factors play an important role in the pathogenesis of FC.

Stool Withholding Behavior

Probably the most important etiologic factor, especially in young children, is stool withholding behavior. This often occurs after a negative experience such as a hard, painful, or frightening bowel movement [22]. Stool withholding behavior can lead to the accumulation of a large fecal mass in the rectum that is difficult to evacuate, also known as fecal impaction. Fecal impaction may lead to overflow fecal incontinence which is the involuntary loss of soft and liquid stools that pass around the solid, obstructing, fecal mass. Stool withholding can lead to a negative chain of events: due to a painful defecation experience, the child voluntarily retains the stools in an attempt to prevent another painful bowel movement, causing the stools to become harder and more difficult to evacuate, leading to more pain during defecation [23].

Impaired Anorectal Function

Withholding behavior may eventually lead to dyssynergic defecation and occurs when the coordination of the muscles involved in defecation is inadequately coordinated during defecation [2]. This is caused by a paradoxical contraction of the muscles in the abdomen and pelvic floor or an inadequate anal relaxation leading to a poorly coordinated attempt at defecation, preventing stools to be expelled from the rectum and sustaining constipation [24, 25].

Colonic Dysmotility

Propagation of feces aborally through the colon is an essential step in the physiology of defecation. Colonic motility dysfunction is thought to be present in a subset of children with FC with delayed transit time and is supported by colonic manometry studies which report that HAPCs occur less frequently in patients with slow-transit FC compared to patients without constipation [20, 26]. It is not entirely clear whether this delay in colonic transit time (CTT) plays a causative role or if it is an effect of long-standing constipation and becomes a perpetuating factor, resulting in a detrimental causal sequence.

Studies utilizing colonic manometry have revealed that in children with intractable FC, several types of colonic dysmotility can be differentiated. In healthy humans, stretching of the stomach after a meal induces an increase in colonic motility via the enteric nervous system and the neuropeptides serotonin, gastrin, cholecystokinin, and prostaglandin E1. This response is better known as the gastrocolic reflex [27, 28]. Colonic manometry studies have shown that this reflex is impaired in a subset of children with FC, which may indicate an impaired extrinsic innervation [20, 29]. Furthermore, it has been shown that a small proportion of children with FC have incompletely propagating HAPCs or a general lack of HAPCs in response to a stimulant laxative, which likely implies an intrinsic (neurogenic or myogenic) pathophysiological process [30]. But it remains uncertain whether these findings are cause, effect, or a combination of both.

Psychosocial Factors

Although the precise underlying pathophysiological mechanisms are not always clear, psychosocial factors such as major life events, socioeconomic status, educational level, and parental child-rearing attitudes might play a role in the pathophysiology of FC [1, 31–33]. Furthermore, behavioral and developmental disorders such as autism spectrum disorders and attention deficit hyperactivity disorder (ADHD) are associated with a higher risk of childhood constipation [34–36].

Genetics

Since FC seems to occur more often in certain families, a genetic predisposition might have a role in the etiology of childhood constipation [37, 38]. A twin study suggested that constipation in children is caused by a genetic predisposition to form hard stools and revealed that 59% of childhood constipation can be explained as a genetic phenomenon [39]. However, studies have failed to identify mutations in specific genes associated with FC yet [40].

Microbiota

The role of the gut microbiota in the pathophysiology of FC is incompletely understood. Gut microbiota differences have been identified between children with and without FC, suggesting that gut microbiota may play a role in the pathogenesis of FC [41–43]. Causality in gut microbiota research remains a challenge. Diet is one of the main key drivers of gut microbiota composition, of which fibers are probably one of the most important. There is some evidence that fiber intake is different between healthy children and those with FC [44–47]. Only few studies have investigated the actual gut microbiota composition in children with FC and findings have been inconsistent [42, 48]. Some of the found associations can be explained by the effect of the gut microbiota's end products, such as short-chain fatty acids (SCFAs). One of these SCFAs is butyrate, which is the main energy source for colonocytes and might have a role in intestinal mucus production, increased colonic smooth muscle contraction, and has been associated with increased fecal water content [49, 50]. Another possible mechanism in which the gut microbiota may potentially influence gut motility is by the production of methane. Anaerobic fermentation of undigested polysaccharides produces hydrogen in the gut which in turn can be the substrate for methane production by intestinal methanogens [41, 51]. There is strong evidence from animal studies that methane delays intestinal transit, possibly acting as a neuromuscular transmitter. Indeed, methane production has been associated with constipation in adults [52, 53]. More studies are clearly needed to unravel the role of the diet and gut microbiota in the pathophysiology of FC in children and thereby find potential microbiota-based interventions such as pre-, pro-, syn-, or postbiotic treatments [54–56].

Bile Salts

There has been an increasing interest in bile salt metabolism as a potential pathophysiological factor in FC. Endogenous deconjugated bile salts have the potential to function as endogenous laxatives by increasing colonic motility and fluid secretion [57]. In a subset of children with FC, bile acid metabolism has been shown to be altered, leading to a decreased secretory activity. This suggests that bile acid metabolism may play a role in the pathophysiology of constipation in a subset of children [58]. Again, there may be a role for the microbiota in this process; only a small portion of deconjugated bile acids end up in the colon where they could exert their laxative effect; however, the gut microbiota will influence their overall physiological effect through dehydroxylation, deconjugation, and desulfation of bile acids [59, 60].

Evaluation

The evaluation of a child with constipation should always aim to differentiate FC from constipation due to an organic cause. The diagnosis of FC is a clinical diagnosis based on a thorough medical history and a complete physical examination. Additional investigations are usually not required (Fig. 41.3) [62].

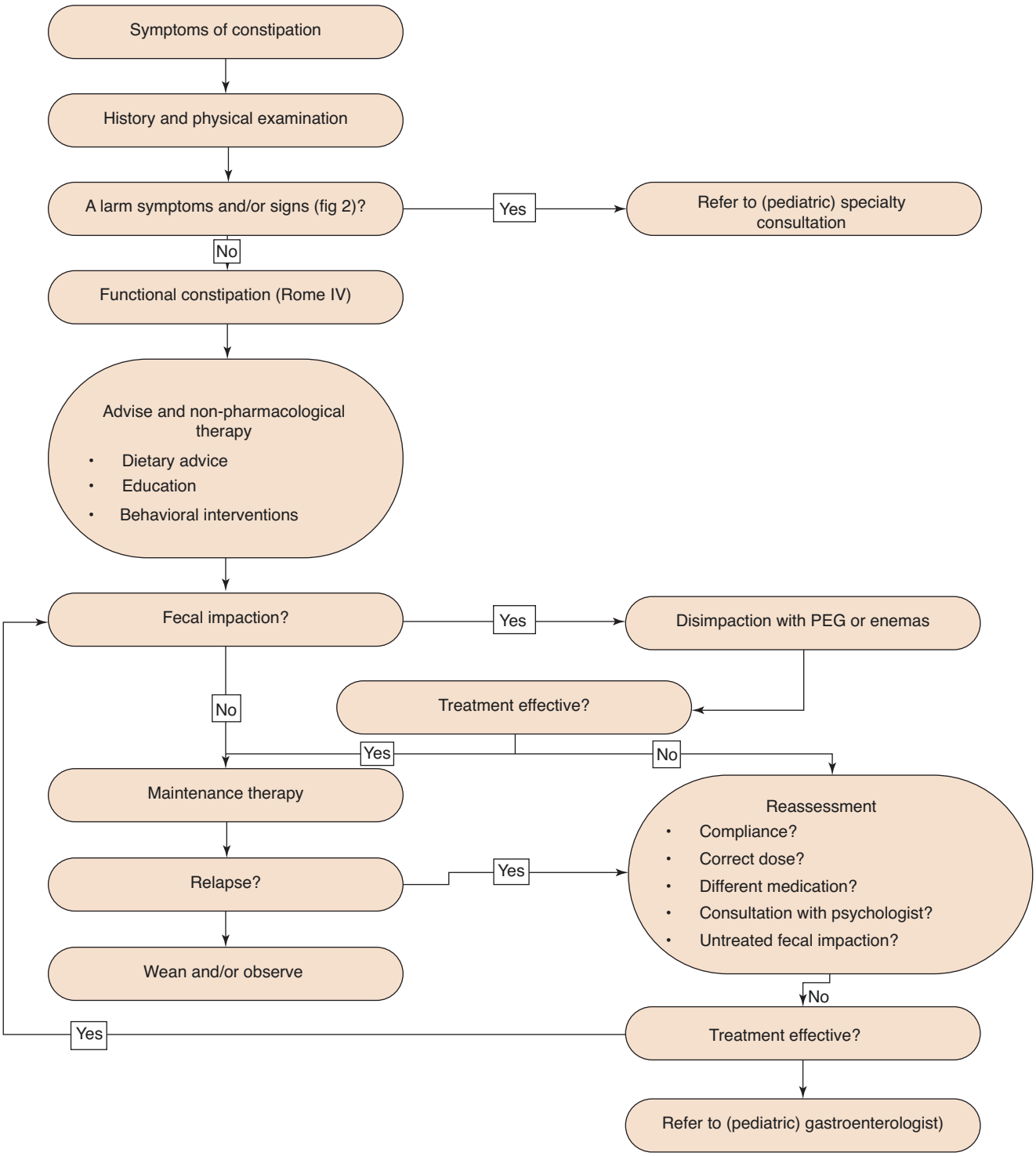

Fig. 41.3 Algorithm for initial evaluation of constipation in children, adapted from [2, 61]

Medical History

The medical history should ask questions about defecation frequency, stool consistency, painful bowel movements, size of the stools, episodes of fecal incontinence, and a history of withholding behavior (Table 41.1). Keeping a daily bowel diary can be useful to gather reliable information about a child's bowel habits. The Bristol Stool Scale or the Modified Bristol Stool Form Scale for Children can be helpful in the assessment of stool consistency in the toilet or in a diaper [63, 64]. Special attention should be paid to questions about withholding behavior, as this behavior may not be recognized as such by parents and may even be wrongfully interpreted as straining to defecate. Questions regarding stool withholding behavior should therefore be clear and illustrated with examples.

In infants, withholding may be characterized by grunting, back arching, and tightening of the legs. In toddlers, squeezing the buttocks together, crossing the legs, standing on the toes, and rocking back and forth are distinctive signs of withholding. The medication history should include the use and efficacy of oral laxatives, enemas, colonic irrigation, and other medications that potentially influence gastrointestinal motility.

Alarm symptoms in children

History

- Delayed passage of meconium
- Early onset (<1 month old)
- Positive family history for Hirschsprung's disease,
- celiac disease or hypothyroidism
- Blood in the stools
- Ribbon stools
- Fever
- Bilious vomiting
- Smearing of feces

Physical examination

- Failure to thrive
- Severe abdominal distention
- Abnormal anal or cremasteric reflex
- Abnormal position of anus or gluteal cleft
- Extreme fear of anal exam
- Scars on anus
- Anal fissures or haematoma
- Abnormal neurological exam
- Hair tuft on spine
- Sacral dimple
- Abnormal thyroid gland

Fig. 41.4 Alarm signs and symptoms in constipation

Alarm Symptoms

In order to differentiate between FC and constipation with an organic cause, alarm symptoms suggestive for an organic cause should be sought out (Fig. 41.4) [2, 62]. They include delayed passage of meconium, which raises suspicion of Hirschsprung's disease. Other important questions include the age of onset, a history of bloody stools without the presence of a fissure, failure to thrive, and severe abdominal distention. Furthermore, a history of smearing feces, detection of fissures, and hematomas or abnormal behavior during physical examination (e.g., sexual acting out, extreme fear) should raise suspicion of sexual abuse [65].

Differential Diagnostic Considerations

Besides organic causes of constipation and psychosocial causes of FC such as sexual or physical abuse, the differential diagnosis should include harmless conditions that may be misinterpreted as FC: infrequent defecation in breastfed infants and screaming or crying before or during defecation in infants can be worrysome to parents but these issues are often innocuous. Approximately 10% of breastfed infants defecate once every 7–10 days, without any other symptom of FC and while still gaining weight normally. This is usually a self-limiting phenomenon related to breastfeeding, with hypotheses ranging from a better digestion of the fat in mother's milk compared to formula milk to a greater number of saccharolytic bacteria that can degrade unabsorbed and unabsorbable sugars and do not require any treatment [5, 66]. Infant dyschezia is a functional gastrointestinal disorder in young children that is defined as straining and crying for at least 10 min before successful or unsuccessful passage of soft stools in an infant younger than 9 months of age without any other health problem [3]. Parents report that their child turns red or purple during defecation, but the infant usually passes soft stools several times daily. This is also a self-limiting condition, which does not require any medication or intervention. It is thought to be caused by a lack of coordination between increased intra-abdominal pressure preceding defecation and relaxation of the pelvic floor [67].

Physical Examination

Assessment of weight and height is of key importance since failure to thrive is a sign of an organic cause of constipation. Physical examination primarily consists of examination of the abdomen, the perianal region, and the lumbosacral region. Abdominal examination mainly focuses on the detection of a palpable fecal mass or scybala. Perianal inspection should be performed in all children; the physician should

look for anatomic abnormalities, perianal feces, fissures, scars, and erythema. The presence of fissures can be a sign of hard or large stools, but can also be a sign of sexual abuse. Hematomas in the perianal region are highly suspicious of abuse as well. Special attention should be paid to abnormal behavior during physical examination (e.g., sexual acting out, extreme fear) [65]. Although digital rectal examination provides valuable information on the presence of a rectal fecal mass, anorectal sensation, and sphincter tone, it is not necessary for the diagnosis of FC if a child already fulfils two or more Rome IV criteria (Table 41.1) [3]. If a child fulfils only one of the Rome IV criteria, a digital rectal examination is recommended since it may help establish the diagnosis of FC. Examination of the lumbosacral region may reveal the presence of a dimple, a tuft of hair, or gluteal cleft deviation, indicative of an organic cause of constipation (e.g., spina bifida).

Laboratory Testing

Laboratory testing in children with constipation should only be performed in the presence of alarm symptoms or signs and it is not part of the routine workup of children with FC. The need for routine screening for cow's milk allergy or hypercalcemia is not supported by current literature [62, 68]. Serological testing for celiac disease and thyroid function is only indicated in children with short stature, unexpected weight loss, persistent gastrointestinal symptoms, or a positive first-degree family history [2]. The prevalence of celiac disease was not found to be higher in children with constipation compared to matched healthy controls, confirming that routine testing of children with constipation for celiac disease is not indicated [69].

Abdominal Radiography

An abdominal radiography is often used as an adjunct to the diagnosis or the management of FC [70, 71]. Extensive literature has shown that a plain abdominal X-ray is not an appropriate test to diagnose constipation. The sensitivity and specificity rates are unsatisfactory, and low inter- and intra-observer reliability have been reported for the different scoring systems (Barr, Leech, Blethyn) that are used to evaluate fecal loading based on abdominal X-rays [72–75]. Moreover, children are exposed to unnecessary radiation. Therefore, abdominal X-rays are only of added value in very limited cases, for example when the medical history is unreliable (e.g., anorexia nervosa, factors that make rectal examination inappropriate or unreliable or too traumatic) [76].

Colonic Transit Time

There is no evidence to support the routine measurement of colonic transit time in the diagnostic workup of FC, but this test can be a useful tool in children with fecal incontinence to discriminate between constipation-associated fecal incontinence or functional non-retentive fecal incontinence (FNRFI), a disorder characterized by fecal incontinence without constipation [62]. The most widely used method to determine CCT is the radiopaque marker test performed by single or multiple ingestion of radiopaque markers and it is calculated by the amount of intra-abdominal markers visualized on an abdominal X-ray once or at several specific intervals [77]. A colonic transit time <62 h is considered to be normal [78]. Patients are considered having slow-transit constipation when transit time exceeds 62 h and when the markers are spread throughout the colon. When >50% of the markers are found in the rectosigmoid, it is labeled as a rectal evacuation disorder, also known as outlet obstruction [79]. Another method to determine colonic transit time is radionuclide scintigraphy; after ingestion of radioactive isotopes, colonic transit is measured with a large-field-view gamma camera. Scintigraphy is a more novel technique than the radiopaque marker test, with the advantage of minimal radiation exposure, but its use is less widespread and more expensive than a radiopaque marker transit test. More importantly, normative values are lacking in the pediatric population [2, 80–83].

Contrast Enema

A contrast enema is a useful tool to identify anatomic abnormalities of the anorectum and the colon. After infusion of contrast fluid into the rectum, an abdominal X-ray is obtained, visualizing the distribution of contrast fluid in the distal gastrointestinal tract. Contrast enemas do not belong in the routine workup of children with FC, but may be useful to evaluate the morphology of the colon to detect mechanical causes or consequences of constipation (e.g., anatomical abnormalities, dilated segments, or complications after colorectal surgery) [84].

Ultrasonography

Transabdominal ultrasonography has been used to measure the transverse rectal diameter [85, 86]. An increased rectal diameter (>30 mm) is often considered to be diagnostic of fecal impaction, but there is major overlap between children with FC and healthy controls [87, 88]. Although transabdom-

inal ultrasonography is a promising technique for assessment of rectal diameter, there is currently insufficient evidence that the transverse diameter can be used as a reliable predictor of constipation and fecal impaction in children [62].

Manometry

Manometry allows for measurement and quantification of intraluminal pressure and contact force in the gastrointestinal tract; this technique can be utilized to gain insights into gastrointestinal motility.

Anorectal Manometry

Anorectal manometry provides information about anorectal neuromuscular function. It can be used to assess the RAIR, anal sphincter pressure, rectal sensation, and defecation dynamics; therefore it is a useful instrument to rule out Hirschsprung's disease and to detect anal sphincter achalasia or dyssynergia [62, 89]. The presence of a normal RAIR is considered to be sufficient to reliably rule out Hirschsprung's disease. However, an absent recto-anal inhibitory reflex is not sufficient to diagnose Hirschsprung's disease; this finding requires confirmation with histochemical evaluation of a rectal biopsy to confirm the absence of enteric ganglia (aganglionosis) [89]. High-resolution anorectal manometry in children with FC with or without fecal incontinence has demonstrated lower pressures in the anteroposterior quadrants at rest and during squeezing in children with FC and FI than in children with FC without FI [90]. Interestingly, children with FC with or without FI showed lower resting pressures, lower maximum squeeze pressure, and higher RAIR values compared to children without lower GI symptoms [90]. The main drawback of the use of anorectal manometry for evaluating defecation dynamics in children is that patients need to be awake and cooperative during the test. In young children, anorectal manometry is therefore sometimes performed with the use of sedation or general anesthesia. Some anesthetics, however, significantly lower the anal resting pressure [91]. The performance and analysis of anorectal manometry are performed in specialized centers and should not be routinely performed in children suspected of FC.

Colonic Manometry

Colonic manometry is a diagnostic test performed to differentiate between normal colonic motor function and colonic neuromuscular disorders in the evaluation of children with intractable constipation (Figure 41.1a, b). In colonic manometry, the quality and frequency of HAPCs are identified during fasting, during a meal, during the postprandial phase, and during a provocative phase in which stimulant laxatives are administered. Abnormal HAPCs may indicate segmental or milder colonic dysfunctioning while absent HAPCs may indicate a severe colonic motility disorder [92]. Many differences exist among centers in the type of catheter used, number of sensors and spacing between sensors, and the protocols for investigations, which makes comparison of data among groups difficult [89]. The introduction of high-resolution colonic manometry allows to not only focus on HAPCs, which are relatively rare events (<2% of all motor patterns) even in a healthy colon, but also on other propagating motor patterns [93]. However, these data originate from adult trials and the clinical relevance, if any, of high-resolution manometry findings still need to be established in pediatrics [89]. Despite differences in execution of colonic manometry studies, this technique is considered a useful tool to rule out neuromuscular motility disorders of the colon associated with slow-transit constipation. Colonic motility testing, such as anorectal manometry and colonic manometry, is performed in specialized centers, usually in an academic setting.

Magnetic Resonance Imaging

To date, evidence does not support the use of magnetic resonance imaging (MRI) of the spine in patients with intractable constipation without other neurologic abnormalities [62]. One retrospective study found lumbosacral spine malformations in 9% of children with intractable constipation, not associated with major neurologic symptoms [94]. Another study in children with defecation disorders including constipation, constipation-associated fecal incontinence and FNRFI, spinal cord abnormalities such as intradural lipoma or tethered cord were found in only 3% of affected children [95]. Recently, a feasibility study has been conducted in adolescents with FC to investigate if MRI could be a noninvasive alternative to colonic manometry. However, results did not overlap in the identification of HAPCs [96]. Therefore, MRI should not be included in the routine workup of children with FC and should only be considered when there is strong suspicion of neurologic disorders such as neurological findings in the lower extremity and midline defect in the skin of the lower back and gluteal cleft deviations.

Management

The ESPGHAN/NASPGHAN guideline includes four phases in the treatment of FC: (1) education, (2) disimpaction, (3) maintenance therapy to prevent reaccumulation of feces, and (4) follow-up [62]. The management of FC in children consists of non-pharmacological and pharmacological treatment modalities. Fig. 41.5 represents a treatment pyramid for the management of children with FC.

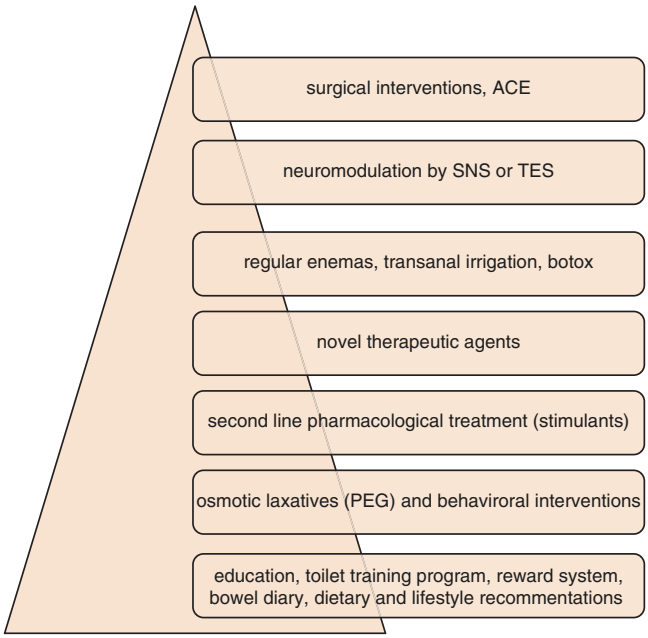

Fig. 41.5 Treatment pyramid for FC. FC is usually treated in a step-up approach, starting with non-pharmacological interventions and osmotic laxatives (bottom of the pyramid). If these measures are unsuccessful, use of more invasive modalities may be necessary (towards the top of the pyramid). PEG, polyethylene glycol; ACE, antegrade continence enemas; SNS, sacral nerve stimulation; TES, transcutaneous electrical stimulation

Education

Education is the first step in the non-pharmacological treatment of FC [62]. This should include an explanation of the physiology of defecation, tailored to the developmental age of the child. The negative chain of events that may have been prompted by experiencing a painful defecation should be explained to parents and, if possible, children. It is important to describe the pathophysiology of overflow incontinence and the pivotal role that withholding behavior plays in this process. Also, the role of parental child-rearing attitudes towards fecal incontinence, such as frustration and overprotection, should be discussed [31]. Lifestyle advice such as dietary recommendations, regular physical activity, and advice on toilet training, toileting posture and behavior should be part of this step and, in the presence of behavioral problems, behavioral therapy should be considered [62, 97].

Toilet Program and Reward System

Toilet training can be challenging for parents, but in case of delayed and unsuccessful toilet training the child must be thoroughly assessed in order not to miss important diagnoses such as spinal cord abnormalities and constipation. In rare cases, delayed toilet training may be a consequence of sexual abuse [98]. In toilet-trained children, stasis of feces in the rectum can perpetuate constipation, therefore it is important to evacuate the rectum regularly. In children with a developmental age of ≥4 years, this can be established by introducing a toilet training program, with scheduled toilet sit times throughout the day, usually after every meal and after coming home from school. The toilet sit times are scheduled after a meal, to take advantage of the gastrocolic reflex [27], which increases colonic peristalsis upon distention of the stomach [27]. During these times, it is advised to have the child pay attention to the body sensation and not divert their attention with reading or screen activities [27]. In order to motivate children to maintain this toilet training program, a reward system can be introduced. By rewarding the child with small gifts for completing toilet training, the child is positively reinforced to comply with therapy. A non-accusatory approach by both physicians and parents is of key importance since affected children may feel guilty or embarrassed, especially when experiencing episodes of fecal incontinence [62]. Only rewarding periods without fecal incontinence is therefore not recommended as this may increase feelings of guilt and can be experienced as punishment for having fecal incontinence.

Dietary Fiber, Fluid, and Physical Activity

Fiber

Insufficient fiber intake has been reported to be associated with FC, and advice on normal fiber and fluid intake and physical activity are the first steps in the treatment of FC [62, 99]. As stated in the ESPGHAN/NASPGHAN guidelines, there is currently insufficient evidence to support the use of supplementary fiber in excess of the daily recommended intake in children with FC [62]. Recent systematic reviews and a meta-analysis found limited high quality studies and give no indications to change the current guidelines of ESPGHAN/NASPGHAN [100, 101]. However, since most children fail to meet the daily fiber recommendations (0.5 g/kg/d for children aged >5 years), fiber intake should be addressed [102, 103].

Fluid

Only few studies have investigated the association between fluid intake and FC [104, 105]. These studies have shown insufficient evidence for a clinical benefit of additional fluid intake on constipation symptoms. Indeed, extra fluid intake in children with FC in excess of a normal fluid intake is not recommended [62]. An exception should be made for extra fluid that is recommended for medication intake, such as polyethylene glycol, which needs to be dissolved in water.

Physical Activity

Although physical activity may be associated with a decreased risk of developing FC at the preschool age [106], no studies have been performed to assess the effect of increasing physical activity to treat symptoms of constipation in children [62, 107].

Probiotics

Studies on the use of probiotics have been conducted in children, but to date there is insufficient evidence to support the use of probiotics in the treatment of childhood constipation [56, 108].

Biofeedback Training

Biofeedback training utilizes reinforcing stimuli in an attempt to achieve a recognizable sensation and encouraging an appropriate learnt response. In theory, this may help children with dyssynergia to optimize their defecation dynamics. However, currently available evidence does not support the use of biofeedback training for the treatment of childhood constipation [62].

Pelvic Floor Physiotherapy

Pelvic floor physiotherapy teaches how to perform pelvic floor muscle exercises and has been reported as potential treatment option for the treatment of children with FC with dyssynergic defecation [109–112]. Three studies showed beneficial effects of pelvic floor physiotherapy in children with FC in addition to standard medical care [109, 110, 113]. On the other hand, a recent randomized controlled trial (RCT) in primary care did not find evidence to recommend physiotherapy for children with FC in primary care [114]. Before recommending pelvic floor physiotherapy in the treatment of FC or as addition to standard medical care, larger studies are needed, also taking cost-effectiveness into account.

Medications

The pharmacological treatment of FC mainly consists of treatment with laxatives and involves three steps: disimpaction, maintenance treatment, and weaning. The pharmacological treatment options, including recommended dosages, are summarized in Table 41.2 [2, 61, 62].

Table 41.2 Pharmacological management of functional constipation in children [2, 61, 62]

Drug	Dosage
Osmotic laxatives	
PEG 3350 (with electrolytes)/4000 (without electrolytes)	Maintenance: 0.3–0.8 g/kg/day in 1–2 doses
	Fecal disimpaction: 1–1.5 g/kg/day (max 7 days)
Lactulose	7 months–18 years: 1–2 g/kg/day, in 1–2 doses
Milk of magnesia (magnesium hydroxide)	2–5 years: 0.4–1.2 g/day, in 1 or more doses
	6–11 years: 1.2–2.4 g/day, in 1 or more doses
	12–18 years: 2.4–4.8 g/day, in 1 or more doses
Lactitol	1–6 years: 0.5–1 g/kg/day in 2–3 doses
	6–12 years: 10–30 g/day in 2–3 doses
	12–18 years: 20–60 g/day in 2–3 doses
Lubricants	
Mineral oil (liquid paraffin)	*Oral*
	3–18 years: 1–3 mL/kg/day, 1 or more doses/day (max 90 mL/day)
	Rectal
	2–11 years: 30–60 mL, in 1 dose/day
	>11 years: 60–150 mL, in 1 dose/day
Stimulant laxatives	
Bisacodyl (diphenylmethane)	3–10 years: 5 mg/day, in 1 dose/day (at night)
	>10 years: 5–10 mg/day, in 1 dose/day (at night)
Senna (anthraquinone)	2–6 years: 2.5–5 mg/day, in 1–2 doses/day
	6–12 years: 7.5–10 mg/day, in 1–2 doses/day
	>12 years: 15–20 mg/day, in 1–2 doses/day
Sodium picosulfate	1 month–4 years: 2.5–10 mg/day, in 1 dose/day
	4–18 years: 2.5–20 mg/day, in 1 dose/day
Rectal laxatives/enemas	
Bisacodyl	3–10 years: 5 mg/day, in 1 dose/day (at night)
	>10 years: 5–10 mg/day, in 1 dose/day (at night)
Sodium lauryl sulfoacetate	1 month–1 year: 2.5 mL/dose (=0.5 enema)
	1–18 year: 5 mL/dose (=1 enema)
Sodium docusate	<6 year: 60 mL
	>6 years: 120 mL
Sodium phosphate	1–18 year: 2.5 mL/kg/dose (max 133 mL/dose)

PEG polyethylene glycol

Disimpaction, Maintenance Treatment, and Weaning

Fecal impaction occurs in approximately 50% of children with FC [23, 61, 115]. Pharmacological treatment consists of two steps: fecal disimpaction followed by maintenance therapy [115].

Disimpaction can be achieved with enemas or high-dosed oral polyethylene glycol (PEG) (1–1.5 g/kg/day) during 3–6 days [115]. High-dose PEG and sodium docusate enemas have been found to be equally effective for disimpaction, and although high-dose PEG is associated with more fecal incontinence during treatment compared with enemas, PEG is recommended as first choice for disimpaction because it is administered orally [61]. After successful disimpaction, maintenance therapy should be initiated to prevent the reaccumulation of feces [115]. The aim of maintenance treatment is to soften the stools and to facilitate easy and frequent bowel movements. Several laxatives are available for maintenance treatment (Table 41.2). PEG is the oral laxative of first choice at a dosage of 0.2–0.8 g/kg/day. Other therapeutic options are discussed below. Depending on the severity of symptoms, the effect of treatment should be evaluated 1–2 weeks after initiation of treatment. Maintenance treatment should be continued and FC symptoms should be resolved for at least 2 months before considering weaning in order to prevent a relapse [62, 115].

Osmotic Laxatives

Maintenance treatment in children with FC usually consists of oral osmotic laxatives; these agents are poorly absorbed, causing water retention in the intestinal lumen. This softens the stools and increases peristalsis through intestinal distention (Fig. 41.6). A number of laxatives are commonly used in children, but PEG is the first choice osmotic laxative in children with FC based on its effectiveness and safety profile [116]. PEG is more effective in increasing stool frequency than placebo, lactulose, and milk of magnesia (magnesium hydroxide) [117]. Even in children less than 2 years of age, PEG has been proven to be effective and safe [116]. PEG combined with electrolytes can be prescribed to minimize the risk of disturbing the electrolyte balance due to osmosis (e.g., in young children). However, the addition of electrolytes affects the taste of the medication, which can result in problems with treatment compliance, but acceptance of PEG-based laxatives was found to be better than non-PEG laxatives [118]. Most commonly reported side effects include fecal incontinence (especially during disimpaction), flatulence, abdominal pain, nausea, and abdominal bloating [27].

Two other commonly used osmotic laxatives are lactulose and lactitol, both synthetic derivatives of lactose, which are fermented into SCFAs such as acetic, lactic, and formic acid by the gut microbiota [61, 119]. Both agents result in intraluminal water retention and a decrease in intraluminal pH, which induces an increase in colonic peristalsis (Fig. 41.6). Bacterial fermentation of these agents also induces gas formation, which leads to additional intestinal distension and increases peristalsis, but may also result in side effects such as flatulence, abdominal pain, and abdominal bloating. Lactulose is less effective than PEG [117], but since it is considered to be safe for all ages, it is recommended in case PEG is not available.

Magnesium hydroxide (also referred to as "milk of magnesia" as suspension) is an antacid with an osmotic laxative effect. It is considered to be less effective than PEG in the treatment of childhood FC [117]. Side effects of magnesium hydroxide include diarrhea, hypotension, weakness, and lethargy [61].

Stimulant Laxatives

Stimulant laxatives have a different action mechanism than osmotic laxatives; these agents act directly on the intestinal mucosa, stimulating intestinal motility or increasing electrolyte and water secretion (Fig. 41.6). Based on expert-opinion, stimulant laxatives may be considered as second-line treatment [116]. Bisacodyl and sodium picosulfate are diphenylmethanes. In the colon, these nonabsorbable agents are hydrolyzed to their active metabolites, which exert a local prokinetic effect and stimulate intestinal fluid secretion [119]. Bisacodyl can be administered orally and rectally; in the latter form its effect is observed rapidly after administration. Long-term use of bisacodyl was not associated with complications or development of tolerance to the medication, and patients were able to be weaned off the medication with minimal reported side effects [120]. Another stimulant and effective laxative is senna, which contains anthraquinones. This agent is also metabolized into its pharmacologically active metabolite by the gut microbiota and the metabolites stimulate colonic motility and the secretion of water and electrolytes, while they inhibit the absorption of water and electrolytes from the colon [119]. The most common side effects of stimulant laxatives are flatulence, abdominal pain, nausea, and diarrhea.

Lubricants

Mineral oil (or liquid paraffin) is a mixture of higher alkanes, often a derivative of petroleum that functions as a lubricant. It is not absorbed by the intestines and may also exert an osmotic effect when it is converted to fatty acids [121, 122]. A Cochrane systematic review found some evidence that mineral oil increased stool frequency, but was also associated with side effects such as abdominal pain, distention, and

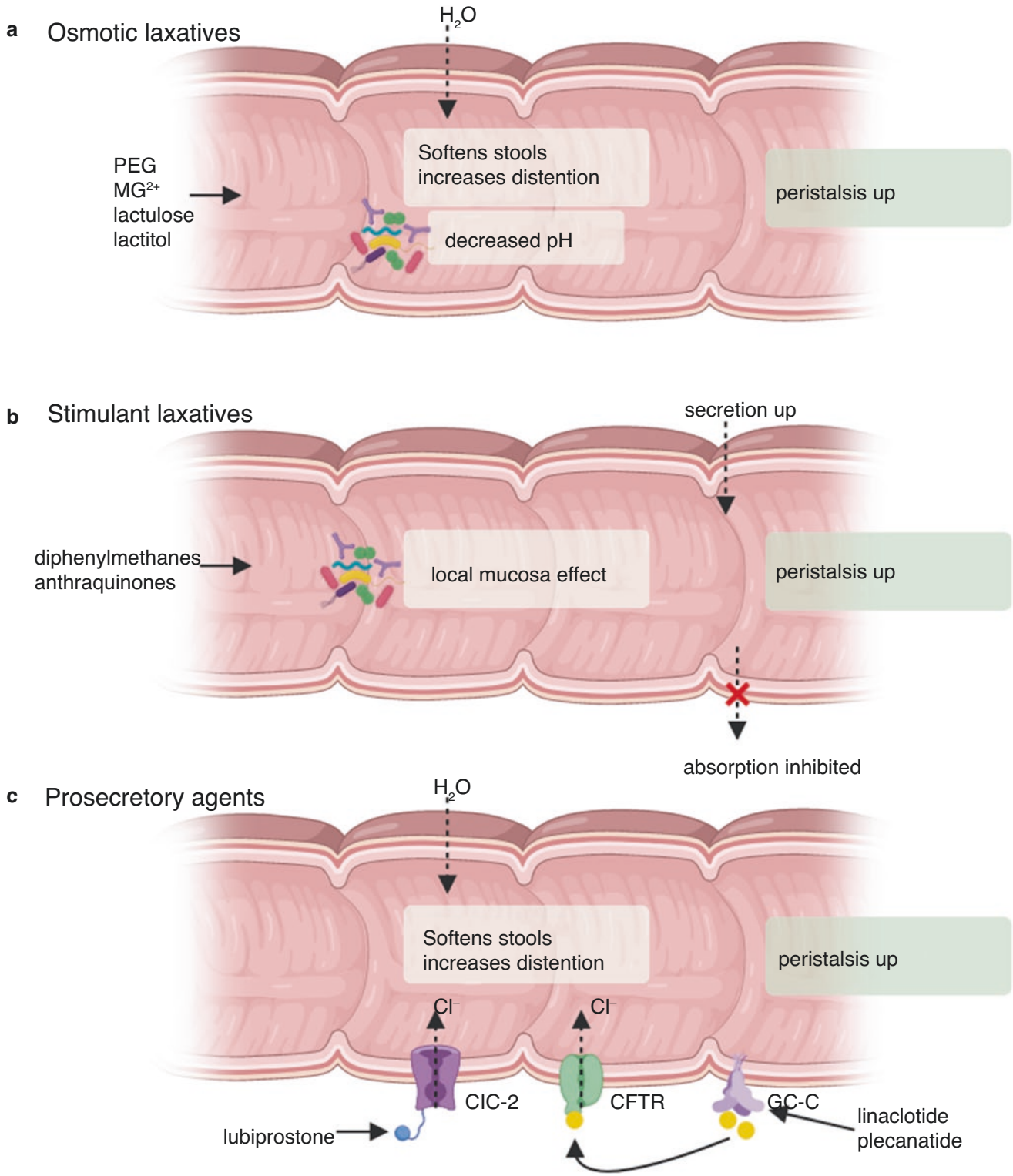

Fig. 41.6 Mechanism of action of different types of laxatives. (**a**) Osmotic laxatives are poorly absorbed by the intestinal wall. This stimulates retention of water in the intestinal lumen, softening the stools, and increasing peristalsis through intestinal distension by increasing stool volume. In addition, fermentation of the disaccharides lactulose and lactitol by the gut microbiota results in a decrease in intraluminal pH, which induces an increase in colonic peristalsis. (**b**) Stimulant laxatives are metabolized into active metabolites by the gut microbiota and act directly on the intestinal mucosa stimulating peristalsis and influencing fluid regulation mechanisms. Diphenylmethane metabolites exert a local prokinetic effect and stimulate intestinal secretion. Anthraquinone metabolites stimulate colonic motility and water and electrolyte secretion, while they inhibit absorption of water and electrolytes. (**c**) Lubiprostone and linaclotide both promote secretion of chloride-rich fluid in the intestine, softening stools and enhancing stool volume. Lubiprostone is a prostaglandin E1 derivative, which activates chloride channel subtype 2 (ClC-2). Linaclotide activates the luminal guanylin receptor (GC-C); this promotes production of cyclic GMP, which in turn activates CFTR channels. Created with BioRender.com

watery stools [117]. Liquid paraffin is considered to be safe and effective in the treatment of FC in children [121], but a bothersome adverse effect is leakage of the agent from the anus, causing irritation, itching, and staining of clothing. Due to incidental reports of the severe side effect of granuloma following absorption and lipoid pneumonia after aspiration [121, 123, 124], liquid paraffin should be considered as an additional or second-line treatment and should not be administered to children under 3 years of age or in children with abnormal swallow dynamics [116, 125].

Enemas

Rectally administered enemas used in the treatment of FC contain chemically active agents that increase gut motility, exert an osmotic effect, or both. They work rapidly, usually within minutes. Different kinds of enemas are available. Sodium lauryl sulfoacetate enemas cause a redistribution of the water that is bound to feces and thereby soften the stools. These enemas do not have an osmotic effect and are therefore often used in infants. Sodium docusate enemas contain the lubricant docusate (sometimes with added sorbitol, a hyperosmolar agent) and sodium phosphate enemas contain a strong hyperosmolar phosphate solution. Adverse effects of enemas include abdominal pain and anorectal discomfort.

Novel Therapeutic Agents

Prosecretory Agents

Prosecretory agents such as lubiprostone, linaclotide, and plecanatide are therapeutic agents that modulate epithelial channels in the gut, promoting the intestinal secretion of fluids and thereby enhance stool volume, resulting in an improved gastrointestinal transit (Fig. 41.6) [126]. These agents have been found to be effective in the treatment of constipated adults [2], but data on the efficacy of these agents in the treatment of FC in children are scarce or not yet available.

Lubiprostone is a prostaglandin E1 derivative that induces intestinal fluid secretion by activating the chloride channel subtype 2 (ClC-2) and cystic fibrosis transmembrane conductance regulator (CFTR), enhancing the secretion of chloride-rich intestinal fluid [127]. Only one study in the pediatric population has been published. This open-label, noncontrolled study showed after 4 weeks of treatment with lubiprostone an increased defecation frequency in 127 children with functional constipation [128]. Reported adverse events included nausea, vomiting, diarrhea, and abdominal pain [128].

Linaclotide and plecanatide promote intestinal fluid secretion by activating the guanylate cyclase C receptor, activating CFTR, and leading to the secretion of chloride-rich intestinal fluid. To this date, no studies were found evaluating its use in children, but studies in adults with linaclotide found improvement in stool frequency and consistency, abdominal symptoms, and global relief versus placebo [129, 130]. Similarly, no studies were found in children evaluating plecanatide; however, in adults the use of plecanatide demonstrated a substantial improvement in stool frequency and consistency compared with placebo [131].

Serotonergic Agents

A number of 5-hydroxytryptamine 4 (5-HT_4) agonists have been developed for the treatment of FC. Serotonin (5-HT) is a central and enteric neurotransmitter that binds to the 5-TH_4 receptors in the gut, thereby increasing the release of acetylcholine which in turn results in an increased secretion and gut motility [132]. Prucalopride is a highly selective serotonin 5-HT_4 receptor agonist which functions as a prokinetic agent. Only two published studies evaluated prucalopride in children with FC and showed in an 8 week open-label controlled study in 37 children improvement in stool frequency and consistency and fecal incontinence frequency [133]. In contrast, another study, a RCT in 213 children with FC, did not find a statistically significant improvement in bowel movements or frequency of fecal incontinence [134]. Reported adverse events included headache, nausea, abdominal pain, and diarrhea [134]. Other serotonergic agents such as velusetrag and naronapride have not yet been investigated in children and have not yet been approved by the FDA or EMA.

Bile Acids

As mentioned above, endogenous deconjugated bile salts have the potential to function as endogenous laxatives by increasing colonic motility and fluid secretion [57]. In adult women, chenodeoxycholic acid, a primary bile acid, was shown to be effective for constipation predominant irritable bowel syndrome in improving stool consistency [135]. But to date, no studies on the use of bile acids in children with FC have been performed.

Cholinesterase Inhibitors

Acetylcholinesterase inhibitors, such as pyridostigmine, increase gastrointestinal motility by increasing the availability of acetylcholine. One study, a case series of four children with gastrointestinal motility disorders using pyridostigmine, suggested a beneficial effect on defecation frequency in one patient with constipation [136].

Transanal Irrigation

Transanal irrigation (TAI) involves infusion of fluids (usually tap water) into the rectum and colon in a retrograde fash-

ion to mechanically clean out the intestine and is typically used in children with FC who are unresponsive to oral laxative treatment [137]. TAI has been well-established for use in patients with neurogenic defecation disorders and anorectal malformations [137], but data on the effectiveness of TAI in children with FC are scarce. Pediatric cohort studies in small populations of children with FC have shown it to be effective in the treatment of constipation with and without fecal incontinence with a high parental satisfaction [138–141]. Transanal irrigations are usually performed with a volume of 10–20 mL/kg of water and the frequency of irrigations is based on the patient's response [137]. In some patients, different irrigation fluids (saline, added laxatives) may be explored to optimize outcome.

Botulinum Toxin

Intrasphincteric injections with botulinum toxin A (botox) have been used in the treatment of FC. By lowering the pressure of the anal sphincter, botox aims at facilitating an easier defecation process. Botox injections have a transient benefit and repetitive injections may be necessary to maintain treatment effect. The injection of botulinum toxin A into the anal sphincter may lead to easier and more frequent passage of stools with less pain in children with intractable constipation, regardless of anal sphincter dynamics, but patients with fecal incontinence are less likely to respond [142]. The dose of botox administration in children ranges from approximately 75–200 U, but 100 U appears to be used the most across studies [143]. However, since this method is rather invasive, other methods like electromotive drug administration (EMDA), in which the drug solution is delivered directly into the target site, are being explored. One recent study compared the effect between regular botox injections and the EMDA botox method in 60 children with FC [144]. EMDA was as effective as an intrasphincteric botox injection of the treatment of FC, but had several advantages, including less comorbidity, lower costs, and most importantly can be performed without general anesthesia [144]. Temporary side effects were fecal and urinary incontinence.

Surgery

In patients with FC unresponsive to medical treatment, surgical treatment may be necessary. Surgical procedures may include antegrade colonic enema (ACE), pelvic floor surgery, botox injections, and colorectal resection [84, 145]. However, the evidence to support their benefit is weak and more studies are needed to identify the subgroups of patients who may benefit from surgical interventions in the treatment of FC. Obviously, one should exhaust every conservative management for patients with FC before moving to these invasive surgical interventions [84].

Antegrade Continence Enemas (ACE)

Antegrade continence enemas (ACE) involve colonic irrigation in an antegrade direction through a surgically created access point into the colon. The most commonly used procedures are the Malone appendicocecostomy and the percutaneous cecostomy [2]. In the Malone appendicocecostomy, the appendix is connected to the abdominal wall creating a valve. In the percutaneous cecostomy, a minimally invasive procedure, an artificial cecostomy tube connects the cecum with the abdominal wall. ACE surgery is considered minimally invasive and excellent clinical outcomes have been reported in children [84].

Colonic Resection

When minimally invasive surgical therapies fail in children with severe cases of intractable FC or when colonic manometry reveals a dysfunctional colonic segment, resection of the affected segment may be beneficial. This can be followed by subsequent colo-anal or ileo-anal anastomosis or creation of a diverting ileostomy or colostomy. In recent years, several studies have been published investigating outcomes of colonic resection in idiopathic constipation in children. One retrospective study in children who underwent ileostomy, colostomy, or (sub)total colectomy found an improvement in symptoms and parent satisfaction of 91%, but also reported high rates of complications such as stoma problems or the need for stoma-revisions [146]. Another retrospective study found that, in the presence of a megarectum, a rectosigmoid resection via laparoscopic video-assisted low anterior resection of the colon was effective in children and better than a Soave pull-through operation [147]. Another retrospective study compared three different types of resection; panproctocolectomy with ileoanal pouch anastomosis, total colectomy with ileorectal anastomosis, and segmental resections and anastomosis. This study found no differences among these types of resection in terms of results or complications and concluded that there might be a role for colonic resection in constipated children. However, authors of this paper estimated that 2/5 will be left with a permanent stoma, an information of which children and parents should be aware [148]. A thorough review on surgical options available for the management of refractory constipation in children concluded that surgical options should be considered as they can lead to significant improvement in symptoms and quality of life [145]. However, due to the small study sizes, lack of prospective randomized studies, large differences in operation techniques, and the high psychosocial and financial impact of surgical interventions, there is a great need for consensus guidelines on surgical decision-making.

Electrical Stimulation/Neuromodulation

Electrical stimulation or neuromodulation involves the generation of currents that cross within the body or are used to stimulate a nerve. The exact mechanism of action is not yet understood, but the current may result in an alteration of neuronal function and increase in colonic motility by stimulating the interstitial cells of Cajal, the pacemaker cells of the gut, and/or enteric or extrinsic autonomic nerves [149].

Transcutaneous Electrical Stimulation (TES)

TES is a noninvasive, pain-free form of electrical stimulation that uses interferential current via electrode pads applied across the skin of the abdomen and lower back. One RCT compared TES with sham stimulation in children with slow-transit constipation and found improvement in CTT and quality of life scores, but defecation frequency did not improve [150, 151]. A long-term follow-up of these studies found that 33% of children with slow-transit constipation had significant improvement in stool consistency and fecal incontinence 2 years after treatment with TES [152].

Percutaneous Tibial Nerve Stimulation (PTNS)

PTNS involves (bilateral) stimulation of the posterior tibial nerve by inserting a needle electrode at the level of the medial malleolus and thereby indirectly stimulating the sacral nerves [2]. Preliminary results of a small study in children with organic causes of constipation found that PTNS is effective for the treatment of fecal and urinary leakage [153]. Despite initial evidence that PTNS or other forms of electroacupuncture may improve motility, such as described in a study in rodents in which they were able to enhance motility via stimulation of autonomic mechanisms, future studies in children with constipation are needed to determine the efficacy of such treatments.

Sacral Nerve Stimulation (SNS)

During SNS, the anterior ramus of sacral spinal nerves S3 and S4 is stimulated via surgically positioned electrodes that are connected to an implanted pulse generator. Efficacy of SNS on fecal incontinence in pediatric patients is well-established, but its mechanism of action and role in treatment of FC is less clear [2]. Small cohort studies in children with FC show promising effects of SNS on defecation frequency [154, 155]. Although considered minimally invasive, high rates of device-related adverse events have been reported such as pain, hematoma, infection, and displacements of the leads [2]. Randomized-controlled studies with long-term follow-up are essential to gain more insights into the potential role of SNS in the management of FC in children.

Prognosis

A large proportion of children with FC can be treated effectively with the therapeutic strategies that are currently available. A systematic review of prospective follow-up studies in the hospital setting concluded that within 6–12 months, approximately 50% of the children recover and are taken off laxatives [156]. An additional 10% of patients will be asymptomatic on treatment and the remaining 40% remain symptomatic despite pharmacological treatment [156]. In children with intractable symptoms, unresponsive to medical treatment, symptoms may persist into adolescence or even adulthood despite laxative treatment [156–158]. Early adequate therapeutic interventions are of key importance; a delay between onset of symptoms and first presentation at a pediatric gastroenterologist is negatively related to recovery [157].

Future Perspectives

The most significant advances in the management of FC in children are likely to result from more precise understanding of the pathophysiology in order to select individualized and novel treatments. These novel therapies might range from acupuncture, specific food exclusion diets, gut-microbiota-directed interventions such as pre-, pro-, syn-, and postbiotics or fecal microbiota transplants, therapies influencing intestinal ion exchanges/transporters and bile acid modulators.

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Fecal Incontinence in Children

42

Jose M. Garza

Fecal incontinence (FI) is defined as the passage of stools into the underwear, either as an unintentional seepage of small amounts of liquid stools (generally referred to as soiling or leakage) or the complete evacuation of formed stools with a developmental age of at least 4 years [1]. Children with FI have significantly worse quality of life (QOL) than their healthy peers. In addition, caregivers of children with FI report an extremely high level of parenting stress [2]. Children with FI often have to deal with feelings of shame, peer rejection, and bullying [3]; this results in a significantly negative impact on their physical and psychosocial well-being [4].

For many years, encopresis was used as a term to describe expulsion of large amount of feces in the underwear and soiling was used to refer to the leakage of small amounts of stool. These terms have been used interchangeably in the medical literature often causing confusion. The Rome criteria [5] have adopted a more neutral term, namely, "functional fecal incontinence" rather than encopresis and soiling.

FI in children can be classified as organic (neurological disorders, anorectal malformations, postsurgical complications) or functional (where no organic cause can be identified). It is important to note that the great majority of children with FI fall into the functional category (around 95%).

Epidemiology

In children, the reported rates of functional constipation vary from 1% to 30% and the rates of FI from 1.6% to 4.4% [6]. Idiopathic FI makes up approximately 3% of all primary care visits [7]. Most children have FI due to fecal retention (75–90%) [1] and it is more common in males than in females. A recent cross-sectional study of children and young adults [8] showed a prevalence of constipation of 15.6% in children and 22.8% in young adults with a prevalence of FI, comparable between both age group cohorts, of about 7%. This study also demonstrated that 43% of children had symptoms for more than 5 years and, more importantly, that 26% of young adults experienced constipation since childhood. These findings stress the fact that a substantive percent of children who have constipation in childhood do not "outgrow" this condition. A large proportion of children with a defecation disorder does not recognize it as a problem and often do not seek help [6]. In other cases parents have been described as incorrectly believing that their child is lazy or indifferent to having accidents, which can lead that affected child to undergo verbal and/or physical abuse. In fact, studies have shown that children with FI are more likely to be victims of emotional, sexual, and physical abuse when compared to their healthy peers [4, 9].

Pathophysiology

FI can be further subdivided into retentive (constipation associated: caused by fecal impaction resulting in overflow incontinence) and non-retentive FI (absence of fecal retention) (Table 42.1) [5]. Regardless of etiology, children with

Table 42.1 Rome IV criteria [5] for functional defecation disorders in children with a developmental age of at least 4 years

Functional non-retentive fecal incontinence	Functional constipation
At least a 1-month history of the following symptoms	Must include two or more of the following occurring at least once per week for ≥1 month with insufficient criteria for the diagnosis of irritable bowel syndrome
1. Defecation into places inappropriate to the socio-cultural context	1. two or fewer defecations in the toilet per week
2. No evidence of fecal retention	2. ≥1 episode of fecal incontinence per week

(continued)

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Table 42.1 (continued)

Functional non-retentive fecal incontinence	Functional constipation
3. After appropriate medical evaluation, the fecal incontinence cannot be explained by another medical condition	3. History of retentive posturing or excessive volitional stool retention
	4. History of painful or hard bowel movements
	5. Presence of a large fecal mass in the rectum
	6. History of large diameter stools which may obstruct the toilet
	After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

FI have lower HRQoL scores compared to children with constipation alone. Furthermore, the emotional functioning components were more negatively influenced by FI than any other aspects when QoL was assessed using disease-specific questionnaires [9–12].

Retentive FI (Constipation-Associated)

This is the most common cause of FI in children (70–95%). Functional constipation is multifactorial, wherein certain events during childhood can predispose to constipation, such as changes in diet during infancy, toilet training, and starting school. Some children after experiencing a painful or difficult defecation begin withholding stool to avoid feeling pain; this leads to stool retention. Subsequently, the colonic mucosa absorbs more water making the retained stool harder and even more difficult and painful to evacuate which in turn results in further worsening of the defecation experience. At this point, the child continues to withhold and, over time, stool accumulation distends the rectum and sigmoid causing rectal hyposensitivity and chronic fecal impaction. Colonic bacteria liquefy the stool in the proximal portion of the fecal mass with resulting seepage leading to fecal incontinence.

Functional Non-retentive Fecal Incontinence (FNRFI)

The reported prevalence of FNRFI ranges from 0% to 1.8% with a pooled prevalence of 0.4% [13]. The pathophysiology of FNRFI is not understood, but several hypotheses have been put forward in the literature. Children with FNRFI have normal defecation frequencies and colonic as well as anorectal motility parameters, including normal resting pressure, squeeze pressure, and rectal sensation to balloon distention. Children with FNRFI often report that they either have no time to go to the toilet or are reluctant to leave activities they are engaged in. Therefore, it is hypothesized that they deny, ignore, or outright neglect the normal urge to defecate [1]. There appears to be a high association of this type of FI and behavioral disorders. For example, a study by van der Plas et al. [14] showed that children with an initial abnormal behavior score who were successfully treated from FI had a significant improvement of their behavioral profile, suggesting that FNRFI is a factor in the occurrence and maintenance of behavioral problems. However, a direct causal association between FI and psychological problems has not been proven. Disorders of sleep organization have been observed in the pathogenesis of enuresis; a recent study generated the hypothesis that the orexinergic system may have a role not only for sleep organization, but for sphincteric control in general and found that children with FNRFI have a reduction in adequate sleep duration and reducing sleep efficiency as well as higher plasma orexin-A levels than controls, supporting sleep organization alterations as a potential contributor to poor evacuation control [15].

Clinical Evaluation

A thorough history and clinical exam are often sufficient for diagnosis, and in rare cases, further tests are required. It is important to establish or rule out constipation (impaction) as the cause of FI. Diagnosis should be based on clinical symptoms and physical exam. (Rome IV criteria; Table 42.1) [5].

History

A detailed description of bowel habits from the parents/primary care takers and from the child who is old enough to report accurately (usually by 8 year of age) is important, including frequency of defecation, stool consistency, and size of bowel movements. It is also helpful to rely on the Bristol Stool Form Scale or any of its modifications to aid in the history taking. In addition, the clinician should ask whether bowel movements are painful or hard, elicit whether there is presence of withholding behavior (which particularly in toddlers some parents confuse with the patient trying to defecate), and assess behaviors towards the use of the toilet (fear, excuses to delay going, etc.). As for episodes of FI, it's important to evaluate frequency, amount or quantity of the stool (smears vs. full bowel movements), situations and time of day of accidents, as well as the presence or absence of nocturnal loss of feces.

Physical Exam

A thorough physical exam is necessary to establish constipation and rule out alarm signs. Stool palpated in the abdomen indicates constipation-associated FI. A thorough inspection of the lower back looks for asymmetry of gluteal region, presence of sacral dimple, tuft of hair or surgical scars. Perineum and anal inspection are key for the evaluation of the position of the anal opening, presence of fissures, bruising, hemorrhoids, scars, erythema, or stool on the perineum. If a diagnosis is confirmed with history and physical exam then a digital rectal examination is not needed, but in cases of diagnostic uncertainty it should be performed as it provides useful information allowing the physician to assess sphincter tone and evaluate for the presence of a large fecal mass in rectum which helps differentiate between constipation-associated FI and FNRFI.

Certain historical features in each patient might help us differentiate between retentive FI and FNRFI:

- Patients with retentive FI tend to have decreased frequency of stools (<2 per week), stools tend to be large, painful, and obstruct the toilet, FI amounts are smaller than the usual amount of stool, and FI can happen during the day and night.
- Patients with FNRFI tend to have normal frequency of stools, stools don't tend to be hard or painful, do not have nighttime incontinence, and the amount of the FI is the usual amount of stool in the toilet.

Diagnostic Tests

Additional investigations are not useful in the routine workup of functional FI; they should be reserved for atypical cases, when conventional treatment fails or to rule out a suspected underlying organic cause.

Abdominal X-Ray (AXR)

AXRs are commonly used in the diagnosis and treatment of patients with defecation disorders, but evidence suggests that they have poor diagnostic accuracy with a sensitivity of 60% to 80% and specificity of 43–99% [16]. Furthermore, there is no association between clinical symptoms and fecal load on abdominal radiography [17], and there is low inter and intra-observer reliability [18]. Fecal load varies day to day, depending on food intake and timing of last defecation. Therefore, both ESPGHAN/NASPGHAN [19] and NICE [20] (National Institute for Health and Care Excellence) constipation guidelines do not recommend the use of AXR for either diagnosis or evaluation of constipation. An argument could be made that AXRs can be helpful in those patients in whom medical history and exam are inconclusive, patients evaluated by telemedicine where an abdominal exam is not possible, and, in the circumstances in which history is unreliable, or psychological factors exist that would make rectal examination inappropriate/unreliable (obese patients, anxiety, suspicion of sexual abuse, etc.). Another potential use is to evaluate the efficacy of a "cleanout" with high volume polyethylene glycol, which, in patients with FRFI, would be associated with clinical improvement and in those with FNRFI no improvement or worsening despite minimal fecal residue.

Colonic Transit Studies

To date, the evidence does not support the routine use of colonic transit studies in the diagnosis of functional constipation or fecal incontinence. Radio-opaque markers help distinguish normal transit, anorectal retention, or slow transit constipation. Several methods have been suggested, the simplest method being the ingestion of a single capsule that contains 24 markers and is followed by a single X-ray on day 5, wherein retention of ≥5 markers is abnormal. Another method used for colonic transit is colonic scintigraphy, which is available in very few centers and is also a radiation exposing test. Regardless of method, measuring colonic transit time in children with functional constipation has limited value in predicting successful outcome. Important signs of functional constipation, such as low defecation frequency and/or a high number of fecal incontinence episodes and/or the presence of a palpable rectal mass, are strongly correlated with a prolonged CTT, especially with retention of the markers in the rectosigmoid [21]. Children with constipation-associated fecal incontinence show a variable delay in colonic transit. In contrast up to 90% of children with FNRFI will have a normal colonic transit [22, 23]. In those patients with uncertain diagnosis and refractory fecal soiling or an unreliable medical history and exam, measuring colonic transit is helpful in differentiating retentive FI from FNRFI.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the spine is not employed in the routine workup for fecal incontinence in children. MRI is helpful in ruling out spinal cord lesions that can lead to FI; however, lumbosacral abnormalities are rarely present and usually don't correlate with treatment success. Moreover, when there are lumbosacral abnormalities present, they are usually associated with clinical abnormalities on exam (tuft of hair and other midline lower back skin manifestations, asymmetry of gluteal cleft, lower extremity

findings, etc.). In any of these aforementioned examples, MRI of the spine is indicated. Patients with spinal cord lesions have changes in anorectal manometry that include a shift in the recto anal inhibitory reflex (RAIR) dose-response curve to the left and presence of anal spasms upon balloon distention and these findings might indicate need for MRI of the spine even in the absence of exam abnormalities [24].

Anorectal Manometry

Anorectal manometry (ARM) is the most commonly performed definitive motility test in children. ARM allows assessment of anal sphincter length, tone and function, anorectal sensory responses, rectoanal reflexes, and ability to squeeze and simulate the process of defecation [25]. In addition ARM is helpful in ruling out Hirschsprung's disease and to detect anal achalasia or dyssynergia. Routine use of ARM in children with FI is not recommended as its usefulness in diagnosis is very limited. Most of the ARM parameters between patients with retentive FI and those with FNRFI show no difference, although those with retentive FI tend to have a higher threshold for rectal sensation [26], thus suggesting a hypercompliant and dilated rectum caused by chronic fecal retention. When evaluating patients with functional constipation without incontinence with those with associated FI, ARM is also not beneficial in evaluation or to guide management [27].

Colonic Manometry

Colonic manometry (CM) evaluates intraluminal colonic pressures and their coordination [25]. CM can help differentiate between functional constipation and intrinsic colonic dysmotility [28] and helps guide surgical interventions [29]. Patients with FNRFI show no abnormalities on colonic manometry [30, 31]. Intraluminal bisacodyl induces high amplitude propagated contractions (HAPCs) in 93% of children with treatment refractory constipation [32]. In patients with constipation-associated FI, CM is typically normal and no single parameter of the CM can identify specific abnormalities related to incontinence or which patient will respond to therapy [29]. Colonic manometry should be performed only after medical interventions have failed and surgical interventions are contemplated.

Treatment

When children and their families present to the clinic with the complaint of FI, they often carry a lot of misconceptions about the underlying causes of the incontinence, including accusing the child of being lazy, having FI on purpose, feelings of guilt, shame, as well as anger. It is of the upmost importance to understand that treatment begins with education and demystification, removing the stigma of FI. The clinician needs to spend enough time explaining the symptoms to caregivers and children (in age-appropriate terms). It is important to recognize when discussing the treatment that it is not a 'one-size fits all' and to be successful requires a personalized long term plan that includes both non-pharmacological and pharmacological interventions.

Toilet Program

All treatments for FI need to include a toilet program. Patients with FI, frequently, have poor toilet habits which both contribute to and exacerbate constipation associated FI [33]. Many of the patients have developed a fear of hard, painful stools and have voluntary stool retention to avoid going to the toilet. Patients should be instructed to sit on the toilet, relaxed, with appropriate positioning with foot support for 5 to10 min, with optimal timing being after meals (to take advantage of the gastrocolonic reflex). In school-aged children, arrangements should be made for school to allow the child to have free access to restroom and the child can substitute sitting after lunch to sitting right when they get home from school, as long as they are not withholding the urge to defecate. This is even more important in children with FNRFI as most of them have accidents between 3 and 6 pm [1]. Parents are encouraged to provide a lot of positive reinforcement. Referral to a clinical psychologist can be helpful in patients with FI who have emotional and behavioral problems. If available, routine psychological assessment for all patients with FNRFI should be performed.

Fiber

Increasing fiber intake when children have normal intake from diet is not recommended in the treatment of functional constipation [19] or FNRFI [34]. In patients with retentive FI, soluble fiber can bulk up stool, making defecation even larger and more painful. Soluble fiber can be used to bulk up stool in those patients in whom high-dose stimulant laxatives are required to achieve defecation, but make the stool too loose.

Biofeedback and Pelvic Floor Therapy

Anorectal biofeedback is used to train patients to strengthen or relax the external anal sphincter, recognize the feeling of rectal distention, and coordinate intrabdominal pressure with

relaxation of the external anal sphincter. Pelvic floor physical therapy improves awareness of body sensations, teaching the child effective ways of expelling stools. Some studies have shown that biofeedback and pelvic floor therapy do not improve retentive FI or FNRFI [14, 34–36]. However, other studies have shown some benefits in the treatment [37–41]. Biofeedback and pelvic floor physical therapy are very safe, of low risk, and show promise for children with constipation [42] and FI. However, currently there is insufficient data to recommend either as the sole treatment of FI.

Pharmacological Treatment

Non-pharmacological therapies are effective complementary therapies for constipation, but they need to be used in conjunction with standard medical therapy [43].

Laxatives

In patients with retentive FI, one of the most frequent causes of treatment failure is not alleviating fecal impaction before starting maintenance therapy; both polyethylene glycol [19] and enemas of sodium phosphate and sodium docusate have been shown safe and effective in relieving fecal impaction [44]. Once fecal impaction has resolved, then daily maintenance therapy needs to be initiated with the goal of avoiding accumulation of stool in rectum by having regular, soft bowel movements with no episodes of overflow fecal incontinence. Both polyethylene glycol and lactulose have been found safe and effective for maintenance therapy [19].

If a patient with retentive FI continues experiencing soiling even after relieving fecal impaction and appropriate doses of osmotic laxatives, the patient could be switched to stimulant laxatives, because in many circumstances rectosigmoid hyposensitivity will make patients not feel an urge to defecate even on osmotic laxatives until they are impacted again. In this circumstance, stimulant laxatives produce cramping which serves as a proxy sensation for the patient to have sensation to defecate so they can then go sit on the toilet and have a successful bowel movement. Stimulant laxatives are widely available and for the most part underutilized in children with FI due to concerns for safety and dependency. Studies have found that both senna [45] and bisacodyl [46] are safe and effective in long term use in children. With aggressive therapy, most patients improve their symptoms irrespective of baseline findings in manometry studies. Once treatment resolves the episodes of FI and produces regular nonpainful stools, then patients should remain on that regimen for at least 2 to 6 months and only then proceed with a slow wean to avoid recurrence of symptoms. If fecal incontinence persists despite maximizing stimulant laxatives, nonretentive fecal incontinence should be ruled out and consider advancing treatment to trans-anal irrigation. Other strategies, discussed below, can also be considered.

Laxatives are not indicated in children with FNRFI as they can worsen symptoms [1].

Antidiarrheals

Loperamide is a μ opioid receptor agonist that acts on circular and longitudinal intestinal muscles to inhibit peristalsis, prolong transit time, decrease fecal volume, and increase tone on the anal sphincter [1]. There is anecdotal evidence that loperamide can improve symptoms in patients with FNRFI [47]. However, more research is needed before it can be recommended as standard treatment.

Botulinum Toxin A

Intrasphincteric injection of *Botulinum* toxin A, an acetylcholine release blocking agent, has been used safely and successfully [48, 49] to treat refractory constipation unresponsive to medical management and complications reported have been self-limiting and did not require intervention. A recent randomized clinical trial [50] compared administration of *botulinum* toxin A through electromotive drug administration (EMDA) which represents a minimally invasive method of administration of medication into deep tissue layers without the need of general anesthesia versus intrasphincteric injection. The study demonstrated that both methods were successful in normalizing stool (73% and 80% respectively) with the advantage that EMDA administration is less costly and associated with less comorbidities; further research is still required on *botulinum* toxin A injection, including the method of administration.

Transanal Irrigation

By regularly irrigating and emptying the distal colon, fecal leakage between irrigations can be prevented. Such irrigation was first introduced in 1987 to treat fecal incontinence in patients with neurogenic disease, and more recently, has been used with good success in patients with both retentive FI and FNRFI. Transanal irrigation has been shown to improve quality of life and prevent surgical interventions in children with FI, with some children able to administer the irrigations themselves [51–55]. Transanal irrigation requires a tailored approach and usually performed with 10 to 20 mL/kg of water or saline solution, with additives like bisacodyl or soap used to improve emptying. When at all possible, transanal irrigation should be tried and troubleshooted before pursuing any surgical interventions.

Surgical Interventions

Antegrade Continence Enemas (ACE)

By providing an antegrade route for enema delivery, patients can more easily self-administer the enema without using the rectal route. ACE significantly improve quality of life in patients with medically refractory FI [56]. To achieve ACE delivery, both appendicostomy and cecostomy have been used. Appendicostomies are made with the purpose of not having to have an indwelling catheter with better cosmetic results, and a cecostomy made to have an indwelling catheter to avoid leakage, as no continence valve is made [57]. Complications of ACE procedures are mostly stoma-related and may require reoperation. Stomal stenosis and leakage are the most commonly reported complications and patient compliance is necessary to achieve less complications and better results [58]. Achievement of fecal continence and improvement of quality of life has been shown to be similar in both procedures [59]. The overall rate of complications is lower in cecostomy patients than appendicostomy. In more recent years, there has been an international move away from the ACE stoma and towards transanal irrigation as an alternative means of colonic washout [60].

Colonic Resection

In constipation, refractory to medical management surgical intervention is considered as a last resort. A permanent intestinal diversion with ileostomy or colostomy is almost never needed [57]. In pediatrics, partial colon resection with colonic anastomosis is the most common intervention [61] and to help maintain continence is important to preserve the rectum [62]. Colonic motility can improve after decompression or after antegrade enemas [63], so it is not unreasonable to propose that ACE should be the first step before more aggressive interventions are tried [64]. A subsequent step could include stomal decompression in hopes that function can be rescued prior to definitive resection. There is no consensus over when or which surgical treatment is indicated; colonic manometry has been shown to help guide surgical management [29]. Judicious use of these surgical procedures in properly selected patients and based on appropriate preoperative testing can lead to excellent outcomes [64]. Whenever possible, if a surgical intervention is being considered or in cases of refractory FI, patients can benefit from a multidisciplinary team approach [65, 66].

Neuromodulation

Neuromodulation is the application of electrical stimulation on nerve fibers to modulate neuronal activity, which is a promising tool in the treatment of fecal incontinence in children. For neuromodulation, invasive and noninvasive techniques are currently available. A systematic review [60] grouped 7 papers [67–72] that included a total of 280 patients who received the implantable sacral neuromodulation technique, aged 6 to 20 years with positive results, showing an increase in defecation frequency and decrease in fecal incontinence with some patients being able to stop or decrease enema use. However, the downside is that 38% experienced a postimplant complication, with 72% of them requiring one or more surgical procedures. Noninvasive techniques such as transcutaneous electrical posterior tibial nerve stimulation, transcutaneous sacral nerve stimulation, and transcutaneous interferential electrical stimulation have the benefit of less complications but require more studies [60].

Conclusion

FI is common in children. Functional constipation and FI have a large impact on the quality of life of pediatric patients and their families. In the great majority of cases, FI is functional and a good history and physical exam are all that is required to diagnose and classify FI as retentive versus nonretentive. Treatment should be aimed at improving bowel frequency and eliminating incontinence and should include education, a structured toilet regimen, and behavioral modifications in conjunction with pharmacological interventions. In some cases, aggressive therapy is needed, and most patients will respond to laxatives. However, if there is no success with adequate doses of osmotic laxatives, therapy should escalate to stimulant laxatives in sufficient doses to produce regular bowel movements. More complicated patients can respond to other therapies including transanal irrigation. Multidisciplinary teams for FI are being more widely employed and available to help evaluate and treat these refractory patients and improve clinical and quality of life outcomes.

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Part VI

Treatments

Drugs Acting on the Gut: Prokinetics, Antispasmodics, Laxatives

43

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Propulsion of gastrointestinal (GI) luminal contents requires coordinated contractions of intestinal smooth muscle in response to input from enteric neurons. The enteric nervous system is capable of independent function, modulated by motor input from the brain through the sympathetic and parasympathetic branches of the autonomic nervous system. GI motility disorders result from weak or uncoordinated contractions due to abnormalities of the bowel neuromuscular apparatus or autonomic regulation of the GI tract. In this chapter we have categorized the drugs commonly used to treat GI motility disorders into three groups: (1) agents that enhance smooth muscle contractions, referred to as prokinetic agents; (2) agents that inhibit contractions, which may be agents that retard normal peristalsis referred to as antimotility agents (opiates and opiate receptor agonists), or agents that reduce abnormally elevated gastrointestinal smooth muscle tone, referred to as antispasmodics (anticholinergics, direct smooth muscle relaxers, and calcium channel blockers); and (3) agents that are used to treat constipation, referred to as laxatives.

Prokinetic Agents

Available prokinetic medications generally fall under three groups of drugs: dopamine receptor antagonists, motilin receptor agonists, and 5-Hydroxytryptamine-4 ($5HT_4$) receptor agonists.

Dopamine-2 (D2) Receptor Antagonists

Domperidone

Domperidone is a peripheral dopamine-2 (D2) receptor antagonist that is used for symptomatic treatment of upper GI motility disorders associated with chronic gastritis or gastroparesis and symptoms of nausea and vomiting. This drug is not approved in the United States and is available via investigational new drug application.

D2-receptors are located both within the brain and in the peripheral nervous system; however, since domperidone has poor penetration of the blood–brain barrier, most of its effects are derived from its action on peripheral receptors. It increases esophageal peristalsis and increases lower esophageal sphincter pressure, increases gastric motility and peristalsis, and enhances gastroduodenal coordination, therefore, facilitating gastric emptying and decreasing small bowel transit time [1]. Domperidone also exerts an antiemetic effect on the chemoreceptor trigger zone, which is not protected by the blood–brain barrier. Domperidone has the ability to cross the placenta and small amounts are excreted in breast milk (2 mg/mL when dosed at 10 mg PO 3 times daily) [2]. It is rapidly metabolized in the liver and has a half-life of 7.5 h [2, 3].

Safety and efficacy of domperidone have not been adequately established for the pediatric population. In children admitted to the hospital for vomiting, compared to placebo and metoclopramide (10 mg), nausea and vomiting were significantly lower using domperidone (30 mg); however, this study was conducted for a 24 h period only [4]. Two systemic reviews of pediatric gastroesophageal reflux disease (GERD) treatments did not recommend the use of domperidone in this patient population due to lack of data showing its efficacy [5, 6]. There are no convincing data for its use to treat infant GERD and may cause prolongation of QTc [7].

For adult treatment of functional dyspepsia, a meta-analysis revealed that there was significant improvement in the patient's global assessment with an OR of 7 (95% CI

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3.6–16); however, there was not enough data to support improvement in gastric emptying [8]. Patients with postoperative nausea as well as nausea from cytotoxic medications have improvement of their symptoms compared to placebo; however, in those studies domperidone was given in the intravenous (IV) form, which is no longer available [9–12]. Similar data in pediatric age group are lacking. There is the potential for prolongation of the QT interval leading to arrhythmias as it acts similar to a class III antiarrhythmic agent. Arrhythmia and sudden cardiac death have been associated with patients given IV domperidone in the setting of hypokalemia and, as a result, the IV formulation is no longer available [13, 14]. Prolonged QTc has been associated with PO domperidone use, although this may not lead to adverse events [15]. However, an increased risk of cardiac events associated with oral domperidone use exists when compared to PPI use, metoclopramide use, or nonuse of either medication with increased events for both serious ventricular arrhythmia and sudden cardiac death [16, 17]. Past use of domperidone has not been associated with increased risk of cardiac events. Risk may also be increased in patients older than 60 years, males, receiving higher doses, and in individuals without diabetes [16–18].

Domperidone is available in oral tablet, oral suspension, and rectal formulations. The recommended dosing is 10–20 mg 2–4 times daily 15–30 min before meals. Pediatric dosing is 0.1–0.3 mg/kg/dose 2–4 times daily, not exceeding adult dose. Tablets may be crushed and given through gastrostomy, nasogastric, or jejunostomy tubes. FDA recognizes that there are some patients with severe gastrointestinal motility disorders that are difficult to manage with available therapy for whom domperidone's potential benefits may justify its potential risks. Patients 12 years of age and older with certain gastrointestinal conditions who have failed standard therapies may be able to receive treatment with domperidone through an expanded access investigational new drug application.

Metoclopramide

Metoclopramide is a dopamine (D2) receptor antagonist that stimulates the stomach and duodenum by causing efferent myenteric cholinergic neurons to release acetylcholine. There is also an increase in the lower esophageal sphincter (LES) tone [19, 20]. Metoclopramide's antiemetic properties are due to its effects on the central nervous system D2 receptors in the chemoreceptor trigger zone. Metoclopramide is recommended for chemotherapy-induced nausea and vomiting (CINV) prophylaxis and for the treatment of CINV that occurs despite prophylaxis in adult cancer patients [21]. It is also recommended for CINV prophylaxis as an alternative to dexamethasone in children receiving moderately emetogenic chemotherapy [22]. A systemic review described the adverse effects associated with the administration of metoclopramide [23]. A total of 108 (57 prospective) studies involving 2699 patients (2745 metoclopramide courses) were included. The most common adverse effects reported in prospective studies of metoclopramide in children were extrapyramidal symptoms (EPS; 9%, 95% confidence interval [CI] 5–17), diarrhea (6%, 95% CI 4–9), and sedation (multiple-dose studies: 6%, 95% CI 3–12). Dysrhythmia, respiratory distress/arrest, neuroleptic malignant syndrome, and tardive dyskinesia were rarely associated with metraclopramide use. These side effects were reversible and of no long-term significance. Adverse effects that were life threatening or slow to resolve were rarely associated with its use in children. Based on the findings of this systematic review and meta-analysis, the adverse effect profile of metoclopramide does not seem to preclude its judicious use in children. EPS can be reversible with timely discontinuation of metoclopramide and administration of diphenhydramine or benztropine. Children receiving metoclopramide and their parents must be made aware of the possibility of metoclopramide-induced EPS, which could be permanent if not quickly recognized treated.

Metoclopramide is available in the PO, SC, IM, and IV forms. A nasal spray formulation is currently undergoing clinical trials [24]. The adult dose is 10 mg 3–4 times daily. The pediatric dose is 0.4–0.8 mg/kg/day divided 4 times a day not to exceed adult dosage. A black box warning issued by the United States Food and Drug Administration cautions that cumulative use >12 weeks in duration increases risk of tardive dyskinesia, which may be irreversible. The half-life in children is around 4 h with 85% being eliminated in the urine, therefore dosing should be adjusted in cases of renal dysfunction. Metoclopramide does cross the placenta, although there may not be teratogenic effects [25], and it is excreted in breast milk.

Motilin Agonists

Erythromycin

Erythromycin is a macrolide antibiotic; it acts as a motilin agonist and a prokinetic. It induces gastric anrum contractions and phase III of the migrating motor complex in the duodenum [26]. Patients usually develop rapid tolerance and tachyphylaxis to erythromycin and loss of therapeutic efficacy. Clinical response usually decreases after 4 weeks; however, some patients may experience some benefit for a longer period. In order to overcome the tachyphylaxis, some experts will use it intermittently to treat children with chronic motility disorders. Indications and use of erythromycin in children with gastroparesis and pediatric intestinal pseudoobstruction are covered in chapters. Erythromycin has

been used to treat infants, especially low birth weight and premature babies with feeding intolerance. Postnatal exposure to erythromycin has been associated with development of infantile hypertrophic pyloric stenosis [27].

Erythromycin may be given through both oral and intravenous routes. Adult dosing ranges from 50 to 250 mg, 3 or 4 times a day and pediatric dosing is typically 5 mg/kg/dose. Different motor patterns are elicited from varying erythromycin dosages [28]. Low dose erythromycin (1–3 mg/kg IV) stimulates the enteric neuronal motilin receptors leading to augmentation of phase 3 of the MMCs [28, 29]. A higher dose of the drug stimulates the smooth muscle motilin receptors, leading to sustained contractions in the antrum and antroduodenal coordination [28–30]. There has been no evidence that erythromycin has any prokinetic effect on the colon [31, 32].

Commonly reported side effects include nausea, vomiting, and abdominal pain. There have been reports of erythromycin being associated with serious cardiac arrhythmias and prolonged QTc [33–35]. Erythromycin should not be used concurrently with medications metabolized by cytochrome P450 3A4 (CYP3A4) such as cisapride, terfenadine, pimozide, or astemizole as it is a CYP3A4 inhibitor. Caution must be used in young infants as there is an eight- to tenfold increased risk of developing hypertrophic pyloric stenosis in term or near-term infants when used within the first 2 weeks of life and when the treatment course is >14 days [36]. There are insufficient data in the preterm infant population as to whether there is increased risk of pyloric stenosis and a recent review did not show increased incidence for this particular population for treatment of dysmotility due to immaturity of the gastrointestinal tract [37]; in fact, feeding tolerance may be improved with erythromycin in preterm infants with very low birth weight [38]. Erythromycin is excreted in breast milk at levels ranging from 50% to 100% of maternal serum levels [39] and should be taken into consideration when treating nursing mothers.

More recently, azithromycin has been considered as an alternative to erythromycin as a prokinetic agent. It has been shown to bind to motilin receptors on enteric neurons and to produce contractions similar to erythromycin [40, 41]. Unlike erythromycin, it is not a CYP3A4 inhibitor so there may be less concern for drug interactions. However, all macrolides have been associated with possible QTc prolongation.

Cholinergic Agents

Bethanechol

Bethanechol is a cholinergic medication, which acts as a muscarinic receptor agonist leading to stimulation of esophageal peristalsis and increased antral contractility. It is also used to treat urinary retention secondary to neurogenic bladder. It causes decreased episodes of esophageal reflux by increasing LES pressure and increasing esophageal clearance [42–45]. Bethanechol's effect on the amplitude and duration of esophageal contractions is more pronounced in the distal esophagus and there is less effect on upper esophageal motility [46]. In patients with normal LES tone and normal esophageal motility, it is questionable whether bethanechol is useful in the treatment of uncomplicated GER and acid suppression may better serve this population [47, 48]. Patients with known esophageal dysmotility and abnormal LES tone, such as those post-tracheoesophageal fistula repair or esophageal atresia, may benefit from bethanechol [49]. It improves smooth muscle function in patients with ineffective esophageal motility documented by esophageal manometry [50].

Bethanechol, a direct cholinergic agonist, is not approved by the FDA for use in children, has been studied in a few trials in pediatric GERD, has uncertain efficacy, and carries a high potential of side effect such as dyspeptic symptoms, drowsiness, dizziness, fatigue, lowered threshold for seizures, headache, breathlessness, and nasal pain. Bethanechol is available by oral and subcutaneous administration only and the onset of action is 30–90 min. Pediatric dosing is 0.1–0.2 mg/kg/dose before meals up to 4 times a day and the adult dose is 10–50 mg 2–4 times a day. Side effects to note include bronchial constriction and it should be used with caution in asthmatics.

Neostigmine

Neostigmine is a parasympathomimetic agent which acts as a reversible acetylcholinesterase inhibitor. The resulting increased acetylcholine activates M receptors. M1 receptors in the salivary glands and stomach promote sialorrhea, gastric secretions, and vomiting. M2 and M3 receptors in the gastrointestinal mucosa and smooth muscle lining produce contraction which hastens gastrointestinal transit time and promotes colonic propulsion. Neostigmine has also been used to treat patients with acute colonic pseudoobstruction (ACPO), also known as Ogilvie's syndrome. Its use as a promotility agent has not been well-studied in pediatric patients [51]. In a group of 10 pediatric patients with hematologic malignancies who experienced ACPO, eight responded to doses of neostigmine at 0.01 mg/kg/dose administered subcutaneously, given twice a day for no more than five doses [52]. One patient reported diplopia and one reported abdominal pain [52]. There are additional case reports of successful treatment of pediatric patients with ACPO [53, 54]. Neostigmine has been shown in pediatric case series to be efficacious in some children for refractory postoperative

ileus. Peterson et al. reported that three pediatric patients who developed refractory ileus post-liver transplant were safely and effectively treated with continuous infusions of neostigmine [55].

5-Hydroxytryptamine-4 ($5HT_4$) Receptor Agonists

Cisapride

Cisapride is a $5HT_4$ receptor agonist which acts on the myenteric plexus and stimulates smooth muscle contraction by release of acetylcholine. $5HT_4$ receptors are found throughout the gastrointestinal tract and stimulation causes increased peristalsis as well as intraluminal fluid secretion. It's action on stomach smooth muscle leads to accelerated gastric emptying. Amplitude of esophageal peristalsis as well as resting LES tone is increased [56]. Cisapride also decreases mouth to cecum time and colonic transit time [57].

While cisapride has never been approved for use in children under the age of 12 years, it has historically been used extensively in pediatric age group. The consensus statements issued by NASPGHAN and ESPGHAN in 2000 state that cisapride is recommended for pediatric GERD when nonpharmacologic treatment fails, but that the medication does require close monitoring and specific precautions should be undertaken [58, 59]. A 2010 Cochrane Review, however, did not show any difference in symptom improvement or weight gain when compared to placebo [60]. Nine studies comparing cisapride with placebo or no treatment that met inclusion criteria were included in the meta-analysis [61–68]. The authors reviewed five studies comparing results of esophageal pH studies in patients being treated with cisapride versus placebo, and while there was improvement in the reflux index, there was not significant improvement in the number of reflux episodes and episodes lasting longer than 5 min. Histologic examination of the esophagus was performed in three studies, and in two ($n - 6$, $n = 20$) studies, there was no statistical difference between cisapride and placebo [62, 66]; however, one study ($n = 17$) did have histologic improvement from baseline. Further large-scale studies are needed to assess the utility of cisapride for GERD, though due to limited access, it is unlikely this information will be obtained. Although cisapride may be efficacious in treating constipation, it is not recommended for treatment of standard constipation as the risks do not outweigh the benefits [69].

Availability of cisapride is restricted due to risk of prolonged QTc interval and serious cardiac arrhythmias and it is only available in most countries through limited-access programs. Multiple studies have shown increase in QTc interval in neonates, infants, and children; however, in many of these cases the medication was dosed above the recommended dosing and some were also taking a macrolide antibiotic concurrently [70–74]. Arrhythmias have also been reported ranging from notched *t* waves to torsades de pointes [70, 73, 75]. In a multicenter, double blind, placebo-controlled trial of 49 children (age 6 months–4 years), a dose of 0.2 mg/kg given 3 times a day in patients without cardiac risk factors for a treatment duration of at least 6 weeks did not show a statistically significant increase in QTc interval and no subjects experienced cardiac events [61].

Cisapride is metabolized in the liver by cytochrome P450 into norcisapride. It is eliminated in urine and feces and its half-life is 7–10 h. Adult dosing starts at 10 mg PO 2–4 times a day 15 min before meals and dose may be increased to 20 mg for efficacy. Pediatric dosing is 0.8 mg/kg/day divided into 3–4 times a day and not exceeding adult dose. In the case of renal or hepatic failure, 50% of the recommended dose should be started. It is contraindicated in combination with macrolide antibiotics, azole antifungals, and any drug that prolongs the QT interval. It should be avoided while CYP3A4 inhibitors are being used and grapefruit juice can also increase cisapride serum concentrations. Caution must be taken in infants who are breastfed as mothers may excrete medications in their breast milk that are contraindicated while using cisapride. Patients with known history of prolonged QTc should not be prescribed cisapride and patients with other known arrhythmias need careful monitoring. Electrolyte imbalance, especially potassium, increases the risk of serious cardiac side effects.

Cisapride is a mixed serotonergic agent that facilitates the release of acetylcholine at synapses in the myenteric plexus, thereby increasing gastric emptying and improving esophageal and intestinal peristalsis. It was withdrawn from the market of most countries more than 10 years ago, after it was found to produce prolongation of the QTc interval, increasing the risk of sudden death. In the USA, cisapride is available only under investigational new device (IND) protocols.

Tegaserod

Tegaserod is a 5-hydroxytryptamine-4 ($5HT_4$) receptor partial agonist. It was previously approved for treatment of females ≤55 years of age with constipation-predominant irritable bowel syndrome (IBS) or for chronic idiopathic constipation; however, it was withdrawn from the US market due to an increased risk of cardiovascular events. In 2019, tegaserod was reintroduced as for use in irritable bowel syndrome with constipation in women under 65 with no cardiovascular risk factors.

While tegaserod was never approved for pediatric use, it has been used off-label in some practices. A report on a sin-

gle center's experience in pediatric patients reviewed 72 patients with a median age of 10 years (1.1–18.3) [76]. Most of these children were treated for functional constipation and the mean follow-up period was 11.3 months (2.3–45.2). Patients reported a statistically significant improvement in bowel frequency and fecal continence. The most common adverse events were diarrhea (20%), abdominal pain (8%), and headache (4%). No cardiovascular events were reported.

Adult dosing is 6 mg, PO, twice daily before meals. Bioavailability is 11% and decreased by up to 65% when taken with food [77, 78]. It is metabolized in the liver and 66% is excreted unchanged in stool and 33% as metabolites in urine. Use is contraindicated in severe hepatic or renal impairment. Adverse reactions include diarrhea, abdominal pain, nausea, flatulence, headache, and back pain.

Prucalopride

Prucalopride is a third-generation, highly selective 5-hydroxytryptamine 4 (5-HT4) receptor agonist. It reduces colonic transit time and is the principle mechanism of action for its use in chronic constipation [79, 80]. Prucalopride may reduce gastric emptying time and has been used to treat gastroparesis. According to a recent post hoc analysis analyzing six phases 3 and 4 randomized, double-blind, placebo-controlled studies of patients with significant abdominal bloating by Lembo et al., treatment with prucalopride improved symptoms compared with placebo, irrespective of baseline bloating severity, and was most effective in women and patients <65 year old with chronic idiopathic constipation [81]. Prucalopride is a highly selective, high affinity 5-HT_4 receptor agonist, which increases colonic motility by stimulating serotonin release leading to giant migrating contractions [82]. Gastro-pyloro-duodenal motility, as well as gastric emptying, is also enhanced in the canine model [83]. A study in healthy adult males replicated the increased gastric emptying as well as acid clearance from the esophagus and decreased proximal esophageal reflux [84]. There was no decrease in LES relaxation or reflux events. Prucalopride is structurally different from previously available 5-HT_4 receptor agonists and, due to its selectivity, the cardiac side effects seen with cisapride and tegaserod have not been reported. Use of prucalopride has mostly been in adult patients with chronic constipation. Prucalopride reportedly lost its efficacy gradually after the first few weeks of favorable and beneficial response in some patients. Tachyphylaxis, the development of tolerance, could cause this incomprehensible phenomenon, leading to drug dose escalation of reaching the same result [85].

Prucalopride has shown efficacy in managing adult patients with constipation who have not obtained relief from laxatives, regardless of subtype or symptom pattern [86, 87]. In children with constipation, prucalopride use did not provide a consistent outcome; some authors reported beneficial effect while others failed to find therapeutic response [88].

There is literature to suggest prucalopride is effective in reducing symptoms of postoperative ileus and chronic intestinal pseudoobstruction in adults [89, 90]. Mutalib et al. reported their experience in the use of prucalopride in children with intestinal pseudoobstruction both in the acute and chronic settings. In this series, the use of prucalopride in children with acute, intermittent, or chronic intestinal pseudoobstruction appears to be safe and effective. None of the children experienced any adverse effect and prucalopride was overall well-tolerated [91].

Velusetrag (TD-5108)

Velusetrag is a next-generation, pan-GI, potent, very selective 5-HT4 agonist with prokinetic activity under investigation for treatment of gastroparesis and other GI motility disorders [92–94]. Velusetrag has no significant affinity for any other receptor types, including 5-HT1, 5-HT2, 5-HT3, and dopamine receptors; ion channels, including human ether-à-go-go–related gene potassium channel; or enzymes tested to date [94]. Consistent with its target specificity, velusetrag does not affect coronary artery tone or human platelet aggregation in vitro [95]. Velusetrag showed efficacy and a favorable safety profile in a large phase 2 study in adult subjects with chronic constipation [93]. A phase to study in adults with gastroparesis reported improvement in gastric emptying both in diabetic and idiopathic gastroparesis [96]. The most commonly encountered side effects were diarrhea, headache, nausea, and vomiting. No cardiovascular adverse events were reported.

Other Prokinetic Agents

Octreotide

Octreotide is a synthetic octapeptide that is a long-acting somatostatin analogue used in many disease processes including gastrointestinal bleeding, pancreatitis, secretory diarrhea, chylous leakage, hypoglycemia, and gastrointestinal dysmotility. For the purposes of this section, only the use of octreotide in gastrointestinal dysmotility will be discussed. Somatostatin, studied in patients with normal gastrointestinal motility as well as the canine model, causes inhibition of gastric activity and stimulation of small intestinal phase 3 of the MMCs beginning in the duodenum [97, 98]. It is commercially available for SC, IV, and IM use.

Subcutaneous absorption is rapid and IM is released slowly in a depot formulation. Metabolism is through the liver with 32% unmetabolized excretion through the urine [99]. Half-life is 1.7–1.9 h, but it is 3.7 h in patients with cirrhosis and 3.1 h in patients with renal impairment [77].

Octreotide has been studied in adult patients with scleroderma and pseudoobstruction; subcutaneous octreotide increased the frequency of intestinal MMCs [100]. A single case report described a 12-year-old girl with chronic idiopathic pseudoobstruction who was successfully treated using 50 mcg of subcutaneous octreotide daily [101].

Methylnaltrexone

Methylnaltrexone is a peripheral μ-opiate antagonist that has been used in the setting of opiate-induced constipation [102]. Opioid-induced constipation is reversed without inducing withdrawal symptoms or decreasing analgesic effect [102–104]. μ-receptors are found throughout the gastrointestinal tract [105] and stimulation leads to delayed transit and nonpropulsive activity [106]. Decreased intestinal secretion as well as increased absorption in the small bowel and colon also contributes to the constipating effect of opioid medications [107].

In treatment of adult patients receiving chronic opioids for nonmalignant pain, doses of 12 mg every day and every other day have been used; both regimens significantly decreased the time to rescue-free bowel movement as well as increased the number of weekly bowel movements compared to placebo [108]. Adults with advanced illness and opioid-induced constipation treated with doses of 0.15 and 0.3 mg/kg had significantly increased rates of rescue-free bowel movements within 4 h of administration compared to placebo [103, 104].

Pediatric data in oncology patients have reported improvement in number and frequency of bowel movements. No major adverse events were reported in these small pediatric studies [109–113].

Methylnaltrexone is available in a subcutaneous form with onset of action between 30 min and 4 h and a half-life of 8–9 h [108, 114, 115]. It is administered every other day with dosing based on body weight (<38 kg: 0.15 mg/kg; 38 to <62 kg: 8 mg; 62–114 kg: 12 mg; >114 kg: 0.15 mg/kg). Excretion is through both urine and feces, primarily as unchanged drug [115]. Side effects include flatulence, abdominal pain, nausea, dizziness, excessive sweating, and diarrhea. Intestinal perforation has been reported with use and it should be used with caution in patients with diminished gastrointestinal wall integrity. Patients with severe renal impairment (creatinine clearance <30 mL/min) should be dosed at 50% of recommended dosing.

Naloxegol

Naloxegol is a newly approved oral peripheral μ-opiate antagonist for use in opioid-induced constipation not associated with pain control for cancer. It is a PEGylated form of naloxone and therefore does not cross the blood–brain barrier. Compared to placebo, a 25 mg/day dose produced significantly higher response rates over a 12 week period with the primary end point being ≥3 spontaneous bowel movements per week and an increase from baseline of ≥1 spontaneous bowel movements for ≥9 of 12 weeks and for ≥3 of the final 4 weeks [116].

In adults, Naloxegol is dosed at 25 mg/day and reduced to 12.5 mg/day if not tolerated [117]. Laxatives should be stopped prior to the initial dose. Renal dosing is 12.5 mg/day if CrCl <60 mL/min, but may be increased to 25 mg if tolerated. Metabolism is hepatic through CYP3A and use should be avoided with CYP3A4 strong inhibitors. Time to peak concentration is 2 h and elimination is in the feces and urine with up to 32% unchanged drug.

Amoxicillin/Clavulanate

In a study of 20 patients undergoing antroduodenal motility testing, administration of 20 mg/kg of amoxicillin/clavulanate into the small bowel induced a duodenal phase III motility pattern in 2 out of 10 patients receiving the medication 1 h after a meal and in 9 out of 10 patients receiving the medication 1 h before a meal [118]. Further studies are needed to determine the role of amoxicillin/clavulanate as a prokinetic agent.

Antimotility Agents

The commonly used agents are the opioid receptor agonists, loperamide and diphenoxylate (Table 43.1).

Loperamide

Loperamide is a synthetic opioid receptor agonist acting on the μ opioid receptors in the myenteric plexus of the large intestine [117]. It has been shown in meta-analysis of randomized controlled trials to be safe and effective in treating acute diarrhea in adults and children [119, 120]. Serious side effects were reported more often in children younger than 3 years old [120]. Loperamide has also been shown in clinical trials to be effective in reducing stool frequency and urgency in patients with diarrhea-predominant IBS [121]. Side effects include abdominal pain and bloating, constipa-

Table 43.1 Antimotility and antispasmodic agents

Medication	Dosing	Notes
Loperamide	Acute diarrhea (first 24 h)	Adult dose acute and chronic diarrhea—First dose 4 mg, then 2 mg after each loose stool, maximum 16 mg daily
	– 2–5 years (13–20 kg): 1 mg 3 times a day	
	– 6–8 years (21–30 kg): 2 mg twice a day	
	– 9–12 years (>30 kg): 2 mg 3 times a day—After first 24 h–0.1 mg/kg doses after each loose stool not exceeding initial dose	
	Chronic diarrhea—0.08–0.24 mg/kg/day divided 2–3 times a day, maximum: 2 mg/dose(PO)	
Diphenoxylate	– 2–5 years—2 mg 3 times a day	Adult dose 5 mg 4 times a day
	– 5–8 years—2 mg 4 times a day	
	– 8–12 years—2 mg 5 times a day (PO)	

tion, sedation, dry mouth, and, rarely, paralytic ileus. This medication should not be used in the setting of acute diarrhea caused by enteric bacterial pathogens such as *Salmonella* and *Shigella* and in acute ulcerative colitis as it can precipitate toxic megacolon. It should also not be used in children <2 years old; indeed, deaths have been reported in young children given loperamide to treat acute diarrhea [122].

Diphenoxylate

Diphenoxylate is a synthetic opioid receptor agonist related to meperidine and fentanyl [117]. Its mechanism of action is similar to loperamide, but can be habit forming. Atropine is reportedly added to the preparation to reduce the abuse potential [123, 124].

Antispasmodics

Antimuscarinics

Antimuscarinics are a class of drugs that work by blocking the action of acetylcholine at postganglionic parasympathetic receptors in the intestinal smooth muscle. The antispasmodics available in North America are alverine, dicyclomine, hyoscyamine, mebeverine, otilonium, pinaverium, and trimebutine for the treatment of chronic abdominal pain in patients with common disorders of gut-brain interaction.

Hyoscyamine

There are no pediatric data regarding efficacy in treating functional abdominal pain or IBS with hyoscyamine [125].

Dicyclomine

Dicyclomine is a smooth muscle relaxant and has been associated with side effects like breathing difficulty. Therefore, it is not routinely used in children less than 6 months. In two randomized, placebo-controlled studies, dicyclomine improved symptoms of IBS relative to placebo [126–133]. One study reported no difference in adverse event (AE) rates with dicyclomine versus placebo [127], whereas the other reported that AEs occurred in a greater percentage of patients (69%) receiving dicyclomine 160 mg/d continuously for 2 weeks versus patients receiving placebo [126].

Scopolamine (Hyoscine)

It has been used to treat various gastrointestinal disorders including IBS and motion sickness [134]. In three studies, hyoscine taken for a duration of 4 weeks to 3 months was more efficacious than placebo at improving IBS symptoms (44–46). Only one study adequately reported AEs [45]. Although all three studies reported favorable efficacy, they differed in treatment duration and definitions of IBS, and two studies lacked separate assessments of abdominal pain [128–130]). Methscopolamine and butylscopolamine are derivatives of scopolamine which have also been used to treat IBS. Scopolamine was found in a meta-analysis study to offer benefit in the treatment of IBS in adults [135]; however, there are no published randomized controlled studies establishing its efficacy in pediatric population.

Common side effects of antimuscarinic agents include dry mouth, urinary retention, blurred vision, constipation, sedation, and palpitations.

Direct Smooth Muscle Relaxers

Mebeverine and related drugs including alverine, otilonium, and drotaverine [136–138] are not available in the USA, but are available in many countries.

OnabotulinumtoxinA (Botox®)

OnabotulinumtoxinA is the drug name for botulinum toxin A (BTX). It is a neurotoxin that acts through a strong binding to the presynaptic cholinergic-nerve terminals, ultimately inhibiting the acetylcholine release from nerve endings. It impairs muscular contractility and may also lower smooth muscle tone in the gastrointestinal (GI) tract. It has been used off-label to treat esophageal achalasia, gastroparesis, anal fissure, and anal achalasia [139].

Botox injection into the lower esophageal spinchter in children with achalasia can transiently improve symptoms and repeated intervention is needed. Data regarding efficacy and side effects are limited in pediatric population and most

experts choose this treatment modality only when dilation or surgical treatment options are not available or considered high risk. A single center reviewed their experience with pediatric patients diagnosed with esophageal achalasia; out of their 33 patients, 7 were treated with Botox [140]. They used 100 U of Botox per session with 25 U injected into each quadrant of the LES. Six of the seven required 2–3 repeated injections and the longest duration of symptom-free period postinjection was 10 months.

In two studies, pediatric patients treated with Botox injections for anal outlet obstruction (postsurgical repair of Hirschsprung disease and primary internal anal sphincter achalasia) had variable outcomes [141, 142]. The dosage used was 3–6 U/kg/session to a maximum of 100 U. In 31–53% of patients, good long-term outcome was reported and 62–89% had initial clinical improvement after a single injection. Complications included pain following the injection and fecal incontinence. In a recent study of 33 children with obstructive symptoms following surgical treatment of Hirschsprung disease who were treated with anal intrasphincteric Botox injection, initial improvement was found in 76% with a medium duration of 4.1 months (1.7–58.8). Long-term response was observed in 49% [143].

Botox injections have also been used to treat chronic anal fissures. In a single center study of 13 children (age 1–10 years) with chronic anal fissures [144], patients under age 2 years were injected with 1.25 U × 2 doses and patients over age 2 years were injected with 2.5 U × 2 doses. Eleven of the 13 patients had resolution of their symptoms within 1 week of treatment and no adverse events were reported. In a systematic review of nonsurgical therapies for chronic anal fissures, Botox was found to be equivalent to topical nitroglycerin in efficacy; however, nitroglycerin itself was only marginally better than placebo [145]. A recent randomized trial compared the efficacy of electromotive delivery of Botox into the anal sphincter in children with intractable constipation. After 1 month follow-up, the stool form normalized in 73.3% (22/30) in electromotive Botox delivery group compared to 80% (24/30) in injection group. The median of constipation score and pain score decreased significantly in both groups after treatment, suggesting noninvasive electromotive Botox is as effective as Botox injection in treating children with chronic constipation [146].

There is a paucity of data on the usefulness of intrapyloric injections of Botox for treatment of gastroparesis. One randomized controlled crossover study of 23 adult patients with gastroparesis showed no benefit of Botox injection (25 U/quadrant; 100 U total) compared to placebo [147]. In a single published retrospective pediatric study of 45 children receiving intrapyloric Botox injection for idiopathic gastroparesis, 66.7% of the patients reported improvement with 90% reporting moderate improvement to complete resolution of their symptoms. The median duration of response to the initial injection was 3 months (1.2–4.8) [148] A recent multicenter retrospective study reported results in 24 children with gastroparesis and efficacy of intropyloric botox injection was comparable to pylorus balloon dilation. Improvement in symptoms was temporary and repetition on intervention was needed [149].

Topical Nitrates

Topical nitrates have been used to treat painful anal conditions. There are three formulations available—mono, di, and trinitrates—all act to relax smooth muscle by stimulating production of cGMP, irrespective of autonomic innervations [150]. The only topical formulation available in the USA is nitroglycerin, which is a trinitrate. Its most common use in gastroenterology is for treatment of chronic anal fissures.

In children with anal fissures, 0.2% glyceryl trinitrate (GTN) applied topically to the distal anal canal twice a day resulted in improvement of symptoms by day 10 of treatment and higher rates of complete resolution after 8 weeks compared to placebo and topical lidocaine [151, 152]. However, one study comparing GTN plus oral senna and lactulose with placebo plus oral senna and lactulose found similar response rates, with 84% healing overall [153]. Concentrations of 0.05% and 0.1% ointments were also found to be effective for fissure healing after 8 weeks of treatment [154]. Results at 8 weeks of treatment were similar to results using a eutectic mixture of 5% prilocaine and 5% lidocaine (EMLA) [152]. Long-term treatment of chronic anal fissure in 31 children using 0.2% GTN resulted in a 32% relapse 1 year after treatment and no relapses for 4 years following initial treatment in 68% [155].

Glycerine trinitrate has also been used to treat proctalgia fugax, which mainly occurs in patients aged 30–60 years [156, 157].

Calcium Channel Blockers

It has been suggested that calcium channel blockers may be effective in the treatment of some gastrointestinal motility disorders because of their ability to relax smooth muscles. Nifedipine and verapamil have been shown to inhibit sigmoid colon myoelectric response to eating in healthy adult volunteers [157] and reduce internal anal sphincter pressures in patients and controls with high resting anal sphincter pressures [158].

Nifedipine has been used to treat disorders of esophageal hypermotility such as nutcracker esophagus and achalasia in children and adults [159–163]. Nifedipine at a dose of 0.2 mg/kg aspirated from Gelcaps and given every 6 h reduced the amplitude and number of simultaneous contractions and resulted in clinical improvement in two toddlers diagnosed with diffuse esophageal spasms on esophageal manometry [164]. Diltiazem has been used anecdotally to treat diffuse esophageal spasm in adolescents [165]. Verapamil has anecdotally been used to treat antral spasms in children [166].

Pinaverium, a calcium channel blocker which acts selectively on the gastrointestinal tract, has been found to reduce the duration of abdominal pain in randomized, placebo-controlled studies of adult patients with IBS [167, 168].

Peppermint oil is believed to be a calcium channel blocker and has been found to relax the LES in healthy subjects as well as reduce colonic spasms in patients undergoing colonoscopy [169, 170]. It has been found in double-blind randomized controlled studies to be effective in treating children and adults with IBS [171, 172], and in meta-analysis studies of published trials, it was found to be effective in the treatment of both adults and children with IBS [173, 174]. A recent meta-analysis of nine studies including 726 patients found peppermint oil to be superior to placebo for improvement of global IBS symptoms with minimal side effects [175]. Side effects of calcium channel blockers include headaches, lightheadedness, and constipation.

In summary, meta-analysis studies of controlled trials of antispasmodics in the treatment of IBS have found them to be somewhat superior to placebo, at least for the short term, in the management of IBS in both adults and children [135, 176, 177].

Laxatives

Laxatives can be divided into osmotic/lubricant laxatives and stimulant laxatives (see Table 43.2). First-line treatment for constipation starts with osmotic/lubricant laxatives followed by stimulants for cases that are poorly responsive to the initial treatment.

Table 43.2 Laxatives

Therapy	Dosage
Osmotic agents	
Lactulose	– 1–3 mL/kg/day in divided doses
Magnesium citrate	– May use divided doses. – <6 years—1–3 mL/kg/day – 6–12 years—100–150 mL/day – >12 years—150–300 mL/day
Magnesium hydroxide	– May use divided doses. – 1–3 mL/kg/day of 400 mg/5 mL solution
Polyethylene glycol	– 1 g/kg/day
Sorbitol	– 1–3 mL/kg/day in divided doses
Lubricants	
Mineral oil	– 1–3 mL/kg/day
Stimulants	
Bisacodyl	– 3–12 years—5 mg/day – >12 years—5–15 mg/day
Senna	– 2–5 years—2.5–7.5 mL at bedtime – 6–12 years—5–15 mL at bedtime
Lubiprostone (adult dosing only)	– Chronic idiopathic constipation—24 mcg BID – Female IBS with constipation—8 mcg BID

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Osmotic and Lubricant Laxatives

Lactulose

Lactulose (1–4-beta-galactosidofructose) is a semisynthetic disaccharide created through the isomerization of lactose [178]. Lactulose increases osmotic load as well as decreases the stool pH thereby increasing colonic propulsion [179]. It passes through the small intestine intact without degradation by disaccharidases and is broken down by bacteria in the colon to produce lactic and acetic acid [180]. Systemic absorption is minimal with majority of excretion through the stool and <3% excretion in urine. Formulations contain both lactose and galactose, so use is contraindicated in patients with galactosemia. Onset of action is 24–48 h and side effects include cramping, abdominal distension, flatulence, diarrhea, nausea, vomiting, and electrolyte imbalances. Long-term use is safe with few reported adverse events [69].

Magnesium Salts

Magnesium salts are available commercially as magnesium citrate and magnesium hydroxide. All magnesium salts promote bowel evacuation by osmotic fluid retention. Absorption is 15–30% and excretion is in the urine. Use is contraindicated in patients with renal failure and renal insufficiency as hypermagnesemia is a significant risk. Caution should be used even in patients who do not have renal dysfunction as excessive ingestion can lead to hypermagnesemia in otherwise healthy children [181, 182]. Other side effects include diarrhea, abdominal cramps, flatulence, hypotension, and respiratory depression. There are few studies evaluating the efficacy of magnesium salts in treatment of constipation; however, compared to a bulk laxative, it may produce more frequent bowel movements [183]. Palatability of magnesium may decrease compliance. When compared to polyethylene glycol (PEG) solution over a 12-month period, 95% of children using PEG were compliant versus 65% using magnesium hydroxide [184].

Polyethylene Glycol

Polyethylene glycol is a high molecular weight, nonsoluble polymer that acts as an osmotic laxative. Hydrogen bonds are formed between PEG and water, which prevents reabsorption of water in the colon. With increased water retention, stool is thereby softened and its bulk is increased. The onset of action is 24–96 h; excretion is 93% through feces with minimal systemic absorption and a bioavailability of 0.2% [185]. Polyethylene glycol has minimal systemic absorption. In one pediatric study blood levels of ethylene glycol (EG), diethylene glycol (DEG), or triethylene glycol (TEG) in nine children receiving daily PEG 3350 therapy were not significantly different compared to 18 age and gender-matched controls. The authors concluded that PEG 3350 therapy in children was not associated with sustained elevation of EG, DEG, or TEG blood levels over levels in

matched controls. Although EG and TEG levels increased after a standard dose of PEG 3350, their peak values remained well below toxic levels [186]. Contraindications to PEG include hypersensitivity, ileus, bowel perforation or obstruction, and toxic megacolon.

PEG is available with or without electrolytes added. In general, PEG with electrolytes is used for colonoscopy preparation or disimpaction. PEG without electrolytes is more commonly used for daily management of chronic constipation, but has been used in children for colonoscopy preparation as well [187, 188]. High-dose PEG without electrolytes can be as successful for disimpaction in the pediatric population [189] with highest success for doses of 1–1.5 g/kg/day [190]. PEG is safe and well-tolerated for long-term treatment of chronic constipation with few noted side effects [184, 191–194].

Sorbitol

Sorbitol is a polyalcoholic sugar and acts as a hyperosmotic laxative. Absorption is minimal and it is metabolized in the liver mainly into fructose. There is a paucity of studies, evaluating the efficacy of sorbitol for treatment of constipation. Compared to lactulose it has similar safety and efficacy in the geriatric population [195]. Excessive ingestion of sorbitol in non-constipated pediatric patients is known to cause loose stool and diarrhea [196, 197]. Side effects include diarrhea, nausea, vomiting, lactic acidosis, and electrolyte imbalances.

Mineral Oil

Mineral oil is a lubricant laxative with minimal systemic absorption and primary elimination in the feces. It is a mixture of hydrocarbons derived from petroleum. The oil lubricates the colon, but it also decreases water reabsorption and softens the stool. It should not be used in infants and patients with swallowing dysfunction since there is a risk for lipid pneumonitis with aspiration [198–200]. Other adverse effects include diarrhea, nausea, vomiting, anal itching, and anal seepage. Chronic use could theoretically decrease absorption of fat-soluble vitamins; however, there is no published evidence to support this [201, 202]. One study showed a reduction in beta-carotene levels after just 1 month of treatment [202].

Stimulant Laxatives

Bisacodyl

Bisacodyl is a diphenolic laxative that stimulates intestinal fluid secretion and motor activity. It induces intestinal fluid secretion by direct action on the enterocyte, activating adenylate cyclase and causing an increase in production of cyclic-AMP [203, 204]. Chloride and bicarbonate ions are actively secreted, while sodium and potassium are passively effluxed into the bowel. Sodium and chloride are then inhibited from reabsorption back into the enterocyte. Contraction of the colonic smooth muscle is caused by increasing the myoelectrical activity through direct irritation of the bowel wall [205, 206]. Systemic absorption is <5% with onset of action between 4 and 6 h for oral administration and 0.25–1 h for rectal administration [206, 207]. The small fraction that is absorbed is conjugated by the liver and excreted in urine. Most formulations are enteric-coated and should not be administered within 1 h of antacids. Side effects include nausea, vomiting, diarrhea, abdominal cramping, proctitis, and electrolyte imbalance.

Bisacodyl and other stimulant laxatives should be used as second-line agents for patients who are refractory to osmotic/lubricant laxatives [69]. There are no data on safety and efficacy of bisacodyl for treatment of constipation, particularly in the pediatric population [208]; however, there is clear evidence that it accelerates colonic transit and stimulates colonic motor activity [209–211]. A recent retrospective review of 164 children with functional constipation refractory to conventional therapy reported significant increase in number of bowel movements per week following treatment with bisacodyl. The median bisacodyl dose was 5 mg/day. Approximately 57% of patients had successful response and 55% of patients were successfully weaned off bisacodyl on long-term follow-up (median duration 18 months). Side effects were reported in 9% of the patients [212]. Chronic and prolonged use of stimulant laxatives may lead to loss of haustra and anatomic changes in the colon, possibly due to muscular or neuronal injury [213, 214]; it is unclear, however, if this is a true risk of long-term usage of bisacodyl [215].

Senna

The mechanism of action of senna as a stimulant laxative is unclear; however, it may increase production of cyclic-AMP in the colon leading to increased ion secretion and increased peristalsis by direct irritation of the colon [216]. Senna is derived from the plant *Senna alexandrina* and has been used for centuries. Absorption is minimal and onset is 6–12 h after ingestion. Senna is metabolized in the liver and excreted through feces and urine. Reported adverse events include hepatitis, hypertrophic osteoarthropathy, analgesic nephropathy, and melanosis coli, which is reversible. There is poor evidence for development of cathartic colon with long-term use of senna [217]. As with other stimulant laxatives, it is a second-line agent and is used in constipated patients failing first-line treatment. Although it is commonly used, there is a

paucity of studies evaluating its efficacy in treatment of constipation [208].

A recent meta-analysis of 18 randomized controlled trials (1643 patients) of osmotic and stimulant laxatives for the management of childhood constipation concluded that PEG preparations may be superior to placebo, lactulose, milk of magnesia, and mineral oil in the treatment of childhood constipation. The analysis also found evidence to support the efficacy of mineral oil. Overall, the authors of this meta-analysis found the quality of evidence to be low due to a number of reasons including inconsistency and high risk of bias [218].

Lubiprostone

Lubiprostone is a prostone that acts locally on the gastrointestinal tract by activation of type-2 chloride channels (CIC-2) [219]. It is approved for use in adults with chronic idiopathic constipation and females older than 18 years of age with constipation-predominant IBS. Prostones are bicyclic fatty acids derived from prostaglandin E_1 that do not significantly act on prostaglandin E or F receptors or cause smooth muscle contractions [220]. Activation of the chloride channels increases intestinal fluid chloride concentration and fluid secretion, leading to increased stool passage without causing significant change in serum electrolyte levels [219]. Lubiprostone worsens gastric emptying while accelerating small bowel and colonic transit time in normal adult volunteers [221]. A single published multicenter study of its use in the pediatric population found it to be efficacious and well-tolerated in the treatment of childhood constipation [222]. Doses used were 12 mcg daily for children <6 years old weighing at least 12 kg and children age 6–11 years old weighing between 12 and 24 kg, 12 mcg twice daily for children 6–11 years old weighing between 24 and 36 kg, and 24 mcg twice daily for all children at least 6 years old weighing at least 36 kg. Adult dosing is 24 mcg PO twice daily for chronic idiopathic constipation and 8 mcg PO twice daily for constipation-predominant IBS. A phase 3, multicenter, randomized, double-blind, placebo-controlled trial of 12-week lubiprostone 12 μg twice daily (BID) and 24 μg BID evaluated its efficacy and safety in pediatric functional constipation. A subgroup of these patients entered long-term, open-label extension of the study. Drug efficacy was assessed using rate of spontaneous bowel movement. Six hundred and six patients were randomized to treatment (placebo: $n = 202$; lubiprostone: $n = 404$). There was no statistically significant difference in overall spontaneous bowel movement response rate between the lubiprostone and placebo groups. Both the 12-μg BID and 24-μg BID doses of lubiprostone were well-tolerated with a safety profile consistent with that seen in adult studies. Lubiprostone did not demonstrate statistically significant effectiveness over placebo in children and adolescents with functional constipation [223]. Lubiprostone is distributed mainly in the gastrointestinal tract with minimal systemic absorption; it is rapidly metabolized in the stomach and jejunum by carbonyl reductase into the active metabolite M3. Sixty percent is excreted in the urine and 30% through the feces. Most common reported side effects include nausea, diarrhea, and headache [224]. There have been no studies on patients with hepatic or renal insufficiency and caution is recommended in these populations. No teratogenic effects have been reported; however, there has been increased fetal loss in the guinea pig model and therefore female patients should have a negative pregnancy test prior to initiation of therapy and be advised on contraception [220].

Linaclotide

Linaclotide is a new guanylate cyclase-C (GC-C) agonist [225] which was recently approved by the FDA (August 2012) for the treatment of IBS-C and chronic constipation in adults. Activation of GC-C leads to activation of the cystic fibrosis transmembrane conductance regulator causing secretion of chloride and bicarbonate into the small intestinal lumen [226]. Visceral hypersensitivity is suppressed by cGMP acting on submucosal afferent pain fibers to decrease nerve reactivity [227] and a decrease in abdominal pain compared to baseline and to placebo has been reported [228]. Doses ranging from 75 to 600 mcg improved bowel habits in men and women >18 years of age with IBS-C [228]. In adult women with IBS-C, colonic transit was improved over a 5-day treatment period with 1000 mcg of linaclotide [229]. For adult patients with chronic constipation, bowel movement frequency, stool consistency, and straining as well as overall quality of life were improved on trials of linaclotide [230, 231]. The approved dose for treatment in adults is 145 mcg QD for chronic idiopathic constipation and 290 mcg QD for constipation-predominant IBS. Clinical trials of linaclotide for treatment of childhood constipation and constipation-predominant IBS are ongoing. A retrospective study in 93 children with functional constipation or IBS-constipation reported positive clinical response based on the physician's global assessment of symptoms documented in patient charts. Sixty patients with functional constipation and 33 IBS patients were included in the study with a median follow-up of 2.5 and 2.4 months, respectively. Forty-five percent of patients with FC and 42% with IBS-constipation had a positive clinical response. Approximately a third of patients experienced adverse events and 27% stopped using linaclotide due to side effects. The most common side effects were diarrhea, abdominal pain, nausea, and bloating [232].

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Drugs Acting on the Brain

44

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Introduction

The relationship between the brain and the intestine, termed the "gut-brain axis," begins during development and persists throughout life. The gut-brain axis links the emotional and cognitive centers of the brain with intestinal functions. It regulates homeostatic functions that were classically thought to be exclusively gut-centric or brain-centric. In the intestine, these functions include sensation and motility. In the central nervous system (CNS), these roles evolve around the control of behavior, cognition, and mental health. Thus, when either system is disturbed, disease states emerge that can affect both systems.

The brain and gut communicate continuously through a number of complex pathways involving the enteric nervous system (ENS), the autonomic nervous system (ANS), the hypothalamus-pituitary axis (HPA), and the CNS. These pathways are highly integrated and regulated by neuronal and neurohumoral factors [1].

Complex mechanisms underlying disturbances in the bidirectional communication between the gastrointestinal tract and the brain play a significant role in the pathogenesis and understanding of functional gastrointestinal disorders (FGID). With the 2016 publication of the Rome IV criteria, FGID have been redefined as disorders of gut-brain interaction (DGBI), characterized by any combination of motility disturbances, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and CNS processing. Dysfunction of the gut-brain axis is the biological basis for these disorders and symptoms. DGBI are common in the pediatric age group and are associated with functional disability, impaired quality of life, and a cost burden on health care.

It has been well-established that patients with DGBI have both symptoms related to the gastrointestinal tract including abdominal pain, nausea, emesis, early satiety, diarrhea, etc., in addition to coexisting psychological symptoms including stress, anxiety, depression, and sleep disturbances [2].

In the treatment of DGBI, pharmacological agents targeting the gut-brain axis, known as neuromodulators, have focused on the HPA axis, serotonergic, noradrenergic, and dopaminergic systems. Thus, antidepressants will have effects not only on psychiatric disorders, but also on chronic GI symptoms routinely found in patients with DGBI.

Currently, the use of neuromodulators in treating pediatric patients with DGBI is neither fully elucidated nor widely accepted, likely due to limited research in the pediatric population. Most studies have small sample sizes, are noncontrolled, open-label or non-randomized, and many have yielded conflicting results, lack of superiority to placebo or small effect size. Despite the above, newer evidence is changing how we think about these disorders and their treatments. Ultimately, the approach is to reduce symptom burden and improve quality of life in patients, while minimizing side effects.

This chapter will provide an overarching review of the current available pharmacologic agents that play a role in modulating the gut-brain axis (Fig. 44.1) and how these therapeutics apply to DGBI. Particularly, we will define how these drugs are utilized in irritable bowel syndrome (IBS), functional dyspepsia (FD), functional abdominal pain (FAP), abdominal migraine, and cyclic vomiting syndrome (CVS) (Table 44.1).

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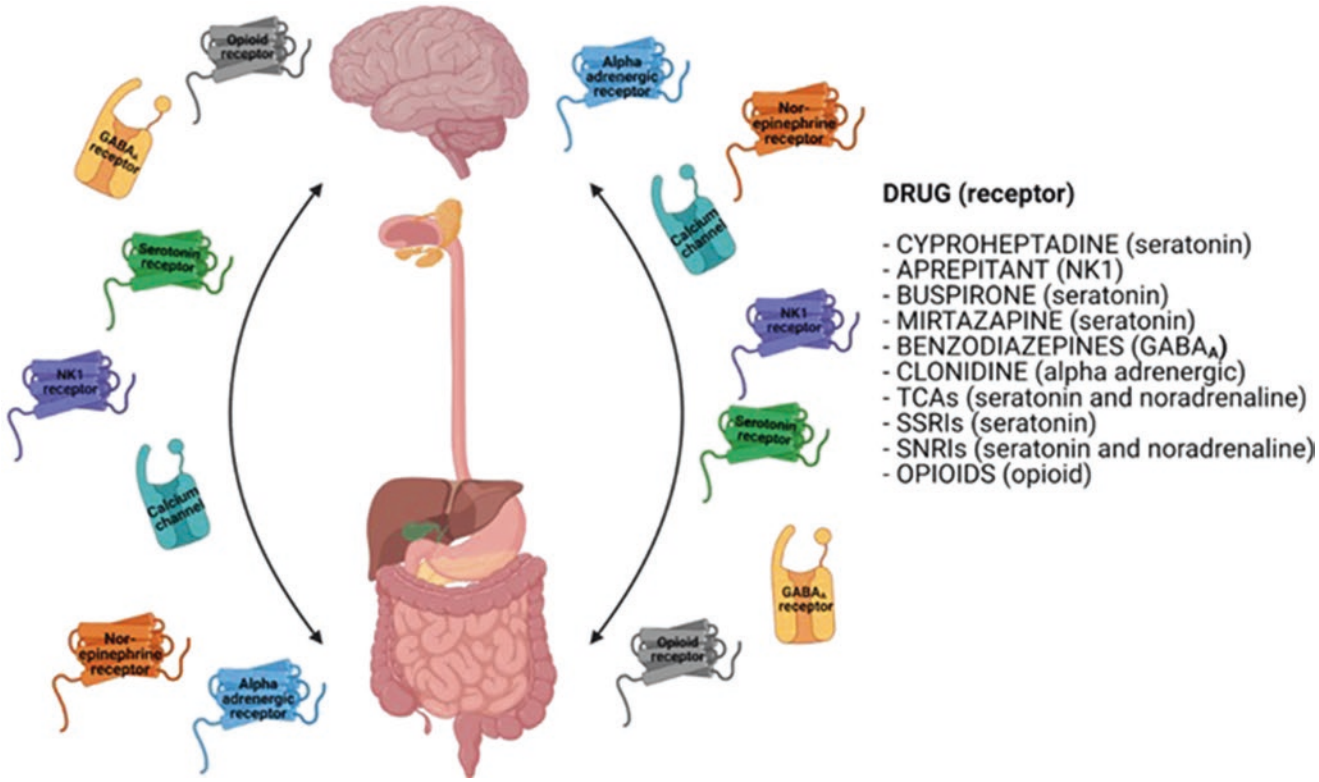

Fig. 44.1 Neuromodulators and associated receptors involved in gut-brain axis. NK1, Neurokinin1; GABA, gamma-aminobutyric acid; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor

Table 44.1 Indications, dosages, and major side effects of neuromodulators with evidence for use in pediatric DGBI

Disorder of gut-brain axis	Drug	Dose	Medication class	Side effect
Cyclic vomiting syndrome	*Prophylaxis*			
	Amitriptyline, in children >5 years	10–50 mg at bedtime	Tricyclic antidepressant (TCA)	Constipation, sedation
	Cyproheptadine, in children <5 years	0.25–0.5 mg/kg/day divided BID or TID	Serotonin, Histamine-1, muscarinic, and calcium channel receptor antagonist	Increased appetite, fatigue
	Mirtazapine	7.5–30 mg at bedtime	TCA	Weight gain, fatigue
	Acute			
	Aprepitant	<15 kg: Day 1: 80 mg orally day 2, 3: 40 mg, 15–20 kg: Day 1: 80 mg, day 2, 3: 80 mg, >20 kg: Day 1: 125 mg, day 2, 3: 80 mg	Neurokinin-1 receptor antagonist	
	Lorazepam	0.05–0.1 mg/kg q6h	Benzodiazepine	Respiratory depression
Functional dyspepsia	*Epigastric pain*			
	Amitriptyline	10–50 mg at bedtime	TCA	Constipation, sedation
	Heartburn			
	Melatonin	5 mg at bedtime	Endogenous hormone	
	Postprandial distress			
	Amitriptyline	10–50 mg at bedtime	TCA	Constipation, sedation
	Cyproheptadine	0.25–0.5 mg/kg/day divided bid or TID	Serotonin, Histamine-1, muscarinic, and calcium channel receptor antagonist	Increased appetite, fatigue
	Mirtazapine	7.5–30 mg at bedtime	Tetracyclic antidepressant	Weight gain, fatigue

Table 44.1 (continued)

Disorder of gut-brain axis	Drug	Dose	Medication class	Side effect
Irritable bowel syndrome	*IBS-D*			
	Amitriptyline	10–50 mg at bedtime	TCA	Constipation, sedation
	IBS-C			
	Imipramine	25–50 mg at bedtime	TCA	Sedation, dizziness
	Citalopram	5–40 mg/day	Selective serotonin reuptake inhibitor (SSRI)	Diarrhea, nausea, fatigue
Functional abdominal pain	Amitriptyline	10–50 mg at bedtime	TCA	Constipation, sedation
	Cyproheptadine	0.25–0.5 mg/kg/day divided bid or TID	Serotonin, Histamine-1, muscarinic, and calcium channel receptor antagonist	Increased appetite, fatigue
	Gabapentin	100–800 mg tid	Antiseizure	Drowsiness
Abdominal migraine	Prophylaxis			
	Amitriptyline	10–50 mg at bedtime	TCA	Constipation, sedation
	Cyproheptadine	0.25–0.5 mg/kg/day divided BID or TID	Serotonin, Histamine-1, muscarinic, and calcium channel receptor antagonist	Increased appetite, fatigue

DGBI disorders of the gut-brain interaction, *IBS-C* irritable bowel syndrome—constipation predominant symptoms, *IBS-D* irritable bowel syndrome—diarrhea predominant symptoms

Classes of Neuromodulators for Pediatric Disorders of the Gut-Brain Interaction (DGBI)

Cyproheptadine

Cyproheptadine, an antagonist of serotonin (5-HT1, 5-HT2A, 5-HT2B, 5-HT2C) receptors, H-1 histamine receptor, muscarinic, and calcium channels [3], has shown efficacy and safety in the treatment of DGBI, including FAP, FD, CVS, and abdominal migraines, as well as in poor growth [4]. For decades, physicians have utilized cyproheptadine's effects on appetite for supportive treatment in children with poor growth both with and without medical diagnoses [5, 6]. In 2014, a retrospective study supported the efficacy and safety of cyproheptadine in children and infants with feeding difficulties and poor growth, who were less than 2 years of age [7]. The mechanism by which cyproheptadine stimulates appetite is not fully elucidated, but may be due to antiserotonergic effects in the hippocampus or effects on insulin-like growth factor and growth hormone [8, 9].

More recently, research has supported the use of cyproheptadine in DGBI. In the treatment of FAP, a randomized, placebo-controlled trial in children showed significant effects of cyproheptadine on pain compared to placebo, with improvement in abdominal pain in 66% and resolution of pain in 20% of patients after 2 weeks [10]. The antiserotonergic properties and calcium channel blocking effects are plausible explanations for its effect on pain. Cyproheptadine has been shown to be effective in the treatment of functional dyspeptic symptoms including postprandial fullness, nausea, post-fundoplication retching, and epigastric pain [11]. A retrospective study including 80 children with refractory dyspeptic symptoms showed improvement in symptoms in 55% of patients [12]. Importantly, there was no relationship found between symptom response and a diagnosis of gastroparesis, supporting its efficacy in functional symptoms without effect on gastric motility disorders. Multiple mechanistic hypotheses have been proposed for treatment efficacy such as increased fundal relaxation via antagonism of fundal serotonin receptors shown in animal models [13, 14], as well as decreased gastric hypersensitivity to distension [10] and anti-serotonergic effects on the CNS [15].

Cyproheptadine is also used as a preventative agent in CVS [16]. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines recommend cyproheptadine as first-line agent in children <5 years of age because of its safety and side effect profile when compared to amitriptyline, although efficacy has been shown to be largely equivalent between the two drugs [17]. Cyproheptadine has been used as a treatment for migraine headaches [15, 18] and seems to be effective in prevention of abdominal migraines, which is characterized as both a subtype of migraines in children and a DGBI. In a retrospective study including children with FGIDs based on Rome III criteria, cyproheptadine was effective in eliminating symptoms in 60% of patients with FAP, 76% of patients

with FD, 72% of patients with abdominal migraine, 100% of patients with IBS, and 75% of patients with CVS [19].

Recommended dose for all indications is 0.25–0.5 mg/kg/day in two or three divided doses with a maximum of 16 mg/day. Tolerance to appetite stimulation appears after roughly 3 weeks, so when used for appetite stimulation, cyproheptadine is cycled 1–3 weeks on and 4 days to 1 week off [7]. Cyproheptadine is available as a liquid or tablet. The main side effect is sedation.

Aprepitant

Aprepitant is a central acting neurokinin-1 receptor antagonist that has been used for the past two decades as an effective antiemetic for chemotherapy-induced nausea and vomiting [20]. While research is limited on its use in pediatric DGBI, it is proposed to affect gastric accommodation and pyloric relaxation [21, 22] and thus may be helpful in nausea predominant disorders such as functional dyspepsia [23]. Further pediatric research is needed for this indication.

In CVS, aprepitant is used as a first-line abortive agent in moderate, severe, and refractory cases and as a first-line prophylactic agent in refractory cases [16]. In a retrospective study of 41 pediatric patients with CVS, 81% had complete or partial clinical response from its use as a prophylactic agent and 76% had complete or partial clinical response from its use as an abortive agent [24]. As a preventative therapy, recommended dose is based on weight and should be given 2–3 times per week. As an abortive therapy, it should be given at the start of the prodromal phase, prior to the emetic phase, and again on day 2 and 3 at a reduced dose based on weight [16]. If oral aprepitant is not tolerated, it is available in IV preparation, fosaprepitantant.

Azapirones

Azapirones, including buspirone and tandospirone, which are typically used in the treatment of generalized anxiety disorder, are pre- and postsynaptic serotonin 5HT1A receptor agonists that increase serotonin in the brain [25, 26]. They are also weak antagonists of the dopamine (D_2) receptor. These agents have been shown to affect the gastrointestinal tract through their inhibitory effects on serotonin receptors in the enteric nervous system [27, 28].

Buspirone was shown to improve gastric accommodation through fundal relaxation, showed positive effects in FD, and provide relief in gastroparesis [29, 30]. In a double blind, randomized placebo-controlled crossover study of 17 adult patients, buspirone significantly reduced severity of postprandial fullness, early satiation, and upper abdominal bloating compared to placebo after 4 weeks. It had no significant effect on gastric emptying of solids or gastric hypersensitivity to distension. Buspirone's utility in DGBI may result from both its direct effects on the gastric mucosa and from its anxiolytic properties given the recognized comorbidity between anxiety and DGBI. In a study examining adult patients with FD, those with gastric hypersensitivity scored higher on a measure of anxiety and scores negatively correlated with discomfort threshold, pain threshold, and gastric compliance [31]. Despite these findings, data remain limited; there is no consensus on the use of azapirones in adults with DGBI [27]. Studies in the pediatric population are scarce; however, a recent randomized double-blinded, placebo-controlled trial examining children with FAP assigned buspirone or placebo for 4 weeks showed no superiority over placebo [32].

Clonidine

Clonidine is an alpha-adrenergic agonist approved for use in hypertension and ADHD. The adrenergic nervous system impacts multiple gastrointestinal functions including motility, tone, and sensation [33]; thus clonidine has been evaluated as an alternative treatment for diarrhea predominant IBS (IBS-D) in adults [34]. Low doses (0.05 mg twice per day) relaxed colonic fasting tone and reduced sensation to distension in healthy adults [35]. A phase IIb double-blind randomized, placebo-controlled, parallel-group trial evaluated dose-related clonidine effects versus placebo in adult patients with IBS-D for 4 weeks and showed that 0.1 mg BID improved stool consistency and comfort with passage although had no effect on gut transit [33]. In a double-blind, placebo-controlled randomized study in adult women with urge predominant fecal incontinence (FI), clonidine did not improve symptoms of FI, although improved stool consistency in those patients with diarrhea as compared to placebo [34]. A systematic review of the literature examining the use of clonidine in diarrhea concluded that while study quality was generally compromised due to biases or small size, overall, clonidine shows favorable effects on stool frequency and consistency [36]. Despite positive effects, significant side effect profile including hypotension, dry mouth, sedation, dizziness, and tiredness limits the use of clonidine, especially in the pediatric population.

Benzodiazepines

Benzodiazepines enhance the effects of neurotransmitter gamma-aminobutyric acid (GABA) at the $GABA_A$ receptor site, thereby inhibiting neural signaling in the brain [37]. They are used in the short-term treatment of anxiety in adults and while they can provide some benefit for IBS in adult

patients with comorbid anxiety, they have not been found to be efficacious at addressing pain. In children, benzodiazepines, especially midazolam, are mainly used as anxiolytics and sedatives for painful or uncomfortable procedures [38]. There is no role for benzodiazepines for chronic DGBI in children or adults [39]. Significant side effects such as dependence, tolerance, and respiratory depression make this class of medications an unsafe choice for prolonged use.

Benzodiazepines can be useful in the treatment of CVS [16]. In children whose CVS episodes are triggered by anxiety, prodromal phase symptoms may be aborted using benzodiazepines as anxiolytics. In the emetic phase, IV lorazepam can be useful as a supportive agent to achieve sedation and improve nausea by acting on central emetic pathways. The recommended dose is 0.05–0.1 mg/kg/dose q 4–6 h.

Atypical Antipsychotics

Atypical antipsychotics are D_2 receptor antagonists; however, olanzapine and quetiapine have effects related to additional alpha-2 adrenergic and serotonin antagonism [40]. In chronic pain syndromes such as fibromyalgia and headaches, quetiapine and olanzapine have been studied as secondary treatment options in adults [4, 41]. Quetiapine showed superior efficacy over placebo in fibromyalgia, although did not show superiority to amitriptyline [42, 43]. While robust data and mechanistic understanding are lacking, the possibility that atypical antipsychotics may play a role in the treatment of refractory DGBI has been postulated [27]. A small pilot retrospective case series evaluating the use of quetiapine as an adjunctive therapy on refractory FGIDs in adults showed some benefit in over half of patients who remained on the drug [40]. In CVS, atypical antipsychotics may be useful as prophylactic agents as a way to reduce anxiety to avoid triggering an episode [27]. Quetiapine can also have antiemetic properties. There is no data on the use of atypical antipsychotics in the treatment of DGBI in children.

Anticonvulsants

Gabapentin and the similar drug pregabalin are lipophilic structural analogues of the inhibitory neurotransmitter GABA and act by binding to a subunit of the voltage-sensitive calcium channels, reducing release of excitatory and pronociceptive neurotransmitters [4]. Gabapentin and pregabalin are primarily anticonvulsants; however, they are also used to treat generalized anxiety disorder, social anxiety, and panic attacks. Additionally, they are used in the treatment of neuropathic pain and fibromyalgia in adults [44, 45]. Their possible central effects on visceral pain have led to consideration for use in DGBI [46]. A double-blinded, randomized controlled study using barostat distension technique on 26 adult patients with IBS showed a higher threshold for pain, desire to defecate, and first sensation with pregabalin use [47]. In another randomized study evaluating 40 IBS-D adult patients, gabapentin increased rectal sensory threshold and increased rectal compliance [48]. A more recent double-blinded placebo-controlled study examining pregabalin in patients with constipation predominant IBS (IBS-C) failed to show benefit over placebo in colonic compliance and tone, sensation thresholds, sensation ratings, and motility index [49].

Gabapentin as an adjunctive treatment may benefit adults with FD; a study evaluating 126 patients on omeprazole alone versus omeprazole and gabapentin showed a greater reduction in severity of reflux, dyspepsia, and abdominal pain in those receiving gabapentin [49]. Given the limited data with inconsistent results, evidence for use in adult DGBI remains low [41]. Newer anticonvulsants, such as zonisomide and levetiracetam, were shown in a small retrospective study to provide benefit as prophylactic medications in adults with refractory CVS unresponsive to tricyclic antidepressants (TCAs) [27, 50]. Data are extremely limited in pediatric DGBI. A Cochrane review included four pediatric studies, but authors were unable to perform a meta-analysis or draw any conclusions due to small study sizes and limited data [45].

Melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine) is an endogenous hormone secreted from the pineal gland, which plays a role in regulation of circadian rhythms [51]. In addition to its use in initiating sleep, its role in the gastrointestinal (GI) tract and theorized antinociceptive properties in the gut have been explored in both preclinical and clinical studies, mainly in adults, over the last decade. Given the association between alterations in the circadian rhythm and functional gastrointestinal symptoms, its use as a treatment for FD and IBS remains of interest, although robust research and mechanistic understanding are lacking [52]. A randomized, double blinded, placebo-controlled study of 40 adult IBS patients with sleep disturbances showed significant improvement in abdominal pain scores and increased threshold for urgency and rectal pain after 2 weeks of treatment with melatonin compared to placebo [53]. Notably, no differences were seen in sleep parameters. Another preliminary double-blinded placebo-controlled trial evaluating 18 refractory adult IBS patients treated with melatonin or placebo for 8 weeks leads to greater improvement in overall IBS and quality of life scores in the melatonin group [54].

Melatonin may also be a useful alternative treatment of dyspeptic symptoms [55], although conflicting results have

been shown. A study randomizing adult patients with gastroesophageal reflux disease (GERD) into treatment with proton pump inhibitor (PPI), melatonin alone, or combination for 8 weeks showed resolution of symptoms in all 3 groups [56]. Another study evaluating 351 adult patients with heartburn who received either PPI or melatonin and various other vitamins showed greater symptom improvement in the melatonin group [57]. A more recent, albeit small, study evaluated children aged 8–17 years with FD who had failed acid suppression therapy in a double blind, randomized, placebo cross-over study [58]. Patients took 5 mg of melatonin nightly for 2 weeks and placebo for 2 weeks and, in contrast to adult studies, melatonin was not more effective than placebo. A positive response was seen in 42% of those on melatonin versus 50% on placebo.

Cannabis

Tetrahydrocannabinol (THC) and cannabidiol are 2 of the 60 naturally occurring cannabinoids that exist within Cannabis plants. The FDA has approved one cannabis-derived drug product: cannabidiol for the treatment of seizures, and two synthetic cannabis-related drug products: dronabinol and nabilone for the treatment of chemotherapy-induced nausea and vomiting in adults (fda.gov). Off-label use in the treatment of DGBI such as FAP, IBS, and chronic nausea is widespread [59]. While cannabinoids have antiemetic properties in the CNS, they also directly affect the GI tract and have been shown in various small trials in adults to reduce gastric emptying [60] and decrease colonic motility [61] as well as tone [62]. In animal models, cannabinoids are suggested to play a role in decreasing visceral hypersensitivity of the gut [63–65]. Research in humans has been limited to adults and has shown mixed results. For example, one randomized, placebo-controlled trial showed that dronabinol increased sensory thresholds to colorectal distension compared to placebo in healthy adult volunteers, and another trial showed no difference in sensory thresholds between dronabinol versus placebo in both healthy volunteers and IBS patients [66]. The use of cannabinoids in the treatment of gastrointestinal symptoms in DGBI requires more robust research, especially in pediatrics.

An area where cannabinoids play a definitive and paradoxical role is in Cannabinoid Hyperemesis Syndrome (CHS) [16]. CHS was described in 2004 as a variant of, although distinct entity from CVS, triggered by long standing, high dose use of cannabis. In CHS, patients experience cyclic episodes of intense nausea and vomiting that may be responsive to compulsive hot bathing though often requiring intravenous fluid resuscitation and hospitalization. Considering the general understanding that cannabinoids function as antiemetics, patients often treat these symptoms by consuming more cannabis, feeding a vicious cycle [59]. The pathophysiology of CHS remains unknown; however, it is hypothesized that the buildup of THC levels in the body may overstimulate enteric nervous system cannabinoid receptor type 1, causing proemetic properties (i.e., prolonged gastric emptying, decreased colonic motility) to outweigh the antiemetic properties in the CNS [67]. The treatment for CHS is cessation of cannabis use.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs), specifically amitriptyline, have shown to affect multiple neurotransmitter pathways to provide pain and other symptom relief. TCAs block reuptake of noradrenaline and/or serotonin, although the mechanism of action in DGBI is not fully understood [68, 69]. One proposed notion is that an increase in available neurotransmitters leads to neuromodulation, given that the response from TCAs is not immediate and tends to improve with longer usage [69, 70]. Another central mechanism for TCA analgesia appears to be increased opioid response via δ opioid receptors [70]. TCAs do not appear to reduce sensation to visceral distension in the esophagus or stomach, likely indicating that central mechanisms play a key role in TCA effectiveness in DGBI [71, 72]. TCAs also block muscarinic cholinergic receptors, which may contribute to improving intestinal spasms and diarrhea, however, as a result can also cause constipation [73, 74]. At lower doses, TCAs have a greater central analgesic effect, whereas at higher doses there are greater psychiatric effect [75].

TCAs have been used with varying clinical data for management of IBS and FD. In adult studies, low dose amitriptyline was shown to decrease perceived symptoms and episodes of loose stool in patients with IBS-D [76–78]. Amitriptyline had superior symptom relief over escitalopram in adult patients with FD, specifically epigastric pain-type dyspepsia, but did not affect gastric emptying [77]. Pediatric data is limited with only two placebo-controlled randomized trials. One study found significant improvement in quality of life with the use of amitriptyline compared to placebo in IBS [79]. The second study showed improvement of symptoms in both amitriptyline and placebo, with no significant differences between the groups; however, only the TCA group had a significant improvement in anxiety scores [80]. Additional retrospective studies show improvement with TCAs; however, one study showed more improvement in patients taking selective serotonin receptor inhibitors than TCAs [81, 82].

Based primarily on adult data, amitriptyline is the first-line treatment for CVS in children greater than 5 years of age with observed moderate to high response rate [83]. A randomized control trial in pediatrics comparing amitriptyline to cyproheptadine found both to be effective without either being superior [17].

There is limited data for use of TCAs in patients under age 5. A small randomized placebo-controlled trial with average age of 3.73 years demonstrated no efficacy using amitriptyline as part of a feeding program to wean children from tube to oral feedings [84]. This study did not report any side effects, including electrocardiogram (ECG) changes.

Other TCAs such as imipramine, doxepin, nortriptyline, desipramine, and clomipramine have been evaluated in DGBI, though studies are limited. Among these medications, there is variability in anticholinergic and antihistaminic effects, resulting in different side effect profiles that often impact the choice of medication or patient compliance [85, 86].

The most common side effects among all TCAs include constipation, dry mouth, headache, dizziness, somnolence, and weight gain [86]. These are more commonly seen with amitriptyline use due to increased anticholinergic and antihistaminergic effects [87]. Although rare, it is important to note increased risk of suicidal ideation, especially in adolescents. TCAs are contraindicated in those with family history of QTc prolongation or sudden cardiac death and in those taking monoamine oxidase inhibitors.

Dosing for amitriptyline varies, but often starts at 1 mg/kg/day up to 50 mg/day. It is recommended to take before bed to aid with sleep. Typically, doses start low around one quarter to one half of final dose, with escalation every 1–2 weeks as tolerated. Dose escalation minimizes side effects and allows providers to titrate to lowest effective dose. Typically, several weeks of treatment with amitriptyline are necessary to observe its neuromodulating effect. When discontinuing amitriptyline, it is important to wean off slowly to prevent side effects such as sleep disturbances [88, 89].

Amitriptyline overdose becomes concerning with doses of 5 mg/kg/day and can cause sedation, seizures, and cardiac arrhythmias and death. On the other hand, at dose of 1 mg/kg/day, there have been no reports of serious side effects [87]. Studies evaluating ECGs in children prescribed low dose amitriptyline found that screening ECG was important to detect unsuspected cardiac arrhythmias and therefore avoid or modulate amitriptyline use; however, follow-up ECGs on amitriptyline did not show significant changes from baseline [90, 91]. The current recommendation is to screen with ECG prior to initiating amitriptyline and repeat once at target dose, especially in patients with personal or family history of prolonged QTC, arrhythmias, or heart disease [83, 92].

Selective Serotonin Receptor Inhibitors

Selective serotonin receptor inhibitors (SSRIs) block presynaptic serotonin (5-HT) transporters and increase the levels of 5-HT in the synaptic cleft available to bind to postsynaptic receptors [93]. Compared to other antidepressants, SSRIs primarily affect 5-HT receptors with weak binding to norepinephrine, increasing the psychiatric benefits over pain syndromes. Commonly used SSRIs in the treatment of depression and anxiety include fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline. Despite its critical roles in CNS development and function, only approximately 3% of the body's serotonin is located in the CNS [94]. The vast majority of serotonin (approximately 95%) is found in the intestine. As a result, SSRIs have shown to increase gastric and small bowel motility and may increase colonic compliance and contractility [93, 95].

A cross-over study looking at citalopram in adults with IBS showed reduced number of pain days per week, improved stool pattern, and decreased bloating compared to placebo [96]. Another study comparing amitriptyline, escitalopram, and placebo in adults found amitriptyline to be more effective at symptom relief over placebo, whereas escitalopram was comparable to placebo [77]. One pediatric RCT looking at citalopram in FAP showed no significant difference at 4 weeks. The authors proposed that longer treatment is likely needed to see full effect. A pediatric retrospective study comparing SSRIs and TCAs in DGBI demonstrated 75% and 61% symptom improvement with SSRIs and TCAs, respectively [82].

Dose of SSRIs typically starts low and can be increased if necessary. It is recommended to wait at least 4–6 weeks before determining if increased dose, additional medication, or change in medication is warranted [97]. SSRIs are believed to have fewer side effects than other antidepressants, such as TCAs, because they do not act on histamine, acetylcholine (except for paroxetine), dopamine, or norepinephrine receptors [98]. Because side effects can differ among SSRIs, providers can consider intra-class change if there is intolerance or lack of response. It is important to monitor and educate patients and families that SSRIs can increase suicidal ideation, especially in teenagers. When stopping SSRIs, it is recommended to gradually taper off the medication to prevent discontinuation symptoms [99].

Serotonin and Norepinephrine Reuptake Inhibitors

Serotonin noradrenalin reuptake inhibitors (SNRIs) inhibit 5-HT and noradrenalin reuptake, increasing the availability of the neurotransmitters in the synapse [93]. Examples of

SNRIs include duloxetine, venlafaxine, and milnacipran, each with varying effects on specific receptors, impacting the drug's function and side effect profile. There are no pediatric studies investigating SNRI use in DGBI. A small observational study found duloxetine improved symptoms in adult IBS patients [100]. An RCT in adults with FD showed venlafaxine was not more effective than placebo [100, 101].

Tetracyclics and Serotonin Antagonist and Reuptake Inhibitors

Mirtazapine increases central serotonin and norepinephrine via antagonistic effects on central presynaptic alpha-2-adrenergic receptors [102]. It also increases energy and metabolism, possibly as a result of norepinephrine impacts on the sympathetic nervous system. Mirtazapine's impact on gastrointestinal symptoms is via the brain-gut axis by altering gastrointestinal hormone levels including increasing ghrelin, neuropeptide, motilin, and gastrin and decreasing leptin, serotonin, and CCK [103]. Mirtazapine does not appear to effect the gastric sensorimotor function [104]. Two small RCTs in adults using mirtazapine for FD associated with weight loss demonstrated improved FD symptoms and weight gain. [103, 105] A study comparing mirtazapine to paroxetine and conventional treatment demonstrated significant improvement in FD symptoms with mirtazapine use compared to the other groups [103]. A pediatric case series of eight patients showed mirtazapine to be effective for chronic vomiting or CVS, with 3 children achieving complete remission; however, when mirtazapine was discontinued during study period, vomiting resumed [106].

Mirtazapine dosing typically starts at 7.5 mg daily and can be increased to 15 mg or 30 mg as needed. Mirtazapine is more sedating at a lower dose due to preferential binding of histamine over serotonin receptors [107]. Histamine tolerance typically occurs around 7–10 days after initiating treatment. Other side effects include weight gain, xerostomia, increased serum cholesterol, and constipation [102]. To prevent serotonin syndrome, mirtazapine should be avoided with monoamine oxidase inhibitors and linezolid, but otherwise has few contraindications.

Trazodone

Trazadone blocks reuptake of 5-HT and the histamine and alpa-1-adenergic receptors [108]. Trazodone is used for migraines and insomnia in pediatrics, with limited evidence. There are no RCTs investigating trazodone for pediatric or adult DGBI.

Opiates

There is no role for the use of traditional opiates, such as morphine, oxycodone, or tramadolin in the treatment of DGBI; chronic use can lead to significant gastrointestinal side effects including constipation, nausea, abdominal pain, and ileus in addition to addiction [109]. Eluxadoline, however, is an opiate that acts on peripheral opioid receptors with both μ opioid receptor agonism and δ opioid receptor antagonism, which allows for decreased visceral hypersensitivity without decreased intestinal motility [110]. A large RCT investigating adults with IBS-D comparing eluxadoline to placebo demonstrated significant reduction in symptoms with sustained efficacy over 6 months [111]. Reported side effects included constipation, abdominal pain, bloating, and pancreatitis. There are no published pediatric trials with eluxadoline.

Placebo Effect

The placebo effect has been shown to play a significant therapeutic role in research studies investigating DGBI [112]. A study investigating fMRI brain activation during placebo effect in adults with IBS compared to patients with inactive ulcerative colitis (UC) and healthy controls (HC) showed that the cingulate cortex, involving affective and cognitive brain regions, is responsible for pain modulation [113]. In contrast to patients with inactive UC and HC, IBS patients were unable to downregulate midcingulate cortex activation in response to placebo given during painful stimulation, effectively blunting the positive placebo effect seen in UC patients and HC. This study also found that depression scores were negatively correlated with the magnitude of placebo analgesia, leading authors to conclude that depression may contribute to inability to downregulate cognitive pain in IBS. In contrast, an earlier randomized controlled trial investigating different components of the placebo effect in IBS showed a graded response to different components; combining placebo and patient-practitioner relationship yielded the highest positive outcomes [114]. In this study, however, it is important to highlight that a very low proportion of included patients had depression, thus possibly allowing for an unopposed placebo effect on pain sensation.

In pediatric trials, positive placebo effect was found in 36% to 53% [115], with the highest placebo effect shown in a multicenter randomized placebo-controlled trial of amitriptyline in children with IBS, FAP, and FD. In this trial, there was no significant efficacy differences between amitriptyline and placebo; authors concluded that both treatment options were associated with excellent therapeutic response in chil-

dren with mild to moderate pain [80]. Another randomized, double-blind, placebo-controlled trial investigating domperidone versus placebo in abdominal pain predominant DGBI showed that while domperidone showed superiority in all primary outcomes, there was still a substantial placebo effect: 50% of placebo receivers had improvement in pain at 8 weeks [116].

Conclusion

It is well-recognized that the bidirectional role of the gut-brain axis plays a significant role in FGID, now reclassified as DBGI. Thus, the notion that neuromodulators may be useful treatment options is gaining more acceptance in clinical practice. Their use in pediatrics, while often based on adult data, is increasing in popularity among gastroenterologists. The area of neuromodulators in pediatric DGBI will continue to grow; however, more robust research studies are needed in this population.

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Electrical Stimulation of the GI Tract

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Peter L. Lu

Introduction

Neuromodulation of the gastrointestinal tract using electrical stimulation is an idea that has been around for over a century, with a report of colonic electrical stimulation delivered via saline enemas to treat constipation and ileus published in 1911 [1]. In 1963, Bilgutay and colleagues reported the effects of transluminal electrical stimulation of the stomach in an effort to promote gastrointestinal motility in patients with ileus [2]. As understanding of the relationship between myoelectrical activity of the gastrointestinal tract and gastrointestinal function grew in the following decades, so did the clinical applications of neurostimulation for treatment of gastrointestinal disorders. Gastric electrical stimulation (GES) and sacral nerve stimulation (SNS) emerged as treatment options for adults with gastroparesis and urinary incontinence, respectively, in the 1990s, with approval from the United States Food and Drug Administration (USFDA) coming for both treatments at the end of that decade [3]. The use of neurostimulation and the number of applications available for adults with gastrointestinal disorders have both since been growing.

There are advantages to neurostimulation that are particularly relevant to pediatric patients. Children with gastrointestinal symptoms refractory to conventional medical treatment can suffer debilitating symptoms with limited remaining treatment options that often require surgical intervention. Neurostimulation can be a less invasive (or noninvasive) alternative that is adjustible in treatment strength and reversible if no longer needed. Although neurostimulation for children with gastrointestinal disorders is less widely used than for adults, its use has been growing steadily and we now have over a decade of experience with more established neurostimulation treatments like GES and SNS [4]. Newer, noninvasive applications like auricular stimulation and posterior tibial nerve stimulation (PTNS) are promising and have the potential to help a much larger population than previous applications requiring surgical implantation. In this chapter, we will review a few of the major neurostimulation treatments available for children with gastrointestinal disorders.

Gastric Electrical Stimulation

GES treatment involves the delivery of high-frequency, low-energy electrical stimulation via electrodes placed along the greater curvature of the stomach. These electrodes are connected to a pulse generator and battery implanted into a subcutaneous pocket in the abdominal wall (Fig. 45.1). GES is used to treat chronic nausea and vomiting refractory to conventional treatment, traditionally secondary to gastroparesis, but also as the result of functional gastrointestinal disorders like functional dyspepsia. Although the healthcare burden of gastroparesis and functional dyspepsia appears to be increasing rapidly over time, treatment options for children with symptoms refractory to dietary and pharmacological interventions remain limited [5, 6].

The precise mechanism by which GES leads to improvement in nausea and vomiting remains unclear, but our understanding of its effects is growing. The electrical stimulation delivered by GES does not entrain gastric muscle and therefore does not actually pace the stomach as a cardiac pacemaker does. GES can have a prokinetic effect in patients with delayed gastric emptying at baseline, but can lead to improvement even in those with normal gastric emptying [3, 7]. Proposed mechanisms therefore include modulation of enteric or afferent neural activity influencing symptom perception, enhanced vagal activity, alterations in central control mechanisms of nausea and vomiting, and enhanced gastric accommodation [8]. A recent study from Abell and colleagues demonstrated several early and late physiological

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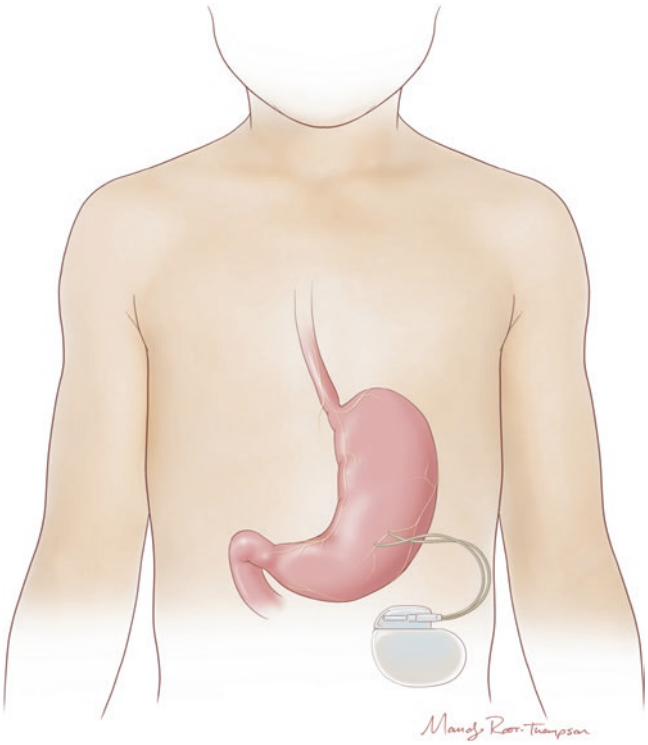

Fig. 45.1 Gastric electrical stimulation involves the delivery of electrical stimulation via electrodes placed along the greater curvature of the stomach. © [Mandy Root-Thompson, MS, CMI]/MedDraw Studio

effects of GES, including an early and sustained antiemetic effect, normalization of gastric dysrhythmias, and modulation of the autonomic nervous system [9].

Stimulator Placement

Initiation of GES treatment often begins with a trial of temporary GES, where electrodes are attached to the gastric mucosa and the pulse generator remains external to the body, in an effort to demonstrate improvement prior to permanent implantation of the electrodes and stimulator (Fig. 45.2). The temporary GES electrode used is a temporary cardiac pacing lead placed through either the nose or an existing gastrostomy site. The lead is then endoscopically secured to the gastric mucosa, generally at the junction of the body and antrum of the stomach using endoscopic clips to hold the lead in place. The lead is connected to an external stimulator that is placed into a telemetry pouch. In general, the lead can stay in place for 7–14 days before eventual dislodgement. Depending on the protocol used, clinical and physiological measurements can be used during the trial of temporary GES to help decide whether to proceed with permanent implantation following the trial. The temporary lead is typically removed endoscopically with gentle traction.

During permanent implantation, the electrodes can be placed laparoscopically or by open laparotomy if necessary due to previous surgeries. Two electrodes 1 cm apart and in parallel alignment are placed along the greater curvature of the stomach at the junction of the antrum and body of the stomach. The electrodes are placed under endoscopic visualization to ensure that the leads are not intraluminal. The electrodes are secured to the gastric wall and connected to the stimulator, which is then implanted into a subcutaneous pocket. Postoperatively, stimulation parameters can be adjusted if the patient does not achieve satisfactory relief of symptoms.

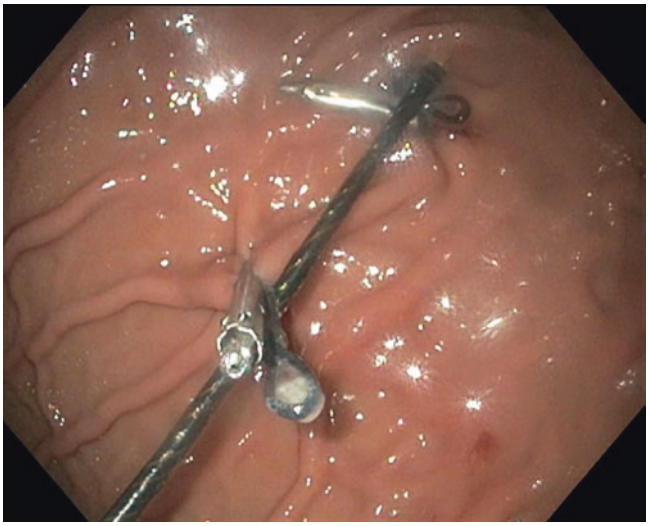

Fig. 45.2 This image taken during endoscopy shows the temporary gastric electrical stimulation lead being secured to the gastric mucosa using a combination of loops of suture and endoscopic clips

Outcomes

GES has been used to treat adults with nausea and vomiting refractory to conventional treatment for over two decades, and the literature supporting its use in adults has continued to grow over time [10]. The USFDA approved the use of GES in 2000 as a humanitarian device exemption for the treatment of adults with gastroparesis. Although there have been a number of prospective studies since then reporting benefit after GES treatment, four have been randomized controlled trials [11–14]. The most recent and largest was a randomized crossover trial published by Ducrotte and colleagues in 2020, which found that in 172 adults treated with GES there was significant improvement in vomiting when the stimulator was on compared to off. The American College of Gastroenterology guidelines for the treatment of adults with gastroparesis recommends consideration of GES for patients with refractory symptoms [15].

Experience with GES treatment in children is more limited, but has been growing over the past decade. Islam and colleagues published the first report of GES treatment in children in 2008, demonstrating symptomatic improvement and decreased hospitalization in a series of adolescents with chronic nausea and vomiting treated with GES [16]. This was followed by several

more case series of children treated with GES, including one published by Elfvin and colleagues in 2011 describing their experience using GES to successfully treat three children with refractory nausea and vomiting all younger than 3 years of age [17]. In 2013, we published the outcomes of our first 24 children treated with permanent GES treatment, which led to not only significant symptomatic improvement and a decreased need for supplemental nutrition, but also improvement in quality of life and perceived overall health [18].

However, in the past few years two larger studies have been published that have furthered our understanding of both the short- and long-term outcomes of GES treatment in children. Islam and colleagues published another review of their experience with GES in 2016, this time in 96 children who underwent a trial of temporary GES and 67 children who underwent permanent GES treatment. The cohort included children as young as 2 years of age and nearly all children had documented delayed gastric emptying. They again demonstrated significant clinical improvement that persisted in those with several years of follow-up data. However, during the follow-up time period 16% required further surgery because of a complication (lead repositioning or device removal) and 19% needed to have their battery replaced. Interestingly, all battery failures were identified because of a return of symptoms [19].

In 2021, we published a prospective study of our 10-year experience with using GES to treat children with refractory nausea and vomiting. Of the 85 children who underwent a trial of temporary GES, 77 children (91%) experienced a positive response and underwent permanent GES treatment. Patients ranged in age from 2 to 19 years and were predominantly (68%) female. Delayed gastric emptying was documented in most (63%) but not all patients. We found significant improvement in symptoms (including nausea, vomiting, early satiety, postprandial fullness, epigastric pain, and bloating) as early as 1 month after starting GES treatment. This improvement remained at 12 month follow-up and at most recent follow-up a median of 3.8 years after starting GES treatment. We also found a corresponding decrease in need for tube feeding or parenteral nutrition, decreasing from nearly 70% at baseline to 30% at most recent follow-up. We did not find any differences in response based on age, presence of delayed gastric emptying, or presence of small bowel dysmotility as demonstrated by antroduodenal manometry evaluation. However, by a median of 4.3 years after starting GES treatment, 18% of our patients required further surgery because of a complication and 38% needed battery replacement. Despite these issues, at a median of 5.6 years after starting treatment, 96% reported perceived benefit and 98% would repeat their decision to start GES treatment [20].

Despite these encouraging findings, questions remain that should be answered prior to more widespread adoption of GES. While it seems clear that gastric emptying does not predict response, our understanding of actual predictors of response remains limited. And while the use of a trial of temporary GES can be very helpful for deciding whether to proceed with permanent GES treatment, particularly in younger children or in those with higher surgical risk, the role of placebo effect remains unclear. Blinded, controlled studies have not yet been performed in children. Although placebo effect probably plays a smaller role in our younger patients who are 2 or 3 years of age (many of whom have already tried other procedural or surgical treatments), it is certainly possible that placebo effect plays a role for our adolescent patients struggling with years of nausea and vomiting who desperately want to feel normal again. Therefore, although GES offers real promise to a population of children with severe and debilitating symptoms, more work needs to be done to ensure we are using this surgical treatment for those who are most likely to experience significant, long-term improvement.

Sacral Nerve Stimulation

SNS involves the delivery of high-frequency, low-energy electrical stimulation of the sacral nerve root via an implanted electrode placed at the S3 sacral foramen. This electrode is connected to a pulse generator and battery implanted within the subcutaneous fat of the buttock (Fig. 45.3). SNS was first

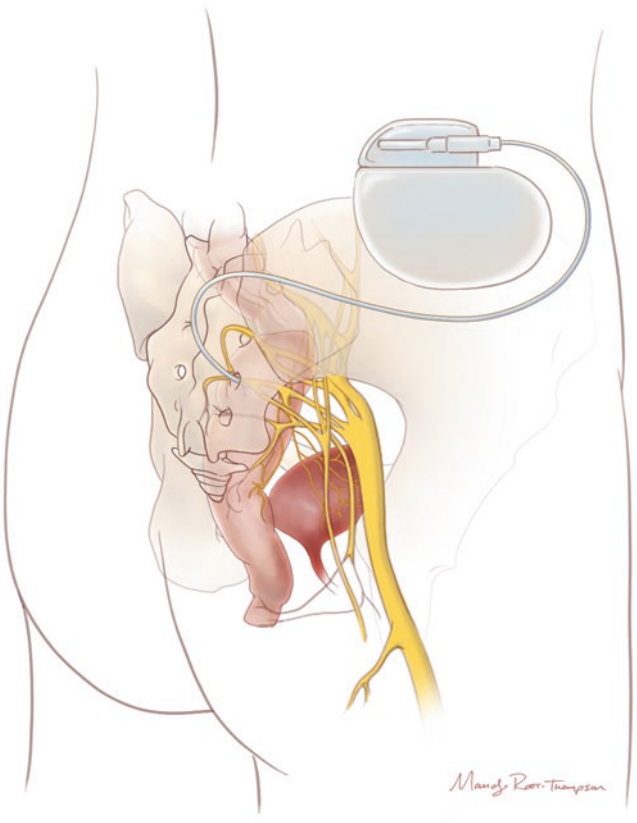

Fig. 45.3 Sacral nerve stimulation involves electrical stimulation of the sacral nerve root via an implanted electrode placed at the S3 sacral foramen. © [Mandy Root-Thompson, MS, CMI]/MedDraw Studio

used to treat adults with urinary incontinence and has since also became an established treatment for adults with fecal incontinence (and is therefore much more widely used than GES). Similarly, in pediatrics SNS was first used to treat urinary incontinence, but over the past decade has also been used to treat constipation and fecal incontinence refractory to conventional treatment. Treatment options for children with refractory constipation and fecal incontinence are limited and often require surgery [21]. Our understanding of where SNS fits into the treatment algorithm for these patients is becoming more clear as experience grows [22]. Studies have shown that SNS can modulate anorectal function in several ways, likely through effects at the pelvic afferent or central level rather than by peripheral motor neurostimulation. Although not consistent from study to study, SNS can alter anal sphincter resting and squeeze pressure, increase rectal sensitivity, and can at times even stimulate series of propagating colonic contractions [23, 24].

Stimulator Placement

Like GES treatment, SNS treatment in children often begins after an initial percutaneous nerve evaluation period during which the stimulator remains external. Lead placement is performed with fluoroscopic guidance in the operating room. With the child in the prone position, the sacroiliac joints are identified by fluoroscopy and a line is drawn between them. Starting 2 cm superior and lateral to the midpoint of the line, the access needle is passed through the skin into the S3 foramen using fluoroscopic guidance to confirm correct positioning. The lead is then inserted by Seldinger technique. Stimulation is then applied to demonstrate a "bellows effect" of the perineum with dorsiflexion of the toes. The lead is then connected to a stimulator that remains external to the body for a 2-week trial period. Depending on the protocol used, clinical and physiological measurements can be used during the trial to help decide whether to proceed with permanent implantation following the trial. If the trial is successful, then the lead is connected to a permanent stimulator and the stimulator is implanted into a subcutaneous pocket over the buttock.

Outcomes

SNS is the most established neurostimulation treatment targeting the pelvic organs. SNS was first used to treat adults with urinary incontinence and was approved by the USFDA in 1997 for this indication. Use of SNS to treat adults with fecal incontinence soon followed and SNS has since become the first-line surgical treatment for adults with fecal incontinence refractory to conventional treatment [25]. The USFDA approved SNS for treatment of fecal incontinence in 2012. However, the efficacy of SNS treatment for adults with constipation is less clear. Despite several initial prospective studies demonstrating improvement in constipation with SNS treatment, more recent randomized crossover studies have not shown benefit when compared to sham stimulation [26, 27]. The applicability of these findings to children is debatable given the differencies in the underlying mechanisms contributing to constipation in children and adults.

As in adults, SNS was first used in pediatrics for children with urinary symptoms, including those with both urinary and defecatory symptoms attributed to dysfunctional elimination syndrome. In the mid-2000s, the initial cohort studies evaluating the effects of SNS on children with dysfunctional elimination syndrome found that in addition to improvement in urinary symptoms, 70–80% of those with constipation and fecal incontinence also experienced improvement [28, 29]. In 2010, Haddad and colleagues published the results of a randomized crossover study using SNS to treat 33 children with urinary and/or fecal incontinence. Children underwent SNS implantation and then were randomized to having the stimulator on or off for 6 months at a time with a 45-day washout period. Of the 24 children with fecal incontinence, 78% experienced a decrease of >50% in fecal incontinence frequency when the stimulator was on compared to 17% when off [30].

Experience using SNS to treat children who primarily have constipation, however, remains limited and only two pediatric institutions have reported long-term outcomes. In 2016, van der Wilt and colleagues reported their experience using SNS treatment for 27 adolescent girls with functional constipation after a median of 22 months of treatment. Although they found overall improvement in bowel movement frequency, abdominal pain, and Wexner constipation score, approximately half were considered not to have had a successful response based on bowel movement frequency [31, 32]. In 2017, we published a prospective study of SNS outcomes in children with constipation who had been treated for at least 2 years. We included 25 children who started SNS treatment at age 6–19 years, most of whom had functional constipation (64%) or anorectal malformation (24%). We did not find significant improvement in bowel movement frequency, but did find a fairly dramatic reduction in fecal incontinence, with the percentage of patients reporting any fecal incontinence decreasing from 72% to 20% at follow-up. Laxative and antegrade continence enema use also decreased and both quality of life measures and patient satisfaction were positive [33]. A more recent comprehensive review of our institutional experience that included 65 chil-

dren treated with SNS for constipation or fecal incontinence supported these findings, demonstrating a decrease in the percentage of patients reporting fecal incontinence from 70% before treatment to 38% at 1 year and 20% at 3 years after starting SNS treatment. Bowel movement frequency did not change significantly [34].

For children with severe constipation and fecal incontinence despite antegrade continence enema treatment, SNS may be a particularly helpful option. In a study of 22 children with constipation already treated with antegrade continence enemas who then started SNS treatment, antegrade continence enema use steadily decreased from 7 enemas per week at baseline to 1 per week 1 year after starting SNS treatment. Half of the cohort was able to stop their use of antegrade continence enemas entirely and nearly half were able to have their cecostomy or Malone appendicostomy closed [35]. However, direct comparison of antegrade continence enema and SNS treatment is more nuanced. In a comparison of children with constipation and fecal incontinence treated with antegrade continence enemas (23 patients) or SNS (19 children), we found that while antegrade continence enemas led to greater improvement in bowel movement frequency and abdominal pain, SNS led to greater improvement in fecal incontinence, suggesting that there may be a role for both treatment options based on the child's predominant symptoms [36].

While the benefits of SNS are encouraging, a major drawback is the relatively high rate of complications requiring further surgery. Although SNS is reversible and less invasive than surgery directly involving the intestine, initiation of SNS treatment already involves 1–2 surgical procedures. In studies evaluating long-term outcomes of SNS, 24–44% of children who had a stimulator implanted experienced one or more complications requiring further surgery after 22–27 months, often related to wound infection, pain, or lack of response [32, 33]. Age, sex, and BMI are not associated with a higher risk of complications [37].

SNS is therefore a promising treatment option for children with constipation and fecal incontinence, but particularly given the associated risk of complications is one that requires a thoughtful approach. The growing literature on SNS treatment for children with constipation and fecal incontinence suggests that it is particularly helpful for those who have fecal incontinence as a primary symptom. Children who have symptoms refractory to antegrade continence enema treatment and those who have urinary symptoms that could also benefit from SNS may be better candidates for SNS treatment. The influence of SNS on anorectal and colonic physiology in children has not yet been studied – perhaps a better understanding will help guide treatment selection for children with constipation and fecal incontinence refractory to conventional treatment.

Auricular Neurostimulation

Experience with GES and SNS has emphasized the need for less invasive or noninvasive neurostimulation applications, particularly for children. One such application is auricular neurostimulation, also termed peripheral electrical nerve field stimulation or PENFS. Auricular neurostimulation involves peripheral noninvasive electrical stimulation using several electrodes placed on specific areas of the external ear that target branches of the cranial nerves innervating the ear (V, VI, IX, and X) (Fig. 45.4). Each electrode consists of a 2 mm titanium needle through which stimulation is delivered. Electrodes originate from a wire harness that is connected to a pulse generator and battery placed behind the ear. The device is applied weekly and provides 5 days of stimulation with 2 days off prior to the next application. Stimulation is thought to modulate central pain pathways and therefore decrease abdominal pain caused by functional abdominal pain disorders like irritable bowel syndrome [38].

In the initial study of auricular neurostimulation for treatment of adolescents with functional abdominal pain disorders published in 2017, Kovacic and colleagues randomized

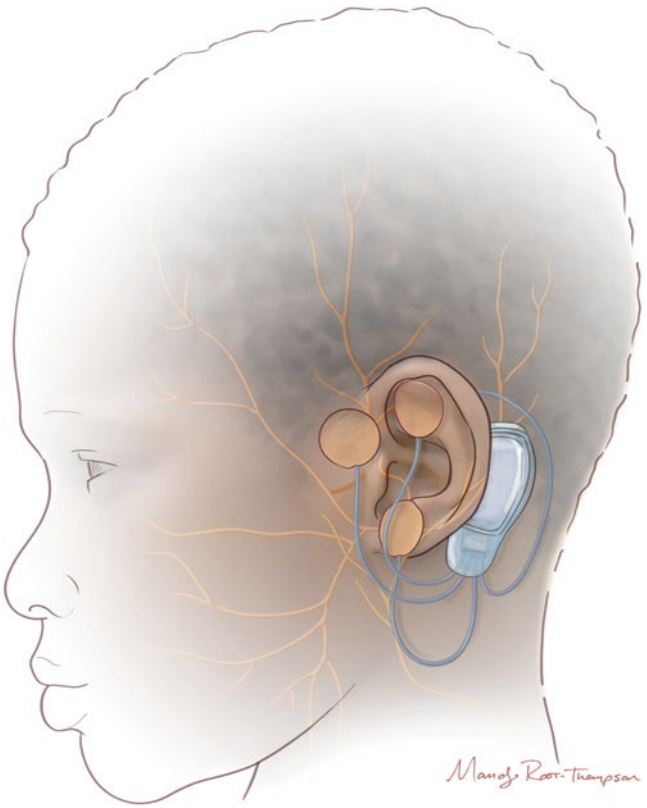

Fig. 45.4 Auricular neurostimulation involves peripheral noninvasive electrical stimulation using several electrodes placed on specific areas of the external ear. © [Mandy Root-Thompson, MS, CMI]/MedDraw Studio

115 patients to receive 4 weeks of auricular neurostimulation or 4 weeks of sham stimulation. Adolescents who received auricular neurostimulation experienced a greater reduction in abdominal pain severity starting at 3 weeks of treatment that persisted even a median of 9.2 weeks after completing neurostimulation treatment. Side effects were infrequent and mild, consisting of discomfort, allergic reaction to adhesive, and syncope due to needle phobia [38]. In a subsequent analysis of 50 participants who had irritable bowel syndrome, Krasaelap and colleagues found that 59% of patients experienced a >30% reduction in pain severity after auricular neurostimulation, significantly greater than the 26% who responded to sham stimulation [39]. Based on these results, the USFDA permitted marketing of auricular neurostimulation for adolescents with irritable bowel syndrome in 2019. Impaired vagal regulation with low baseline vagal efficiency seems to predict improvement in pain with treatment [40].

Auricular neurostimulation therefore represents perhaps the first of several applications of noninvasive neurostimulation that have the potential to transform the way we treat children with disorders of gut-brain interaction. When we consider that the quality of evidence supporting the efficacy and safety of auricular neurostimulation is already superior to the majority of treatments currently used to treat children with functional abdominal pain disorders, it is perhaps not a stretch to envision auricular neurostimulation treatment soon positioned before some of our established pharmacological or procedural treatments. Adoption of auricular neurostimulation in clinical practice has been growing and is sure to accelerate once barriers to its use (insurance approval, institutional adoption, logistical challenges) have been addressed.

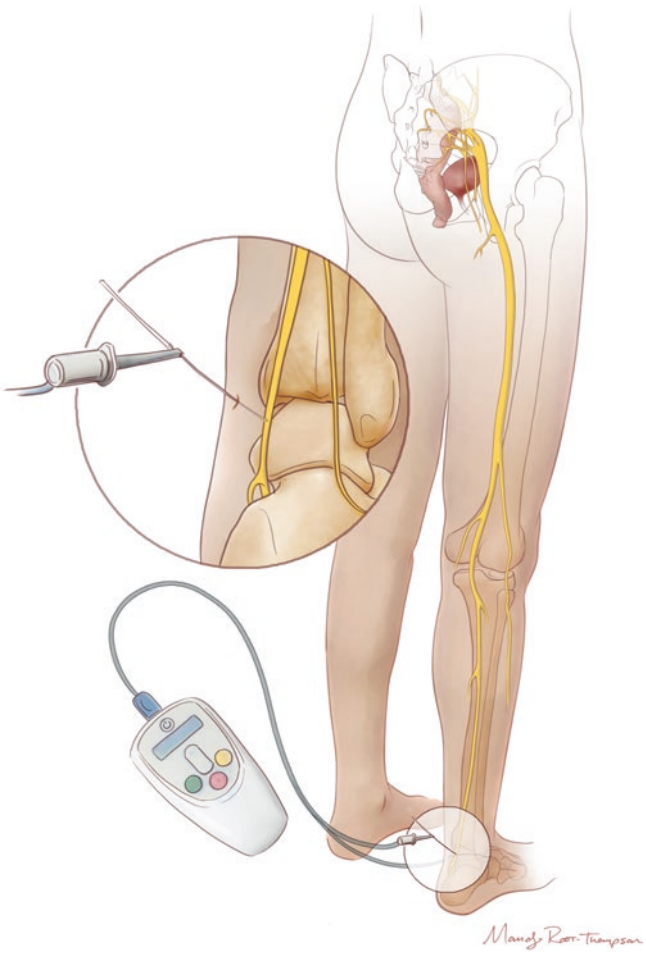

Fig. 45.5 Posterior tibial nerve stimulation involves peripheral noninvasive electrical stimulation of the posterior tibial nerve at the level of the ankle, generally delivered percutaneously using a thin needle placed near the medial malleolus. © [Mandy Root-Thompson, MS, CMI]/MedDraw Studio

Posterior Tibial Nerve Stimulation

PTNS is a noninvasive neurostimulation application showing promise for children with defecatory dysfunction. PTNS involves peripheral noninvasive electrical stimulation of the posterior tibial nerve at the level of the ankle, generally delivered percutaneously using a thin needle placed near the medial malleolus (Fig. 45.5). Electrical stimulation can also be delivered transcutaneously using an electrode placed on the overlying skin. The electrode is placed during treatment sessions and connected to a handheld stimulator. PTNS is thought to modulate urinary and defecatory function by stimulating the sacral nerve roots, therefore exerting an effect similar to that of SNS [41].

PTNS has been used to treat urinary dysfunction and more recently has been used to treat adults with fecal incontinence. Several studies, including multiple randomized controlled trials, have demonstrated its benefit for adults with fecal incontinence, but variability exists in how the PTNS was used, including in how stimulation was delivered, the frequency of treatment sessions, and the duration of treatment [42]. The evidence for use of PTNS to treat adults with constipation is more limited, with cohort studies showing only partial benefit [41, 43].

PTNS has primarily been used to treat children with urinary dysfunction, but experience using PTNS to treat children with defecatory dysfunction is growing. In 2015, Lecompte and colleagues used daily home-based transcutaneous PTNS to treat a small, heterogeneous cohort of children with fecal incontinence primarily due to organic etiologies like anorectal malformation and Hirschsprung disease. Seven of eight children experienced improvement after 6 months of treatment and five children experienced resolution of fecal incontinence. Two children had recurrence after stopping PTNS treatment [44]. Preliminary data from a prospective study of 20 children with functional constipation treated with 10 daily sessions of PTNS showed improvement in hard stools and fecal incontinence [45]. Several other studies on the use of PTNS for children with constipation are ongoing.

Conclusion

Electrical stimulation of the gastrointestinal tract has become not only an established treatment modality for adults with a variety of gastrointestinal disorders, but has also been used to treat children with these disorders for over a decade. The use of neurostimulation in medicine is growing rapidly and its application to pediatrics, particularly as experience with noninvasive treatment options increases, will only become more widespread. There are several other examples of neurostimulation of the gastrointestinal tract not mentioned in this chapter: electrical stimulation of the lower esophageal sphincter has been tried for adults with gastroesophageal reflux disease, abdominal transcutaneous electrical stimulation has been used for children with slow-transit constipation, and recently translumbosacral neuromodation therapy has been used for adults with fecal incontinence, all with encouraging findings [46–48].

Although technological advancement will continue to improve the delivery of noninvasive neurostimulation treatment, a major limitation thus far in the adoption of neurostimulation treatments for children with gastrointestinal disorders has been the lack of high-quality evidence for its use. Randomized controlled trials are certainly more challenging for surgical treatments like GES and SNS, but the ability to adjust stimulation parameters could be incorporated into study designs that account for the role of placebo effect. A positive randomized controlled trial has accelerated the adoption of auricular neurostimulation, and hopefully similar quality data will be available for PTNS and other noninvasive treatment modalities as well. Given the differences in pathophysiology of disorders like gastroparesis and fecal incontinence between children and adults, it is not sufficient to simply extrapolate findings from adults studies to children [6, 49]. High-quality evidence to demonstrate long-term efficacy and safety is a critical step before more widespread adoption of neurostimulation for children with gastrointestinal disorders.

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Hypnotherapy in Functional Gastrointestinal Disorders

46

A. M. Vlieger and Marc A. Benninga

Introduction

Brain-gut interactions are essential in the pathogenesis of functional gastrointestinal disorders (FGIDs), making treatments focusing on the body-mind connection appealing therapeutic options. A body-mind technique that seems to be very useful in children with FGIDs is gut-directed hypnotherapy. Hypnotherapy (HT) is the oldest form of Western psychotherapy and a powerful treatment for numerous disorders. In gut-directed HT, a hypnotic trance is induced in which patients are given suggestions directed toward control and normalization of gut functions. There is strong evidence supporting hypnotherapy in FGIDs, especially in functional abdominal pain and irritable bowel syndrome [1, 2]. This chapter describes what hypnotherapy is, gives an overview of the studies performed in children with functional gastrointestinal disorders, discusses potential working mechanisms, and gives directions towards implementing hypnotherapy in clinical practice.

What Is Hypnosis?

Hypnosis is defined as "a state of consciousness (i.e., a trance) involving focused attention and reduced peripheral awareness characterized by an enhanced capacity for response to suggestion" [3]. This hypnotic trance is a normal phenomenon, comparable with the trance that people often experience while watching a movie or daydreaming. In these situations, people become entirely absorbed by images or thoughts and are less aware of their surroundings. Therefore, we often describe hypnosis to children as "daydreaming with the purpose of helping yourself".

A therapist can use hypnosis for both medical and psychological disorders by eliciting images while giving hypnotic suggestions for change in physiology, sensations, emotions, thoughts, or behavior. Examples of these suggestions are provided in Box 46.1. Therapists often apply metaphors during treatment, for instance, a calmly flowing river in patients with either diarrhea or constipation. In sensitive, introvert children with functional abdominal pain, the image of a sponge filled with emotions and thoughts can be used. Sessions are often being recorded, and clients are invited to listen to the hypnotic recordings daily to have more impact. For most problems, four to six sessions in a 3-month treatment period are sufficient in children; in adults, up to 12 treatment sessions may be necessary [4, 5]. Hypnotherapy can be delivered in various ways. Traditionally, clients visit a therapist for individual treatment. In recent years, studies have shown effectiveness for other forms of HT in GI disorders, like home-based HT using standardized audio hypnosis exercises, group hypnotherapy, and hypnotherapy delivered by Skype [6–8]. These forms make hypnotherapy more widely available, especially in areas with a lack of well-trained hypnotherapists, and they can reduce costs.

Children generally respond very well to HT since their suggestibility is higher than in adults [9]. They like listening to the audio exercises and creating their own stories with their vivid imagination. Treatment can focus on different parts of the pathophysiological mechanism of the GI disorder. Since stress plays an essential causal role in almost any functional disorder, suggestions for relaxation are a standard part of the HT. Also, many children suffer from anxiety or depression, so HT sessions can focus on creating happy feelings with ego-strengthening suggestions. Images of a healthy gut (and sometimes immune system) can be incorporated into the treatment plan. If no improvement is noticed, hypno-analysis can be added. During hypno-analysis, a qualified and experienced therapist uses the hypnotic trance to explore underlying psychosocial issues that need to be addressed, like problems at home or school.

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Side effects are infrequent during hypnosis [10]. Sometimes, dizziness is reported, which can be prevented by lying down during the hypnosis sessions. In addition, some patients may experience emotions like sadness that can come up during hypnotic relaxation or hypno-analysis. An important advantage of HT is that children can continue using the skill of self-hypnosis in the years after treatment by inducing the hypnotic trance themselves while repeating positive suggestions, for example, to improve sleep or concentration.

Hypnotherapy in Pain-Related Functional Gastrointestinal Disorders

Functional abdominal pain (FAP) and irritable bowel syndrome (IBS) in childhood are pediatric abdominal pain-related FGIDs, characterized by chronic or recurrent abdominal pain and no evidence of an underlying organic disorder. Functional abdominal pain-related FGIDs are common clinical entities with a worldwide prevalence of 3–16%, depending on country, age, and sex [11]. Among these disorders, IBS is reported most frequently (8.8%, 95% CI 6.2–11.9); they occur significantly more in girls (15.9% vs. 11.5%, pooled OR 1.5) and are associated with the presence of anxiety, depression, somatization, stress, and traumatic life events [12, 13].

Standard medical treatment usually consists of dietary advice, education, and/or pain medication. Sometimes patients are referred to a child psychologist for cognitive behavioral therapy [14]. All these interventions may result in a reduction of symptoms, but approximately 40% of children continue to experience symptoms for years, even into adulthood, demonstrating the need for other effective treatments [15, 16].

Brain-gut interactions have been recognized to be important in the pathogenesis of FAP and IBS, making body-mind medicine an appealing therapeutic approach. A body-mind technique that has been shown to be very useful in treating both adults and children with FAP and IBS is gut-directed hypnotherapy [1, 2]. In this therapy, a hypnotic trance is induced in which patients are given suggestions directed towards control and normalization of gut function in addition to relevant ego-strengthening interventions. Studies in adults and children have not only demonstrated long-term efficacy on IBS symptoms, but have also demonstrated improvement in noncolonic symptoms, anxiety, quality of life, and reduced healthcare utilization [5, 17].

To date, five RCTs have been published evaluating the effect of hypnotherapy, either as individual therapy or as standardized self-hypnosis exercises at home, using a CD. These studies included 412 children, 6–18 years of age with IBS or FAP- NOS [6, 14]. All studies showed substantial long-lasting beneficial effects on quality of life, number of doctor visits, and missed days of school with a number needed to treat of 3. Positive results of hypnotherapy are long-lasting, with 85% of patients receiving hypnotherapy being symptom-free at 1-year follow-up and 68% after 5 years follow-up. These figures were only 25% and 20%, respectively, in the control group [17].

Shortcomings of hypnotherapy may include limited access, its rare coverage by commercial health insurances, and the lack of adequate well-trained hypnotherapists. Therefore, two of the five trials examined the use of a home-based treatment with standardized hypnosis exercises on CDs [6, 18]. The first study compared this with a waitlist control group. About two-thirds responded favorably to this therapy compared to only 27% in the control group, and the effects were maintained for at least 6 months [18]. The second study, in 260 children, compared home-based treatment to individual hypnotherapy provided by a therapist. The CDs contained similar exercises as used during individual HT. Treatment success rates and the number of patients reporting adequate relief were comparable in the groups, but costs were significantly lower in the CD group [6]. Therefore, audio-recorded self-hypnosis can become an attractive first-line therapy for children with FAP or IBS because of its low costs and direct availability, either using a mobile app [19] or online (hypnosis-4abdominalpain.com).

Mode of Action of Hypnotherapy in Pain-Related FGIDs

The precise mechanisms by which hypnotherapy has an impact on pain-related FGIDs are poorly understood. It is likely through a combination of effects on gastrointestinal motility, visceral hypersensitivity, and psychological factors. Whorwell et al. demonstrated already in 1992 that induction of hypnotic relaxation as well as happiness can lead to a profound reduction in fasting colonic motility. In contrast, hypnotic-induced anger and excitement increase colonic motility [20]. So far, it is unknown whether this effect on motility persists when the patient is no longer in the hypnotic state. It has also been shown that gut-oriented hypnosis can shorten gastric emptying in adult dyspeptic patients [21].

Studies on the effect of hypnosis on visceral sensitivity show contradictory results. Two studies revealed an overt reduction in rectal sensitivity after hypnosis [22, 23], whereas other work in adults and children failed to find such an effect [24–26]. These inconsistent data may have been caused by differences in methodology. A study using functional MRI to measure cortical activation patterns during rectal distensions in adult IBS patients indicated that hypnotherapy can have a normalizing effect on the central processing of visceral signals (Fig. 46.1) [27].

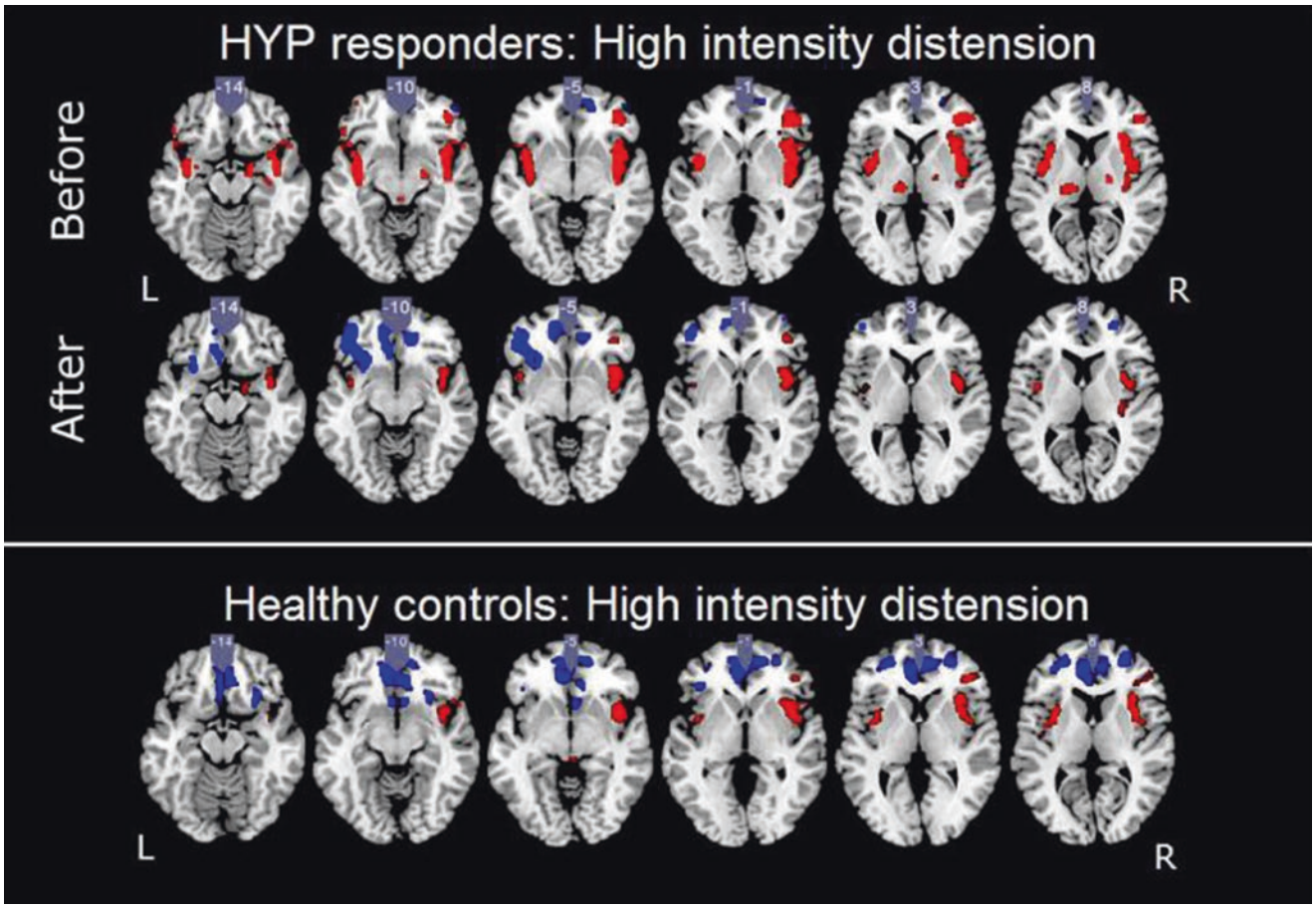

Fig. 46.1 Blood oxygen level-dependent response during high intensity rectal distension before (top panel), after (middle panel) a course of successful hypnotherapy in IBS patients. Blood oxygen level-dependent response to the same stimuli in healthy controls is shown in the bottom panel. Red color represents increased and blue color decreased blood oxygen level-dependent response. No differences were found anymore between healthy controls and IBS patients after a course of successful hypnotherapy [27]

Improvement in IBS symptoms after hypnotherapy often parallels improvement in psychological symptoms. [4, 6, 24] In children with IBS or FAP, treatment success was associated with improvement in feelings of depression & anxiety, somatization, health-related quality of life (QoL), pain beliefs, and coping strategies [4, 6]. Whether these psychological changes are the cause of the improvement of abdominal complaints or a consequence remains to be elucidated.

In recent years, a role for the gut microbiome in the pathophysiology of pain-related FGIDs has been suggested. Gut microbial alterations have been found in both adults and children with IBS [28, 29]. A small study in 38 adult IBS patients investigated the effect of hypnotherapy on the microbiome. Reductions in IBS symptoms and psychological burden were observed after gut-directed hypnotherapy, but only minor changes were found in intestinal microbiota composition. This suggests that hypnosis may act independently from microbiota composition, but more studies are necessary to confirm this finding [30].

Hypnosis in Functional Nausea

In 2016, the Rome IV pediatric adolescent committee introduced three new diagnoses; functional nausea and two subtypes of functional dyspepsia: postprandial distress syndrome type and epigastric pain type [31]. Children are diagnosed with functional nausea when they have the following complaints for the last 2 months: (1) bothersome nausea as the predominant symptom, occurring at least twice per week, and generally not related to meals; (2) not consistently associated with vomiting; and (3) after appropriate evaluation, nausea cannot be fully explained by another medical condition. Children diagnosed with the postprandial distress syndrome have bothersome postprandial fullness or early satiation that prevents finishing a regular meal, and supportive features include upper abdominal bloating, *postprandial nausea*, or excessive belching. Functional nausea (FN) and functional dyspepsia (FD) affect approximately 0.5% and 4.5–7.6% of children worldwide, respectively, and are asso-

ciated with substantial physical and psychosocial distress, school absences, and decreased social functioning [32–34].

The treatment of children with either FN or FD with prominent nausea is primarily symptomatic. Surprisingly, clinical evidence from RCTs is lacking regarding the efficacy and safety of available drugs to reduce nausea with or without dyspeptic symptoms in children [35]. Currently, most healthcare professionals individualize the patient's medical treatment, including prokinetics, antiemetics, antacids, and herbal products, according to their symptoms and associated comorbidities [35]. The disadvantage of this approach is that this treatment is symptomatic. This implies that drugs often need to be used for as long as patients suffer from nausea, which may take years [36]. Several pathophysiological mechanisms have been proposed to play a role in the etiology of FN and FD, including delayed gastric emptying, impaired gastric motility, and/or abnormal central nervous system processing of gastric stimuli through the gut-brain axis [33]. Also, there are indications that psychological factors, including anxiety and stress, may increase the severity of nausea through the gut-brain axis [33]. As in children with functional abdominal pain disorders, gut-directed hypnotherapy (HT) may have the potential to reduce symptoms of nausea in these children. Several studies in both adults with FD and children with chemotherapy-induced nausea and vomiting have clearly shown positive and long-lasting results of HT [37, 38]. A recent study in a 100 children (ages, 8–18 year) with chronic nausea and fulfilling the Rome IV criteria for FN or FD demonstrated that both medical treatment and hypnotherapy were able to reduce symptoms of nausea. In the subgroup of patients with FN, hypnotherapy was more effective than medical treatment [39].

Hypnotherapy in Other Gastrointestinal Disorders

Since some evidence exists that gut-directed hypnotherapy affects colonic motility [20], it is conceivable that hypnotherapy can be a helpful adjunct in treating children with functional constipation. In adults with IBS, it has already been shown that stool habits improve after gut-directed HT [40], but data in children are scarce. So far, only one report has described self-hypnosis as an adjunct in the treatment of children with severe constipation, but to date, no trials have been performed [41]. Awaiting future studies, it might be worthwhile to try hypnotherapy in addition to laxative therapy in children with refractory constipation.

Hypnosis may also be a valuable intervention for patients with globus sensation. Kiebles et al. described 10 adult patients with persistent globus sensation, unresponsive to anti-reflux medication, and with normal oesophageal manometric assessment. They were treated with seven sessions of hypnotically assisted relaxation. Nine of ten subjects reported a substantial improvement in their globus sensation [42]. The authors have also successfully treated several children with globus complaints with hypnotherapy (data not shown), but well-designed trials are needed in these patients.

Hypnosis can also significantly influence gastric acid production [43]. Moreover, gut-oriented HT has a prokinetic effect on gastric emptying [21]. These data suggest a potential role for hypnosis in treating patients with gastroesophageal reflux disease (GERD) and other gastric or esophageal FGIDs. Two adult studies have shown an improvement in functional heartburn symptoms, but data in patients with GERD, especially in children, are lacking [44, 45].

Due to its effect on psychological factors, hypnotherapy can also be added to the medical treatment in children with other gastrointestinal disorders, especially in those who experience stress, depression, anxiety, and/or a lower quality of life. For example, a recent study in adolescents with Crohn's disease demonstrated that HT is an acceptable and feasible adjunct in the treatment of these patients and may improve quality of life and abdominal pain [46]. Another study compared standard medical treatment to hypnotherapy in adults and teenagers whose inflammatory bowel disease was in remission, but suffered from ongoing IBS-type symptoms [47]. In this group of patients, hypnotherapy was not superior to standard medical therapy, making both treatment strategies, or a combination of the two, reasonable options.

Implementation of Hypnosis in Clinical Practice

It seems realistic to offer hypnotherapy to those children who are most likely to respond. However, studies performed in children with pain-related FGIDs have not shown many predictors of treatment response. The degree of anxiety, depression, severity of abdominal pain, age, and expectations do not influence treatment results. Only a longer duration of symptoms was associated with a worse outcome in children with IBS and FAP, six suggesting that hypnotherapy should not be postponed. Not every clinician, however, feels at ease in advising hypnotherapy to patients. This might be because misconceptions surrounding hypnosis are still common, caused by movies or popular stage hypnotists. Especially the lingering myth that hypnosis is a form of mind control in which the patient has no free will may hinder both doctors and patients from discussing this treatment option. It is, therefore, important to emphasize that hypnotherapy is quite the opposite: hypnotherapy is a very safe treatment in which patients gain more control over their body and their feelings and that "medical hypnosis is very different from stage hypnosis" (Box 46.2). We recommended that pediatricians and pediatric gastroenterologists have a network of skilled health care professionals in their area who can provide gut-directed hypnotherapy, either as a stand-alone treatment or in combination with cognitive-behavioral therapy. When well-trained

therapists are unavailable, referral to online treatment with standardized hypnosis exercises is a valuable and cost-effective alternative [6]. These exercises are now available in English, Spanish, German, and Dutch [48].

Conclusion

Hypnotherapy is an effective treatment option for children with pain-related functional gastrointestinal orders. In other disorders like nausea, reflux, or constipation, only scarce but positive data are available, suggesting that it might be considered here as well, but more studies are needed. The availability of online exercises for children with chronic abdominal pain makes this treatment now easily accessible and cost-effective.

Box 46.1: Examples of Hypnotic Suggestions in FGIDs

Every day, by practicing your breathing, slowly in and out, your belly will feel more and more relaxed.
Like the water flowing in this imaginary river, easy and steady, food and drinks in your stomach and intestines will also flow steadily, effortlessly, at the right pace.
The more you imagine yourself in this colorful balloon, the more your body will be filled with feelings of confidence and happiness, until 1 day you no longer need to think of this balloon, because these feelings of confidence and happiness have become a part of who you are.
You are really good in doing this and therefore, you are also really good in helping yourself and helping your belly, so you will have nice, comfortable feelings again.

Box 46.2: How to Discuss Hypnotherapy with Patients

Hypnosis is sort of like daydreaming. You likely have experienced this before. You're sitting in the classroom, thinking of your favorite sport or the nice vacation at the beach, and you totally forget that you are sitting in the classroom, because you're completely absorbed in your imagination.
Now hypnosis is daydreaming with a purpose. Hypnosis invites you to focus your imagination on bringing about something you want-- for example, going to sleep easier, doing better on tests at school, or training your belly to be happier, relaxed and more comfortable. Hypnosis is the experience of using your imagination in a deliberate and focused way. And the good news is that everyone can do it because it's a natural ability! Interestingly, the more you do it, the better you get and the better it works.
Some people think that hypnosis is losing control, but that's not true! In fact, when it's properly used in medicine, you get even more control over your body and more control over your feelings. And it is like learning a new sport, the more you practice, the better you will become. Thousands of children have already used it successfully for their abdominal complaints and most of them really liked using it. I wonder how good it will work for you!

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Cognitive Behavioral Therapy for Disorder of Brain-Gut Interaction

47

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Introduction

The use of psychological treatments for disorders of brain-gut interaction (DGBI) has a long history. Where these treatments were originally implemented to address the supposed psychogenic cause of the symptoms, presumably stress or anxiety, nowadays their application is placed in a biopsychosocial framework. This means psychological treatments are offered in combination with medical treatments to address brain-gut interaction dysregulation. Recently, they have been renamed 'Brain-Gut Behavior Therapies' [1, 2] to reflect this focus. In addition, this renaming indicates Brain-Gut Behavior Therapies focus specifically on treatment of the GI symptoms, rather than comorbid psychological factors such as anxiety and depression. This is an important distinction that affects everything from deciding who should receive treatment, referral, treatment considerations, etc.

Among the various Brain-Gut Behavior Therapies for DGBIs, cognitive behavioral therapy (CBT) has the widest popularity and largest evidence base. This is largely driven by the fact that current training for therapists is strongly rooted in CBT. Evidence for hypnosis for the treatment of DGBIs is growing and its popularity increasing. Hypnosis is discussed in Chap. 10 in this volume. Other treatment paradigms are used in practice, but lack wide-based evidence in pediatric DGBI. However, over time we will likely see their applications grow. These include meditation, for which there is some evidence in adults with DGBI, and acceptance and commitment therapy, for which there is evidence from child chronic pain literature [3].

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What Is CBT?

CBT has three basic components, addressing thoughts, emotions, and behaviors (see Fig. 47.1). CBT recognizes that how we *think* can affect how we act and feel, how we *feel* influences our thoughts and behaviors, and how we *behave* influences how we think and feel. When our thinking, feeling, and behaviors become maladaptive, they can increase gut symptoms, disability, and reduce quality of life. For example, by fearing minor nausea may become uncontrollable, a child may avoid going to school, or, by worrying about a parent's negative reaction to a stooling accident, a child may hide the urge to go to the toilet. In CBT, both behavioral and cognitive interventions are applied to change all three factors. This makes CBT highly adaptable to various disorders and each patient to maximize therapeutic benefit. This also means that the content of CBT can be very different across therapists, disorders, age range, and other individual or situational characteristics. Many studies allow protocols to be individualized to maximize therapeutic benefit, mean-

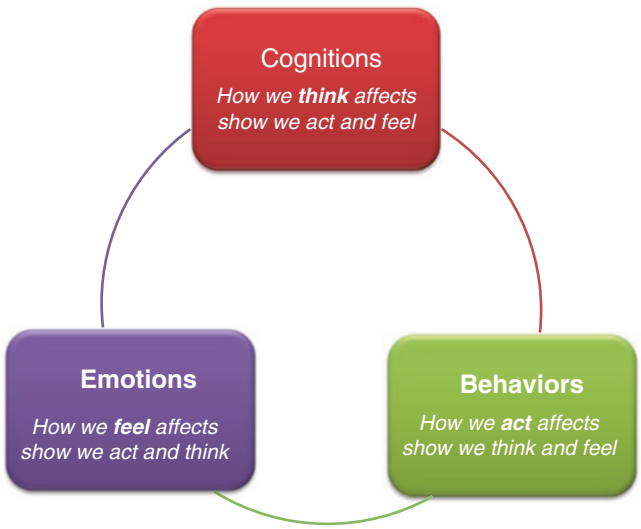

Fig. 47.1 Cognitive behavioral model

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ing that even within randomized controlled trials the treatment is often highly variable across subjects.

The particular therapeutic techniques vary within CBT and include, as the name suggests, both cognitive and behavioral approaches. Cognitive therapy questions and tests cognitions, assumptions, evaluations, and beliefs that might be unhelpful or unrealistic. A child will learn skills on how to recognize these unhelpful cognitions and replace them with more adaptive cognitions. Given that this requires insight into thoughts and verbal fluency to communicate these thoughts with a therapist, CBT is usually recommended for children of school-age or older. However, some components of CBT, especially behavioral therapy, can be applied to children of younger ages. Behavioral techniques include gradually facing activities which may have been avoided, trying out new ways of behaving and reacting, and relaxation exercises such as progressive muscle relaxation, deep-breathing, mindfulness, or guided imagery. Many of these components can also be used as stand-alone therapies, but in that case would not be considered CBT. A third important component of CBT is homework. Skills need to be repeated to be learned and a therapist therefore assigns homework of both cognitive and behavioral components. Lastly, it is important to emphasize that CBT is a time-limited therapy. Session can range from 3 to 12 in children. Unlike psychotherapy or counseling, in which long-term relations are formed between the therapist and client, CBT is brief due to its structured nature and emphasis on teaching children skills that can be used after treatment termination.

CBT only involving the child is a missed opportunity. Children are not islands, and their environment plays a major role in shaping how they respond to and think about symptoms. Recently, evidence has been mounting on the role of the family in maintenance and exacerbation of symptoms and disability in children with DGBI [4]. Parents take primary responsibility for teaching the child how to cope with symptoms, and often are the main decision makers affecting child's disability. For example, parents, rather than children, take the decision on when a child is well enough to go to school. Thus, ideally, both parent and child should participate in CBT, as maladaptive response to symptoms can be reinforced or modeled by parents [5].

When school absences play a major role, therapists may reach out to and collaborate with school personnel as well. School nurses and teachers may send the child home for relatively mild symptom, and this behavior and related cognitions can increase school avoidance and disability. Although school personnel are usually not part of CBT treatment, they can be provided psychoeducation – a component of CBT. Thus, CBT for DGBIs focuses on the child as well as their environment.

Evidence for CBT in DGBI

CBT is widely used for many DGBI. However, data are lacking on efficacy of CBT for the majority of these disorders. For example, there is one uncontrolled study in six children with Functional Dyspesia, although this study also included children with Functional Abdominal Pain [6]. In addition, one case study describes CBT for Cyclic Vomiting Syndrome [7], and several case reports exist of integrative care for rumination including psychological approaches [8, 9]. The most evidence for CBT is in functional constipation and functional abdominal pain disorders, which will be described below.

CBT for Functional Constipation

Functional constipation in children is usually a learned behavior [10]. Fear to defecate leads the child to postpone defecation. Retained stool increasingly becomes more painful to defecate, and the child gradually becomes more afraid of painful bowel movements. In those with fecal incontinence embarrassmeant also plays a role. This in turn increases fear, stool withholding, and hard stools. Standard medical intervention for functional constipation already involves behavioral elements such as education and daily toilet sitting to address the stool withholding. Medical treatment is associated with 60% success rate [11]. Given that many children with functional constipation are too young to receive CBT, and parents often have misconceptions of the causes of functional constipation and fecal incontinence [12], the cognitive element of CBT is often directed at parents, while the behavioral component is directed at the children. The cognitive element often is restricted to psycho-education, which by itself, can change how parents think, feel, and behave towards their child's symptoms. In a small study it was shown that explanation of the cause of fecal incontinence by a pediatric gastroenterologist, decreased blaming and punishing the child and increased helping behaviors [12].

Very few studies have been conducted testing if CBT adds to standard medical-behavioral therapy. A study in 1986 showed no difference between psychotherapy and medical-behavioral therapy, but little information is available about the psychotherapy and children were not randomized to treatment [13]. In a more recent randomized controlled trial, similar results were found: the number or treatment responders was not significantly different between those who received CBT (51.5%) and medical-behavioral treatment (62.3%) [14]. These authors did find a reduction in the number of children with behavior problems after CBT. For children with fecal incontinence due to constipation, there is

evidence that Enhanced Toilet Training (ETT) is helpful. ETT includes many behavioral elements such as education, teaching proper defecation skills, reducing fear to defecate, addressing social isolation, and parent-child conflict. Two randomized controlled trials have shown the efficacy of ETT both in person and through internet-delivery [15, 16]. Thus, the evidence for CBT in functional constipation is limited, but the evidence suggests it may be effective in helping those who suffer from fecal incontinence [17]. There is a lack of recent literature [17] which may suggest that CBT has limited perceived efficacy for child constipation. A recent study by Santucci and colleagues discovered that self-efficacy predicted treatment success of standard medical care [18]. Self-efficacy can be addressed in CBT, but no trials are yet available to determine if this may be helpful for children with constipation.

An additional behavioral treatment in functional constipation is biofeedback. Some evidence has been found for biofeedback for dyssynergic defecation [17], though the evidence is not always in agreement and the quality of trials is generally low. Discussion of biofeedback is outside of the focus of this chapter. Biofeeback is usually a stand-alone treatment, rarely combined with CBT.

CBT for Functional Abdominal Pain Disorders

Functional Abdominal Pain Disorders (FAPD) include Irritable Bowel Syndrome (IBS), Functional Dyspepsia, Abdominal Migraine, and Functional Abdominal Pain not otherwise specified [19]. In most trials of CBT, the focus is on FAP nos and IBS, in fact these two groups are often combined. CBT for FAPD focuses on changing maladaptive cognitions, emotions, and behaviors related to pain. Common maladaptive cognitions in FAPD are pain catastrophizing (Assuming the worst pain outcome, while feeling helpless to change the course), and pain threat (My pain means something is seriously wrong), and for parents the feeling of being inadequate as a parent. Common behaviors are avoidance of situations/behaviors that may increase pain (e.g., avoiding eating certain foods or wearing tight clothes) and avoidance of activities (e.g., missing social activities, school).

Given that increased anxiety and depression are found in patients with FAPD [4], it may seem logical that treating these can help FAPD. However, there is plenty of evidence suggesting anxiety may not directly affect pain, but drives pain through other psychological factors [4]. To date, only one study directly addressed if treating general anxiety is helpful in FAPD. They found that pain is not affected by treating anxiety [20]. Thus, the focus of CBT in FAPD generally is on pain-specific cognitions, behaviors, and emotions. Where the first approach invites physicians to refer children with anxiety and depression for therapy – and unintentionally reinforce the idea that the pain is 'all in the child's head'- the second approach invites physicians to refer children with poor coping abilities and high disability to a therapist. The latter reinforces the idea that these symptoms can be challenging, but their impact is reduced by learning coping skills, an idea that is more acceptable to most families.

How to Control for the Placebo Effect in CBT Trials?

Several randomized controlled trials have evaluated the efficacy of CBT for FAPD and these will be discussed below. Before delving into this evidence, it is important to understand the challenge of controlling for the placebo effect. Since the participants can tell they are receiving CBT, giving a placebo pill as a control would unblind the participants to what treatment arm they are assigned to and make the placebo ineffective. The standard solution is to control for three aspects that together constitute the placebo effect: Time, Attention, and Expectations. Time can heal wounds, as most patients will enroll in a trial when symptoms are high and over time these can be expected to regress to the mean. Attention refers to the healing effect of personal attention by healthcare providers. Lastly, the expectation to get better is probably the most well-recognized part of the placebo effect. Thus, behavioral trials should include a control group that: (1) Is followed for the same amount of time, (2) Gets the same exposure to study personnel (e.g., visits of equal length, as well as frequency), and (3) Is delivered an intervention that has equal expectation of effect but is relatively ineffective (measuring expectancy is the only way to assure this was achieved). The latter is difficult to attain, and most adequately controlled trials have control conditions that are known to have some effect (hence are not completely equivalent to placebo). This means that any well-controlled behavioral study probably has higher efficacy than reported. Unfortunately, as discussed below, trials that adequately control for all these three aspects are hard to find.

Evidence for CBT from Randomized Trials

Taken together it seems the overwhelming evidence suggests CBT is effective for FAPD in children. However, most trials did not adequately control for the placebo effect. Let's examine some of this evidence more closely. The majority of randomized trials compared CBT+ standard medical care to standard medical care alone [21–24]. Humphreys and Gervitz [25] compared CBT to a specific medical treatment: Fiber. All these studies found significant reductions in pain, and some also in school absences and quality of life. This controls for time but not attention or expectancy. In these trials, children who receive CBT have contact with a therapist for two to six sessions, which is not equivalent to the atten-

tion and time they receive from their physician, hence it is unknown if effects are due to increased attention by a health care professional or the treatment itself.

To control for both attention and time, CBT was compared to an equivalent number of sessions with the physician in two studies [23, 26]. These studies found pain improved equally on both treatment arms, while one study reported a higher number of pain-free children with CBT. Warschburger and colleagues [27] compared CBT to a specific attention control and found no initial difference between the two. Over a period of 1 year posttreatment, CBT showed decreased pain intensity/duration, disability, and increases in quality of life compared to attention control. Thus, the evidence is mixed on whether CBT is effective when comparing to attention and time control. However, it is not known if the children expected the attention control to help with their pain, which may explain some of the negative results.

A better approach is to compare CBT to another treatment. This treatment should be the same in time, attention, and credibility as a treatment for FAPD but of lesser efficacy. In a small study by Alfven and Lindstrom [28] ($N = 48$ children), CBT+ physiotherapy was compared to physiotherapy alone. The authors did not report differences in pain between groups. This study presumed there was equal expectancy of treatment benefit, but failed to measure the latter. In addition, physiotherapy may be an efficacious treatment in itself for FAPD. For example, there is some evidence that exercise such as yoga and dance has a medium to high effect on abdominal pain in girls with FAPD [29]. Hence, physiotherapy may not be a low efficacy treatment and hence not an ideal comparison group. Only one study adhered to recommended control for the placebo effect. In a large study by Levy and coauthors [30, 31] ($N = 200$), a 3 session CBT was compared to three session of dietary education (=credible but low efficacy). Care was taken that both were equal in time, attention, and credibility. This study added a new aspect to CBT by specifically focusing on parental modeling and reinforcement of pain. Reductions in gastrointestinal symptom severity were observed up to 1 year after treatment [31].

Exposure CBT therapy is new approach for FAPD. It addresses the fear and avoidance of gut sensations that contribute to pain. Threat of visceral sensations is addressed through cognitive restructuring, interoceptive, and in vivo exposure exercises (e.g., wearing tight clothing or eating feared foods). This treatment is of interest and will likely become more mainstream over time. At this point, the evidence comes solely from one research group in Sweden and includes two uncontrolled trials in children with FAPD and one large randomized trial for IBS where exposure CBT was compared to wait list control [32, 33]. The latter controls for time but not attention or treatment expectancy. The evidence suggests exposure therapy can improve pain and quality of life in children with FAPD, but no adequately controlled trial has been conducted.

In a groundbreaking paradigm, Levy and colleagues ran a trial testing the efficacy of parent-only CBT. It is known that parents can unintentionally reinforce and model maladaptive pain cognitions and behaviors [5]. Children learn these maladaptive thoughts and behaviors from their parents. The authors hypothesized that by changing maladaptive parental thoughts, feelings, and behaviors, child pain outcomes may improve. Levy and colleagues ran a large ($N = 316$) randomized trial comparing a brief parent-only CBT to an education control condition of equal attention, time, and expectancy. No differences between groups were found for child pain, but compared to the education condition, children in the CBT group had fewer school absences and healthcare visits. This makes sense as parents are often the main decision makers on when to take a child to a doctor or out of school. Thus, a parent-only intervention may help reduce child's disability.

In summary, there is wide evidence for the use of CBT to improve pain, disability, and quality of life in children with FAPD. The majority of this research still struggles with adequate controls for the placebo effect. Better well-controlled trials are needed. Even with this caveat, the use of CBT is widely recommended for the treatment of FAPD. However, access remains an issue with lack of trained therapists in DGBI. There is now evidence that treatment can be delivered remotely by phone [34] or virtually [35] without loss of efficacy. Developments of phone apps and virtual reality will also improve access to care for patients [36, 37].

Mechanism of CBT

As discussed above, CBT can involve multiple cognitive and behavioral approaches that vary across each patient, disorder, and therapist. The question becomes what are the mechanisms by which CBT affects outcomes? Identifying the most effective approaches would better tailor this treatment to the patient population. A few studies have addressed this question in children with FAPD. They found that changes in both pain-specific cognitions as well as behaviors mediate the effect of CBT (see Table 47.1) [38–40]. Notably, none of the studies found general anxiety is a mediator of treatment

Table 47.1 Evidence-based treatment targets for CBT in children with FAPD

Child cognitions/emotions	Catastrophizing
	GI-specific anxiety
Child behaviors	GI-specific avoidance
Parent cognitions/emotions	Catastrophizing
	Pain threat
Parent behaviors	Protectiveness

efficacy. Furthermore, a meta-analysis suggested there are no changes in anxiety with CBT treatment for child chronic pain [41]. These findings emphasize the need to tailor treatment to gut-specific cognitions, emotions, and behaviors rather than general anxiety.

Given these are Brain-Gut Behavioral Therapies, changes in the gut may be expected as well. In a first-of-its-kind trial, the effect of CBT on gut microbiota was examined among adults with IBS [42]. CBT responders were characterized by changes in microbiota particularly increases in *Bacteroides*. These microbiota changes were associated with changes in brain connectivity particularly a reduction in connectivity between the salience and sensorimotor networks. This suggests gut symptoms may become less salient to patients after CBT. These findings align with the observations in Table 47.1 that the effect of CBT is mediated by reductions in catastrophizing, pain fear, and GI anxiety which all affect salience of gut symptoms. More work is needed to understand the brain-gut connectivity changes with CBT, but this initial evidence supports the focus on pain-specific targets for CBT.

Implementation of CBT

A treatment is only effective if you can implement it. Unfortunately, for most patients with DGBI, psychological treatment is not an option. This has two main reasons: Stigma, and access to therapists. First, DGBIs are stigmatized diseases. The biomedical model (see Chap. 10 in this book) implies that if symptoms are 'medically unexplained', they must be psychiatric in nature. Patients encounter high levels of stigma and disbelief surrounding their symptoms from their family, peers, school, and healthcare providers. A common theme is that symptoms are not real and faked or that one is crazy [43, 44]. These stigmatizing experiences hamper referral to a therapist. Many families may see referral to a mental health care provider as a suggestion that the pain is all in the child's head. This is exacerbated by negative test results (if there is no medical cause, it must mean one is crazy). Best practice is for the physician to give a positive diagnosis ("your child has a condition called IBS"), explain the brain-gut axis (metaphors are very helpful here such as a child's nervous system being like a car alarm that is too sensitive), and introduce the rationale for brain gut behavior therapies (= help cope with gastrointestinal symptoms).

Ideally, a therapist is integrated in the GI practice. Joint appointments or warm hands offs communicate that the therapist is part of the medical team taking care of the patient and reduce stigma around seeking mental health care help. If hiring a therapist in a GI practice is not feasible, physicians and therapists should proactively seek each other out and educate each other about DGBI and psychogastro treatment and determine how to communicate joint treatment plans and progress notes. Ideally, this is accomplished before seeing a patient. During the visit, physicians can explain to the family the benefits of communication with the therapist and asking for HIPAA release forms. Patients who are sent out to find their own therapists often do not follow through (for various reasons) and if they do, may be treated for general anxiety instead of their gut symptoms. This is not helpful for anyone and can increase request for help to medical providers over time.

Physicians should make a follow-up appointment after the end of the therapy and give clear rules on when to reconnect during therapy (e.g., when blood appears in stools, or pain wakes child up at night). This clearly communicates that the physician remains involved in the patient care, and mental health care is part of the treatment plan. Otherwise, families may feel the physician ships off the patient to therapy to 'get rid of them'.

Even with these strategies, some families will be resistant to referral. In general, only families who admit a role of non-medical factors in FAPD should be referred. Although all children can benefit from Brain-Gut Behavioral, those with high levels of disability such as school absences or high levels of (child or parent) pain catastrophizing are likely the best candidates for referral. General anxiety in and off itself should not factor in the referral for Brain-Gut Behavioral Therapy. Comorbid anxiety disorder requires a referral to a general psychologists or psychiatrist for treatment of anxiety, not to help with the pain. It is important to make that distinction to the family to address the stigma discussed above. In many cases, the same therapist can take care of both, and treatment can overlap, but it is important to be very clear to the patient about the reasons for treatment. Additional factors that may require referral to a general psychologist/psychiatrist include: Trauma/Abuse history, eating disorders (other than ARFID which would fit in a GI-oriented treatment team), clinical depression/suicidality, and other comorbid disorders such as Autism, developmental delay, etc. How and who to refer is summarized in Table 47.2.

Remember it is up to the physician to refer for Brain-Gut Behavioral Therapy. It is up to the therapist to decide which modality will be best. Referral specifically for CBT or hypnosis may work counterproductive if the therapists don't agree this is the best treatment plan.

Table 47.2 Referral guidelines for CBT

How to refer to brain-gut behavioral therapies	Who to refer
I. Before patient appointment:	I. Family accepts role of nonmedical factors in child's symptoms
• Integrate therapist in GI practice	II. High levels of disability (e.g., school absences, not participating in social activities)
• Proactively reach out to outside therapists	III. High levels of maladaptive child or parent cognitions such as catastrophizing
• Develop systems for referral, treatment coordination, progress notes, HIPAA forms for sharing information	IV. The following is NOT a reason to refer to brain-gut therapies but should be referred for general or other appropriate mental health care. Clearly communicating the referral is for a comorbid condition, not focused on the child's GI symptoms:
II. During patient visit:	1. Anxiety
• Give positive diagnosis not based on exclusion	2. Depression/suicide ideation
• Explain brain-gut axis	3. Eating disorders*
• Explain reason for brain-gut behavioral therapy (manage symptoms)	4. Trauma/abuse history/PTSD
• Warm hand-off or joint visit with therapist if possible	5. Autism, developmental delay
• Give clear guidelines on when to contact physician office when symptoms change	
• Schedule follow-up visit for after treatment	
III. After referral	
• Coordinate treatment goals with therapists	
• Communicate about treatment progress	

[a]ARFID is best treated by Brain-Gut Behavioral Therapy

Conclusions

Changing maladaptive cognitions, behaviors, and feelings is at the heart of CBT therapy and ultimately its success. CBT treatment is an important addition to medical therapy for many DGBIs. Support for efficacy is available for FAPD, but studies are largely lacking for other DGBIs. Access to treatment remains an issue and development of long-distance and mobile applications is needed to increase use of CBT. As clinicians become increasingly comfortable with the understanding of the role of the brain-gut axis in the etiology of DGBIs, it is expected that they ultimately will begin to offer CBT delivered in a variety of novel ways much earlier in the treatment paradigm rather than waiting for other comorbid conditions to develop such as anxiety, depression, and impaired function which may lead to a more refractory patient.

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Complementary and Alternative Treatments for Functional Gastrointestinal Disorders

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The term complementary and alternative medicine (CAM) refers to a group of highly diverse health care systems, practices, and products that are not considered part of conventional medicine. The US National Institute of Health National Center for Complementary and Integrative Health (NCCIH) defines a complementary therapy as a non-mainstream practice used *together* with conventional medicine. In contrast, alternative medicine is a non-mainstream practice used *in place of* conventional medicine [1]. CAM incorporates many different approaches and methodologies ranging from ancient techniques like acupuncture and Ayurvedic medicine to chiropractic, homeopathy, spiritual healing, food supplements, and body-mind medicine. CAM has significant popularity in pediatric patients with functional gastrointestinal disorders (FGID) with reported CAM use between 38% and 69% [2, 3]. Because of this high prevalence and the fact that some complementary therapies are not without adverse effects and may interfere with allopathic medications, pediatricians and gastroenterologists need to become familiar with these therapies.

CAM is mostly used by children who have low perceived effect of conventional treatment and/or experience significant school absenteeism [2]. Both situations frequently occur in children with FGID. For example, 30–50% of the children with functional constipation continue to have severe complaints despite intensive treatment with laxatives [4, 5]. Many patients are therefore dissatisfied with conventional treatment options. Also for pain-related disorders like infantile colic or functional abdominal pain and irritable bowel syndrome, treatment options can have limited efficacy, resulting in dissatisfied patients and parents. With the current popularity of CAM in mind, it seems just a matter of time before patients with chronic abdominal pain will consider an alternative or complementary therapy. Another reason parents use CAM is fear of side effects from allopathic medications [2]. Many parents harbor the belief that CAM therapies are more "natural" and thus safer and "gentler" than modern medicine's armamentarium. This may explain why even in young infants with regurgitation CAM use is around 40% [2].

In this chapter, we will discuss CAM treatment options for those pediatric FGID in which CAM is used relatively often: infantile colic, gastroesophageal reflux, abdominal pain-related disorders, and functional constipation. Since CAM treatments may vary widely and research on safety and efficacy of these treatments in children with these disorders is very limited, we will focus on those treatments that have been studied best and/or are being used most, including herbs, acupuncture, homeopathy, yoga, and manual-based therapies like chiropractic. Probiotics and hypnotherapy are not discussed in this chapter, because they have become more mainstream medicine in the last decade due to increasing evidence for their effectiveness.

General Remarks on Safety of CAM Therapies

Many CAM users consider CAM therapies "natural" and equate this concept with safety. They are often unaware that many of these therapies have the potential to be directly or indirectly harmful. Several nationwide surveillance studies report severe adverse events in children after CAM use, mostly indirect due to delaying or ending more effective conventional treatment [6–8]. Also, direct effects have been reported, such as damage due to manual pressure, drug interactions, and toxic effects of herbs or supplements [6–8]. Toxicity and drug interactions can be even more noxious in young children and infants whose metabolism and organ function are immature and less tolerant of even subtle changes. Only scant data on the frequency of adverse effects

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of individual CAM therapies in children are available to date. A review on the safety and efficacy of acupuncture in children found a risk of adverse events of 1.55 in 100 treatments [9]. The authors concluded that acupuncture is a safe CAM modality for pediatric patients. However, for an individual patient, safety may be hard to determine because certain children, such as immunosuppressed patients, can be predisposed to an increased risk, and because acupuncturists may differ with respect to their qualifications, skills, and knowledge. Another study determined the frequency of concurrent use of conventional medications **CAM Therapies** and natural health products and their potential interactions in 1800 children [10]. Concurrent use of allopathic drugs and natural products was documented in 20% of patients with potential interactions in one-quarter of them. The authors did not investigate whether these interactions resulted in clinical symptoms. Still, the significant number of children who used both conventional drugs and natural products stresses the importance of studies investigating natural health products safety. A meta-analysis on adverse events associated with pediatric spinal manipulation identified 14 cases of direct adverse events involving neurologic or musculoskeletal events [11]. Incidence rates, however, could not be inferred from these observational data. Finally, over-the-counter homeopathic remedies are popular and often used for common self-limiting conditions [12]. There is little published data on the safety of homeopathy. The few studies, which have been performed on this subject, show that adverse events to homeopathic drugs exist but are rare and not severe.

As mentioned above **CAM Therapies**, CAM therapies can also have indirect harmful effects due to missed diagnoses, delay of more effective treatments, or discontinuation of prescribed drugs [6–8]. These indirect effects are probably less of a reason for concern in FGIDs, for which conventional treatment options are often limited and not life-saving.

Infantile Colic

Infantile colic is a functional disorder observed in 10–30% of infants [13]. It occurs mostly in healthy infants and is characterized by paroxysms of excessive, inconsolable crying, frequently accompanied by flushing of the face, drawing-up the legs, meteorism, and flatulence. These crying episodes tend to increase at the age of 6 weeks and usually resolve spontaneously at the end of 3 months. The etiology is not clear, and the limited treatment options frustrate both parents and physicians. It is therefore not surprising that many parents turn toward CAM treatments for their infant.

Acupuncture

Acupuncture has long been used for infantile colic, especially in China. In 2018, two systematic reviews (SRs) evaluated the effect of acupuncture on infantile colic with opposing conclusions. The first SR included four randomized controlled trials (RCTs) that used minimal acupuncture, without strong stimulation, at L14, ST36 and Sifeng [14]. The authors concluded that acupuncture may be effective for reducing crying, feeding, and stooling problems in infantile colic. Only minor side events, such as losing a single drop of blood or crying briefly after needle insertion, were reported. Due to the different outcome assessment in the studies, it was not possible to perform a quantitative meta-analysis. Subsequenly, Skjeije et al. also performed a SR and included three of the same trials as the SR mentioned earlier [15]. They invited the trialists of the eligible studies to take part in a collaborative group and asked to provide their raw data, making it possible to perform a meta-analysis. Using this method, no statistically significant benefit of acupuncture on crying time in infants with infantile colic was found. Considering the small sample sizes and the contradictory results of these reviews, more research is needed to evaluate the effect of acupuncture in infantile colic.

Homeopathy and Herbs

Homeopathic treatments, especially over-the-counter remedies such as fennel extracts, are often used in infantile colic [12, 16]. A recent high quality SR including five studies with a total of 491 colicky infants evaluated the effect of different herbal medicines [17]. Four studies evaluated the effect of different preparations of *Foeniculum Vulgare*, frequently combined with other herbs. All studies showed a significant reduction of crying compared to standard care or placebo. No significant effect was found on the duration of crying using peppermint oil for infantile colic. It should be noted that the methodological quality of the individual studies was very low to moderate.

Manual-Based Treatments

One of the most frequently used treatments for infantile colic is spinal manipulation, applied by chiropractors, manual therapists, osteopaths, or craniosacral therapists. A SR published in 2020 included four RCTs investigating the effect of manual treatments on crying symptoms [18]. Manual therapies reduced crying time by 33 to 76 min per 24 h, but studies were of low to moderate quality to draw firm conclusions. Moreover, several severe to even fatal adverse reactions after

manual therapy have been reported demonstrating that spinal manipulation is not without risks and therefore should not be recommended for treatment of infantile colic [11, 19].

Gastroesophageal Reflux

Gastroesophageal reflux (GER) is defined as the passive flow of gastric contents into the esophagus. It is important to recognize that GER is a normal physiologic phenomenon and occurs to some extent in all infants and children. Symptoms, especially regurgitation, are very common in infancy and are reported by parents to occur on a daily basis in more than a quarter of the infants. In more than 95% of the infants, symptoms disappear by 12 months of age. In children older than 18 months, discrepancy regarding the prevalence has been reported in different studies, abd overall symptoms are present in more than 10% of the children on a weekly basis and in 25% on a monthly basis [20].

Parental education, guidance, and support are usually sufficient to manage healthy, thriving infants with physiologic GER. If symptoms persist despite these conservative measures, it can be helpful to eliminate cow milk from the infant's diet (or in case of breastfeeding, from the mother's diet). Therefore, formula-fed infants with recurrent vomiting may benefit from a 2- to 4-week trial of an extensively hydrolyzed protein formula [21, 22]. Furthermore, thickening feeds has been shown to decrease the frequency of visible regurgitation but the impact on non-regurgitation symptoms is less clear and thickening feeds does not decrease acid exposure [21, 23, 24]. In addition, studies have been performed looking at the effect of specific postures on reflux symptoms. Compared to supine position, prone position significantly reduces the number of acid GER episodes but increases the risk for sudden infant death syndrome, thus no position other than supine is recommended [25–28].

The major pharmacologic agents currently used for treating GERD in children are gastric acid-buffering agents, mucosal surface barriers, and gastric antisecretory agents.

Although many of the simple therapeutic interventions are helpful in infants and children with GER, 40% of the parents still seek help in the complementary medicine circuit. It is unclear however whether the benefits that some patients derive from CAM are related to the treatment recommended or to the consultation process as some of these healthcare provider visits are more involved than conventional medical visits [29].

Acupuncture

Transient lower esophageal sphincter relaxations (TLESR) have been shown to underlie most GER episodes in healthy volunteers and healthy premature infants as well as in adult and pediatric patients with GER disease [30]. TLESR are mediated via a vago-vagal pathway initiated by tension receptors located in the proximal stomach musculature [31].

The mechanism by which acupuncture improves GERD-related symptoms remains to be elucidated. Some studies investigated the impact of acupuncture on the basal lower esophageal sphincter (LES) pressure. It has been shown that electric acupuncture at zusanli (ST36) can both increase as well as decrease the basal LES pressure [32]. Transcutaneous electric nerve stimulation (TENS) at specific acupuncture points in the hands increases the degree of LES relaxation in healthy volunteers [33]. Others have suggested that TENS at neiguan may inhibit the rate of TLESRs triggered by gastric distention and reduce the perception to gastric distention [34, 35].

In 2017, Zhu et al. performed a SR to assess the effect of acupuncture on reflux symptoms in adults. They combined 10 Chinese and two English trials and performed a meta-analysis to establish the efficacy of acupuncture. Acupuncture appeared to be equivalent to Western Medicine, and the combination of acupuncture and Western Medicine was significantly superior to Western Medicine alone [36]. Lower recurrence rates were reported in the acupuncture group. Nevertheless, a limitation of the study was the generally poor quality of the included trials. None of the included trials were blinded, and the randomization and allocation concealment were unclear [36]. Some literature points out that superficial (needling of the skin), sham (needling of non-acupuncture points), and placebo (needling with blunt tip that does not penetrate the skin) acupuncture also provide a therapeutic effect [37]. No such studies have been performed in either infants or children with GERD.

Manual Treatment

Neu et al. randomized 36 infants with GERD to massage or sham therapy (including rocking and holding) [38]. In both groups, symptoms, measured by the I-GERDQ-R, decreased and weight increased. Moreover, significant improvement was observed in the proportion of subjects crying less than 10 min and in those crying less than 1 h in the massage group, while there was no significant improvement in the sham group. Interestingly, the pretreatment salivary cortisol levels significantly decreased in the massage group while increased in the sham therapy group. A limitation of the study was the small sample size.

Herbs

A retrospective study assessed the effect of *Rikkunshito,* a traditional Japanese herb, in infants with severe GERD

symptoms and failure to thrive [39]. Compared to mosapride, the babies in the *Rikkunshito* group gained significantly more weight and reduced vomiting. However, the methodolical quality of the trial was low and the sample size was small.

Functional Abdominal Pain and Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) and functional abdominal pain (FAP) in childhood are pediatric FGIDs, characterized by chronic or recurrent abdominal pain, without evidence of an underlying organic disease. By definition, altered bowel movements and/or relief of pain after defecation are seen in IBS, while defecation pattern is normal in patients with FAP [40]. IBS and FAP are among the most common abdominal pain complaints in childhood with reported prevalence's between 3% and 16%, depending on age, sex, and country [41, 42]. Quality of life scores of IBS and FAP children are significantly reduced, and many children suffer from depression, anxiety, being bullied, and unhappiness, highlighting the clinical impact of these conditions [43, 44]. Standard medical consists of dietary advice, education, and/or medications. Sometimes patients are referred to a child psychologist for behavioral therapy or hypnotherapy. These interventions may result in reduction of symptoms, but up to one-third continue to experience symptoms for years, even into adulthood. It is therefore not surprising that up to 69% of patients considers alternative treatments [2, 3]. Given the high placebo response shown in IBS/FAP studies, many patients experience at least a short-term benefit from any of these treatments [45].

Acupuncture

A Cochrane review searched English and Chinese databases and included 17 RCTs with 1806 adults with IBS using acupuncture [46]. They found no improvement with acupuncture relative to sham (placebo) acupuncture in symptom severity or quality of life. A GRADE analysis indicated that the overall quality of the evidence for the primary outcomes in the sham controlled trials was moderate due to sparse data. Eighty-four percent of patients in the acupuncture group had improvement in symptom severity compared to 63% of patients in the pharmacological treatment group. Another more recent meta-analysis combined 41 RCTs and showed comparable results [47]. The results of these two reviews suggest that acupuncture has a potential role in the treatment of IBS, but its effect might be nonspecific. Schneider et al. however showed that real acupuncture in comparison to sham acupuncture had more specific physiological effects with a more pronounced decrease in salivary cortisol and an increased parasympathetic tone [48]. They concluded that different mechanisms seem to be involved in sham and real acupuncture-driven improvements, but the specific mode of action of acupuncture in IBS remains unclear and deserves further evaluation. A possible mechanism could be that acupuncture downregulates brain-gut peptides, involved in the control of gastrointestinal motor and sensory functions [49]. A study evaluating colonic biopsies showed that the colonic mucosa associated neuropeptide substance P and vasoactive intestinal peptide were downregulated after acupuncture, which may contribute to the improving of symptoms [49]. Whether acupuncture is also effective in the treatment of children with IBS or FAP is unknown, since trials in pediatric patients are lacking. Awaiting such studies, physicians might consider acupuncture as a potential treatment option in children with refractory IBS or FAP, since acupuncture is considered a safe CAM modality for pediatric patients [9].

Manual-Based Therapies

Only few studies have been performed using manual-based therapies in adults with IBS or FAP. Müller et al. performed a SR to assess the effectiveness of osteopathic manipulative therapy (OMTh) for managing the symptoms of IBS in adults [50]. OMTh is a manual treatment which relies on mobilizing and manipulating procedures in order to relieve complaints. Their search identified only five studies (204 patients) meeting the inclusion criteria. The studies had a low risk of bias, although heterogeneity in the outcome measures and control interventions was present. All the included studies reported more short-term improvement with osteopathy compared to sham therapy or standard care. However, caution is required in the interpretation of these findings because of the limited number of studies available and the small sample sizes. Studies in children using this treatment are lacking. Another SR assessed whether Tuina (traditional Chinese therapeutic massage) was effective and safe for adults with IBS [51]. A total of eight Chinese trials were included and showed that Tuina combined with standard care was more effective in treating diarrhea in IBS patients than standard care alone. The included studies used different types of Tuina and the methodological quality of the trials was low. More studies from countries other than China are needed to confirm the findings before osteopathy and Tuina can be advocated as a treatment option for IBS/FAP.

Yoga

Yoga originated in India >4000 years ago and consists of a combination of mind–body exercises. It has been widely used to reduce stress and anxiety in patients with chronic

conditions (e.g., cancer patients, postmenopausal women with rheumatic arthritis, Crohn disease, and hypertension) as well as in healthy adults [52, 53]. These mind–body exercises are simple and can be easily applied at home. In Western civilization, yoga is most often associated with physical postures, breathing techniques, and meditation to promote physical and mental wellbeing [54].

In the last decade, several trials have investigated the effect of yoga on functional abdominal pain disorders in children. Three studies including 122 children with either IBS or FAP assessed the effectiveness of yoga on pain intensity, pain frequency, and functional disability [55–57]. The largest study (69 children with either IBS or FAP) found no significant differences between those children who had undergone yoga compared to usual care (21.2% for yoga compared to 20% for control). At 12-months follow-up, a significantly higher treatment success, a decrease of combined abdominal pain scores (frequency and intensity) of greater than 50%, was reported by those in the intervention group compared to those in the usual care group (58.1% compared to 28.9%, respectively). None of the three studies reported beneficial effects of yoga compared to control on pain intensity or showed significant effects of yoga intervention on social or psychological functioning [57].

Herbs and Homeopathy

Herbs and botanicals have been used for hundreds of years for abdominal complaints in both adults and children. Unfortunately, the majority of research for herbs is conducted in adults, with just a few pediatric studies available.

Traditional Chinese herbal medicine (CHM) has been most frequently evaluated in adult patients with IBS. More than 90% of the studies were performed in China and high quality trials are lacking. According to the fundamental principles of traditional Chinese medicine, treatment should be tailored to the individual clinical presentation of patients, even though they all may have the same conventional medical diagnosis [58]. Furthermore, treatment needs to be modified at different stages of the patient's illness or recovery. In an elegantly designed trial, 116 adults with IBS were randomly allocated to either individualized Chinese herbal formulations (n = 38), a standard Chinese herbal formulation (n = 43), or placebo (n = 35). Patients received five capsules 3 times daily for 16 weeks and were evaluated regularly by a traditional Chinese herbalist and a gastroenterologist. Compared with patients in the placebo group, patients in the standard and individualized CHM group had significant improvement in bowel symptom scores and global improvement as rated by patients and by gastroenterologists. Chinese herbal formulations individually tailored to the patient proved no more effective than standard CHM treatment. At 14 weeks after completion of treatment, only the individualized CHM treatment group maintained improvement [58]. An Australian placebo-controlled trial in 125 adult patients with IBS evaluated the effect of a Chinese Medicine formulation consisting of seven plant herbs with antispasmodic, laxative, and analgesic properties. CHM reduced symptoms of IBS-constipation predominant, increased bowel satisfaction and stool consistency, and reduced straining and hard lumpy stools, compared with placebo. No significant improvement over placebo was found for abdominal pain, bloating, or overall IBS-QOL measures [59]. A Chinese randomized placebo controlled trial in 1044 adult patients with IBS compared Tongxie with placebo. After 4 weeks, Tongxie lead to a significantly greater reduction in abdominal pain and improvement in defecation parameters, such as frequency and consistency of stools, than patients given the spasmolytic, pinaverium [60].

Peppermint oil is commonly found in over-the-counter preparations for IBS. It appears that peppermint oil may have several mechanisms of action including smooth muscle relaxation (via calcium channel blockade or direct enteric nervous system effects) and visceral sensitivity modulation [61]. A recent SR identified eight trials of peppermint oil in adults with IBS; three were of low risk of bias. It was concluded that peppermint oil was significantly more efficacious than placebo after 4 to 12 weeks of treatment. Adverse events did not occur more often in the peppermint oil group than in the placebo group [62]. After publication of this SR, Weerts et al. performed a double-blind trial including 190 adult patients with IBS (Rome IV criteria), and compared 182 mg small-intestinal-release peppermint oil, with 182 mg ileocolonic-release peppermint oil, or placebo for 8 weeks [63]. Neither small-intestinal-release nor ileocolonic-release peppermint oil produced statistically significant reductions in abdominal pain response or overall symptom relief. The small-intestinal-release peppermint oil did, however, significantly reduce abdominal pain, discomfort, and IBS severity. The authors suggested that these findings do not support further development of ileocolonic-release peppermint oil for treatment of IBS. In the recently published American guidelines on adults with IBS, peppermint oil is recommended as one of the treatment options [64].

In children with IBS, the use of peppermint oil seems to be both safe and beneficial: in a small randomized, double-blind controlled 2-week trial, 76% of the patients receiving enteric-coated peppermint oil capsules reported a decrease in symptom severity versus only 19% in the placebo group [65]. In a larger Iranian RCT, the efficacy of peppermint oil in the treatment of functional abdominal pain disorders was investigated. A total of 120 children, 4–13 years of age, were treated either with Colpermin capsules or probiotic tablets, or folic acid tablets as the placebo. When compared with the placebo, peppermint oil significantly reduced the duration of

pain (minutes/day), frequency of pain (episodes per week), and severity of pain. In comparison with probiotics, peppermint oil significantly reduced the duration of pain (minutes/day) and the severity of pain. No adverse events or side effects of peppermint oil were reported [66]. Another popular herb in IBS is ginger (*Zingiber officinale*), especially used by patients with nausea and dyspepsia as one of the main complaints [67]. It has a prokinetic action probably mediated by spasmolytic constituents of the calcium antagonist type [68]. Ginger has been proven effective for reducing postoperative nausea and vomiting as well as nausea in early pregnancy [69, 70]. It seems to be relatively safe, although abdominal discomfort has been noted in some patients. No RCTs researching the efficacy of ginger have been performed in children with IBS or FAP. STW 5 is a liquid formulation of nine herbs including extracts from bitter candytuft (Iberis amara), angelica root (Angelicae radix), milk thistle fruit (Silybi mariani fructus), celandine herb (Chelidonii herba), caraway fruit (Carvi fructus), liquorice root (Liquiritiae radix), peppermint herb (Menthae piperitae folium), balm leaf (Melissae folium), and chamomile flower (Matricariae flos). Randomized placebo controlled clinical trials evaluating the use of STW 5 in children with FAPDs are lacking. A retrospective surveillance study including 1042 children with functional dyspepsia reported a success rate of STW in 96.8% of the cases with minimal side effects [71].

One small study evaluating the efficacy of Aloe vera and asafetida reported a reduction in global IBS symptoms in adults with IBS [72]. Studies in children with IBS evaluating the efficacy of these herbs are lacking.

In 2019, a Cochrane review included four randomized trials assessing the effectiveness of homeopathy in adults with IBS [73]. Two types of homeopathic treatment were evaluated: clinical homeopathy in which a specific remedy is prescribed for a specific condition and individualized homeopathic treatment, where a homeopathic remedy based on a person's individual symptoms is prescribed after a detailed consultation. A meta-analysis of two studies assessing the efficiency of asafoetida in 171 adults with IBS-C (clinical homeopathy) was conducted. At short-term follow-up of 2 weeks, global improvement in symptoms was experienced by 73% of asafoetida participants compared to 45% of placebo participants. In the other study, a combination of asafoetida and nux vomica was used with 68% (13/19) experiencing global improvement after 2 weeks versus 52% (12/23) in the placebo arm. For individualized homeopathic treatment, a slightly higher benefit was shown for homeopathic treatment compared to usual care. The results for the outcomes assessed in this review are fairly vague, and therefore, no conclusions regarding the effectiveness and safety of homeopathy for the treatment of IBS can be drawn [73].

Constipation

The diagnosis of functional constipation in infants and children is based on a combination of symptoms in the absence of an underlying organic cause [42]. A recent systematic review reported that the prevalence of childhood constipation in the general population ranges from 0.5% to 32.2%, with a pooled prevalence of 9.5% [74]. Chronic symptoms of functional constipation are associated with a lower quality of life, as measured with generic questionnaires [75]. The backbone for treatment of functional constipation consists of education, behavioral modifications, and laxative therapy [76]. Once disimpaction is accomplished, maintenance therapy is essential to prevent re-accumulation of feces. Daily oral laxative therapy needs to be continued for 3 months or longer at a dose that produces a daily soft stool without side effects. In many children, symptoms of constipation resolves within this period. However, persistence of symptoms is reported in 30–52% of children in studies with at least 5 years of follow-up [77]. Not surprisingly, we showed that 36% of patients with constipation visiting a gastroenterology outpatient clinic used a least one CAM modality [2].

Acupuncture

A recent meta-analysis including 28 RCTs with 3525 adults with functional constipation demonstrated that acupuncture significantly increased stool frequency, alleviated constipation symptoms, and improved quality of life [78]. However, the quality was relatively low. More high-quality trials from other countries than China are needed. Little effort has been made to investigate the efficacy of acupuncture on constipation in children. In 2012, a retrospective study including 10 children with constipation received bilateral stimulation of acupuncture point LI11 using fixed acupuncture needles (0.9 mm long). Acupuncture was feasible in all children, and application of the needles was tolerated without fear. Side effects were not observed. After a median of 3 days, all children defaecated within 2 h after LI11 stimulation. No patient required conventional constipation therapy [79]. Clearly, an adequately powered, randomized sham controlled study is necessary to confirm these positive results.

Acupuncture may accelerate the release of opioid peptides in the central nervous system, but its effect on opioid activity and constipation is not known. One study evaluated the effect of acupuncture on symptoms and on basal plasma pan-opioid levels in children with chronic constipation [80]. The study regimen consisted of 5 weekly placebo acupuncture sessions followed by 10 weekly true acupuncture sessions. A significant increase in frequency of bowel movements occurred in both boys and girls after treatment.

The pan-opioid activity was lower in the control children and increased only in the children who received the true acupuncture sessions. Out of 27 children enrolled in the study, 10 did not complete it due to poor compliance.

Another review identified 29 clinical studies evaluating the complementary effects of auriculotherapy in functional constipation. All of the studies reported that auriculotherapy was effective in managing constipation. Generalization of these findings is however limited because of significant methodological flaws. Uncertainty in accurate acupoints identification and subjects compliance to instructions resulted in varied doses of intervention received and consistent intervention protocols and therapeutic outcome criteria made comparison among different studies difficult [81].

Herbs

Herbs and botanicals, and especially traditional Chinese medicine, have been used in many cultures over 1000 of years for defecation disorders in both children and adults. Although there are many CHM interventions available, and some have been utilized in clinical trials, their efficacy and safety are still questioned by both patients and health-care providers worldwide. A 2009 SR of the literature reviewed 35 studies including a total of 3571 patients, ranging in age from 1 month to 93 years [82]. Although the authors concluded that the results favored the tested CHM interventions in comparison with controls, the results of these trials should be interpreted with caution due to the generally low methodological quality of the included studies. First, all studies provided insufficient information on how the random allocation was generated and/or concealed. Second, none of the studies used any blinding method. Third, none of the included studies addressed incomplete outcome data, such as missing data due to attrition or exclusions. Fourth, none of the studies had been registered, and finally, the majority of experimental CHM interventions were prepared by the investigators without detailed information on formulation, dosage, and manufacturing process.

An observational study investigated the use of a Japanese herbal medicine, Dai-Kenchu-To (DKT), composed of three herbs, zanthoxylum fruit, ginseng root, and dried ginger rhizomes, in 10 children with non-defined severe constipation over a 3–12-month period [83]. In this small study, the authors concluded that DKT had a favorable clinical effect on symptoms of constipation in children such as fecal incontinence. No data were, however, provided about the effect on defecation frequency, consistency of stools, and abdominal pain.

Historically, the botanical agents *Rhamnus purshiana* and *Senna* (Sannae folum) have been used as stimulant laxatives and are approved by the Food and Drug Administration for the treatment of constipation in children over 2 years of age; however, studies evaluating safety and efficacy of these stimulants are lacking. The literature suggests that *Cassia Fistula,* originating from the same genes as *Senna,* may provide beneficial effects in children with functional constipation. The herb is popular in the tropics and is widely used in different traditional medicines to treat functional constipation in children and pregnant women. A trial that compared *Cassia Fistula* to mineral oil in children with functional constipation found that the defecation frequency, severity of pain during defecation and consistency of stool significantly improved in the *Cassia Fistula* group compared to the laxative group [84]. There was no difference in the number of fecal incontinence episodes. A similar trial, including 109 children with functional constipation, comparing *Cassia Fistula* to polyethylene glycol, found comparable results [85]. It was demonstrated that after 4 weeks of treatment, severity of pain, consistency of stool, fecal incontinence and retentive posturing improved in both groups, without any significant difference. Frequency of defecation was significantly more improved in the *Cassia Fistula* group compared to the laxative group. Both trials reported side effects; 25–32% of the children in *Cassia Fistula* group reported diarrhea, which was resolved after dose reduction. The methodological quality of both trials was low.

Reflexology

Reflexology is based on the notion that different areas on the hands and feet correspond to glands, organs, and other parts of the body and that pressure on those specific areas can have a therapeutic effect. The mechanism underlying this treatment is unknown, but many believe that the effect is caused by an improvement of blood flow that encourages relaxation and the healing response [86]. The effect of reflexology has been studied in 50 children, 3–14 years of age, with functional constipation and fecal incontinence [87]. After 6 weekly reflexology sessions of 30 min, there was an increase in defecation frequency and a decrease in fecal incontinence episodes. No side effects were reported. In contrast, no differences were found with respect to defecation parameters when comparing foot massage for 10 min 5 times a week to toilet/diet/motivation training for 30 min once a week in 37 children with functional constipation. Larger well-designed randomized controlled trials are necessary to establish whether there are benefits of reflexology in the treatment of functional constipation in children [88].

Massage

Abdominal massage for the relief of constipation was a commonly practiced therapy in India, China, Arabia, Egypt, and

Greece, but its use declined over time. As for other complementary therapies, there is now a resurgence of interest in the role that abdominal massage may play in relieving symptoms related to constipation. Although preliminary studies have been disappointing many patients perceived the therapy as agreeable [89]. It has been suggested that the combination of exercises that stimulate and relax the abdominal muscles, in coordination with diaphragmatic breathing, may trigger contraction of the intestinal and rectal muscles and bring relief to patients with functional constipation [90]. Seventy-two children with functional constipation, 4–18 years of age were randomized and received either medication plus physiotherapy (isometric training of the abdominal muscles, diaphragmatic breathing exercises and abdominal massage, exercises were employed during twelve 40 min sessions twice a week by a trained physiotherapist), or laxatives. After 6 weeks of treatment, the defecation frequency was significantly higher in the physiotherapy group [5.1 (2.1) days/week] than in the medication group [3.9 (2.0) days/week]. The frequency of fecal incontinence was not different between the groups [3.6 (1.9) days/week versus 3.0 (2.1) days/week] [90].

Conclusion

Some CAM therapies, and especially acupuncture, show considerable promise in the treatment of children with FGID. Since so many patients are using CAM and because some of these modalities are not always devoid of risks, it is important for pediatricians and pediatric gastroenterologists to be familiar with these therapies. Moreover, given the ongoing interest in CAM by pediatric patients, it is in the public interest to establish more rigorous evidence on efficacy and safety of these therapies. Only this way, we can head toward integration of evidence-based CAM modalities into pediatric FGID. Until then, one should try to acknowledge both benefits and limitations of CAM therapies in discussing these treatment options with parents and patients.

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Cellular-Based Therapies for Paediatric GI Motility Disorders

49

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Currently, the therapeutic options for many gastrointestinal (GI) motility conditions, especially the most severe, remain woefully inadequate. For these disorders, such as esophageal achalasia, paeditric intestinal pseudo-obstruction, and Hirschsprung disease, treatments are limited to palliative interventions such as surgery and/or the provision of artificial nutrition. This highlights the fact that current treatments aim to prevent mortality and limit the morbidity associated with the most significant complications of the diseases but are not designed to be curative.

Although it is clear that both surgery and parenteral nutrition (PN) have revolutionised the management and overall survival of children suffering from severe intestinal motility disorders, most of whom would otherwise not have survived beyond the neonatal period [1–3], these conditions continue to be associated with high levels of morbidity and mortality. Mortality rates still remain in the order of 8–20% and mostly relate to iatrogenic complications of central venous catheter-related sepsis and PN-related liver failure [1–6].

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The poor outcome of gut motility disorders is perhaps best exemplified by Hirschsprung disease (HSCR) where despite substantial surgical expertise and relatively rare use of PN, the post-operative morbidity data are compelling [7–15]. A long-term follow-up study of 48 HSCR patients with total colonic aganglionosis (TCA) by Tsuji et al. showed that 94% survived. Among the survivors, faecal incontinence was present in 82% of patients at 5 years, 57% at 10 years, and 33% at 15-years follow-up. On anthropometric follow-up, 63% of patients with TCA were failing to thrive at 15 years [7]. These findings are supported by recent systematic reviews [12, 15]. Other studies suggest that such problems occur irrespective of the extent of aganglionosis [8] and persist in a significant number of HSCR patients into adulthood [9, 14].

Such data highlight the need for improved, curative therapies for gut motility disorders, including those designed to definitively restore missing components or rescue dysfunctional ones. With particular attention to enteric neuropathies, this chapter summarises the tremendous progress that has been made, and the challenges that remain, in the development of new curative cellular therapies for gut motility disorders.

Stem Cell Therapies for ENS Disorders: Background and Concepts

Recent advances in molecular biology and genetics have significantly enhanced our understanding of the development and function of the gut neuromusculature, especially its intrinsic innervation, the enteric nervous system (ENS). This not only has facilitated our appreciation of the pathogenesis of gut motility disorders but also has allowed the identification of novel tools and targets for therapy [16, 17]. Stem cells, defined by their unique ability to self-renew, proliferate extensively and differentiate into multiple lineages, provide one such tool. For the purposes of this chapter, the term "stem cell" has been used to denote both progenitor cells, with limited self-renewal and differentiation capacities, and stem cells in the truest sense.

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Successful stem cell therapy has already been performed for many years in the form of bone marrow transplants, and there is currently enormous interest in the potential of stem cell therapy to treat diseases of both the central nervous system (CNS) [18] and ENS [19–21]. Compared with other systems, the use of stem cell therapy for treating diseases of the ENS has some potential advantages including accessibility to source and delivery of cells, as well as the possibility of autologous transplantation.

Sourcing Stem Cells for ENS Therapy

In the quest to develop cellular therapies for ENS disorders, a number of tissue sources have been explored to identify a cell type capable of generating ENS components upon transplantation. These are discussed and summarised in Table 49.1.

Table 49.1 Possible sources of stem cells to generate a putative ENS

Source	Selection/ propagation	Recipient or host tissue	Differentiation in host tissue	Function	References
PSC (ES/iPS)					
Mouse ES cells	EB	Mouse renal capsule	N, M, ICC and EP	Regular slow wave activity and spontaneous spike potentials	[22–25]
Mouse ES cells	Sox10	Aneural hindgut explant from mouse embryo in vitro	N	ND	[26]
Human PSC	SOX10, CD49D	Colon of Ednrb−/− mouse	N+G	Prolonged survival of mice with HSCR	[27]
Human PSC	+RA; Sorted SOX10:GFP+/p75+	Rag2_/_;gc_/_;C5-/- mice	N	Long-term colonisation	[28]
CNS					
Embryonic mouse brain	NS	nNOS−/− mice stomach in vivo	N+G	Improved gastric function	[29, 30]
Embryonic rat brain	NS	Chemically denervated rat rectum in vivo	N+G	Restored rectoanal inhibitory reflex	[31]
Embryonic rat neural tube	NS	Chemically denervated rat colon in vivo	N+G	Improved colonic motility	[32]
Neural crest ENS					
Embryonic mouse gut	Sorted Ret+ cells	Aganglionic gut explant from Ret−/− mouse embryo in vitro	N+G	ND	[33, 34]
Embryonic/postnatal mouse gut	NS	Aganglionic gut explant from Ret−/− mouse embryo in vitro	N+G	ND	[35]
Postnatal/adult rat gut	Sorted p75+/α4 integrin+ cells	Aganglionic gut explant from Ednrb−/− mouse embryo grown on chorioallantoic membrane of chick embryos	N	ND	[36–38]
Embryonic rat gut	Sorted p75+/α4 integrin+ cells	Ednrbsl/sl rat bowel in vivo, i.p.	N+G	ND	[39]
Embryonic/postnatal human gut	NS	Human gut explant in vitro	N	ND	[40]
HSCR patient gut	NS	Aneural hindgut explant from mouse embryo in vitro	N+G+ICC	Restored motility patterns to hindgut	[41, 42]
Postnatal human gut mucosa	NS	Explant from aganglionic region of HSCR patient in vitro	N	ND	[43]
ENS cell line from immortomice	Sorted p75+ cells	Piebald or nNOS−/− mice colon in vivo	N	Improved colonic motility	[44]
Embryonic mouse gut	Sox2	Aneural hindgut explant from mouse embryo in vitro	N	ND	[45]
Postnatal mouse gut	Sorted ENCCs (Wnt1-Cre/YFP mice)	Wild-type mouse colon in vivo	N+G	Functional integration with host neurons by Ca2+ imaging	[46]
	Sorted ENCCs (*EdnrbKik* mice)	Wild-type mouse colon in vivo	N+G	Functioning neurons by intracellular recording	[47]

Table 49.1 (continued)

Source	Selection/ propagation	Recipient or host tissue	Differentiation in host tissue	Function	References
Other NCCs					
Embryonic mouse neural tube	Neural tube explant	Dom/+ mouse colon in vivo, i.p.	N+G	ND	[48]
Embryonic rat peripheral nerve	Sorted p75+/α4 integrin+ cells	Into migratory pathway of embryonic chickens in ovo	Gut; no, peripheral nerve; N+G	ND	[36, 37]
Diphtheria toxin receptor mouse	Enteric neural-crest derived cells	Injected into ablated area	N+G	ND	[49]
Hypoganglionic rat model using BAC	ENCCs with RHO inhibitors	Injected into ablated hypoganglionic area		ND	[50]

CNS central nervous system, *EB* embryoid body, *ENCCs* enteric neural crest cells, *ENS* enteric nervous system, *EP* epithelium, *ES* embryonic stem (cells), *G* glial cells, *HSCR* Hirschsprung's disease, *ICC* interstitial cells of Cajal, *i.p.* intraperitoneally, *iPS* induced pluripotent stem (cells), *M* myofibroblasts, *N* neuron, *NCCs* neural crest cells, *ND* not determined, *NS* neurospheres, *PSC* pluripotent stem cells

Embryonic Stem (ES) Cells

Embryonic stem (ES) cells derived from the inner cell mass of the blastocyst are pluripotent and capable of giving rise to all the cell types in the body [51]. Their initial discovery [52, 53] and subsequent isolation from human embryos [54] led to significant interest for their use in regenerative medicine, especially given their potential to generate "unlimited" quantities of cells for replacement therapies. ES cells from both mouse (mES) and human (hES) are capable of producing a range of neural cell types [55–61], including enteric neurons [26, 62, 63]. Kawaguchi et al. demonstrated that neural crest (NC) progenitors (Sox10 expressing) derived from mES cells can colonise and give rise to neurons (Hu and TuJ1 expressing) within explants of aneural hindgut of mouse embryos [26]. Neural progenitors derived from hES cells also appear capable of generating NC-like cells that migrate along established NC migratory pathways in quail embryos in vivo and colonise explants of embryonic mouse gut in vitro where they give rise to neurons [62, 64]. To date, a number of studies have described the most efficient induction of NC and generation of ENS progenitors and neurons from pluripotent stem cells [27, 28, 65–67]. These are described below.

Apart from neurons, mES cells also appear capable of generating "gut-like" structures [22–24, 68–71]. These structures are 0.2–1.5 mm in diameter and contain an endodermal epithelium, intestinal epithelial stem cells, a layer of smooth muscle cells and interstitial cells of Cajal (ICCs); they also exhibit spontaneous contractions [22–24, 68–71]. Although they show some similarities to normal gut organogenesis [24], the requirement for brain-derived neurotrophic factor (BDNF) for neuron development differs from normal enteric neuron development, which does not require BDNF [24]. It is still unclear whether gut-like structures derived from ES cells will be useful for cell therapy, whereas generation of functioning gut epithelial tissue in vitro will provide a platform to study a wide spectrum of GI conditions. It has been shown that these "organoids" can be manipulated to mimic human GI diseases, including Menetrier disease; hence, they can be used as disease models [71].

Induced Pluripotent Stem Cells (iPSC)

Arguably, one of the most exciting and promising advances in the search for a regenerative medicine solution for the most severe gut motility disorders has been the generation of induced pluripotent stem (iPS) cells by the reprogramming of mouse embryonic or adult fibroblasts back to a pluripotent state by introducing four transcriptional factors, namely, Oct4, Sox2, Klf4, and c-Myc [72]. Successful reprogramming of differentiated human somatic cells into a pluripotent state raised the possibility of creating patient-derived stem cells [72], which would bypass both immunological problems and bioethical issues associated with hES cells or those obtained from foetal brains. In terms of the GI tract, iPS cells can produce intestinal tissue and gut-like structures in vitro. Three-dimensional intestinal organoids were derived from human iPS cells using activin A treatment to induce endoderm formation, followed by FGF4 and WNT3A manipulations to develop hindgut and intestinal specification [73]. Gut-like structures can also be derived from mouse iPS cells that contain a lumen with three distinct layers (epithelium, connective tissue, and muscle layer), neuronal networks and ICCs, and which exhibit spontaneous contractions [74]. It is unknown whether iPS cell-derived gut-like structures or neurons will have any therapeutic relevance for the treatment of

enteric neuropathies. Studies will be required to elucidate the mechanisms of reprogramming of somatic cells into enteric neurons using exogenously delivered transcription factors and to establish a method of purifying desired cells with 100% efficiency in vitro. Interestingly, in recent years, protocols have been developed in vitro whereby both human embryonic stem cells (hESCs) and human pluripotent stem cells (hPSCs) were converted into neural crest cells (NCC) [75–77]. This was achieved either by the addition of small molecules (SB431542) and Noggin [75] or by activating Wnt signalling using CHIR99021 (Chir), which works by selectively inhibiting glycogen synthase kinase 3β (GSK-3β) [77, 78] or using the stromal-derived inducing activity of PA6 fibroblast co-culture [76]. These culture conditions favour generation of neural crest cells (NCC).

To date, a number of studies have described the generation of ENS progenitors and neurons from pluripotent stem cells [27, 28, 65–67]. Fattahi et al. demonstrated neural crest induction of hES and the efficient derivation and isolation of ENS progenitors from hPSCs and their further differentiation into functional enteric neurons [27, 79]. Importantly, in vivo engraftment and migration of these hPSC-derived ENS precursors rescued disease-related mortality in HSCR mice (EDNRBs-l/s-l), although the mechanism of this action was unclear. More recently, Frith et al. [28] confirmed that hPSC could be converted to ENS progenitors in the presence of retinoic acid. These progenitors gave rise to neurons both in vitro and in vivo upon transplantation into the gut of immunodeficient mice with long-term colonisation in the ENS of adult mice [28]. hPSC-derived therapy for human enteric neuropathies is an important advance and could pave the way to develop individualised therapy for different ENS diseases.

Mesoderm-Derived Enteric Neurons

It has long been proposed that neural crest stem cells persist throughout life and remain dormant until injury when they can differentiate to form new ENS. Zhang et al. [80] have shown, using chick/quail transplantation of vagal neural crest cells from progressively older stages, that the capacity to form ENS reduces with age. Therefore, they suggest that whilst considering cell transplantation for ENS rescue, (younger) embryonic cells would be better. However, studies also suggest that perhaps there may be another cell type that could replenish the ENS at older stages. Kulkarni et al. (BioRxiv 262832 [Preprint]. August 25, 2020. Available from: https://doi.org/10.1101/2020.08.25.262832), have shown that the NC derived neurons are replaced by mesoderm derived neurons in adult. The proportion of the NC derived and mesoderm derived populations maintains a healthy functional gut. This study suggests that transplanting only NC derived cells may not be sufficient for restoration of function and a mixture of these two cell populations could be necessary.

CNS-Derived Stem Cells

Although it had long been believed that the CNS in mammals is incapable of regenerating after birth, adult neurogenesis is now well established, including in humans [81–87]. This neurogenesis appears to be affected by a population of self-renewing, multipotent progenitors known as neural stem cells (NSCs) [88, 89]. CNS–NSCs were one of the first cell types tested for ENS therapy as several features were thought to make them suitable [20]. Transplanting CNS–NSCs into the pyloric wall of an animal model of gastroparesis (nNOS−/− mice), Micci et al. showed that these cells predominantly gave rise to neuronal nitric oxide synthase (nNOS) expressing neurons, which resulted in significant improvements in gastric emptying and in electric field stimulation-induced relaxation [29]. Although the mechanisms underlying such improvement of gastric function were unclear, the study provided the first demonstration that NSCs transplanted into the bowel were able to ameliorate a motility disorder [19]. More recently, transplantation of foetal cerebral cortex-derived CNS–NSCs into the rectum of adult rats, where enteric neurons had been destroyed chemically, resulted in the generation of neurons and glial cells, an increase in both the expression of nNOS and choline acetyltransferase (ChAT) and restoration of the rectoanal inhibitory reflex [31].

Cells isolated from the mid-embryonic rat neural tube or "neuroepithelial stem cells" have also been shown to give rise to enteric neurons in vivo in experimental animals similar to that described above [32, 90]. Transplantation of these cells appeared to result in nNOS- and ChAT-expressing neurons and improvements in colonic motility in recipient colons in which the ENS had been chemically destroyed [32, 90].

Neural Crest Stem Cells

Perhaps, the most attractive tools for ENS therapy are derivatives of the neural crest (NC) cells that gave rise to the ENS itself. This phenomenon is described in detail in earlier chapters. Briefly, during embryogenesis NC cells emigrate from

the NC, a transient structure that forms at the dorsolateral surface of the developing neural tube, and migrate along defined pathways to give rise to diverse structures including the ENS [91–93]. Vagal (hindbrain) NC cells arising adjacent to somites 1–7 [91–93] enter the foregut and migrate along the developing GI tract to give rise to the majority of the ENS [94–96]. The capacity to rescue the ENS appears to be limited to NC cells fated to give rise to the ENS itself [36], and although there is some data to suggest that vagal NC have some therapeutic potential [48], the most promising avenue appears to be the use of NC derivatives isolated from the gut.

Enteric Neural Crest Stem Cells (ENS Stem Cells)

Non-human studies: Several studies have demonstrated that multipotent cells, with the ability to form the ENS when transplanted to uncolonised or aganglionic gut, are present within the GI tract during development and into postnatal life [33, 34, 37, 38, 47, 97, 98], including from the ganglionic portion of the gut from an HSCR mouse model (miRet51) [35, 99]. The methodology used to isolate such cells is the culture of dissociated gut to give rise to neurospheres (NS) or neurosphere-like bodies (NLBs), akin to stem cell-containing CNS neurospheres. In addition to differentiated neurons and glia, NLBs also contain proliferating undifferentiated cells that not only express putative stem cell markers (e.g., Sox10) but also are capable of self-renewal and giving rise to both enteric neurons and glia. Grafting of postnatal NLBs into aganglionic embryonic mouse gut revealed that donor cells were able to colonise the gut and differentiate into appropriate enteric phenotypes, at the appropriate locations [35].

Recent in vivo studies have shown that ENS stem or progenitor cells have the potential to migrate, proliferate and differentiate into appropriate phenotypes when transplanted into the colon of postnatal mice [39, 47, 100–105]. Such cells can be isolated from the embryonic (E14.5) and postnatal mice gut, survived for at least 16 weeks and formed enteric ganglion-like clusters containing neurons and glia. Graft-derived neurons expressed some enteric neuron subtype markers, including NOS, ChAT, calbindin and calretinin. Importantly, intracellular electrophysiological recordings from graft-derived neurons showed that they fired action potentials and received fast excitatory postsynaptic potentials (fEPSPs) demonstrating that the graft-derived neurons had incorporated into the enteric circuitry [47]. Furthermore, optogenetic activation of ENS stem cells following transplantation to mouse colon demonstrated that graft-derived neurons integrate into the neural circuitry of the host ENS [105]. In an nNOS knock-out mouse model for slow transit constipation, transplanting yellow fluorescent protein positive enteric NC stem cell-containing NS into the colon not only showed these cells were not only capable of generating nNOS neurons and colonizing recipient gut but also effected functional rescue [106, 107]. Following transplantation into the large intestine of nNOS knockout mice, the delayed whole gut transit time that characterised these mice improved and was no longer significantly different compared to controls (untransplanted and sham transplanted nNOS knockout mice). Electrophysiological studies of transplanted tissue further showed rescue of previously absent nNOS neuronal function.

Human Studies: a number of groups, including ours, have reported the harvesting of ENS stem cells from postnatal human gut [40–43, 102, 108–110]. Although initial studies suggested this required full-thickness tissue for a source of cells, our work showed that gut mucosal biopsies obtained by routine endoscopic procedures can be used as a source of stem cells [43]. Neurospheres were generated in cultures of mucosal tissue from endoscopic biopsies obtained from children from the neonatal period up to 16 years, including HSCR patients (Fig. 49.1). The neurospheres were equivalent to those generated from human embryonic and full-thickness postnatal gut tissue and contained putative ENS stem cells. When transplanted into segments of aganglionic gut, including human HSCR gut maintained in vitro, the neurosphere-derived cells colonised the recipient gut and generated neuronal phenotypes. These studies highlight a significant advance by identifying a regenerating cell source to generate ENS stem cells and confirm the feasibility of autologous transplantation. Although there are data suggesting that transplanted human cells are capable of influencing mouse embryonic gut function [42], it is still unclear if recipient postnatal gut exhibits functional rescue following human ENS stem cell transplantation in vivo [109] (Fig. 49.2).

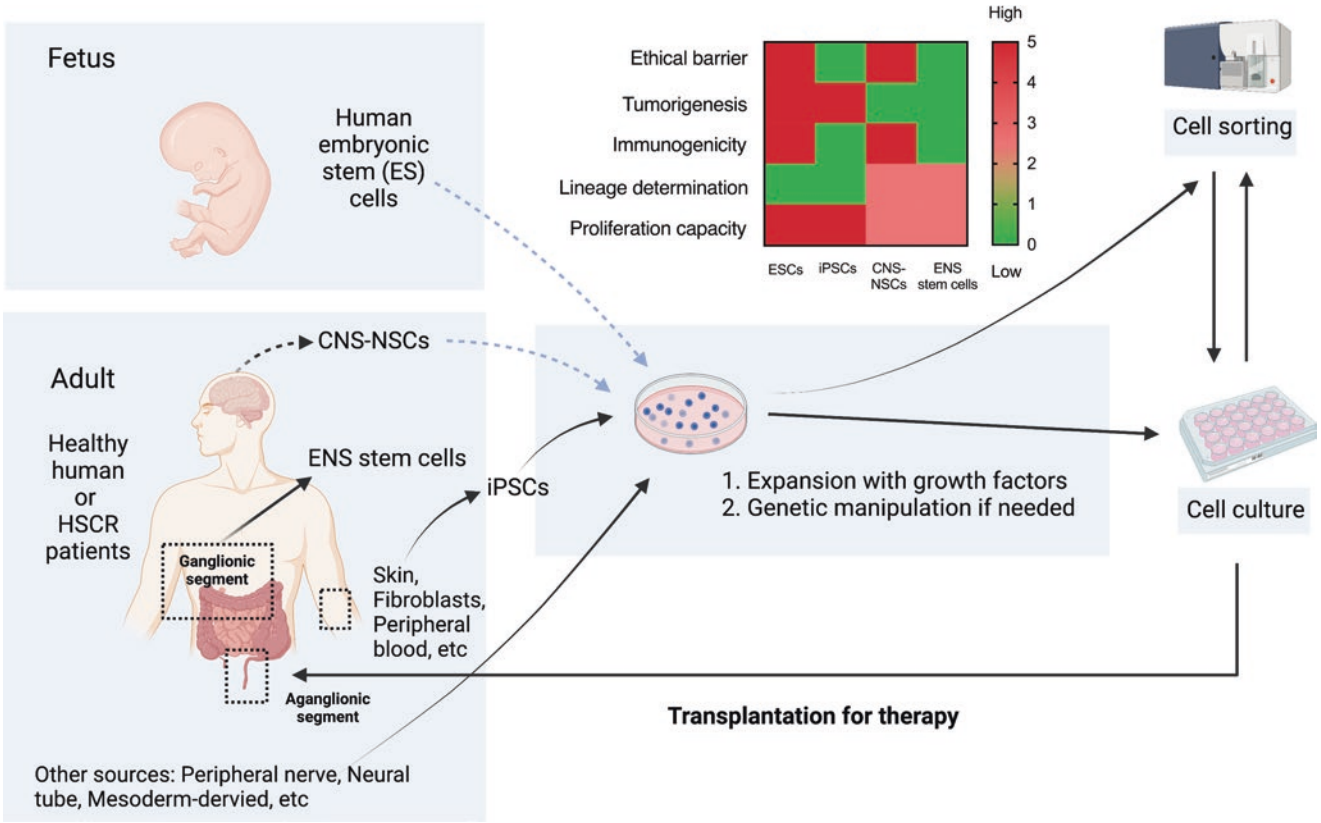

Fig. 49.1 Strategy for cell-based approach for the treatment of enteric neuropathies. Donor cells can be harvested from fetal or postnatal tissue, with potential cell sources including ESCs, iPSCs, CNS-NSCs, ENS Stem Cells, or other novel sources such as peripheral nerve-, neural tube-, or mesoderm-derived neural progenitors. Cells are expanded in culture, with the option of performing genetic modification and/or cell sorting prior to transplantation into the affected segment of the GI tract. Each cell source has potential ethical barriers, tumor risk, immunogenicity, lineage potential, and proliferation capacity, as summarised above. For example, ESCs have the advantage of pluripotency and a robust proliferation capacity but present ethical, tumorigenic, and immunogenicity challenges. iPSCs show similar tumor risk and proliferation capacity as ESCs, but if derived autologously, the immunogenic risk is avoided. CNS-NSCs have potential advantages but cannot be derived autologously, whereas autologous ENS Stem Cells have high lineage determination given their neuronal commitment, lower proliferation capacity than ESCs and iPSCs, and low tumorigenicity and immunogenicity. HSCR, Hirschsprung disease; ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells; CNS-NSCs, central nervous system-neural stem cells; ENS Stem Cells, enteric nervous system stem cells

Fig. 49.2 Enteric neural stem cell-containing neurospheres can be harvested from postnatal gut. (**a**) Fluorescent immunostaining of day 14 cell cultures generated from postnatal mouse gut showing the presence of spherical multicellular aggregates of cells, termed neurospheres. These contain cells positive for Sox10 (*red*) and for S100 (*green*). Positivity for both markers (*arrow*) suggests the presence of glial cells, whereas the presence of cells positive for Sox10 only (*arrowheads*) suggests neural crest-derived undifferentiated progenitors or stem cells. (**b, c**) Low-power (**b**) and high-power (**c**) bright field images of cell cultures (day 21) generated from dissociated human colonic mucosal biopsies obtained from a 6-year-old patient by conventional endoscopy. The cultures show numerous characteristic neurospheres, which have been shown to contain enteric neural stem cells and can be transplanted into recipient gut

Practical Challenges in Developing Cell Therapies

Although there has been much progress in the sourcing of cells with potential for therapy for gut motility disorders, some key challenges still need to be addressed before effective clinical application. These have been discussed in a "white paper" produced by an international consortium of scientific and clinical experts in the field [111].

What Is the Ideal Target Disease?

HSCR has provided the archetypal disease for ENS stem cell therapy. The ENS deficiency (distal intestinal aganglionosis), however, is absolute and extensive, and it is unclear whether replenishment of the complex ENS circuitry is truly achievable. In view of this, disorders with a less severe anatomical or functional phenotype may be more amenable to therapy.

In oesophageal achalasia, in the early stages of disease, functional and presumably neuronal loss appears more restricted to the lower oesophageal sphincter presenting a smaller therapeutic target. Furthermore, recent less invasive surgical iniatives aimed at this area, namely per-oral endoscopic myotomy (POEM) may also hold promise for the delivery of therapeutic cells [112, 113]. The underlying immunologically mediated pathogenic processes [114], however, may need to be controlled prior to transplantation to prevent destruction of a neo-ENS. In intestinal pseudo-obstruction and slow transit constipation, the overall ENS 'scaffold' appears intact but is clearly dysfunctional possibly due to deficiencies of particular elements of the neuromuscular circuitry [115–117]. These elements, once identified, may be easier to replenish than the entire ENS. Generalised involvement of significant lengths of the GI tract may, however, limit success, as would potential limitations in migration of transplanted cells [118, 119]. It is clear that all these potential disease targets need more detailed characterisation of their specific defects and aetiology prior to the development of any tailored replenishment strategies. Recent international initiatives to address these hold promise [120].

It should also be noted that complete ENS restitution may not be necessary. Studies of the ageing gut, where despite substantial neuronal loss, a scanty surviving ENS functions in the absence of any overt functional obstruction, suggest that partial ENS reconstitution may be sufficient to restore some balance between inhibitory and excitatory influences within the neuropathic gut [121, 122]. This suggests that delivery of smaller number of appropriate cells may be an acceptable therapeutic goal. Furthermore, where segments of diseased dysmotile gut cannot simply be rescued by the delivery of cells (e.g., where there is also loss of viable gut length as is seen in long-gap esophageal atresia), progess, using combinations of many of the cell-based technologies described in this chapter, is being made towards the generation of whole segments of multilayered gut for clinical application [67, 123–128].

What Is the Ideal Therapeutic Cell Type?

It is likely that the therapeutic requirement for individual disorders will determine which cell source is most suitable, e.g., whether to use multipotent stem cells (e.g., from hES, iPS) or more committed neuronal precursors (e.g., "adult stem cells" or precursors sourced from gut). Limitations exist for each source ranging from uncontrolled proliferation and potential tumour formation (ES cells) to restricted harvesting and differentiation potential (adult stem cells).

The production of unlimited quantities of enteric neurons by direct induction of ES cells remains an exciting possibility, but there are concerns about their potential to form tumours [54, 129] and unwanted cell types. Strategies have been proposed to prevent this including partially differentiating ES cells, enriching for appropriate cell types and then screening for undifferentiated cells [129–131]. Certainly it could be advantageous to differentiate them into specific neuronal subtypes before transplantation. Protocols for such specific differentiation from each stem cell type have yet to be established although some progress has been made. Stem cells from foetal brain (CNS–NSCs) also have the ability to divide, form neurospheres and differentiate into neurons and non-neuronal cells [132]. Micci et al. reported that CNS–NSCs preferentially differentiate into nNOS neurons [29, 30], which may be promising for conditions such as oesophageal achalasia. For many patients, clinical practitioners and the general public at large, however, there are ethical problems associated with the use of hES cells and CNS–NSCs from fertilised human eggs and aborted foetal brain tissues, respectively.

Due to the issues outlined above, much focus has therefore shifted to "adult" stem cells, especially given their presumed role in maintaining and repairing the tissue in which they are found and restricted potential to generate only those cell types (e.g., neurons and glia) of the required tissue (e.g., ENS), which limits the need for cell programming and reducing the risks of generating "ectopic" cell types and malignancy. Such cells, however, are present in much smaller numbers and appear to have a reduced potential to proliferate. Kruger et al. reported that NC stem cells comprise only <0.2% of cells within the gut wall of postnatal day 22 rats [38], and human studies have suggested that the generation of ENS stem cell-containing neurospheres declines with increasing postnatal age [43]. Although it is possible to enrich and expand neural stem cells obtained from the ENS

[35, 40–43], it is not known whether the therapeutic potential is compromised with prolonged in vitro propagation. The paucity of specific markers for stem cells presents a further potential obstacle for the field. ENS stem cell harvesting has largely been restricted to their isolation within neurospheres, structures composed of a heterogeneous mix of cells consisting of, in addition to the stem cells, differentiated cells including neurons, glia and smooth muscle cells [35, 43]. It may be argued that pure isolation of stem cells is perhaps not necessary as neurospheres exist as potential ready-made stem cell niches and complete therapeutic packages capable of colonising aganglionic gut [35, 41, 43]. However, unless specific isolation is possible, the manipulation of cells within, and generation of targeted cell types from, the heterogeneous cellular pool within neurospheres is likely to be a major problem.

As discussed above, recent studies by Fattahi et al. [27] and Frith et al. [28] have demonstrated that enteric neural crest (ENC) cells can be derived from hPSC. These authors induced neural crest cells from hPSCs followed by treatment with retinoic acid to obtain functioning ENC cells. Fattahi et al. showed that survival of *Ednrb*-null mice (mouse model for HSCR) was improved following transplantation of these cells. This work provides significant validation for the use of hPSCs for the treatment of enteric neuropathies. However, it remains unclear how transplanted cells were able to elicit the rescue of animal survival in this study [27]. It also remains to be determined whether transplanting a mixed population of ENS–NCC would be better given, for example, that other cell types may provide paracrine factors for maintenance and differentiation, or if transplanting an enriched population (e.g., nNOS neurons) known to be deficient or dysfunctional in a specific disease, would be better therapeutically.

As mentioned above, another population of NC, derived from mesodermal cells, has recently been suggested by Kulkarni et al. (BioRxiv 262832 [Preprint]. August 25, 2020. Available from: https://doi.org/10.1101/2020.08.25.262832). It has been suggested that in adult life, the NC derived neurons are replaced by mesoderm derived neurons and these two cell types are present in a proportion important for normal gut function. If so, this would suggest that if cell replacement therapy is being planned and depending on age, appropriate proportions of both populations will need to be considered and generated for transplantation.

Overall, studies such as the above suggest that the ideal cell type for replacement therapies is likely to be a NCC phenotype rather than a generic stem cell population, and deriving them from stem cells may have the advantage of generating adequate cell numbers. However, much work is needed to investigate the function and safety aspects of these cells.

Is Cell Manipulation Prior to Transplantation Likely to Be Necessary?

The finding that stem cells can be generated from innervated or ganglionic portions of diseased gut or from the thickened nerve trunks characteristic of the aganglionic region of HSCR gut [133] makes it likely that in some cases, especially with autologous transplantation, genetic modification of the cells may be necessary before transplantation. Stem cells derived from the normo-ganglionic or aganglionic part of HSCR gut may have defective biological function due to underlying genetic mutations causing the disease, underlining the inability of their predecessors to form a complete or functional ENS [134]. In support of this idea, enteric progenitors isolated from the monoisoformic Ret51 (miRet51) HSCR mouse model show delayed differentiation compared to controls [135]. Thus defective cells may need to be rescued by genetic manipulation, given that reintroducing the Ret9 isoform within the miRet51 ENS progenitor cells reverses the differentiation deficits [136]. The advent of novel targeted genome-editing approaches, such as the CRISPR-Cas9 system [137], with their ability to alter genome sequences and gene expression, is likely to provide a significant advance for this aspect of novel stem cell therapy application in humans.

Injection of stem cells in conjunction with delivery of missing neurotrophic factors may be beneficial for cell survival, migration and differentiation [21]. Recent data suggest this may be possible. Endothelin 3, for example, inhibits reversibly the commitment and differentiation of ENS progenitor cells along the neurogenic and gliogenic lineages, suggesting a role for this factor in the maintenance of multilineage ENS progenitors [138]. Glial cell line-derived neurotrophic factor (GDNF) acting in the presence or absence of endothelin 3 significantly increases the proliferation of ENS progenitors as well as increasing neurite outgrowth [138–140]. In a very interesting recent study, HSCR model mice, when given rectal enemas containing GDNF, showed significantly prolonged mean survival times compared with control mice [141]. Furthermore aganglionic mice given GDNF developed neurons and glia in distal bowel tissues, had a significant increase in colon motility, and had fecal microbiomes similar to those of wild-type mice. GDNF application to cultured explants of human aganglionic bowel induced proliferation of Schwann cells and formation of new neurons.

Such findings and studies have enormous implications for pre-transplantation priming of ENS stem cells as well as the creation of receptive environments within recipient aganglionic gut.

Is the Gut Environment Suitable for Cell Replenishment?

In HSCR the average aganglionic segment measures almost 10 cm in length. Yet data from several groups, including ours, suggest that longitudinal migration of transplanted cells within recipient embryonic gut maintained in organ culture may be limited to a few millimetres at best [43]. The limited migratory capacity of grafted stem cells is a potentially important issue, especially in adolescent or older patients, as it appears that the migratory ability of CNS–NSCs and enteric neuronal precursors is limited in more mature gut in which the mesenchyme has already differentiated [29]. It is possible that the local gut environment of patients with congenital gut motility disorders might be defective and/or not be permissive for the grafted cells to survive or differentiate into appropriate cell types. For example, there are reports of decreased expression of GDNF in the aganglionic region of patients even in the absence of mutations in *GDNF* [142]. GDNF has been implicated in the directed migration of NC-derived ENS progenitors within the developing gut during embryogenesis [135, 143]. Therefore, recipient gut may require pretreatment with growth factors, e.g., GDNF, to optimise stem cell transplant success although a recent study using Ednrb-null mice demonstrated that aganglionic gut lacking Ednrb signalling was permissive to transplanted isogenic enteric neuronal progenitor cells, which were able to engraft and exhibit neuroglial differentiation [104]. As described above GDNF treatment of the distal colon appeared to increase neuron and glia development and exert effects on its structure [141] (e.g., decreased epithelial permeability and muscle thickness). More work needs to be done to confirm that the pretreatment of cells, or of the recipient gut of patients, does not have any adverse effects in other aspects of their health.

Finally, immunological rejection of transplanted cells within the gut is also likely to be a problem [144]. This may well be overcome with improving protocols of immunosupression already in use with solid organ and cellular transplantation and/or by using autologous cells for transplantation.

What Is the Most Effective Route of Administration for Stem Cells to the Gut?

The gut is easier to access compared to the brain or spinal cord, and cells have been introduced into the gut wall of animals through the serosa via laparotomy [31, 32, 48, 144]. Stem cells have also been injected intraperitoneally into animals to replace enteric neurons, but further work is needed to identify all the sites colonised using this method [39, 48]. A recent study has revealed the potential of NC stem cells to give rise to a small number of neurons and glial cells when injected into the peritoneal cavity of *Ednrbsl/sl* rat, but none of the injected cells were found in the aganglionic colon [39]. Injecting cells intravenously could allow cells to be delivered to a broader area which would be an advantage over using multiple injections. However, the vasculature has not yet been explored extensively as a delivery route for cells to the gut.

Endoscopy is routinely practised to deliver drugs into the gut wall. This may be a better way for not only harvesting cells but also for their delivery into recipient guts, as has recently been shown using Ednrb−/− mice [103] especially when combined with imaging techniques for better precision (e.g., ultrasound, confocal). Disadvantages include the need to intubate entire segments of diseased GI tract, some of which, e.g., mid-small intestine, remain relatively inaccessible, and would require more complicated enteroscopy techniques.

What Is the Best Measure of the Success of Cell Therapy?

The main aim of cell replacement therapy is to restore function to the diseased gut. Grafted human ENS stem cells have been reported to differentiate into glia and neuronal subtypes reminiscent of a functional ENS within explants of aneural hindgut from chick and mouse embryos [38, 39]. Hotta et al. went on to show that transplanted enteric neural progenitor cells were capable of generating electrically functional enteric neurons in the bowel of postnatal mice [43]. Human PSCs-derived enteric NCCs transplanted into an animal model of HSCR showed extensive migration and neuroglial differentiation. More importantly, survival of transplanted animals was significantly improved compared to controls [27]. Although this work had significant bearing on realising the potential of cell therapy for the treatment of enteric neuropathies, it remains unclear how the transplanted cells were able to elicit the improvements in survival. In studies by McCann et al. the ultimate measure of success was rescue of the delayed gut transit exhibited by the untransplanted (or sham transplanted) nNOS knockout mice. This was further supported by tissue physiology tests that confirmed the restoration of nNOS-specific function within the transplanted guts [106, 107].

In terms of safety it has been demonstrated that transplanted ENS stem cells show long-term viability following transplantation without tumor formation or ectopic spread [46]. However, although it seems that transplanted cell-derived neurons are capable of forming functional connections to other target cells, including neurons of neuropathic

gut that has retained an ENS, albeit dysfunctional, and smooth muscle, it remains unclear whether they are capable of forming an ENS with the appropriate circuitry to produce functional recovery on its own accord, particularly when introduced into an aganglionic region. It is likely that functional data will only truly be understood within the context of in vivo studies, by studying parameters ranging from simple gut transit to definitive measurements of peristaltic activity and sphincter function. With increasing access to tissue of the GI tract with minimally invasive techniques (e.g., laparoscopic assisted, POEM) it is possible that tissue assessment with histology and, importantly, physiology (e.g., RAIR) may also provide additional evidence of transplant success.

Summary and Future Directions

Cell therapy for GI motility disorders is an exciting and promising prospect and, even in the few years since the last edition of this textbook, has shown significant advances. The ENS has many potential advantages that favour the success of transplantation therapies. These include accessibility to both source and delivery of cells, as well as the possibility of minimising immunological rejection by expanding neural stem cells obtained from unaffected regions of the intestine, for autologous transplantation.

The evidence to date suggests that cells with the potential of generating components of the ENS can be harvested from a range of allogeneic and autologous sources, be propagated and cultured in large numbers and have their biological properties manipulated, and ultimately be transplanted into diseased or dysmotile gut to replenish components of the ENS and rescue function. Although a number of significant hurdles remain, all is perhaps not so bleak. Ageing-related neuronal loss is not associated with functional failure giving hope that restitution of a fully normal ENS, in terms of neuronal number and cellular diversity, may not needed. Gene therapy is already established in clinical therapies and rescue of defective ENS stem cells derived from murine models of HSCR possible. Tissue transplantation and management of immunological aspects is well studied and could potentially be overcome with the use of autologous transplantation. Recent work has shown that minimally invasive procedures such as endoscopy can be used to isolate ENS stem cells from a regenerating source of intestinal tissue and ultimately be used to deliver them back into the gut. Transplantation of such cells into models of aganglionic and neuropathic gut suggests they are capable of colonisation, generating components of the ENS and effecting functional change. Although encouraging progress has been made with enteric neuropathies, other motility disorders such as myopathies and mesenchymopathies will need to see similar initiatives in terms of understanding disease pathogenesis/pathology before ultimately progressing to the development of targeted cellular therapies.

There is no doubt that children and adults with gut motility disorders represent a significant challenge in management. Huge strides have been made in unraveling the processes that underlie the complex workings of the gut neuromusculature, especially the ENS, and have given us tremendous insight into pathogenesis and the identification of putative treatments. Cellular therapies should now be considered alongside other approaches as they have the potential to herald a shift towards definitive cures for gut motility disorders.

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Surgery in Motility Disorders

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Abbreviations

CC	Chicago classification
DES	Diffuse esophageal spasm
EA	Esophageal atresia
EGJ	Esophagogastric junction
ERAS	Enhanced recovery after surgery
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology, and Nutrition
FI	Faecal incontinence
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
HAEC	Hirschsprung-associated enterocolitis
HD	Hirschsprung's disease
HRM	High-resolution manometry
IAS	Internal anal sphincter
IFALD	Intestinal failure associated liver disease
JH	Jackhammer esophagus
LES	Lower esophageal sphincter
LHM	Laparoscopic Heller's myotomy
MEN2A	Multiple Endocrine Neoplasia type 2A
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
NI	Neurological impairment
PEG	Percutaneous endoscopic gastrostomy
PEG-J	Percutaneous endoscopic gastro-jejunostomy
PIPO	Pediatric intestinal pseudo-obstruction
PN	Parenteral nutrition
POEM	Peroral endoscopic myotomy
PPI	Proton pump inhibitor
RAIR	Recto-anal inhibitory reflex
TCA	Total colonic aganglionosis
TLESR	Transient Lower esophageal sphincter relaxation
TPN	Total parenteral nutrition

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Introduction

Gastrointestinal motility disorders pose a major clinical challenge because of the limitations of diagnostic tests and the lack of efficacious therapeutic options. Gastrointestinal motility disorders comprise heterogeneous conditions that may affect any area of the digestive tract resulting from abnormality of enteric neuromuscular function. Motility disorders are frequently chronic and may markedly affect patients' quality of life. Despite significant progress has been made over the last years, the exact nature and pathophysiological mechanisms of most gastrointestinal motility disorders remain largely unknown. Unfortunately, most dysmotility disorders cannot be cured and treatment are only offered to relieve symptoms, reduce morbidity and mortality, and improve quality of life. Surgery has a pivotal role in managing patients with motility disorders representing the treatment of choice in different conditions or an important intervention to be associated with medical therapies.

This chapter discusses surgical approaches to the main motility disorders focusing on indications, techniques, and postoperative outcomes. Principal areas of controversy and risks/benefits considerations concerning surgery for motility disorders are debated.

Since the needs of patients with complex medical conditions, as children with gastrointestinal motility disorders are, exceed the boundaries of competence of a single specialist,

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the incorporation of medical and surgical skills is strategic, as suggested by Peter Cotton [1] who firstly described the advantages of the integrated activity of the "digestivists."

Achalasia

Achalasia is a life-long rare debilitating condition characterized by an incomplete lower esophageal sphincter (LES) relaxation and absence of esophageal peristalsis, which leads to slow or absent bolus transit into the stomach (Chap. 22). Diagnosis of achalasia in children is generally made between 7 and 15 years of age, with a mean age of 10.9 years and predominance for male sex. Because of the improved knowledge about achalasia, incidence is constantly increasing and ranges between 0.1 and 0.18/100,000 children per year [2, 3].

Clinical presentation of achalasia in adults and adolescents includes dysphagia (94%), regurgitation (76%), heartburn (52%), chest pain (41%), and weight loss (35%) [2]. Younger children and infants may also present atypically with recurrent pneumonia, nocturnal cough, aspiration, hoarseness, feeding difficulties, and failure to thrive. Achalasia in children is often misdiagnosed as gastroesophageal reflux disease (GERD) or may present in a similar fashion with other conditions, such as eating disorders, eosinophilic esophagitis, or asthma, which often result in a significant diagnostic delay [3, 4].

Clinical history, upper endoscopy, and esophagogram are useful to suspect achalasia and to exclude other conditions such as structural (e.g., peptic stricture, congenital stenosis), and mucosal esophageal disease (e.g., eosinophilic esophagitis). The clinical reference for the diagnosis of achalasia is the high-resolution manometry (HRM) which allows to easily identify impaired relaxation of the lower esophageal sphincter and aberrant peristalsis. Achalasia is categorized by using Chicago Classification 4.0 (CC) into three subtypes according to HRM patterns of esophageal body contractility: type I, minimal/absent contractility in the esophageal body; type II, intermittent periods of panesophageal pressurization; type III (spastic) with premature or spastic esophageal contractions. By using metrics from HRM CCv 4.0 defines other esophageal motility disorders that may benefit from surgical treatment such as esophagogastric junction (EGJ) outflow obstruction (EGJOO), diffuse esophageal spasm (DES), and nutcracker/jackhammer esophagus (JH) [5].

Classifying achalasia subtypes by the Chicago Classification may offer valuable data on prognosis and can be used to direct treatment choice [6].

As no curative treatment is currently available, once the diagnosis is established, the therapeutic aim is the disruption of non-relaxing circular muscle of esophagus and esophagogastric junction (EGJ), in order to facilitate the passage of the bolus into the stomach and to prevent further esophageal dilatation, resulting in an improvement of symptoms [7].

Traditional management of pediatric achalasia includes step-wised esophageal dilation and surgery [6, 8].

The surgical approach in pediatric esophageal achalasia has progressed from an open surgery to a minimally invasive surgery, comprising laparoscopic or robotic Heller's myotomy (LHM) with or without Dor's anti-reflux fundoplication, and peroral endoscopic myotomy (POEM) techniques [9].

In selected patients who are not eligible for definitive surgical management, alternative less effective long-term options include Botulinum toxin injection, calcium channel blockers, and long-acting nitrates, treatments used mainly in adult population, with variable results [10].

Laparoscopic or Robotic Heller's Myotomy with or without Fundoplication

Since satisfactory outcomes occurred in almost 95% of patients, minimally invasive treatments for achalasia are equally effective to open techniques. Laparoscopy is now the preferred approach for Heller's myotomy [9, 11].

The patient is supine in reverse Trendelenburg position. Endotracheal intubation is required for the procedure. A big orogastric tube is generally inserted.

The key elements of Heller's technique are as follows:

(A) incision of the umbilicus
(B) introduction of the 30° laparoscope through the Hassan trocar and, therefore, of the remaining trocars under direct visualization
(C) exposure of the gastroesophageal junction
(D) section of the phrenoesophageal ligament to expone the anterior esophagus and cardias
(E) myotomy
(F) Dor's fundoplication (optional)
(G) entry points closure

One of the most debated aspects surrounding Heller's myotomy concerns the opportunity to perform an antireflux procedure after the esophageal myotomy to compensate the mobilization of cardias. A prospective randomized trial by Richards et al. showed that the addition of an anterior partial fundoplication significantly decreased the incidence of postoperative gastroesophageal reflux, when compared with no fundoplication. Thus, according with main evidence, routine application of Dor fundoplication is the standard approach. The addition of a Dor fundoplication seems not to affect the postoperative functional outcome of an esophageal myotomy [11, 12]. Similar results are reported with the Toupet technique [13]. We must consider that an impaired esophageal emptying is frequently reported, especially in type I achalasia. The workup or recurrence is often more complicated when a flap valve is associated.

Furthermore, despite laparoscopic myotomy is an overall safe technique with excellent outcomes, complications can occur even in expert hands: rates of esophageal mucosal layer perforation up to 15% have been reported, especially after preoperative treatments (e.g., pneumatic balloon dilatation) [14–16].

The latest technological advances suggest how robotic Heller myotomy, combined with a fundoplication, incorporates all of the advantages of laparoscopic surgery with the added benefits of improved 3-dimensional visualization, increased degree of instrument freedom, human tremor control, and restoration of proper hand-eye coordination. These aspects combine to determine a decreased rate of complications, especially regarding the risk of intraoperative perforation (reduced from 15% to 0%), while maintaining the same effectiveness of traditional laparoscopic myotomy [15–18]. Disadvantages of the robotic approach are the high costs and increased operative times due to the setting of the robot, which can be partially reduced by improving the training of the operative team [16, 17].

PerOral Endoscopic Myotomy (POEM): A New Incisionless Approach to Esophageal Achalasia

POEM Technique

POEM is a well-established treatment for achalasia first described by Pasricha et al. in 2007 in a porcine model, performed by H. Inoue et al. in 2010 in humans [19, 20] and recently introduced into pediatric surgical and gastroenterological practices [10, 21–23].

This technique represents an incisionless approach both to the esophagus and the LES made possible by the ingenious concept of creating a submucosal tunnel preventing mucosal thermal damage during the myotomy. Once submucosal tunnel has reached the gastric side, a myotomy is performed for the total length of the tunnel itself. The mucosal incision is closed by using standard clips.

Thus, the elements of POEM technique are as follows (Fig. 50.1):

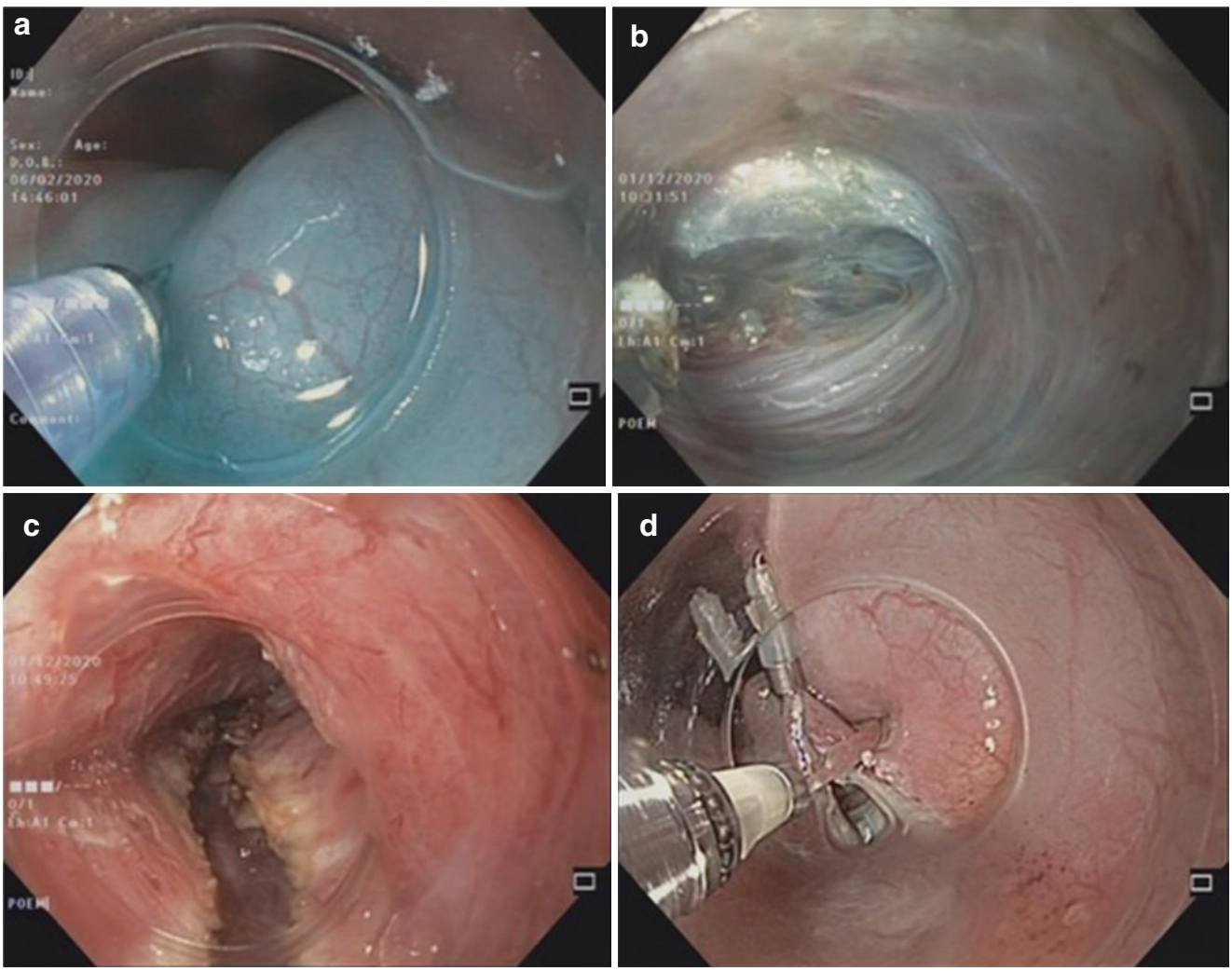

Fig. 50.1 POEM technique. (**a**) Mucosal incision; (**b**) submucosal tunnel creation; (**c**) myotomy; and (**d**) entry point closure

(A) mucosal incision
(B) submucosal tunnel creation
(C) myotomy
(D) entry point closure

The entry point site varies depending on the manometry findings but is typically 10–15 cm proximal to the EGJ.

The tunnel can be created in the anterior (2 o' clock) or posterior (5 o' clock) wall of the esophagus according to the operator's preference and previous treatments in patient's history. This possibility to choose between two alternative tunnel's orientations is particularly profitable in the management of recurrent symptoms after POEM or LHM as it allows to avoid the fibrosis caused by previous myotomy [24].

Risk of GERD and Comparison with LHM

Because no anti-reflux flap valve is generally created, gastroesophageal reflux disease (GERD) after POEM is postulated to be higher than LHM. In a comparative trial, POEM was associated with an increased risk of post-intervention GERD when compared with LHM, with high concordance rates across the three main parameters assessed: reflux- symptoms, abnormal pH-monitoring and endoscopic diagnosis of esophagitis [8]. A recent systematic review estimated a cumulative after-POEM gastroesophageal reflux rate of 17.8% (CI 95%, 14.2–22.0%) [25] compared to a risk between 4% and 16.8% of postoperative GERD in patients undergoing LHM in different studies [8, 26–28]. However, the risk of severe, unresponsive esophagitis is quite low [5]. There are conflicting opinions on the value of adding fundoplication at the time of myotomy. Some authors, in fact, have questioned the real utility to perform an anti-reflux procedure immediately after myotomy, because of the residual impairment of esophageal peristalsis [29]. Furthermore, an outlet obstruction can impair the post-surgical evaluation of a recurrent dysphagia.

Therefore, the management of recurrent dysphagia is easier after POEM comparing to LHM because no flap valve is performed. For this reason, supported by many studies reporting complete GER resolution with medical management[30], many pediatric surgeons perform Heller procedure without flap valve as first choice in children with achalasia and a second anti-reflux procedure only in selected patients with GERD unresponsive to proton pump inhibitor, after the pubertal spurt.

Nevertheless, a diligent follow up with pH-impedance monitoring and endoscopic surveillance of patient underwent POEM is required, to prevent the long-term theoretical risk of chronic esophageal inflammation.

Regardless of the risk of postoperative GERD, because of the different development eras for the two techniques, it remains difficult to compare the effectiveness of POEM and LHM. Both procedures appear to be safe and effective in symptoms relief. The hospitalization is also comparable [31]. The main advantage of POEM over LHM lies in its ability to access the thoracic esophagus, to adapt the length of the myotomy to the manometric findings and to avoid distal inflamed mucosa. POEM is particularly indicated in patients with type III achalasia who benefit from an extended tailored myotomy that involve the entire length of the spastic segment noted on esophageal HRM, which is unfeasible with LHM [6, 32].

Effectiveness and Safety Profile

Clinical success after POEM is most evaluated using the Eckardt score [33]: a score of ≤ 3 is judged to be a clinical success. However, this score only evaluates any weight loss, but does not consider the growth trend and its post-operative recovery, a critical aspect in the evaluation of post-surgical outcome in children.

Other more objective post-procedure efficacy indicators are esophageal HRM and timed barium esophagogram [34].

Mid-term effectiveness results in adults are extremely satisfactory: Eckardt score is less than three points in 98% of patients and post-operative stay is generally around 3–4 days.

Regarding the manometric parameters, a meta-analysis by Akintoye et al. showed that the average LES and IRP measured before the procedure, 33 ± 1.7 and 30 ± 1.4 mmHg, respectively, decreased to 14 ± 1.2 and 13 ± 1.6 mmHg, respectively, 6 months after the POEM. The timed barium esophagogram also recorded equally satisfactory results: prior the procedure the average heights of the barium column were 14 ± 2.3 and 9.7 ± 1.9 cm at 1 and 5 min, respectively; the column heights decreased to 4.2 ± 0.77 and 2.6 ± 0.72 cm at 1 and 5 min, respectively, after the POEM [34] (Fig. 50.2).

Data in pediatric population are quite limited, despite the increasing spread of this technique even in children in the last decade. Recently, a systematic review by Zhong et al. analyzed 11 of the most authoritative studies of last years for a total sample of 385 children undergoing POEM, demonstrating cumulative technical and clinical success rates of 97.4% (CI 95%, 94.7–98.7%) and 92.4% (CI 95%, 89.0–94.8%), respectively. After POEM, the Eckardt score was significantly decreased by 6.76 points (CI 95%, 6.18–7.34, $p < 0.00001$) and the lower esophageal sphincter pressure was significantly reduced by 19.38 mmHg (95% CI, 17.54–21.22, $p < 0.00001$).

Safety profile in expert hands is extremely satisfactory, with a pooled major adverse events rate of 12.8% (CI 95%, 4.5–31.5%) in the meta-analysis of Zhong et al. [25]. Overall, the most common complication is represented by mucosal

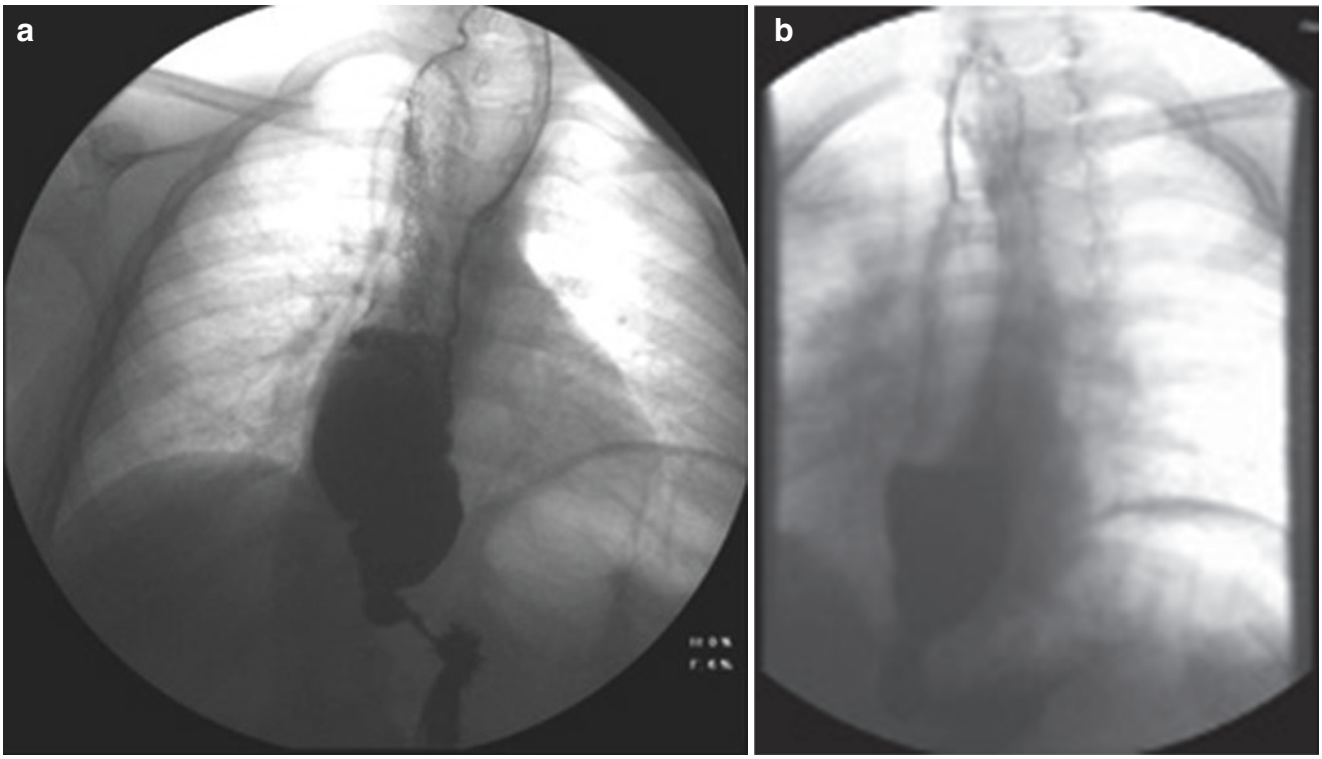

Fig. 50.2 Barium swallow before (**a**) and after(**b**) POEM in a 16-year girl with type I achalasia and a sigmoid esophagus

perforation that is reported in up to 3% of POEMs, and it is generally demonstrated by day after endoscopy or esophagogram. Management of mucosal perforation after POEM is generally conservative (prolonged fasting, antibiotics, and endoscopic treatment). Capnoperitoneum/capnomediastinum requiring decompression, pleural effusion, and submucosal bleeding are also reported as major adverse events. No mortality or emergency surgery after POEM has been reported [35].

Conclusions

In conclusion, a high index of suspicion and prompt investigations are required to detect achalasia in children. Esophageal HRM has a key role in diagnosing achalasia and, by categorizing the disorder in subtypes, it offers important information on prognosis and in driving the choice of treatment.

POEM is a safe and effective emerging technique in the pediatric endoscopy settings with high levels of expertise, according to the most recent literature and to the experience with the adult population. With rates of efficacy, safety and long-term effects largely comparable to those of LHM, POEM could quickly become the first-line therapy of pediatric achalasia when an expert operator is available.

Gastroesophageal Reflux Disease

Although antireflux surgery for gastroesophageal reflux disease (GERD) is one of the most performed procedures in pediatric surgery [36], indications are poorly defined. Therefore, there is a large degree of heterogeneity among centers regarding approaches of surgery for GERD [37]. It should be pointed out that, despite fundoplication has an unquestioned value in preventing reflux-related complications and improving quality of life in many selected children, it is far from an uncomplicated procedure especially when offered to the "wrong" patient. Indeed, the procedure permanently alters gastroesophageal anatomy and function, and may promote a variety of complications [38].

Current guidelines on pediatric gastroesophageal reflux disease (GERD) of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) stated that "*only patients with clearly proven GERD should be considered for surgery*" but they also highlight that obtaining un objective and definitive proof of GERD in children is still an unresolved issue. Indeed, guidelines pointed out also that "*to date no gold standard diagnostic tool exists for the diagnosis of GERD in infants and children*" [39].

Indications for Antireflux Surgery

In clinical practice, children candidate for surgery usually exhibit persistent symptoms despite optimized medical therapy with proton pump inhibitors (PPIs) are suffering from GERD-related complications (e.g., reflux-related pulmonary aspiration or peptic esophagitis) or have predisposing anatomic anomalies (e.g., a large hiatal hernia). Selection of patients for antireflux surgery in pediatrics is traditionally based on a combination of symptoms attributed to reflux, the presence of underlying pathologies that may predispose the development of severe GERD (e.g., neurologic impairment, esophageal atresia), and a preoperative workup that mainly includes upper gastrointestinal endoscopy, esophageal pH monitoring (or pH impedance) and upper gastrointestinal contrast studies [40]. Nonetheless definitive indication for antireflux surgery predominantly relies on individual experience and attitude that greatly varies among centers. Most of the pediatric literature consists of retrospective series in which details concerning diagnosis of GERD and previous medical therapy are lacking [39].

Therefore, recommendations on antireflux surgery in infant and children are only based on expert opinion and suggest that surgery can be considered when GERD is associated with:

1. life-threatening complications (e.g., cardiorespiratory failure) of GERD after failure of optimal medical treatment.
2. symptoms refractory to optimal therapy, after appropriate evaluation to exclude other underlying diseases.
3. chronic conditions (i.e., neurologically impaired) with a significant risk of GERD-related complications.
4. the need for chronic pharmacotherapy for control of signs and/or symptoms of GERD [39].

Over the last years, the number of surgical fundoplication in adults has steadily declined owing to concerns about complications, limited durability, and the need for reoperation in some patients [41]. In line, data collected from a national administrative dataset including 52 children's hospitals across the United States documented a threefold decrease in volume for fundoplication in children with GERD over the last decade [42].

Fundoplication

Different surgical options have been described to treat GERD, but the most common operation is the fundoplication. During fundoplication the gastric fundus is wrapped around the lower part of the esophagus to create a mechanical valve at the level of the esophagogastric junction. This operation decreases the amount of reflux by increasing the baseline tone of the lower esophageal sphincter (LES), decreasing the nadir pressure during swallow induced LES relaxation and the number of transient LES relaxations (TLESRs), and, by lengthening the intra-abdominal portion of the esophagus, accentuates the angle of His, and, when present, reduces a hiatal hernia [38].

Different fundoplication approaches exist, but they can be broadly differentiated in total fundoplication (Nissen procedure), which wraps the fundus 360 degrees around the esophagus, and partial fundoplication, with less than 360-degree wrap (the most common are 270° posterior fundoplication [Toupet procedure] and a 180° anterior fundoplication [Dor and Thal procedure]).

All types of fundoplication can be carried out as either open or laparoscopic surgery [43]. Follow-up studies suggested that laparoscopic fundoplication was associated with improved outcomes (hospital stay, costs, infection and surgical complications, and unplanned readmissions) compared with the open procedure [44, 45]. Therefore, laparoscopic fundoplication is currently regarded as the operation of choice by most pediatric surgeons [46, 47] and considered the gold standard for surgical treatment of severe GERD [47]. However, findings from randomized studies failed to show that laparoscopic fundoplication is superior to open approach with regard to short-term clinical outcomes while, in the long-term children operated with laparoscopy have a higher recurrence rate of GERD. Despite laparoscopic approach leads to a reduced incidence of retching, it shows a higher recurrence rate of GERD than open surgery [48–50]. A meta-analysis comparing open and laparoscopic fundoplication in six studies (four retrospective and two prospective studies) for a total of 721 patients showed no significant differences in GERD recurrence at 12 months, while other outcomes (operative time, hospital stay, start of feeding, and 30-day morbidity) generally favored laparoscopic approach. The significant heterogeneity among studied and the overall poor methodological quality considerably limit the interpretation of these results [51].

Data comparing the fundoplication technique and in particular outcomes of partial versus complete fundoplication in children are even more scarce. A single randomized controlled trial compared outcomes between partial (Thal) versus complete fundoplication in children found that in the long-term Nissen fundoplication had a significantly lower recurrence rate of symptoms than a Thal fundoplication in patients with neurological disorders while no significant difference between them was observed in non-neurologically impaired children. However, patients undergoing partial fundoplication have a statistically significant lower risk of postoperative dysphagia requiring endoscopic dilation compared to children undergoing complete fundoplication [52].

Other Anti-Reflux Operations

Esophagogastric Disconnection or Dissociation

Total esophagogastric disconnection is a radical procedure that has been developed to treat children with neurological impairment (NI) with intractable GERD unresponsive to other approaches. It involves the disconnection of the esophagus from the stomach and anastomosis with the jejunum. The patient is then fed through a permanent gastrostomy without risk of reflux [53].

This procedure has been advocated for NI children with severe neurological compromise with inability or contraindication (unsafe swallowing) to be orally fed [54, 55].

Prolonged postoperative care and occurrence of possible complications including malabsorption, need for prolonged enteral feeding, dumping syndrome, and Barrett's esophagus have been reported after total esophagogastric disconnection [56–60].

ESPGHAN guidelines recommend restricting the indication for total esophagogastric disconnection, as an alternative of classical antireflux surgery, to selected cases in children with NI [61].

Jejunal Feeding

Post-pyloric feeding has been proposed as an alternative to antireflux surgery in patients with severe GERD. Indeed, it represent a less invasive and reversible procedure compared with fundoplication. Gastrojejunostomy (PEG-J) is preferred procedure to gain jejunal access, alternatives are naso-jejunal tube placement or surgical transcutaneous jejunostomy. To minimize the risk of dislodgement in the stomach, the tube needs to be ideally passed beyond the ligament of Treitz. When PEG-J is in place, the gastric port can be used to give medications, vent air, and drain fluids while jejunal nutrition can be simultaneously given through the jejunal port. Main drawbacks are the need of continuous feeding regimes and the risk of frequent jejunal tube dislodgement requiring replacement, while major surgical complications have recently been identified in 6% of patients [62]. A metanalysis comparing outcomes for fundoplication and PEG-J in children with NI failed to show significant superiority of one over the other approach [63]. In another study, neither treatment option is clearly superior in preventing the subsequent aspiration pneumonia or improving overall survival for NI children [64].

Considering the risks and benefits associated with the therapeutic options, it is advisable that the choice of one over the other should involve a decision-making process fully shared with families.

Surgical Techniques

As stated, laparoscopic technique via transabdominal is preferred over open surgery for most patients undergoing fundoplication.

The basic laparoscopic equipment includes insufflation with CO_2, monitors, laparoscopic instruments (30-degree angled laparoscope, four trocars ranging from 3–5 to 10 mm, liver retractor, laparoscopic needle holder, laparoscopic grasper, electrosurgery hook, scissors), suction/irrigation system, electrocautery, and/or laparoscopic ultrasonic energy device dissector.

To perform laparoscopic fundoplication, the patient is placed supine in the reverse Trendelenburg position, with the legs abducted on straight leg boards, with the surgeon between the patient's legs, the assistant surgeon on the patient's right, and the camera holder to the left.

The initial port (5 or 10 mm) is placed at the level of the umbilicus, using a closed or open technique, and three additional ports are placed under direct vision of the laparoscope.

The laparoscopic procedure ensures a meticulous dissection and full mobilization of the lower esophagus (Fig. 50.3). These preconditions are of great importance in performing safely a floppy wrap.

Thal Fundoplication

Thal fundoplication is a simple intervention which fixes the distal esophagus within the abdomen and produces an acute angle of His. It is a 90-degree anterior wrap.

The procedure involves three steps:

1. Dissection of the abdominal esophagus and crura, then ligation of the esophageal hiatus on the dorsal side of the esophagus with non-absorbent sutures.

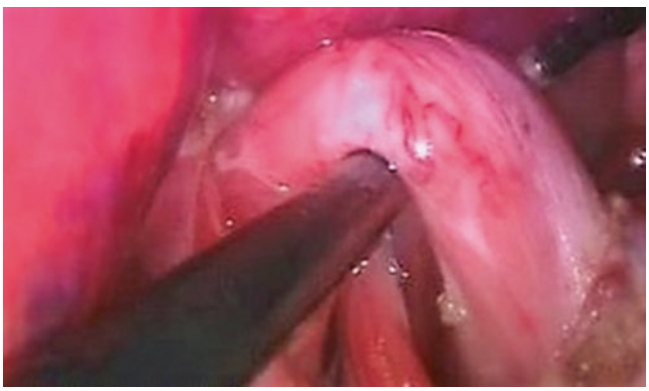

Fig. 50.3 Laparoscopic view of dissection and mobilization of the intra-abdominal segment of the esophagus. A retroesophageal window is created bluntly to perform a floppy wrap

2. Reconstruction of His angle through two more sutures between the left wall of the abdominal esophagus and the fundus of the stomach. Anchoring suture is added to the left crus of the diaphragm.
3. Anterior wrapping: The greater curvature of the stomach dome is sutured to both the right wall of the abdominal esophagus and the right crus of the diaphragm to prevent wrap migration. The stomach and the right wall of the esophagus are sutured with two more sutures and wrapping it over 180° anterior [65].

Dor Fundoplication

Dor fundoplication is an anterior 180-degree wrap originally described by the surgeon Dor in 1962.

The technique implicates the dissection of the hiatus using a vessel sealer or an electro-cautery shears or hook. The gastro-hepatic ligament is opened to find the right crus, then the dissection is continued across the apex of the hiatus to expose the left crus to the base of the angle of His. The esophagus is dissected until the anterior mediastinum in order to ensure adequate intra-abdominal esophageal length. Any herniation is repaired with two to three interrupted not absorbable stitches between the right and left crura. Approximation of the crura is usually performed posterior to the esophagus, although anterior closure may be appropriate.

An anterior 180-degree Dor fundoplication is created by suturing the anterior wall of the gastric fundus to the left and right crura and the diaphragmatic hiatus (Fig. 50.4). Stitches are placed through the right side of the fundus and through the adjacent left crus to recreate the angle of His. An apex suture is placed through the top of the fundus and the apex of the diaphragmatic hiatus. The posterior left fundus is then sutured to the right crus to complete the 180-degree fundoplication [66].

Toupet Fundoplication

Toupet fundoplication is first devised in 1963 by Andre Toupet.

It is a 270-degree posterior wrapping of the stomach around the esophagus, that leave the anterior esophageal hemicircumference free to avoid the inability to belch.

The procedure includes the division of the gastro-hepatic ligament using the ultrasonic shears oh hook, the diaphragmatic crura dissection and the mobilization of the abdominal esophagus. A retroesophageal window is created bluntly from the right side with care not to injure the posterior vagus nerve. After that, the posterior wall of the fundus is pulled behind the esophagus to the right side and it is fixed to the esophagus and to the right crus with three to five not absorbable sutures. The same procedure is performed on the left side, where the fundus is fixed to the esophagus and the left crus (Fig. 50.5). The vagus nerve should be identified and preserved at all steps of the operation. The hiatus should be closed by one or two stitches when it is very enlarged (Fig. 50.6) [67].

Nissen Fundoplication

Nissen fundoplication, a total (360°) wrap fundoplication, is the most common antireflux operation, performed by Rudolph Nissen [68].

Fig. 50.4 Dor anterior 180-degree wrap: the fundus is wrapped halfway around the front of the abdominal esophagus and attached to part of the diaphragm tissue

Fig. 50.5 Toupet 270-degree posterior wrap: the fundus is wrapped about two-thirds of the way around the back side of the bottom of the distal esophagus

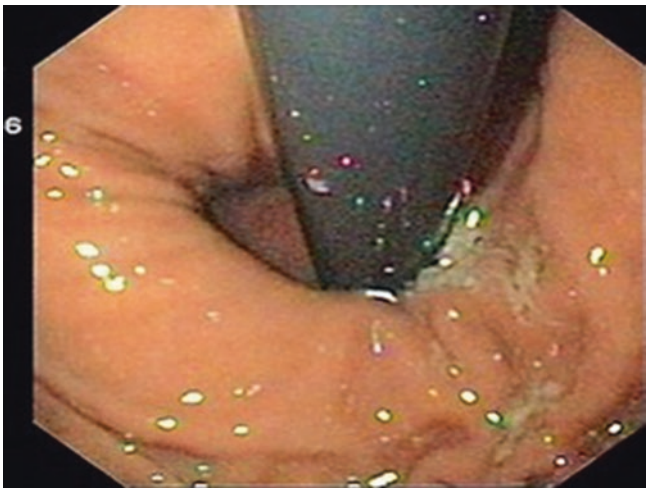

Fig. 50.6 Retroflexed endoscopic view of hiatal hernia

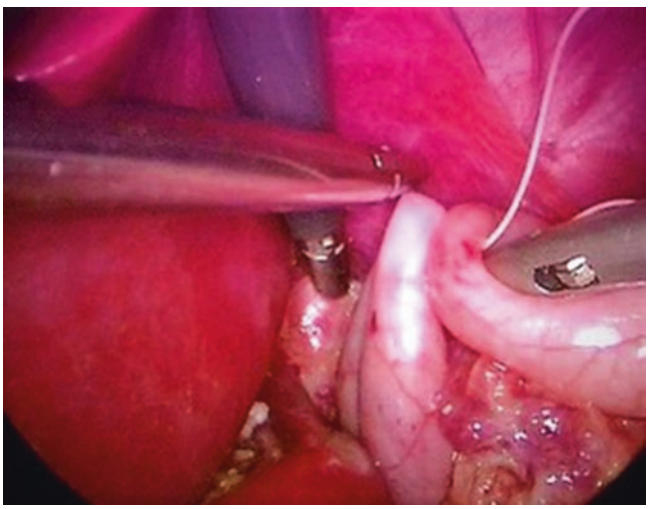

Fig. 50.7 Laparoscopic Nissen 360-degree fundoplication: the fundus is passed behind the esophagus from left to right and it is closed anteriorly using two or three non absorbable sutures

The first steps of the procedure are the same as the Toupet fundoplication and consist mainly of left and right crural dissection, mobilization of the intra-abdominal esophagus, and division of the short gastric vessels. Preservation of vagus nerves is recommended to ensure a better functional outcome. In cases of hiatal hernia, in which the fundus may slide up through the enlarged esophageal hiatus of the diaphragm, the right and left crura should be reapproximated posteriorly, utilizing two or three permanent sutures. To conclude, the posterior fundus is passed behind the esophagus from left to right and it is closed anteriorly using two or three non absorbable sutures (Figs. 50.7, 50.8, and 50.9). The most superior suture can incorporate a small piece of anterior esophagus and right crus to help secure the wrap. An orogastric tube can also be used to calibrate the wrap and prevents excessive narrowing of the esophagus.

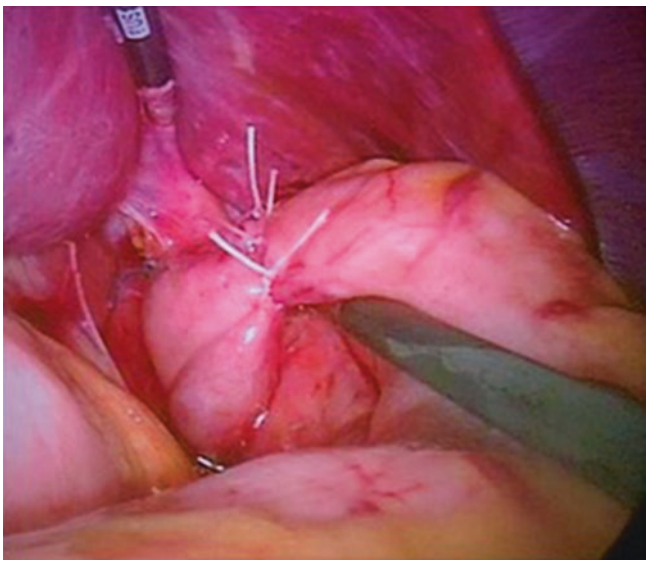

Fig. 50.8 Floppy Nissen fundoplication: laparoscopic view

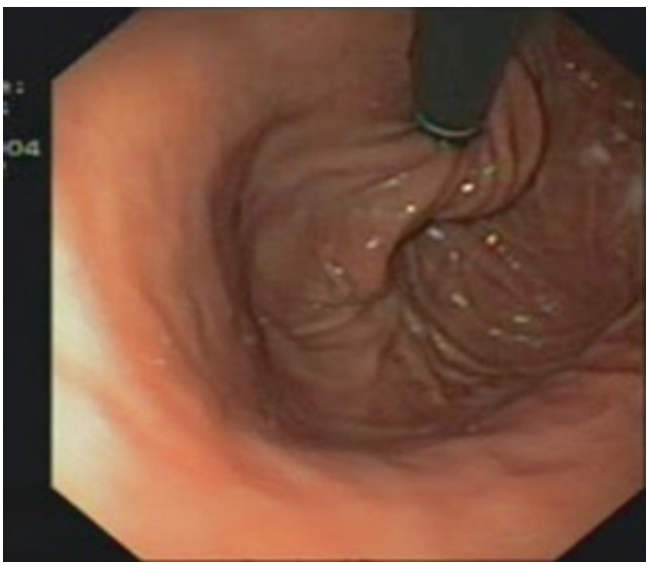

Fig. 50.9 Retroflexed endoscopic view of Nissen fundoplication

Esophago-Gastric Dissociation

The esophago-gastric dissociation is an alternative antireflux surgery for neurologically impaired children, described in 1997 by Adrian Bianchi.

The original technique (Fig. 50.10) involved a fully mobilization of the distal esophagus that was transected above the gastroesophageal junction; the gastric end was over sewn. An isoperistaltic Roux-en-Y loop of jejunum on a convenient mesenteric vascular pedicle was brought without tension through the transverse mesocolon, passing behind the stomach to anastomose with the lower esophagus. An end-to-side jejuno-jejunostomy restored the bowel continuity at 40 cm from the esophago-jejunal anastomosis. When possi-

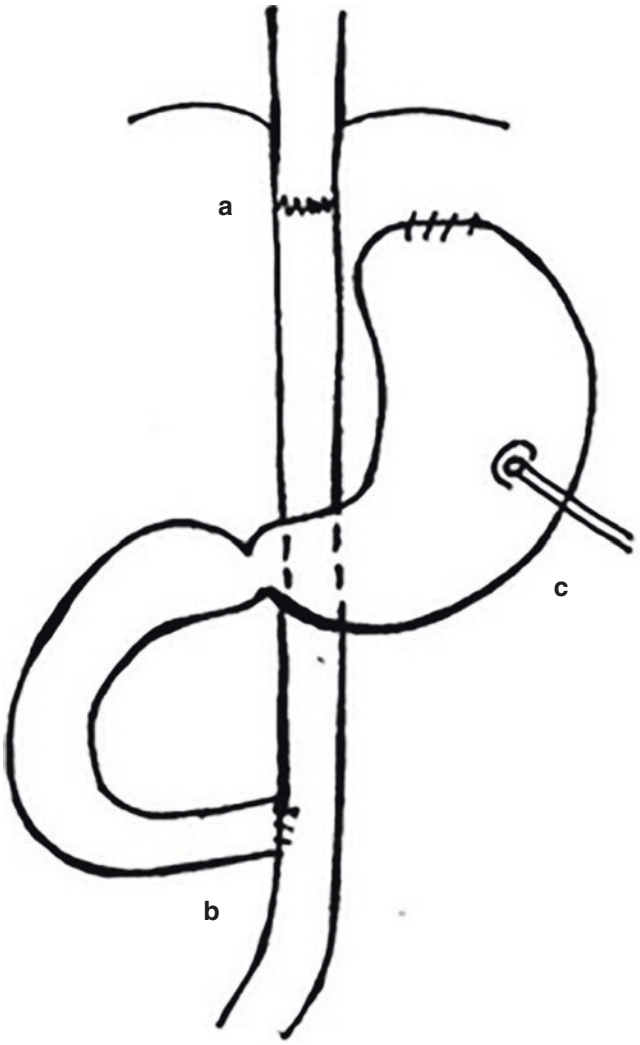

Fig. 50.10 Esophago-gastric dissociation: (**a**) end-to-end esophago-jejunal anastomosis; (**b**) end-to-side jejuno-jejunostomy anastomosis (isoperistaltic Roux-en-Y loop); and (**c**) gastrostomy

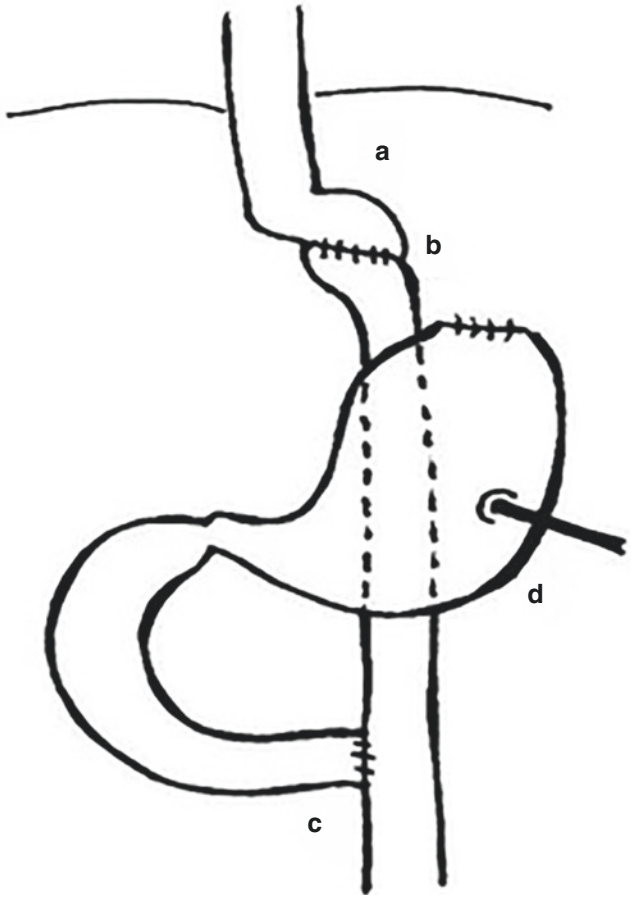

Fig. 50.11 Technical modification of the esophago-gastric dissociation procedure: the oesophageal-gastric stump (**a**) and the isoperistaltic jejunal roux loop are stapled together (anastomosed) (**b**); (**c**) end-to-side jejuno-jejunostomy anastomosis; and (**d**) gastrostomy

ble, a preexisting gastrostomy was preserved; otherwise, a new gastrostomy was fashioned [53, 59].

Recently, a technical modification of the technique has been proposed towards a more secure esophago-jejunal anastomosis (Fig. 50.11). It consists in the creation of an esophago-gastric stump using an articulated 5 mm laparoscopic Endo-GIA stapler; afterwards, a mechanical anastomosis between the esophago-gastric stump and the isoperistaltic jejunal roux loop is created [69].

Complications

The benefit/risk ratio of performing antireflux surgery even in patients with severe GERD is not clear.

Beyond the early post-operative complications (e.g., infection, bleeding, and perforation) that can happen after any gastrointestinal surgery, different complications directly related to the procedure of fundoplication may significantly impair or worsen quality of life.

Despite most long-term follow-up studies report successful outcome in more than 90% of children undergoing fundoplication, data on the true incidence of patients experiencing complications are very limited and derived from studies of poor methodological quality. Therefore, they would not seem to reflect what happens in real life. Indeed, complications are probably underreported in the literature as a result of the common tendency in clinical studies to publish positive results, and in this context, interpretation of results should consider that the great majority of papers are published by experienced and successful surgeons reporting their results of retrospective series [38]. Existing data show that complications are more common in children with underlying diseases as NI and previous esophageal atresia repair [70] that are, unfortunately, in exactly those conditions considered at high-risk for severe GERD accounting for the majority of indications for pediatric fundoplication [71].

Post-surgery issues can be due either to the persistence of symptoms prompting fundoplication, or to the side effects of surgery [72].

Former post-fundoplication complications may be related to a "bad diagnosis" in which the symptoms are incorrectly attributed to GERD. Guidelines on pediatric GERD and those specifically designed for the management of both children with NI and esophageal atresia recommend to objectively measure GERD before surgery [61, 73]. However, due to difficulties in obtaining an objective diagnosis of GERD, and due to the establish belief that most of symptoms experienced in these specific population are GERD-related, in clinical practice indication for surgery are often empirical and only based on center attitude and experience.

Upper gastrointestinal symptoms following fundoplication might be directly produced by the wrap that causes an antegrade obstruction that generates dysphagia, and/or a retrograde obstruction that produces inability to vent gas from the stomach and to vomiting that causes gas-bloat syndrome [72]. Moreover, fundoplication changes the morphology of the stomach by reducing its volume to create the wrap but it may also be potential cause of a variety of changes in gastric sensorimotor functions such as altered afferent input and development of visceral afferent hypersensitivity, gastrointestinal dysmotility, and changes in reflex pathways, including the gastric accommodation reflex and the emetic reflex [74, 75].

Mechanisms leading to disturbances in the gastric accommodation are not clear. Proximal gastric wall dysfunction, vagal injury, or mechanical effects have been reported as a cause of reduced gastric accommodation after surgery [76, 77].

Decreased gastric accommodation leads to impaired distribution of intragastric contents with the foods reaching and distending the distal stomach earlier than physiologically expected; reduced gastric compliance may lead to stimulation of visceral afferents producing visceral hypersensitivity and retching [78]. The rapid gastric emptying may also cause postprandial diarrhea, reactive hypoglycemia and dumping syndrome, reported in 30% of children after fundoplication [79].

Animal model showed that there is evidence that emetic sensitivity is increased post fundoplication [74]. Moreover, the operation may induce gastric dysrhythmia and loss of central inhibition of the gastric emetic reflex [80]. The activation of the emetic reflex leads to retching. Since fundoplication acts as a mechanical impediment to the final act of vomiting, gastric contents remain retained in the stomach, emetic reflex stimulus persists, and the retching continues [81].

Patients with fundoplication may experience gas-bloat syndrome that is characterized by abdominal bloating, postprandial fullness, inability to burp and vomit, and abdominal discomfort. It is more common in patients who have undergone complete laparoscopic Nissen fundoplication than partial fundoplication [82]. The inability to vent gas from the stomach due to the obstructive effect of the wrap may result in gastric distension with air that, if there is impaired accommodation of the fundus, may also lead in symptoms of retching and gagging. Venting gastrostomy between feeds will remove this accumulation of air, reduce overall gastric volume and help to prevent the resultant bloating [83].

Dysphagia is the most frequently reported postoperative complication [52]. Post-operative dysphagia is caused by outlet obstruction created by the wrap at the level of the esophagogastric junction. Early post-operative dysphagia generally resolves in the short term [84]. However, a subset of patient may develop long-term post-operative dysphagia that can mar otherwise successful GERD treatment [85, 86].

The risk of post-fundoplication dysphagia is significantly increased in patients with esophageal dysmotility since it may arise from insufficient esophageal peristaltic vigor to overcome the obstructive effect of the fundoplication [87]. Therefore, the integrity of esophageal motility is an important factor predicting outcomes following fundoplication. Preoperative and postoperative evaluation of the motility pattern on esophageal manometry could be useful to predict post-surgery outcome and to guide management of patients, even though existing data does not demonstrate a strong correlation between manometric changes and post-operative dysphagia [88, 89]. In this context, novel esophageal pressure-flow variables on high-resolution esophageal manometry with impedance demonstrates a high degree of prognostic value for prediction of postoperative new-onset dysphagia [86, 90].

Wrap failure due to a loose or disrupted wrap, or hiatal herniation, and recurrence of reflux, occurs in approximately 5–15% of children [47, 71]. Risk factors for fundoplication failure include younger age, preoperative hiatal hernia, postoperative retching, postoperative esophageal dilation; underlying disorder, such as esophageal atresia and NI, increased the risk of failure [71, 91, 92]. Wrap failure most occurs 1–3 years after fundoplication and is typically diagnosed due to recurrent GERD symptoms [71, 93].

Specific Patient Populations

Children with Neurological Impairment

Patients with NI are suffering from esophageal motor dysfunction directly related to central nervous system damage [94] that together with other predisposing condition, such as prolonged supine position and the increased intra-abdominal pressure secondary to spasticity, scoliosis or seizures, contribute to the risk of severe GERD [95]. In children with central nervous system disease, the incidence of GERD has been reported to be as high as 70% [61]. Even though children with NI account for the great majority requiring antireflux surgery in the pediatric surgical field, there have been very

few studies that have evaluated the GERD of NI patients before surgery in relation to the outcome [96].

Pharyngo-esophageal motility dysfunctions in NI children may also produce a misdiagnosis of GERD and predispose to post-fundoplication complication.

For example, fundoplication is often pursued for NI patients with intractable aspiration with the idea they are at greater risk of aspirating gastroesophageal reflux contents. However, evidence failed to show a consistent benefit of fundoplication for the treatment of aspiration pneumonias, and, in some cases, aspiration can even worsen after fundoplication due to pooling of saliva and food above the wrap [64, 97, 98].

It has been reported that NI children undergoing feeding gastrostomies placement are at greater risk of development or worsening of GERD [99–101] and therefore "prophylactic" antireflux surgery has been historically advocated in this specific population. However, fundoplication is associated with a high occurrence rate post-operative morbidity (up to 50%) with a 1% to 3% mortality rate [74, 100–103]. Moreover, data on infants with NI who underwent fundoplication at the time of gastrostomy placement demonstrated that reflux-related hospitalizations were comparable with those of patients who underwent gastrostomy placement alone [104] and several studies evaluating the relationship between gastrostomy and GERD using pH/impedance monitoring failed to evidence a significant aggravation of GERD after placement of gastrostomy [99, 105]. Owing these data, ESPGHAN guidelines suggest that routine fundoplication at the time of gastrostomy would unnecessarily expose a large proportion of children with NI to antireflux surgery complications and recommends that it should not be performed [61].

ESPGHAN guidelines recommend that fundoplication be considered in cases of failure of optimized medical therapy for GERD in children with NI, and despite the overall limited predicting value of testing [106] extensive evaluation of GERD with endoscopy, contrast studies, gastric emptying studies, and pH-impedance should be always performed before performing surgery.

In general, it is important to highlight that, due to the considerable unpredictability of the surgery for GERD in NI children, surgeon should ensure that parents are fully informed as to the risks and benefits of the procedure.

Children with Esophageal Atresia

GERD is considered the most frequent gastrointestinal complication after surgical repair of esophageal atresia (EA) [73] responsible for several short- and long-term sequelae such as peptic complications (erosive esophagitis, gastric metaplasia, Barrett's esophagus, and adenocarcinoma), anastomotic stricture formation and pulmonary complications (aspiration pneumonia, increased airway reactivity, chronic lung disease, and worsened tracheomalacia) [107–110]. Based on that, all EA patients are systematically treated with PPIs since surgical repair until 1 year of age, and most of them continue the treatment in the long term [73].

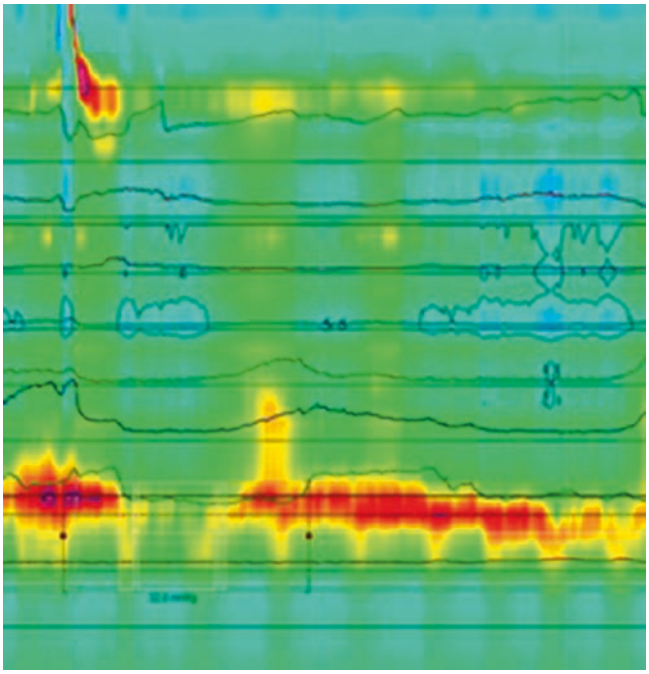

Fig. 50.12 Esophageal high-resolution impedance manometry in a 17-year-old female with previous esophageal atresia repair experiencing severe post-fundoplication dysphagia. Pressure topography shows a iatrogenic achalasia-like pattern characterized by the absence of peristalsis and the presence of outflow obstruction at the level of esophagogastric junction denoted by the elevated integrated relaxation pressure (IRP) and by the elevated intrabolus pressure. Of note, impedance tracing shows impaired bolus clearance

Fundoplication is performed in up to 45% of EA patients and almost all long-gap EA patients even if the indications for fundoplication are not clearly delineated as no controlled trial has been reported regarding the role of surgical management of GERD in patients with EA [110–113]. It is important to emphasize that, since virtually all EA survivors exhibit esophageal dysmotility [114], careful attention must be paid when fundoplication is considered because the outflow obstruction generated by the wrap is more likely to worsen the symptoms of esophageal dysmotility or produce new-onset of symptoms, in particular postoperative dysphagia (Fig. 50.12).

Current recommendations indicate to consider fundoplication in presence of poorly controlled GERD despite maximal PPI therapy, recurrent anastomotic strictures, especially in long-gap EA, long-term dependency on trans-pyloric feeding, acute life-threatening event [73].

It is noteworthy that data on prevalence of GERD demonstrated a high variability, ranging from 20% to 70% [115,

116], and that they are mainly obtained from studies using non-objective measures of GERD, such as the presence of symptoms [73]. However, although clinical suspicion has a main role in diagnosis GERD, it is important to highlight that esophageal symptoms in EA patients may be misinterpreted because of other comorbidities such us dysmotility, eosinophilic inflammation, anastomotic strictures, or other associated malformations [73].

Nevertheless, different studies recently published underestimate the true burden GERD and questioned about the widespread use of PPIs and the extensive indication for fundoplication [117–120]. Indeed, neither PPI treatment nor antireflux surgery have been found able to prevent the occurrence of esophageal histopathological complications that remain highly prevalent despite the extensive use of these treatments [117–119]. On the other hand, pressure-flow analysis on high-resolution impedance manometry revealed that abnormal peristalsis and impaired bolus transport are associated to histological changes [121]. These observations are raising the hypothesis that most EA patients might suffer from "retention esophagitis", which is secondary to the impaired motility, rather than GERD-related esophagitis [120, 122].

GERD is also considered an important risk factor for recurrence of anastomotic strictures. Therefore, although its pathogenesis of is not fully understood [123], the occurrence of refractory anastomotic stricture represents a main indication for systematic PPI treatment and antireflux surgery [73]. However, different studies demonstrated that treatment with PPIs is unable to prevent anastomotic structuring in EA children questioning the real pathophysiological role of GERD in anastomotic stricture formation [124–127].

These findings coupled with the widely reported poor outcomes of fundoplication in EA patients [128, 129] require a necessary reconsideration of the extensive use of antireflux surgery in this specific population. It is established that fundoplication has an unquestioned value in improving quality of life in many EA children, but there must be a clear awareness that a significant portion of patients may experience worsening of their clinical condition. Although we are currently unable to predict which EA patient may benefit from antireflux surgery, a thorough multidisciplinary evaluation of the benefit-risk balance and extensive preoperative workup, incorporating the whole diagnostic armamentarium, should always be done before considering antireflux surgery in EA population.

Pediatric Intestinal Pseudo-Obstruction

Pediatric intestinal pseudo-obstruction (PIPO) is the most severe form of intestinal dysmotility in children.

Surgery and endoscopy are generally involved in outcome of PIPO patients: full thickness biopsy specimen to improve diagnosis, central catheter placement for parenteral nutrition support, decompressive intervention through enterostomies to manage abdominal distension, nutritional enterostomies to allow enteral autonomy, and major surgery for complication and/or for congenital association (malrotation) and intestinal transplantation. Patients often require surgical approach combined to medical and nutritional treatment to reach growth and development, to avoid disease complications and to improve quality of life.

A high complication rate after enterostomy formation and after surgical intervention is often detected; right indications and timing and specific technical expedients may be multidisciplinary decided and planned, individualizing the choices to each patient.

Pediatric Intestinal Pseudo-Obstruction: The Diagnostic and Therapeutic Role of Surgery

Pediatric intestinal pseudo-obstruction (PIPO) is the most severe form of intestinal dysmotility disorders in children, difficult to diagnose and treat. Most cases occur during neonatal period [130].

PIPO is characterized by an impairment of coordinated propulsive activity of the gastrointestinal tract, resulting in recurrent obstructive symptoms, without mechanical reasons.

PIPO diagnosis is a multistep path that relies on clinical picture and radiology (abdominal radiology, contrast study of small intestine, etc.), together with specialised tests (e.g., intestinal manometry) and surgery to obtain histopathology, in order to rule out the secondary causes of obstruction [131–133].

Therapeutic approaches are variable with high morbidity and mortality rate. Medical and surgical treatments are used to support the nutritional status, to prevent sepsis, and to restore the intestinal motility.

Despite the well-known certitude stating that in PIPO patient the surgical approach should be limited to biopsies (not systematically needed according to the ESPGHAN recommendations [131]) and eventually stoma creation, patients with PIPO frequently undergo repetitive and useless surgical procedures, often performed during newborn period also in non-specialized centre [130, 134, 135].

Unnecessary surgery exposes these patients to potential severe complications such increased risk of prolonged ileus, adhesions, leading to a possible progressive reduction of intestinal function up to the irreversible intestinal failure.

In all patients with suspect of PIPO, even if surgery represents one of the diagnostic and therapeutic tools, a dedicated

trained medico-surgical multidisciplinary team should always discuss the indication.

Patients with evidence of PIPO from clinical and radiologic presentation should not be operated for diagnosis [135].

Surgical approach may be performed by laparotomy or laparoscopy depending on surgical expertise; laparoscopy may be challenging in newborn because of small operative space and dilation of the small bowel. Laparoscopy can be performed in children who had undergone previous laparotomy.

The indication for surgery allows two crucial points in the management of this complex disease:

1. Diagnostic to exclude specific anatomical obstruction or congenital diseases (i.e., Hirschsprung's disease);
2. Therapeutic: enterostomy formation, treatment of associated malformations and resective surgery; intestinal transplantation.

Diagnostic Surgery

In newborns or children with persistent bowel obstruction without clear clinical, radiologic and/or manometric etiologic evidence, a diagnostic exploratory laparotomy or laparoscopy should be performed looking at the following steps.

Firstly, all gastrointestinal tracts should be carefully evaluated, from stomach to rectum to exclude causes of mechanical obstruction such as congenital stenosis or atresia/diaphragm, meconium ileus, duplication, abnormalities of intestinal rotation and fixation, the latter may be associated in 30% of cases of PIPO [131].

Secondly, in these patients without specific mechanical causes, serial full thickness biopsies from proximal jejunum to rectum should be performed for histopatologic analysis to assess nerve, muscle, Interstitial Cells of Cajal [136]. During surgery, extemporary frozen sections of rectal biopsies are mandatory to assess the presence of ganglion cells to exclude Hirschsprung's disease.

Finally, as reported above, avoiding multiple surgeries is the goal of our practice; therefore, if patient is candidate to therapeutic surgery, (enterostomies) simultaneous biopsies should be considered as evidence and consensus statement recommendation of ESPGHAN proposed in 2018 [131].

Therapeutic Surgery

Therapeutic aims of surgery involve avoiding useless surgery and specific indications to required surgery:

(A) Nutritional (enterostomy); decompressive (enterostomy).
(B) Treatment of associated anomalies (malrotation); treatment of complications (stoma prolapse, post-surgical mechanical occlusion, colonic or small bowel volvulus).
(C) Replacement (transplantation).

Enterostomies

Enterostomy is often performed as one of the first therapeutic measures. Bypassing the functional obstruction and obtaining digestive decompression, it may offer the chance to restore an intestinal transit allowing feeding and reducing parenteral nutrition (PN). The location of enterostomy is a matter of debate [135].

In 1985, Pitt et al. already stated that patients with chronic Intestinal pseudo-obstruction who receive total parenteral nutrition (TPN) at home and have a venting enterostomy could be safely managed for prolonged periods and require fewer hospitalizations for obstruction [137, 138].

Furthermore, Goulet et al. confirm that decompression ileostomy and colostomy represent one of the most useful tools to allow survival to adult life, together with careful treatment of urinary tract infections and bacterial overgrowth, and judicious use of PN [135].

Nutritional strategies tailored to the single patient enable one to reach enteral autonomy in several cases. As most of the patients requires PN to maintain normal growth and development, it is important to allow partial or total intestinal autonomy through gastrostomy and jejunostomy also like feeding routes with specialised feeds (e.g., hydrolysed protein feeds, amino acid formula, etc.). When PIPO is suspected, during explorative laparotomy, actual recommendations suggest gastrostomy insertion and ileostomy formation at the same time of full-thickness biopsies with the aim to minimize the number of procedures [131].

Gastrostomy and Proximal Jejunostomy

PIPO patients, because of severe pan-enteric motility troubles, experienced recurrent acute episodes of gastric outlet or duodenal functional obstruction, gastrectasis, preventing feeding and requiring decompression. Creating a gastrostomy, sometimes associated to a proximal jejunostomy (Fig. 50.13), is of great benefit because it avoids the recurrent placement of nasogastric tubes, allows the venting of the gastric content, decompresses the stomach, duodenum, and first jejunal loops, promoting a restoration of some degree of bowel movement with consequent enteral feeding tolerance.

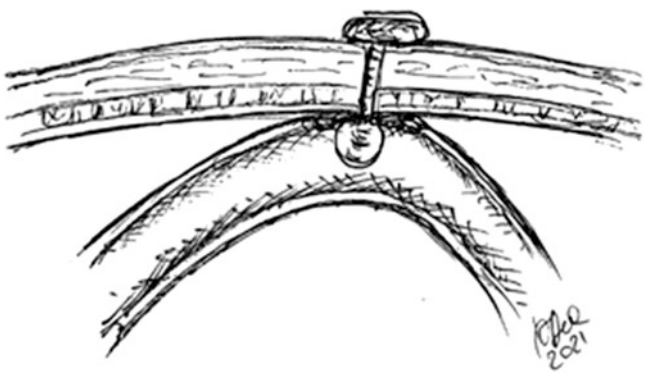

Fig. 50.13 Jejunostomy: low profile device

In these patients that experience prolonged PN, enteral feeding, also if minimal and for short periods, should be considered an indispensable therapeutic weapon because of its protective effect from TPN associated complications particularly on liver function (intestinal failure associated liver disease IFALD), avoiding or retarding liver deterioration with consequent possible indication for intestinal transplantation. Since enteral feeding should always be preferred than using PN, intragastric administration of feeding may be achieved by the gastric or jejunal tube as continuous or bolus enteral feeding. Percutaneous endoscopic gastrostomy (PEG) or gastro-jejunostomy (PEG-J) tube placement is easily achieved in these children and should be preferred as first choice because it avoid laparotomy and intestinal manipulation with increased risk of prolonged intestinal postoperative obstruction, adhesion formation, and surgical complications. Pull or push technique, according to centre expertise and patient's characteristic and requiring, is recommended for endoscopic placement of gastrostomy or gastro-jejunostomy [139, 140].

When surgery is required, surgical gastrostomy should be considered during the same procedure.

Distal Ileostomy or Colostomy

ESPGHAN expert group recommends considering the formation of a decompressive enterostomy in all patients with PIPO on parenteral nutrition [131].

Furthermore, other authors underline as the enterostomies, such as ileostomies and/or colostomies, as distal as possible, represent the most logical approach to enable transit and to resume the obstructive episodes, obtaining some degree of intestinal autonomy with variable dependence from artificial nutrition [135].

However, despite stoma surgery is quite easy, in PIPO patients, it represents a challenge for several reasons.

Firstly, in most cases, the motor function is impaired throughout the intestine then, the choice of bowel segment for diversion is tricky, particularly in newborn and small children. A more proximal stoma such as a more distal stoma can have a worse effect on intestinal function related to high output fluid and electrolytes loss or persistence of obstruction, respectively. Even if ESPGHAN expert group does not recommend the use of scintigraphy for the measurement of small bowel and colon transit given that it has not been validated in the paediatric age, this investigation can add more information on the right and best site for enterostomy.

Second, the present knowledge in PIPO physiology highlights as the motor function of the bowel often is variable during the time alternating periods of occlusion to periods of restored transit therefore, a terminal enterostomy could be inaccurate as choice because it excludes a variable length of bowel which could retain some degree of active absorptive role during the periods of restored motor activity.

Finally, children with gastrointestinal motility disorders had high complication rate after enterostomy formation more as compared to children without motility disorders. Stoma prolapse, diversion colitis and electrolyte and fluid imbalance are the most common complications reported in these patients [141].

According to all reported above, a side-to-side Mikulicz or side-to-end Santulli enterostomy might be the choice better than terminal enterostomy (Figs. 50.14 and 50.15). Their advantages are represented by the restoration of intestinal transit, recruitment of the distal efferent bowel during the possible transient period of restored motility with increase of absorptive intestinal surface, and consequent possible reduction of the parenteral nutrition dependence.

Ideally, enterostomy formation should be done at the same time of intestinal biopsies.

Enterostomy represents a milestone in the management of PIPO patients so that about more or less of 50% of patients

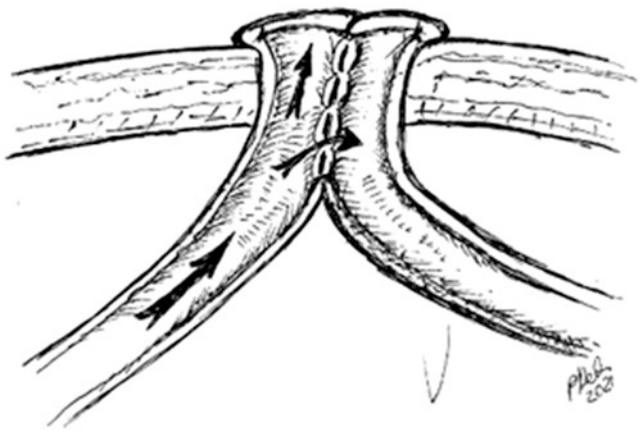

Fig. 50.14 Side-to-side Mikulicz enterostomy

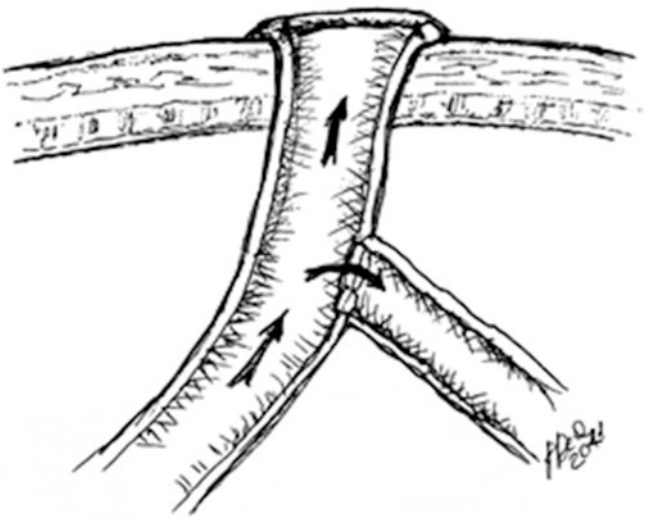

Fig. 50.15 Side-to-end Santulli enterostomy

improve after enterostomy as to be weaned from PN; in patients in which clear improvement from ileostomy is observed, with PN weaning and at least 2 years follow up on enteral/oral feeding without exacerbations, total colectomy and ileorectal anastomosis with the Duhamel procedure could be considered [135].

Surgery of Associated Malformations or Complications

PIPO patients are exposed to variable risk of mechanical occlusion or postsurgical complications related to associated intestinal anomalies, chronic segmental bowel dilation, postoperative adhesions, and stoma prolapse.

During radiologic assessment in patients with suspected PIPO, upper gastrointestinal contrast study is mandatory to evaluate the configuration of the duodenal C- loop, the duodenojejunal flexure position and the position of the small bowel loops. If small bowel malrotation is confirmed, Ladd procedure should be performed at the same time of intestinal biopsies and enterostomies formation. In fact, conditions such as anomalies of intestinal fixation and rotation, observed in about 30% of PIPO, or segmental chronic colonic dilation and elongation related to prolonged stasis associated to motility troubles, may expose these patients to acute life-threatening complications such as midgut or segmental colonic volvulus, respectively.

Mechanical intestinal occlusion related to acute midgut or segmental colonic volvulus or postoperative adhesions may present as an acute episode of obstruction; in PIPO patients, this diagnosis may be challenging and delayed, because of misunderstanding with functional acute pseudo-obstructive episode. Mechanical occlusion may be suspected when occlusive symptoms and signs persist associated to clinical deterioration, despite correct conservative management by fluid and electrolytes balance and infusion, bowel venting manoeuvres (nasogastric tube, open gastrostomy and jejunostomy tubes, fasting, enterostomy tube placement), and intravenous antibiotic administration. Moreover, caution should be exercised during the occlusive episode, when abdominal distension and bowel loop dilation are overcoming the habitual dimension for the patient, on physical and plain radiographic examination [142]. In this situation, an abdominal CT scan coupled with contrast enema is helpful and recommended before surgery. In case of confirmed colonic volvulus, colonoscopy may be attempted before surgery (Fig. 50.16). If strongly suspected small bowel mechanical obstruction (i.e., volvulus, strangulation, kinking) or failed colonoscopy, an emergency laparotomy is mandatory.

Stoma prolapse is frequently observed in PIPO. While its pathogenesis is multifactorial, the variability and anarchy of the bowel movements probably play the main role.

The length of prolapsed bowel may be different even in a few hours observing few tens of centimetres into the ostomy bag. Signs and symptoms are not related to the length of the prolapsed intestine. Manual reduction or surgical correction of the prolapse can be frustrating with high recurrence rate so, the treatment should be carefully evaluated on a case-by-case basis, to avoid unnecessary surgery. If required, because of symptoms such as bleeding, obstruction, intestinal impairment, re-do stoma formation represent the best choice, avoiding, if possible, resection of the prolapsed bowel.

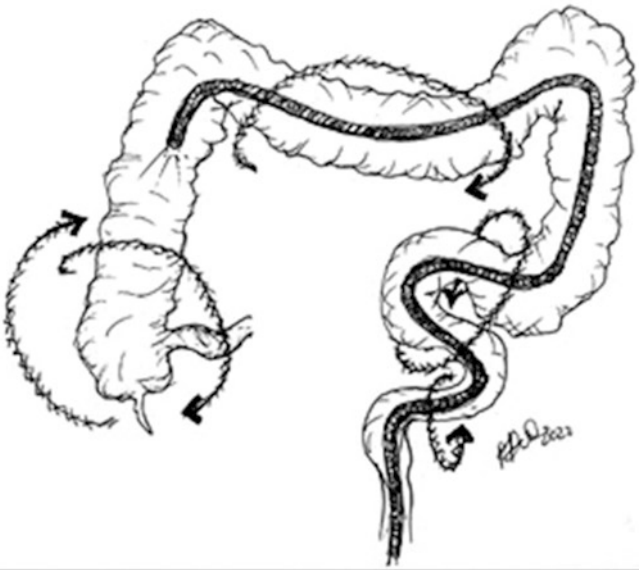

Fig. 50.16 Site of colonic volvulus in PIPO and colonoscopy treatment

Transplantation

Intestinal transplantation, either isolated small bowel or multi-visceral, should be considered in patients presenting with life threatening TPN related complications such as intestinal failure associated liver disease (IFALD), or in patients whose intravenous access has become unreliable and precarious because of repeated sepsis and extensive thrombosis and finally, in patients with poor quality of life with high risk of morbidity and mortality related to frequent pseudo-obstructive episodes with difficult fluid electrolyte imbalance due to excessive fluid shifts necessitating repeated hospitalizations [131]. Transplant procedure varies according to the need of replacing liver and to the experience of the transplant surgical team.

Conclusions

Digestive Endoscopy and surgery represent challenging diagnostic and therapeutic tools in the armamentarium of the multidisciplinary dedicated medico-surgical team in PIPO patients. Surgical interventions should be minimised to avoid potential related complications (adhesions, prolonged paralytic ileus, etc.), which could worsen the outcome of these patients. Resective surgery (gastrectomy,

colectomy, and small bowel resection) is often affected by failures, complications, and inadequate responses, compared to expectations [143]. An enterostomy is often performed as one of the first endoscopic or surgical therapeutic measures. Full thickness biopsies are mandatories to classify PIPO and they must be carried out at the same time of surgery for enterostomy creation. Enterostomies are very commonly used to decompress and reduce pseudo-obstructive events, to allow nutritional feeding through gastrostomy and jejunostomy reducing PN during the life of patients. Emergency laparotomy should be reserved only when a mechanical obstruction is assessed. Intestinal transplantation should be reserved only in selected cases with life threatening PN related complications or loss and unreliability of intravenous access.

When possible, endoscopy and surgery in children with suspected or known diagnosis of PIPO should be restricted to centres and practitioners with great experience in managing such patients with the aim to propose a structured approach.

Hirschsprung Disease

Hirschsprung's Disease (HD), also known as "congenital aganglionic megacolon", is a rare motor disorder of the gut, which is caused by a failure in the cranio-caudal migration of the neural crest cells during the 5–12 weeks of gestation, resulting in an aganglionic intestinal segment.

The incidence of HD is reported in about 1:5000 live births; the male to female ratio in recto-sigmoid disease is 4:1, but in longer segment disease is 1:1–2:1 [144, 145].

Intestinal aganglionosis extends proximally from the rectum for a variable length, with a recto-sigmoid involvement in about 80% of patients; a long-segment type in 15–20% of cases and a total colonic aganglionosis (TCA) in approximately 5% of subjects. In rare cases, a total intestinal aganglionosis with absent ganglion cells from the rectum to the duodenum is described. In ultra-short HD type, the aganglionic tract is limited to the distal 2–3 cm of the rectum [146, 147].

Antenatal suspicion and/or diagnosis of HD is rare. Most patients are diagnosed in neonatal period or even later, due to the variability in clinical presentation, which is dependent on the length of the aganglionosis.

Genetics

HD occurs as an isolated condition in 70% of the cases, associated with additional congenital anomalies in 18% of patients (cardiac defects 8%, genitourinary 6%, gastrointestinal abnormalities 4%), and as a part of a genetic syndrome in up to 12% of cases (i.e., Down Syndrome, Waardenburg syndrome, Mowat-Wilson syndrome, MEN type 2A) [146].

Several genes have been found to be involved in HD (i.e., GDNF, NRTN, SOX10, EDNRB, EDN3 ECE1, ZFHX1B, PHOX2B, KIAA1279, TCF4, L1CAM, and IKBKAP) [148, 149].

The major susceptibility gene is proto-oncogene RET, which is implicated in about 50% of family forms, in 40–45% of sporadic cases, and in a higher percentage of long than of short type HD (76% vs. 32%) [150–154].

More than 100 different mutations have been described in the RET gene [150], some of which are also associated with the development of Multiple Endocrine Neoplasia type 2A (MEN 2A), a cancer syndrome characterized by medullary thyroid carcinoma, phaeochromocytoma of the adrenal glands, and hyperplasia of the parathyroid glands [155].

Therefore, ERNICA guidelines for HD suggest, in non-syndromic cases, to offer referral to parents or patients who wish to have a genetic screening and recommend genetic consultation for subjects with a family history of HD, where the incidence of RET mutations is even higher. In syndromic types, the genetic screening must be associated with the specific gene of the syndromic phenotype [156].

Clinical Presentation

HD should be suspected in any newborn with intestinal obstruction, in any infant and child with refractory severe constipation, chronic abdominal distention and history of delayed or failed passage of meconium within the first 24–48 h of life. This latter is the cardinal clinical feature in about 80–90% of infants with HD but also in 30–40% of healthy children and in 30–35% of preemies [144].

Intestinal obstruction symptoms (bilious vomiting, abdominal distension, and constipation), spontaneous intestinal perforation or episodes of acute "toxic" enterocolitis are typical findings during the neonatal period in the recto-sigmoid or in longer types of HD [150, 157–159].

Explosive bowel movements caused by functional colonic obstruction and enterocolitis-related diarrhoea rather than constipation are possible symptoms in infants with HD [160].

Refractory constipation, frequently associated with abdominal distension and failure to thrive, seems to be the only symptom in the ultra-short form and in older children. Rectal examination usually reveals a tight anal sphincter and explosive discharge of stool and gas.

Diagnosis

Tests available for diagnosing HD include manometric, radiological, and histological studies.

Anorectal manometry assesses the correct innervation of the internal anal sphincter (IAS) eliciting the recto-anal

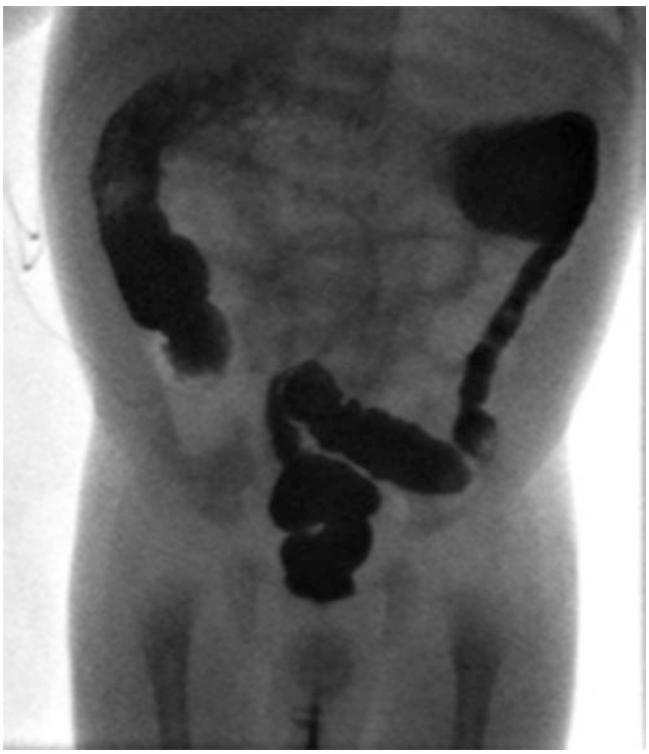

Fig. 50.17 Contrast enema shows a transition zone at the splenic flexure. At the operation, the transition zone correlated with the histological findings

inhibitory reflex (RAIR) via the myenteric plexus. RAIR is a relaxation response in the IAS, namely a pressure drop of at least 25% in the anal canal following rectal distension. The absence of RAIR is indicative of HD [161].

Contrast enema is a useful screening test for a pre-operative morphological evaluation of the colon. The finding of the pathognomonic sign of "transition zone" (Fig. 50.17), a funnel-shaped segment between the narrowed aganglionic rectum and the proximal normally innervated segment, may aid in surgical procedure planning since the location of the radiographic transition zone correlates with the level of aganglionosis in 63% to 90% of cases [162–164].

Unfortunately, the transition zone may not be detected in neonates, because of insufficient time to develop the dilation, or in infant treated by frequent saline rectal irrigations.

Rectal suction or full-thickness biopsy remains the gold standard test in the diagnostic workup of HD. The tissue samples should be taken a minimum of 2 cm above the dentate line to avoid the physiologic aganglionic/hypoganglionic zone of the distal rectum [165], specimens should be at least 3 mm diameter and one-third of them should comprise submucosa [166, 167].

The absence of ganglion cells confirms the clinical and radiological suspicion of HD.

Differential diagnosis may consider meconium ileus secondary to cystic fibrosis, gastrointestinal malformations (intestinal atresia, malrotation, duplication cysts), multiple endocrine neoplasia type 2A (MEN 2A), intestinal neuronal dysplasia, meconium plug syndrome, small left colon syndrome, chronic intestinal pseudo-obstruction, and hypothyroidism [146].

Surgical Techniques

The aim of treatment in HD is the resection of the aganglionic segment, the anastomosis to the anus of the normally innervated bowel, and the preservation of the anal sphincter function.

Historically, colostomy was performed at diagnosis of HD and colonic pull-through was scheduled 6–12 months later. Thanks to the improvement of diagnostic and surgical techniques, surgery shifted from multistage to single stage.

Temporary stoma is indicated in presence of intestinal perforation or acute enterocolitis unresponsive to non-operative treatment and when rectal washouts are not effective to decompress the bowel [168].

In emergency settings, the level of the stoma should be proximal to the site of perforation or empirical in the distal ileum. In elective conditions, the stoma may be performed above the transitional zone (also known as "leveling stoma"), in a normal neuronal pattern bowel segment, detected by peri-operative biopsies [169].

According to ERNICA HD guidelines, the pre-operative management includes: 1–3 times per day saline rectal irrigations to decompress the bowel until the definitive pull-through operation; contrast enema, that may help to define the level of aganglionosis with possible identification of the transition zone, although it does not replace the need for histological assessment; pre-operative one dose of broad-spectrum intravenous antibiotics, which should be continued for 24–48 h post-operatively [156].

Different surgical options are available using an abdominal and/or trans-anal approach and the choice of procedure is usually based on the training and experience of the surgeon.

Full-thickness biopsies should be performed intra-operatively to define the correct level of aganglionosis and identify the normally innervated colon to bring down to the anal canal for anastomosis [156, 170].

Swenson Procedure

The Swenson procedure, first performed in 1948, was the original pull-through procedure used to treat HD. The technique consists of a deep pelvic dissection with mobilization of rectum and left colon to bring normal bowel down the perineum. The rectum is intussuscepted through the anus and an incision is made 1.5 cm above the dentate line of the anal

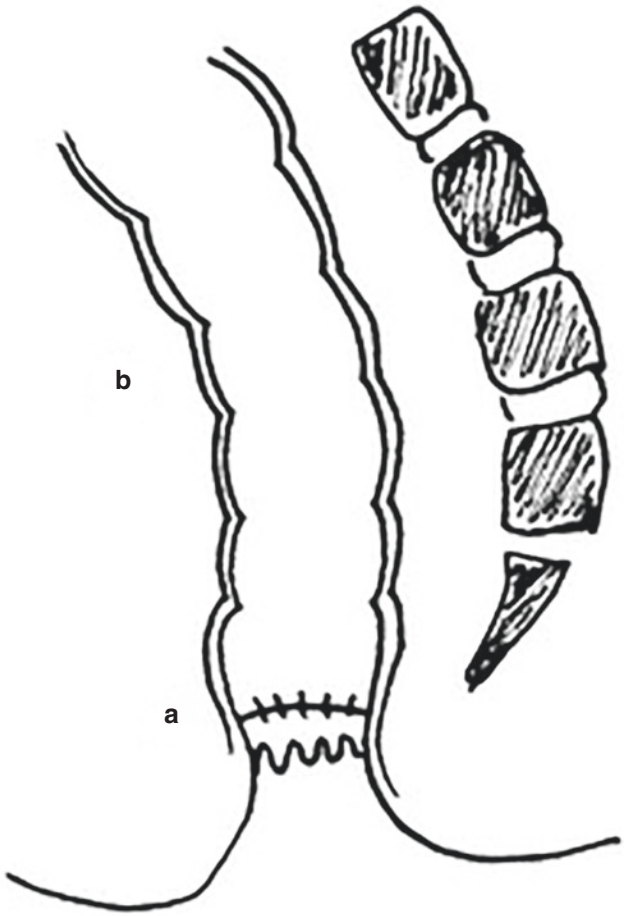

Fig. 50.18 Swenson procedure: the aganglionic bowel is resected and an end-to-end anastomosis (**a**) of the normal colon (**b**) to the low rectum is performed. This operation is done through a laparotomic, or laparoscopic approach and the anastomosis is performed from a perineal approach after eversion of the aganglionic rectum

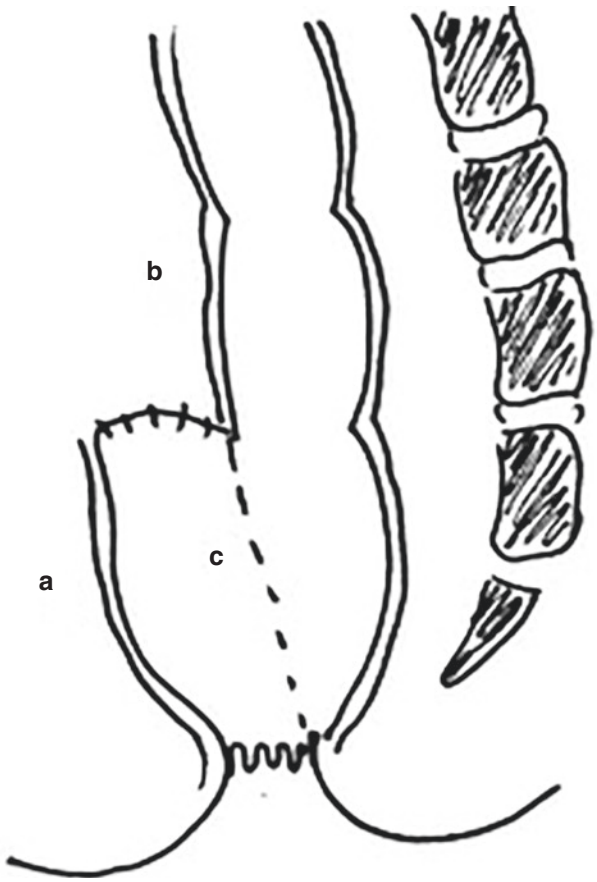

Fig. 50.19 Duhamel procedure: The aganglionic colon is resected to the rectum; a residual pouch of aganglionic rectum is left intact (**a**) and the normally innervated bowel (**b**) is attached behind the rectum with an end-to-side anastomosis (**c**). By joining the two walls, a new lumen is created which is aganglionic anteriorly and normally innervated posteriorly

canal, in the anterior zone of the circumference, in order to preserve faecal continence and facilitate voluntary bowel movements. The intussuscepted colon is pulled through until the correct level is visualized. An anastomosis between pulled-through ganglionic colon and anal canal is performed obliquely outside the anus as the bowel is divided and removed (Fig. 50.18). Finally, the anastomosis is returned to the pelvis [171, 172].

Duhamel Procedure

The Duhamel procedure, described in 1956, requires much less pelvic dissection than the Swenson procedure with a lower risk of incontinence. The aganglionic bowel is resected down the rectum that is maintained in situ. The ganglionic bowel is brought down to the level of anal canal through a bloodless retro-rectal space between rectum and sacrum. A side-to-side anastomosis between the anterior aganglionic rectal stump and the posterior pulled-through ganglionic bowel is performed using a linear stapler which simultaneously joins the two segments and divides the common wall between them to create a single lumen (Fig. 50.19) [173].

Soave Procedure

The endorectal pull-through operation was first described by Soave in 1964 and later modified by Boley. An accurate trans-abdominal submucosal dissection of the aganglionic segment of the colon is extended down to the anal canal, leaving the muscular coat of the rectum intact, avoiding lesions of pelvic innervation. The ganglionic bowel is pulled through the muscular cuff and anastomosed to the anal canal about 1 cm above the dentate line. The original procedure left a 5- to 10-cm length of the pull-through colon hanging out through the anus and the final anastomosis had to be created several weeks later [174].

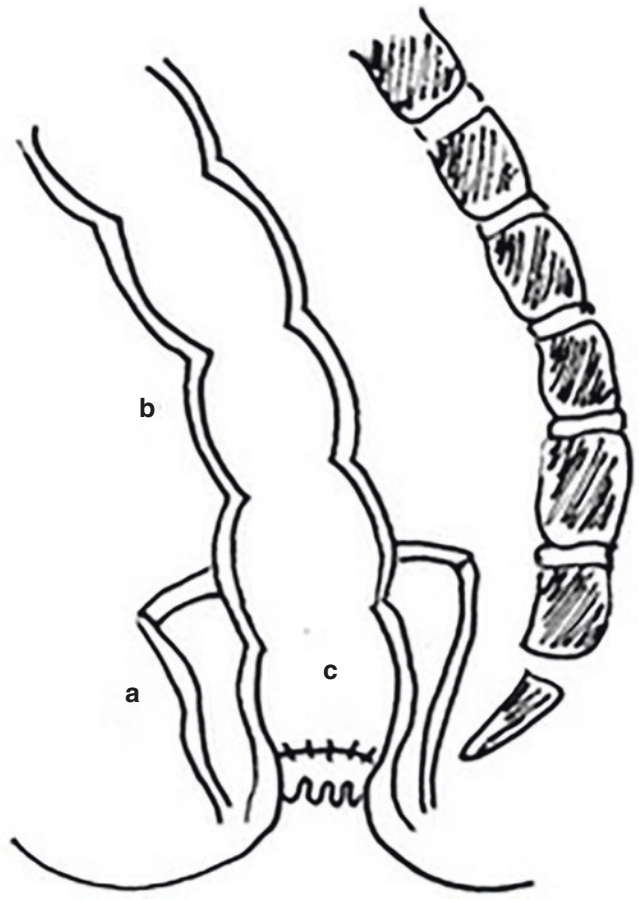

Fig. 50.20 Soave/Boyle procedure: The mucosa and submucosa of the rectum have been removed. The outer layer of the aganglionic rectum (**a**) is left in place and the ganglionic colon (**b**) is pulled through within the muscular cuff with an end to end primary anastomosis (**c**) at the anus

Boley modified this procedure, performing a single stage operation with primary anastomosis at the anus with or without splitting of the aganglionic muscular cuff (Fig. 50.20) [175].

Transanal Endorectal Pull-Through

The transanal endorectal pull-through was introduced by De la Torre-Mondragon and Ortega Salgado in 1998, as a modification of the Soave procedure [176, 177].

This technique consists of a totally transanal endorectal pull-through without any laparotomic or laparoscopic mobilization.

As first step, the rectal mucosal layer is incised 0.5–1 cm above the dentate line and a rectal mucosal cylinder is dissected as far as the peritoneal reflexion. Multiple 5-0 silk traction sutures are placed in the mucosa to facilitate its separation from the muscular wall (Fig. 50.21).

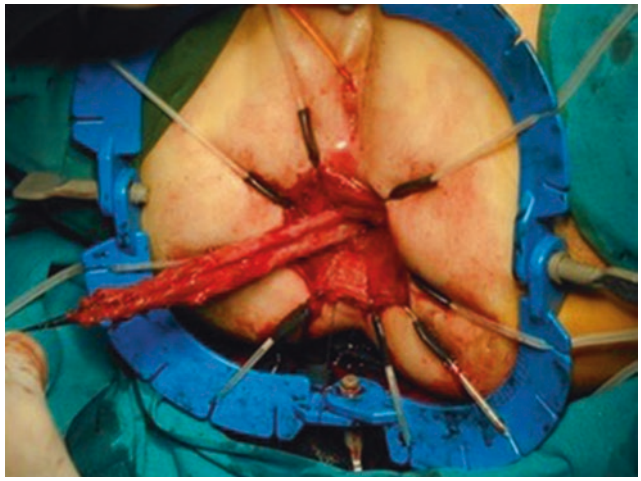

Fig. 50.21 Trans-anal endorectal pull-through procedure, first step. The rectal mucosal layer is incised 0.5–1 cm above the dentate line and a rectal mucosal cylinder is dissected as far as the peritoneal reflexion

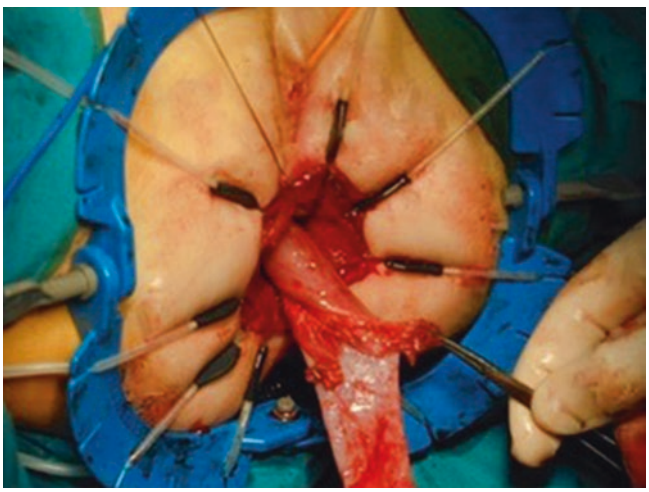

Fig. 50.22 Trans-anal endorectal pull-through procedure, second step. The division of the muscular rectal wall is continued circumferentially, freeing the intra-abdominal colon from the muscular sleeve

The division of the muscular rectal wall is continued circumferentially, freeing the intra-abdominal colon from the muscular sleeve (Fig. 50.22). A posterior myotomy of the muscular sleeve is made above the place where the anastomotic line should be created (Fig. 50.23).

Once the muscular sleeve is prepared and liberated, the rectum is pulled down and perirectal tissues are easily exposed and the mesenteric vessels are dissected, tied, and divided. Thus, the colon is pulled through the rectal muscular sleeve onto the anus (Fig. 50.24).

During this step, full-thickness biopsy specimens of the colon are examined through frozen sections to assure normoganglionic level. The aganglionic colon is resected, and a primary anastomosis is made between the normally ganglionic colon and the rectal mucosa.

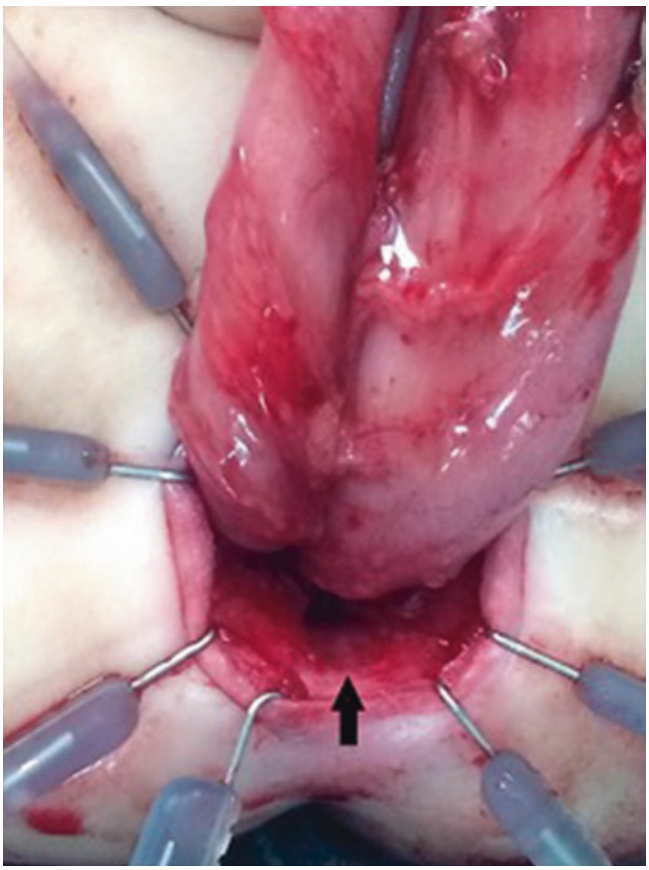

Fig. 50.23 Trans-anal endorectal pull-through procedure. The rectal muscular cuff is incised posteriorly

Laparoscopic- and Robotic-Assisted Colon Pull-Through

Laparoscopic-assisted colon pull-through procedure exploits the well-known advantages of laparoscopy, such as less postoperative pain, quicker recovery, less adhesive bowel obstruction and wound complications, better cosmetic results and, furthermore, gives the opportunity to perform intraoperative multiple biopsies, visualizes the pulled through colon, and prevents twisting of the bowel.

The sigmoid colon and the rectum can be mobilized laparoscopically; a submucosal sleeve is crafted trans-anally to meet the dissection from above. The ganglionic colon is then pulled down in continuity, divided above the transition zone and anastomosed to the anal mucosa 5 to 10 mm above the dentate line [178].

During the last decade, the robotic assisted pull-through procedure has been used to treat infants, even younger than 12 months of life, and children suffering from recto-sigmoid HD, long segment HD and TCA [179–181].

Some potential advantages of robotic surgery include greater surgical precision, increased range of motion, improved dexterity, enhanced visualization, and better access to hard-to-reach areas.

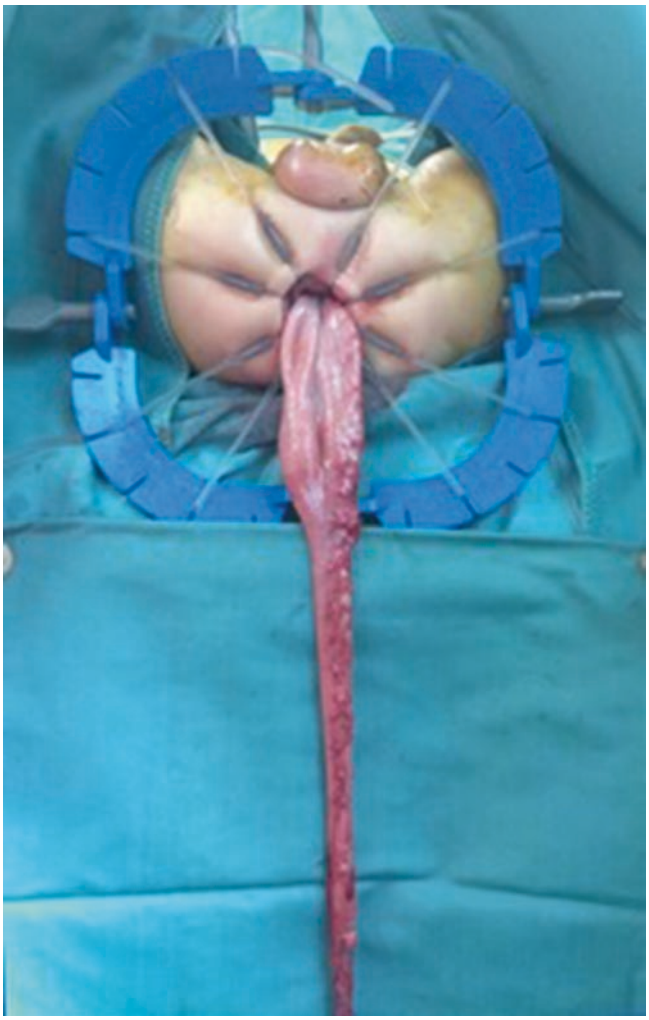

Fig. 50.24 Trans-anal endorectal pull-through procedure, final step. The aganglionic segment (narrow colon), the transition zone and the normal ganglionic bowel (dilated bowel) are pulled through transanally

Four trocars are needed to perform the intraoperative seromuscular levelling biopsies and to mobilize the rectum down to the anal canal with an intracorporeal endorectal cranial dissection; the rectal cuff is divided posteriorly, the previously isolated colon is then pulled-through and a colo-anal anastomosis is achieved at the pectinate line by an endoanal approach.

The first results are encouraging in terms of intra−/post-surgical complications and continence outcomes.

Future studies are needed to compare the long-term data of this approach with the open and laparoscopic techniques [179].

Total Colonic Aganglionosis (TCA)

Surgical treatment for TCA is a challenge for surgeons (Fig. 50.25). To this aim, various techniques have been per-

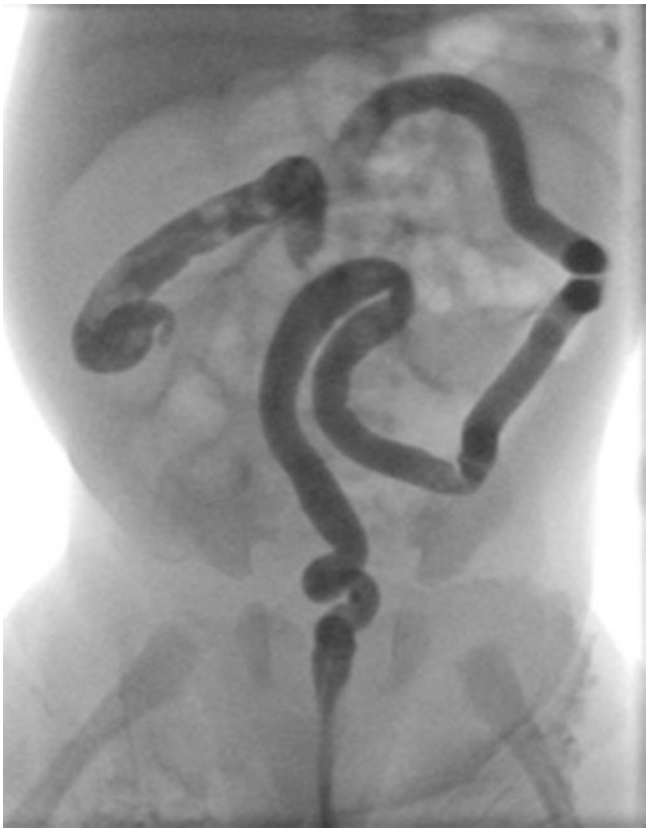

Fig. 50.25 Total colonic aganglionosis. 1-day-old-term male baby with obstructive symptoms and family history of HD. The contrast enema detects a microcolon. Histology confirmed aganglionosis involving colon and terminal ileum (approximately 30 cm)

formed, including a long longitudinal side to side anastomosis between the aganglionic bowel and the pulled-through ganglionic healthy bowel (Lester Martin procedure) [182]; a longitudinal side-to-side ileocolostomy between the normal ileum and the aganglionic ascending colon forming a colonic patch graft (Kimura procedure) [183] and proctocolectomy with J pouch-ileoanal anastomosis [184–186].

Ultra-Short HD

The ultra-short form of HD is an aganglionic segment of less than 2 to 3 cm histologically characterized by the absence of both hypertrophic nerves and abnormal cholinesterase staining [187].

The treatment of ultrashort-segment HD is controversial, so that different therapies, such as intrasphincteric botulinum toxin injections, simple anal sphincter myectomy and excision of the aganglionic segment with bowel pull-through, are taken into consideration [188, 189].

Early Postoperative Management

ERNICA guidelines recommend to adopt the Enhanced Recovery After Surgery (ERAS) protocols in paediatric colorectal surgery to improve surgical outcomes and efficiency of care [156].

Items of ERAS include use of minimally invasive surgical techniques, opioid-sparing analgesia, early post-surgical re-feeding, and judicious use of drains and catheters. ERAS pathways have demonstrated to reduce length of stay and complication rates, with an increment of patient satisfaction [190].

Early Post-Surgical Complications

Anastomotic leak and cuff abscess are rare early post-surgical complications, reported in 1–10% and in 5% of cases, respectively [191–194].

The risk is increased in presence of tension or ischemia of the anastomosis, poor nutritional status, steroid usage, and residual aganglionosis. A water-soluble contrast enema may be useful to make a diagnosis. Treatment may include surgical exploration, diverting colostomy, and revision of anastomosis [146].

Anastomotic strictures are a potential complication after pull-through surgery with an incidence up to 10.6% (range: 0–18.9%) [195].

Predisposing factors include ischemia, anastomotic leakage, and anastomotic tension. The risk is lower after Duhamel procedure since the colo-rectal anastomosis is wider. Calibration of the coloanal anastomosis is advisable at around 2–3 weeks after pull-through surgery, while daily anal dilatations are suitable in case of stricture [146].

Long-Term Post-Surgical Complications

Despite surgical techniques and medical care have improved over recent years, severe constipation (9–40%), faecal incontinence (FI; >8–74%) or Hirschsprung-Associated Enterocolitis (HAEC) (25–37%) can persist after pull through surgery in a long-term outcome [169, 196–203]. According to ERNICA guidelines for HD, a careful re-evaluation of these patients is mandatory to ensure a functional improvement and to prevent a psychosocial unrest [156].

The first step comprises clinical and nutritional check with full survey of the stooling pattern, dietary history, and development.

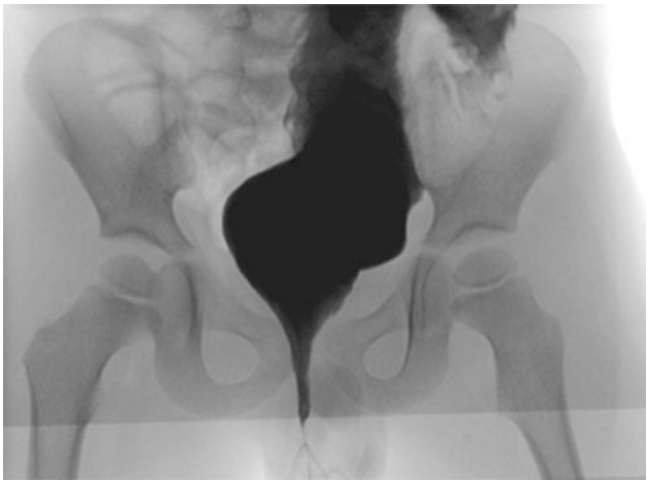

Fig. 50.26 Four-year-old male patient underwent trans-anal endorectal pull-through for diagnosis of recto-sigmoid HD at the age of 14 months. Persistent constipation after surgery. Contrast enema identifies a narrowing (stenosis of rectal cuff) of the distal portion of the pulled colon and a proximally dilated colon. Intraoperative biopsies confirmed a normal ganglionic pattern; a redo myotomy of the rectal cuff has been performed

In persistent post-operative **constipation** or in case of **obstructive symptoms**, anatomical (mechanical or histological) and functional aetiologies should be considered [169].

Rectal examination and contrast enema are required in Soave and in De la Torre-Mondragon procedures to rule out mechanical causes, such as anastomotic stricture, rolled or stenotic muscle cuff (Fig. 50.26) and twisted pull-through; in Duhamel technique occurrence of rectal spur.

Histological review of the proximal margins of the originally resected bowel and/or repetition of rectal biopsies are necessary to exclude an aganglionic residual segment or a pulled-through transition zone.

In accordance with the findings, anal dilations for anastomotic stricture or redo surgery (section of rectal spur; surgical revision of cuff stenosis or bowel torsion; redo pull through in twisted colon and in residual aganglionosis or in incomplete resection of transition zone) should be considered [203, 204]. If no mechanical or histological complications are documented, botulinum toxin can be administered to relax the internal anal sphincter and facilitate the passage of stool [205, 206].

Bowel management programme is recommended to non-responders after repeated (>3) botulinum toxin injections. There are various management options available (retrograde enemas or antegrade continence colonic irrigations through appendicostomy or cecostomy) which can be suggested by the patient.

Faecal incontinence (FI) is another problem after pull-through surgery, that implies evaluation of the anorectum and colon to distinguish between overflow or retentive and non-retentive type.

Overflow or retentive FI may depend on mechanical obstruction with faecal impaction and overflow of liquid stool; in other cases, hyperperistalsis of the pulled-through bowel determines recurrent soiling, despite normal sphincter function.

Non-retentive or true FI is secondary to anal sphincter injuries or abnormal rectal sensation.

A careful clinical inspection of the anal canal under anaesthesia is mandatory to exclude anatomical causes of retention and to document the site of the anastomosis in relation to the dentate line and its circumferential integrity, necessary to distinguish between gas, liquid, or solid stool [207].

A complete assessment of anal sphincters includes endoanal ultrasonography, which aids in the diagnosis of anal sphincter injuries, and anorectal manometry, which offers useful data about rectal sensation, pelvic floor dyssynergia, and anal pressures [208, 209].

Intestinal peristalsis (hypo- or hypermotility) and dilatation of pulled colon should be evaluated by motility tests (colonic manometry, colonic scintigraphy, and radiopaque markers) and a morphological study (contrast enema), respectively.

Successful management of FI depends on a clear understanding of the underlying problem. Thus, laxatives should be administered in case of intact anal canal, dilated colon and constipation (hypomotility colon); constipating diet, loperamide and bulking agents (pectin, psyllium) are useful for patients without colonic dilatation and a tendency to lose stools (hypermotility colon); a bowel management programme should be proposed in non-retentive FI to completely empty the colon; biofeedback training may be effective in pelvic dyssynergia [156].

Enterostomy remains a rescue option if the other treatments fail to control symptoms.

Hirschsprung-associated enterocolitis (HAEC) is a common and sometimes life-threatening complication of HD. Long-segment disease, older age at radical surgery, Down's syndromee and previous episodes of HAEC are recognised predisposing factors for recurrent HAEC [210].

The aetiology is probably multifactorial; alterations in the intestinal barrier, dysbiosis of the intestinal microbiota, bacterial translocation and impaired gastrointestinal mucosal immunity can contribute to the development of this severe condition [211].

Clinical presentation can include fever, abdominal distension, explosive foul-smelling bloody diarrhoea, lethargy; on this occurrence the abdominal X-rays usually show multiple air–fluid levels, dilated loops of bowel, and pneumatosis (Fig. 50.27a–c).

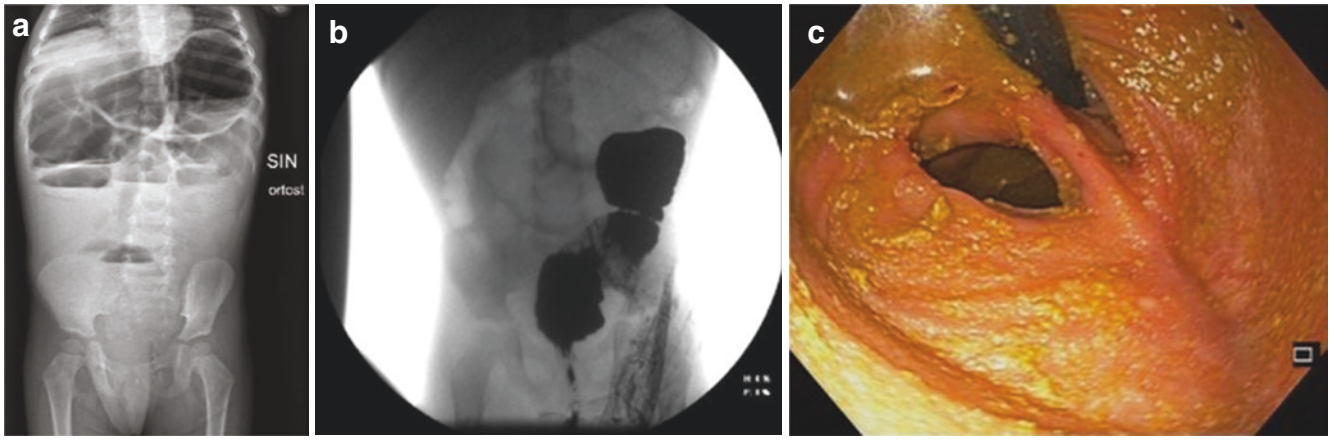

Fig. 50.27 Three-year-old female patient operated on long segment HD at birth (Duhamel procedure). Episodes of HAEC with fever, vomiting, dehydration, abdominal distension, pain, foul smell stools. (**a**) Plain abdominal X-ray: multiple air–fluid levels and dilated loops of ileum. (**b**) Contrast enema: suspect of intestinal stenosis. (**c**) Ano-ileoscopy: no anastomotic stricture, no rectal spur; mucosal bridge and dilation of the ileum

In acute forms, intravenous fluid resuscitation, broad-spectrum antibiotics, and saline rectal washouts to decompress the bowel are recommended [212].

The risk of HAEC may be decreased by using preventive measures such as routine irrigations or/and chronic administration of metronidazole; intra-sphincteric botulinum toxin injection is a valid and minimally invasive therapeutic option, that reduces the incidence of HAEC in 62–89% of HD patients [205, 213–218].

Redo surgery (i.e., posterior myotomy or redo pull-through according to the underlying causes) is indicated in case of mechanical obstruction.

Surgical Procedures and Outcome

In literature, no agreement has been reached about the optimal surgical approach to treat HD. Heterogeneity in the results depends on various parameters such as type of HD, presence of a colostomy, operation timing, complexity of the operation and experience of the surgeon.

Trans-abdominal endorectal pull through techniques spare the perirectal innervation, with a low rate of incontinence and sexual problems. Trans-anal endorectal pull through adds the typical advantages of minimally invasive procedures even if the anal sphincter may be overstretched during anal traction, leading to permanent incontinence/soiling. However, manometric comparison between perineal and abdominal approach shows that the postoperative sphincter function does not decrease in patients undergoing trans-anal endorectal pull through [219, 220].

Likewise, the occurrence of incontinence after the Duhamel operation is like that after the trans-anal endorectal pull through intervention, probably due to minimal pelvic dissection that avoids autonomic nerve damage [221].

As regards constipation, there is no significant difference between the Soave group and the trans-anal endorectal pull through population [222] and between Soave and Swenson operation, notwithstanding the incomplete excision of the aganglionic rectal wall in the first of the two [223, 224].

Chatoorgoon et al. reported a high risk of constipation in patients with a mega Duhamel pouch [225], while Widyasari et al. documented a higher constipation rate in the Soave respect to the Duhamel group, as the latter offers the advantage of a wide anastomosis [226].

A systematic meta-analysis comparing Duhamel with transanal endorectal pull-through procedures in infants and children testified similar results regarding rate of postoperative fecal incontinence and operation time; anyway, Duhamel procedure seems to be associated with longer hospital stay and lower rate of enterocolitis [221].

All the techniques can be performed via laparoscopic surgery, which results in minor trauma, smaller amounts of blood loss, lower intraperitoneal contamination, and less intestinal adhesions [221].

In any case, in a long-term follow up, more than 90% of HD affected individuals relate satisfactory outcomes and approximately only 1% suffers from debilitating incontinence requiring a permanent colostomy [227].

Subjects with chromosomal abnormalities and syndromes or with TCA, have a worse prognosis [228].

Conclusions

HD is a rare, congenital, and complex motility disorder caused by a lack of ganglion cells in the enteric neural plexuses of the intestine. The treatment is primarily surgical and aims at the resection of the aganglionic segment and at a re-anastomosis with ganglionated bowel. Different surgical

options are available and ensure good clinical results in most patients. In any case, a follow up to adulthood, within the context of an interdisciplinary care team, is recommended because of the risk of recurrent enterocolitis, persistent constipation, or faecal incontinence.

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51 Gut Dysmotility and Transplantation: Long-Term Outcomes with New Insights into Surgical Integration and Allograft Motility Disorders

Mohammed Osman, Ayat ElSherif, Charles B. Chen, Masato Fujiki, Giuseppe D'Amico, Kadakkal Radhakrishnan, and Kareem Abu-Elmagd

Introduction

The disorders of the gut neuromuscular system (GNS) were first reported in the late 50's [1]. Patients commonly experience recurrent episodes of bowel obstruction without evidence of mechanical etiology. Over the years, the disorder was increasingly recognized as a primary or secondary chronic intestinal pseudo-obstruction (CIPO) with disabling persistent abdominal pain and progressive oral intolerance [2–5].

With further advances in molecular diagnostics and genetics, the different entities of the clinical gut dysmotility (GD) syndrome are expected to be better defined. In the interim, a well-designed clinical study and an international consensus report have been recently published identifying two new entities of GD; enteric dysmotility (ED) and pediatric intestinal pseudo-obstruction (PIPO) syndrome [6, 7]. With better understanding of the complexity of GNS and the enigma of the gut-brain-axis (Fig. 51.1), effective molecular, genetic, and surgical treatment modalities are highly anticipated.

With disease progression, severe malnutrition and intermittent or irreversible gut failure (GF) develop with the ultimate need for intravenous total parenteral nutrition (TPN) in up to 80% of the pediatric and 60% of the adult patients [8]. Quality of life is also severely impaired due to persistent digestive symptoms and incapacitating chronic abdominal pain [8]. With the diagnosis of recalcitrant GD and development of TPN-associated complications, surgical interventions including gut transplantation (GT), and remodeling reconstructive techniques are the only currently available effective and life-saving treatments [9].

Since its 1990 inception, GT has been increasingly utilized to rescue patients with GD particularly those with TPN-associated life-threatening complications [9]. With the observed maintenance immunosuppression-associated morbidities, a new therapeutic dimension was added utilizing the new Trifecta procedure. In the context of an integrated surgical approach, an unprecedented statistical model was established to predict the probability of restoring nutritional autonomy (RNA) [10].

In addition to a brief description of the embryonic development of GNS and pathophysiology of GD, this review focuses on the current surgical management of GD in both children and adults. The survival and functional outcomes including re-establishment of nutritional autonomy are discussed. In addition, the potential risk and pathogenesis of allograft dysmotility are addressed in milieu of the recently published experimental and clinical data. Finally, an algorithmic management strategy is outlined to further advance the current standard of care for the different entities of GD.

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Development of the Gut Nervous System

The gut nervous system (GNS) is the most complex portion of the peripheral nervous system; often referred to as the first brain [11]. It comprises intrinsic neuroglial circuits forming two main plexuses; the submucosal and the myenteric (Auerbach's) plexuses (Fig. 51.1a). There is a bidirectional axis between the GNS and the central nervous system (CNS) (Fig. 51.1b). The distinctiveness of the GNS originates from being neither sympathetic nor parasympathetic system; rather, having inputs from both autonomic system divisions [11]. The GNS has more than 100 million neurons with 18 subtypes; motor neurons, intrinsic primary afferent neurons (IPANs), interneurons, secretomotor, and vasomotor neurons [12].

The GNS develops from the neural crest cells (NCC); a highly migratory mesenchymal-like cell type. The neural crest cells migrate in a cranio-caudal fashion to result in an axial development of different cell types in different organs [13]. The process involves migration, colonization in the gut tube, proliferation, and finally differentiation. The progenitor cell pool migrate in a chain behavior in an organized and timely fashioned process. Reduced size of the progenitor cells, low proliferation rates, lack of the chain behavior, premature, or delayed differentiation can lead to hypo or aganglionosis [13]. The process is under control of different molecules, including glial cell line-derived neurotrophic factor, endothelin (ET)-3, transcription factors such as SOX10 and PHOX2B as well as adhesion molecules. This complex developmental process including migration and differentiation is illustrated in Fig. 51.2 and fully described in a recent publication [13].

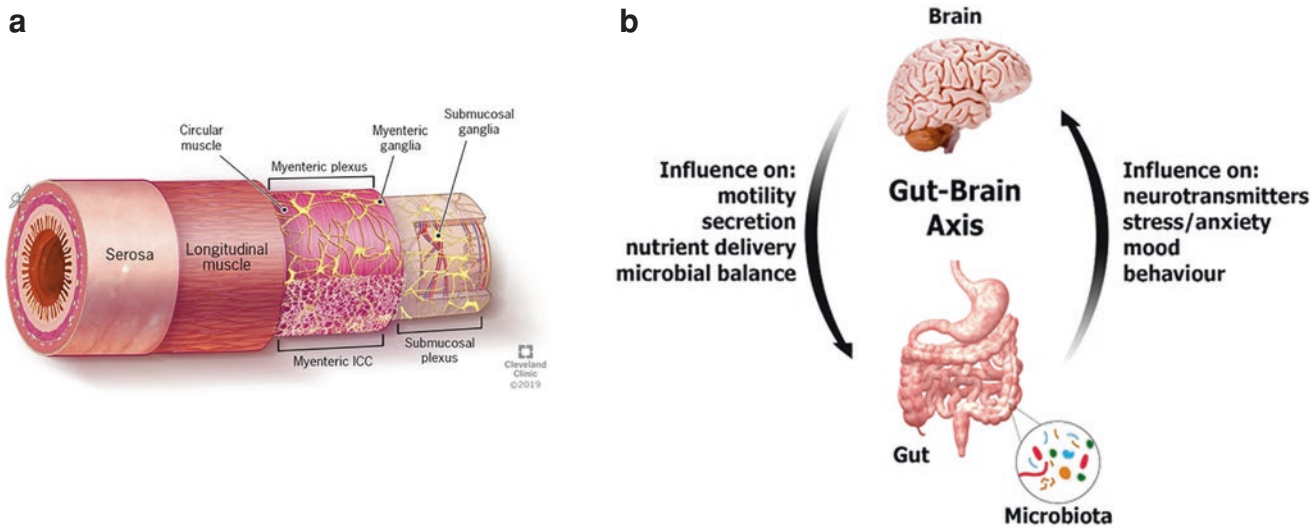

Fig. 51.1 The enteric neuromuscular system. Note the complexity of the neural network and the myogenic compartments (**a**) and the bidirectional gut–brain axis interaction (**b**)

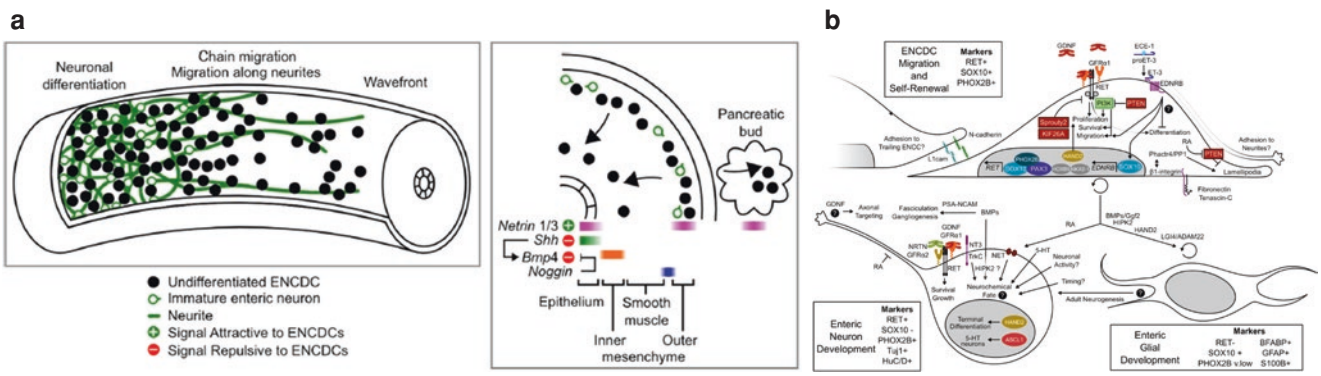

Fig. 51.2 The migration, differentiation, and maturation of the enteric nervous system. (**a**) Primary and secondary migration of the enteric neural crest-derived cells (ENCDCs); while the wave front of ENCDCs in the bowel moves steadily rostrocaudally, individual ENCDCs have complex and unpredictable behaviors. (**b**) Molecules and pathways implicated in ENS development. Roles of molecules and pathways are shown in the contexts of ENCDC migration (top), neuronal differentiation (bottom left), and glial differentiation (bottom right) (used with permission from Ref. [13])

Pathobiology and Nomenclature

Pathobiology

With recent advances in radiologic imaging, manometric studies, molecular diagnostics and genetics, GD has been classified into three categories: primary, secondary, and idiopathic [2–5]. While the primary disorder is caused by intrinsic neuropathies, myopathies, and/or mesenchymopathies (interstitial cells of Cajal), the secondary type is mainly caused by systemic disorders [2–5]. GD is primarily congenital in 80% of the pediatric cases [7]. Of the linked genetic mutations are ACTG2, MYH11, and RAD21 [14–17]. Full details are comprehensively addressed throughout the different chapters of this edition.

With uncertain overall prevalence, current published data declared the rarity of GD which occurs in less than 1 every 100,000 children [7, 18, 19]. The disorder is commonly associated with significant morbidities and mortalities. GF and poor quality of life are documented in up to 80% of the pediatric patients with an overall mortality rate up to 25% [7].

New Nomenclature

With cumulative clinical experience and robust data distinguishing the multifaceted aspect of GD, two different entities were defined [6, 7]. A well-designed European study identified enteric dysmotility as a new entity in patients with non-dilated visceral organs and less risk of associated morbidities including GF [6]. More recently, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and international experts proposed "Pediatric Intestinal Pseudo-obstruction" (PIPO) as a new nomenclature for the disorder among children [7]. To define this pediatric entity, a comprehensive scoring system was utilized with different levels of evidence. With early onset of GD, sometimes in utero, urological abnormalities, and congenital malrotation are distinctive of PIPO [7, 20]. The common association between gut malrotation and GD are further documented in one of a recent publication [21].

The ESPGHAN and international expert meeting recommended abdominal imaging including water soluble contrast series, antroduodenal manometry, and full thickness biopsy as key diagnostic tools. Such a historic meeting also called for the establishment of robust national and international registries, development of specialized referral centers, and adoption of a multidisciplinary management approach. Finally, the expert group addressed the role of surgical intervention with GT being recommended for children with life-threatening TPN-associated complications [7].

Surgical Management

The surgical management of GD has evolved over the last few decades. Historically, digestive surgery was limited to diverting and reductive procedures to overcome the obstructive symptoms and improve oral tolerance [22]. In 1990, clinical intestinal and multivisceral transplantation were introduced to be the most effective rescue therapy with reestablishment of nutritional autonomy. More recently, the concept of surgical remodeling was introduced as a part of an integrated management strategy for most of the GD patients including those with ED-associated GF [10].

Gut Transplantation

Indications & Evaluation

From the outset, GD has been one of the common indications for GT (Fig. 51.3) [9, 23]. According to the 2015 intestinal transplant registry (ITR) report, 18% of the children and

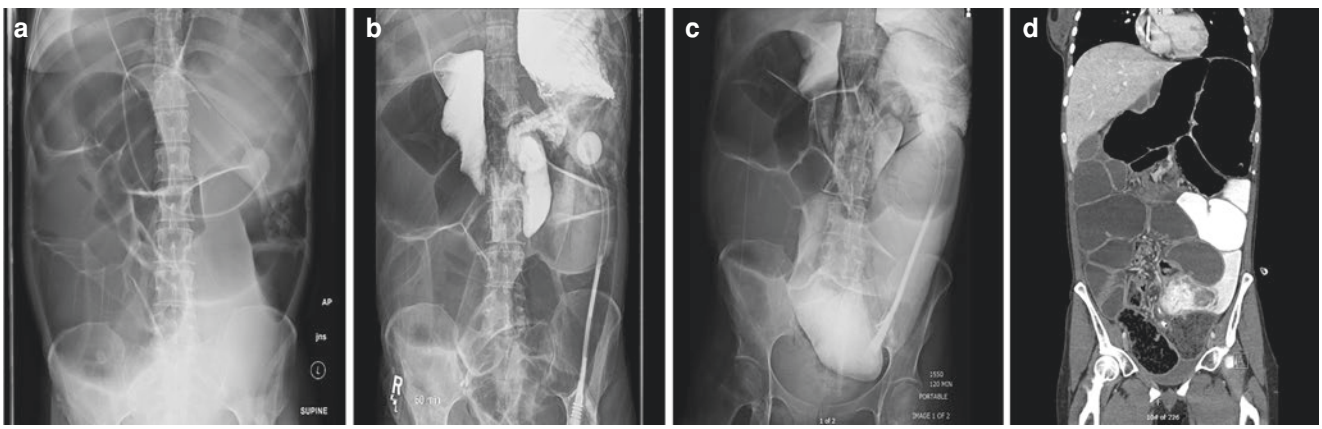

Fig. 51.3 Radiologic features of gut dysmotility. (**a**) Plain abdominal X-ray with diffusely dilated small bowel loops with no evidence of collapsed distal bowel. (**b** and **c**) Upper GI series with retained contrast after 60 (**b**) and 120 (**c**) minutes in the stomach and proximal jejunum with no ileal opacification or evidence of a transition point. (**d**) Coronal section of abdominal CT scan with hugely dilated air and fluid-filled proximal and distal intestinal loops

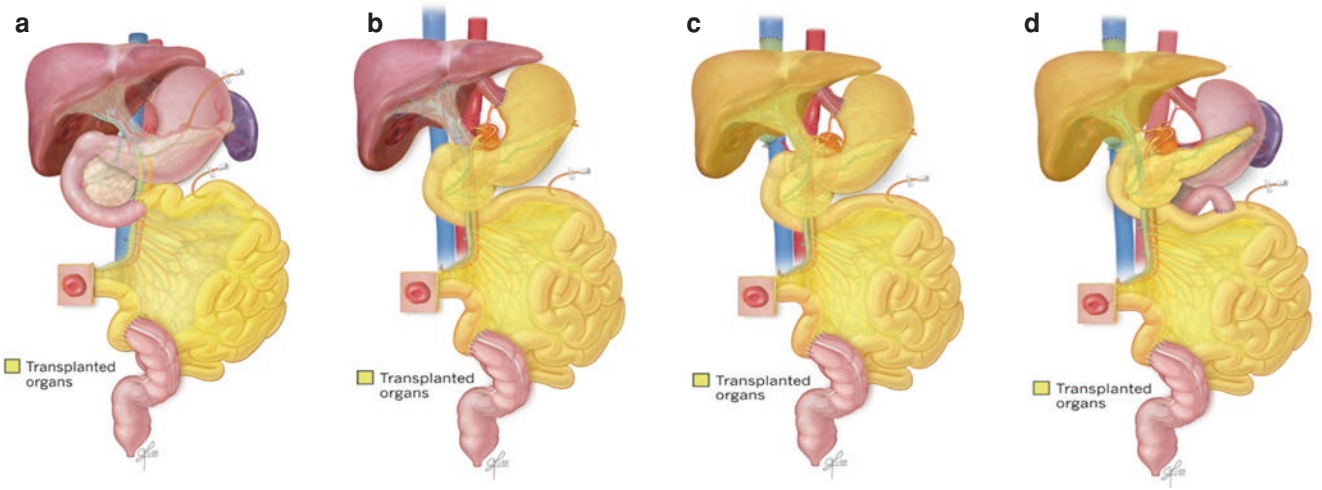

Fig. 51.4 The four main types of gut transplantation. (**a**) Isolated intestinal transplant, (**b**) Modified multivisceral transplant with en-bloc inclusion of the stomach, duodenum, pancreas, and intestine, (**c**) Full multivisceral transplant containing the stomach, duodenum, pancreas, intestine, and liver, and (**d**) Combined liver and intestinal transplant with inclusion of the pancreas

11% of the adult recipients suffered GF due to end-stage GD [23]. The development of irreversible GF with the permanent need for TPN therapy continued to be the standard selection criteria. Candidates should also experience TPN-associated life-threatening complications including recurrent line infection, central venous thrombosis, and hepatic injury as comprehensively outlined in the 2000 Center of Medicare and Medicaid Services (CMS) memorandum [24–26]. It remains to be seen if some of these restrictions could be lifted and preemptive transplant should be considered in patients with GF and severely disabling symptoms, particularly after the failure of the Trifecta.

The pre-transplant evaluation aims to confirm the diagnosis and assess candidacy for transplant [27]. Targeted clinical, laboratory, radiologic, endoscopic, manometric, immunologic, genetic and histopathologic assessments are utilized to define entity, underlying etiology, disease severity and other associated organ dysfunctions. The presence of contraindications for GT is also examined including severe congenital/hereditary anomalies, immunodeficiency syndromes and poor socioeconomic status including Munchausen by proxy [10, 21].

Types of Allograft

The four different types of intestinal and multivisceral allografts are utilized for both the pediatric and adult GD patients (Fig. 51.4). The allograft type is commonly dictated by the degree of foregut involvement and status of the associated solid organs particularly the liver. Patients with preserved gastric motility and solid organ functions often require intestine-only transplant (Fig. 51.4a). We often recommend modified multivisceral transplant (Fig. 51.4b) for global dysmotility with pseudo-obstructive features and severe gastroparesis or prior gastrectomy. Full replacement of the abdominal digestive organs including the liver and pancreas (Fig. 51.4c) is life-saving for patients with GD-associated end-stage liver failure and those with diffuse portomesenteric thrombosis. En bloc inclusion of the pancreas is required to maintain the axial blood supply and continuity of the transplanted organs [24]. Combined liver-intestine transplant (Fig. 51.4d) is utilized by centers who do not advocate or have experience with multivisceral transplantation.

In our recently published series of 55 GD patients, children commonly required isolated intestine and adults often needed modified multivisceral transplant [8]. Such a distinctive difference may signal overtime progression of the gut disorder among the adult population [8].

Controversies still exist concerning inclusion of the stomach in the visceral allograft [8]. Some centers on both sides of the Atlantic do not advocate gastric replacement regardless of the severity of gastroparesis. Alternatively, gastrojejunostomy with and without gastric reduction is commonly performed. Despite satisfactory initial outcomes, failure to fully restore nutritional autonomy was reported in 20% to 40% of these recipients with the continual development of TPN-associated complications [26, 28–33]. This policy has been recently disputed by the proven survival advantages of the modified multivisceral transplant [8]. However, the availability of these stomach-containing allografts has been difficult because of the decades of disparity in the United Network of Organ sharing (UNOS) Allocation policy [8, 34]. In brief, current policy continued to prioritize allocation of the pancreas with the kidney. In addition, liver surgeons are

often unwilling to allow retrieval of the celiac trunk with the en-bloc abdominal visceral organs. Nonetheless, such a legitimate dispute may continue to be fueled by the diversity and current ambiguity of the pathogenesis of the gut motility disorders with the lack of evidence-based criteria that guide en-bloc gastric replacement [8].

Technical Innovations

The intestinal and multivisceral transplant procedures witnessed three modifications specific for GD [9, 35, 36]. In 1993, hindgut reconstruction was first described; subtotal resection of native colon with ileo-rectal anastomosis between the allograft ileum and native rectum (Fig. 51.5a) [37]. A diverting chimney or simple loop ileostomy was also created to be taken down within the first 3–6 months after transplantation. This modification enhanced the gut absorptive functions and improved quality of life.

In 1999, preservation of the native spleen and pancreas along with a short duodenal segment was adopted with establishment of a side to side anastomosis between the native duodenal conduit and the transplanted duodenum or proximal jejunum (Fig. 51.5b) [35]. Preservation of the recipient spleen is shown to be protective against the development of post-transplant lymphoproliferative disorders (PTLD) and graft versus host disease (GVHD) [36]. Retention of a short duodenal conduit eliminates the need for biliary reconstruction. Preservation of the native pancreas along with the transplanted gland augments the islet cell mass and exocrine functions [36].

In 2008, a pull-through operation utilizing the donor colon en-bloc with the visceral allograft can be successfully performed in selected cases with preserved anal sphincter (Fig. 51.5c) [38]. The procedure successfully restored hindgut continuity with further enhancement of allograft functions and patient quality of life.

Postoperative Course

The immunosuppressive regimens utilized throughout the evolutionary phases of GT were similar to the non-GD recipients with indiscriminative early postoperative course [8, 9, 23, 39]. Immunologic monitoring of the intestinal allograft and infectious prophylaxis were also similar. Radiologic imaging was more utilized for the GD recipients particularly those with overt allograft dysfunction (Fig. 51.6).

With longitudinal follow-up, the risks of rejection, infection, PTLD, and GVHD were similar comparing the GD to the non-GD recipients [8, 9]. However, the pediatric GD recipients experienced higher risks of PTLD and GVHD compared to the adult GD cohort.

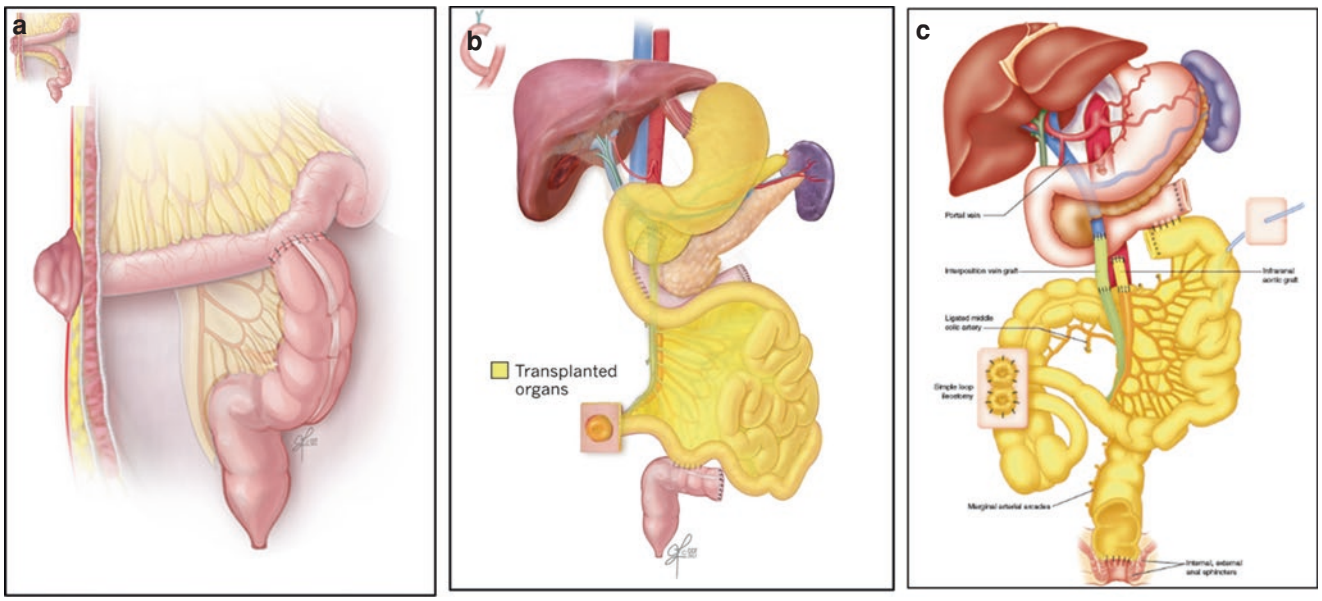

Fig. 51.5 Modification of the recipient and donor transplant surgical techniques for patients with gut dysmotility. (**a**) Hindgut reconstruction with restoration of gut continuity after closure of a temporary chimney or simple loop (insert) ileostomy. (**b**) Preservation of the native pancreas and spleen along with a duodenal conduit with a side-to-side anastomosis between the native and transplanted duodenum to avoid biliary reconstruction (insert) and maintain the immunologic and metabolic functions of the native spleen and pancreas, respectively. (**c**) A pull-through operation utilizing the donor colon en-bloc with the intestinal allograft to restore hindgut continuity for the gut dysmotility patients with preserved anal sphincter with prior proctocolectomy and those with severely diseased residual native colon

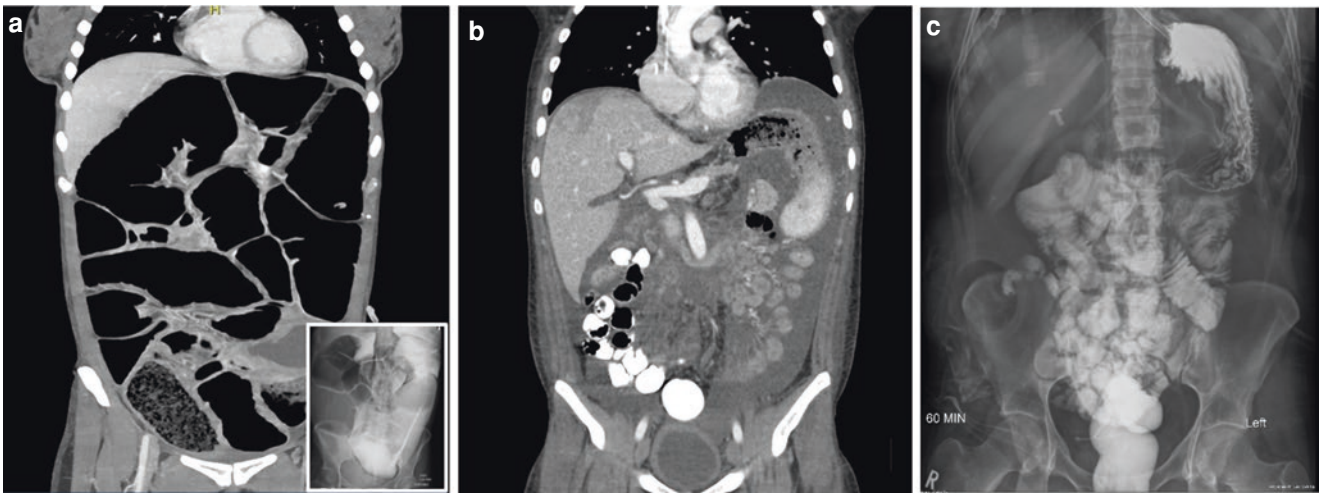

Fig. 51.6 Global gut dysmotility and gut transplantation. (**a**) Abdominal CT and gastrografin follow-through (insert) showing massive dilation of the small and large bowel defining the classic roentgenographic features of chronic intestinal pseudo-obstruction (CIPO) as a common variant of gut dysmotility. (**b**) CT imaging of a modified multivisceral allograft (stomach, duodenum, pancreas, and intestine) 3 months after surgery with residual chylous collection. (**c**) Gastrografin follow-through with 60 min transit time and slightly dilated native rectum one year after stoma closure

Survival Outcomes

The first scientific publication that addressed the utilization of GT for GD stemmed from the early Pittsburgh experience [40]. The study demonstrated the survival advantages of GT as a rescue therapy in 8 out of a total of 27 children referred with end-stage GD. After two decades of experience, a series of 55 consecutive pediatric and adult patients was recently published documenting a cumulative patient survival of 89% at 1 year and 69% at 5 years with respective overall graft survival of 87% and 56% (Fig. 51.7) [8]. Compared to the non-GD patients, the total GD recipients experienced unadjusted better patient (Fig. 51.7a) and graft (Fig. 51.7b) survival. Interestingly, adults experienced better survival outcome than children (Fig. 51.7c, d).

Over the years, the literature witnessed a few publications in both children and adults (Table 51.1). The relatively small sized international series reported similar or inferior survival outcomes compared to the Pittsburgh experience [26, 28–33, 40, 41]. The observed variation in outcome is most probably due to disparity in center experience, sample size, allograft type, immunosuppression, follow-up period, and disease gravity in the milieu of diverse hereditary and neuromuscular disorders.

Regardless of the cause of GF, the survival advantage of GT continued to improve with technical innovation, novel immunosuppression and enhanced postoperative care [9, 23, 42]. Similar to other GF patients, recipient preconditioning with anti-lymphocyte preparations significantly improved patient survival (Fig. 51.8a) with better primary graft survival (Fig. 51.8b). Pertinent to the GD patients, en-bloc inclusion of the stomach improved the long-term survival of the liver-free allografts (Fig. 51.8c, d). These results favor the simultaneous replacement of the stomach en-bloc with the intestine. Nonetheless, rejection, infections, PTLD, and GVHD continued to be the leading causes of death and graft loss [8].

A few collective review articles compared the survival benefits of transplantation to the survival of patients who continued to tolerate TPN therapy using compiled Medicare and European survey data [43–45]. It is sensible to believe that such a comparison is invalid since GT is mostly utilized to rescue the patients who no longer can be maintained on TPN. In contrast to the low transplant survival rates quoted in these articles, the quoted herein 5-year survival is similar or even higher than that reported with TPN in some of these publications [46]. With restored nutritional autonomy, transplantation has the additional advantages of being cost effective with improved quality of life [42, 47].

Nutritional Autonomy

Most of the GD patients achieve nutritional autonomy a few weeks after transplantation [26, 28–33, 40, 41]. Similar to other GT patients, recipients commonly require intermittent therapy for diarrhea and bacterial overgrowth with prokinetic agents for those who received gastric-containing allografts particularly during the early postoperative period [42]. Loss of the early restored nutritional autonomy in some recipients was observed in those with late destructive alloimmunity including intractable acute and progressive chronic rejection

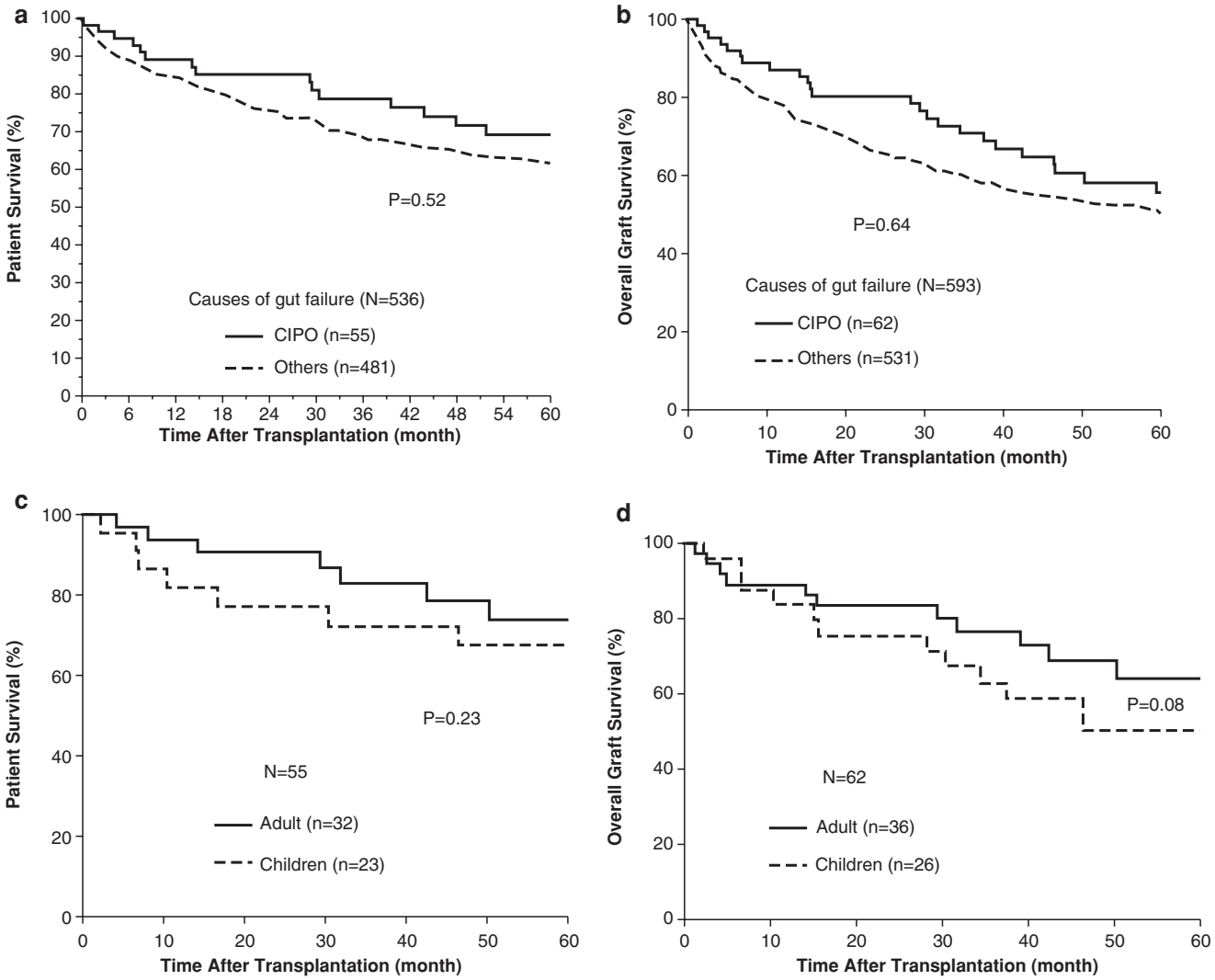

Fig. 51.7 Cumulative (Kaplan-Meier) patient and graft survival. The gut dysmotility (CIPO) transplant recipients achieved better patient (**a**) and graft (**b**) survival compared to the non-gut dysmotility (others) population. Of the gut dysmotility patients, adults achieved better patient (**c**) and graft (**d**) survival compared to children used from Ref. [8])

Table 51.1 The worldwide published series of intestinal and multivisceral transplantation in patients with gut dysmotility

				Number of patients				Patient survival		
	Author	Center	Year	Child/adult	Total	Age (year)	Follow-up (year)	1 year	3 year	5 year
1	Sigurdsson et al. [40]	Pittsburgh, PA	1999	8/0	8	1–19	0.2–5	75%*	NA	NA
2	Masetti et al. [41]	Miami, FL	1999	3/0	3	0.6–2.8	0.1–1.4	66%*	NA	NA
3	Iyer et al. [28]	Omaha, NE	2001	8/0	8	0.7–12.8	1.0–6.0	88%	NA	NA
4	Bond et al. [26]	Pittsburgh, PA	2004	17/7	24	1–47	NA	82–85%	75%	53%
5	Masetti et al. [29]	Modena, Italy	2004	0/6	6	21–37	1.2–3.0	83%	NA	NA
6	Loinaz et al. [30]	Miami, FL	2005	12/0	12	2.0–8	0.7–1.5	67%	50%	NA
7	Sauvat et al. [31]	Paris, France	2006	6/0	6	0.5–14	0.5–10.5	NA	71%	NA
8	Millar et al. [32]	Birmingham, UK	2009	12/0	12	NA	NA	61%	50%	50%
9	Lauro et al. [33]	Bologna, Italy	2013	0/11	11	NA	0.2–10.6	77%	70%	60%
10	Sogawa et al. [8]	Pittsburgh, PA	2021	23/32	55	1–49	0.2–16	89%	NA	69%

The study patients reported in Reference [8, 30, 33] and were part of earlier series reported from the same center
[a]Crude Survival; *NA* not available

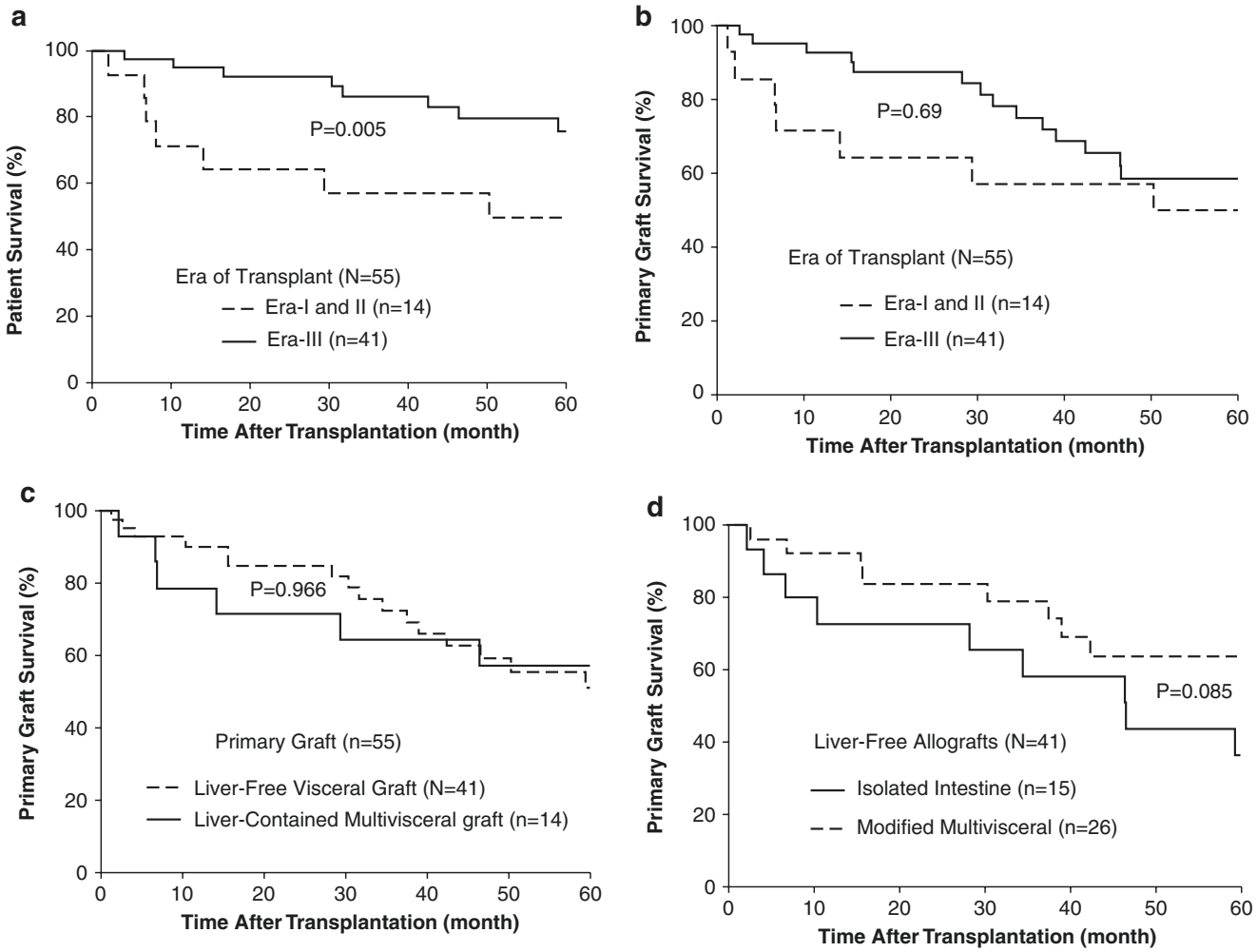

Fig. 51.8 Kaplan-Meier patient and graft survival. The cumulative patient (**a**) and graft (**b**) survival markedly improved with the utilization of recipient preconditioning (Era III) utilizing a single dose of anti-lymphocyte antibodies (Thymoglobulin or Campath-1H). The survival of the liver-free and liver-containing allografts where similar (**c**) while the modified multivisceral allograft achieved better survival compared to the intestine-only transplant (**d**) (Used from Ref. [8])

[26, 28–33, 40, 41]. Progressive dysmotility of the remaining native and transplanted visceral organs was also observed in a few cases [9, 26, 28–33, 40, 41]. The higher attrition rate of nutritional autonomy among the GD patients compared to the other GF patients was clearly demonstrated in two of the recently published Pittsburgh series addressing the long-term outcome among the total and GD patients as shown in Fig. 51.9 [8, 42].

Quality of Life

The detrimental effect of the severely disabling gut motility disorders on digestive health and overall quality of life has been clearly reported in the literature [48–52]. Compared to healthy control, GD significantly impairs the health related quality of life (HRQOL) issues in both patients and primary care givers with depressed scores worse than those observed with other chronic gastrointestinal disorders (Fig. 51.10a) [8, 48]. There is also a strong correlation between disease gravity and the level of impairment of HRQOL measures.

With successful transplant, most of the dedicated studies documented improvement in many of the HRQOL indices among the GD patients including the psychosocial and emotional domains (Fig. 51.10b) [8, 33, 42]. Interestingly, the improvement in physical activity, wellness and socioeconomic milestones were observed at a lower rate compared to the overall transplant population [42, 53]. These results could be partially due to the chronicity and incapacitating nature of GD. Other implicated factors are the cumulative side effects of maintenance immunosuppression and progression of some of the associated comorbidities including autonomic, connective tissue and muscular disorders. Recent studies have also suggested the potential harmful effect of altered gut microbiota and circulating neuropeptides on the gut-brain axis [8, 54, 55].

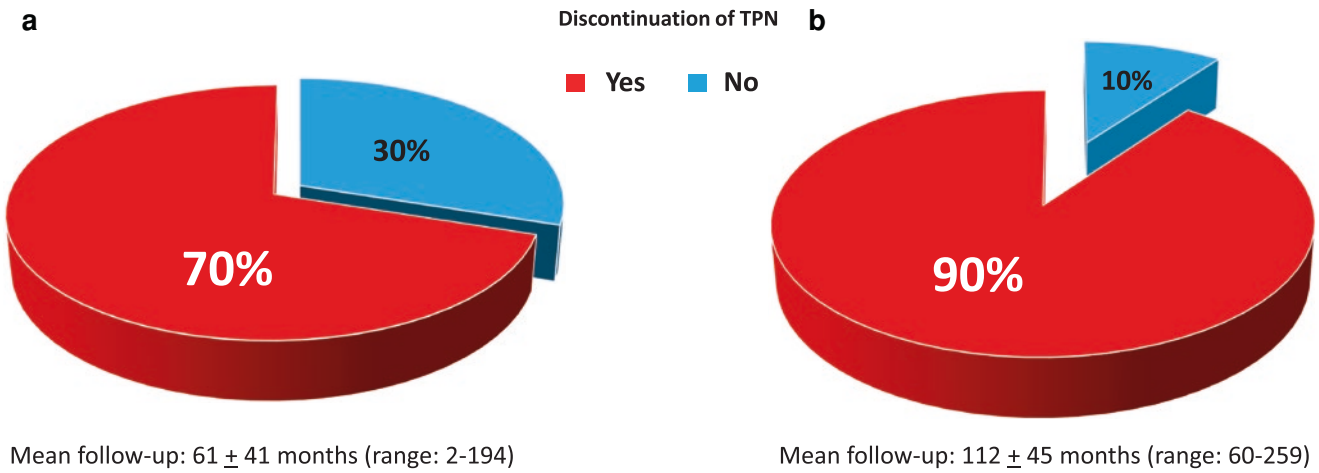

Fig. 51.9 Nutritional autonomy with discontinuation of total parenteral nutrition (TPN) after gut transplantation among the gut dysmotility (**a**) and other gut failure (**b**) patients. Note the two-digit lower rate of restoring the gastrointestinal nutritional autonomy among the gut dysmotility recipients compared to those who were transplanted to other causes of gut failure despite a shorter duration of follow-up (Used from Refs. [8, 42])

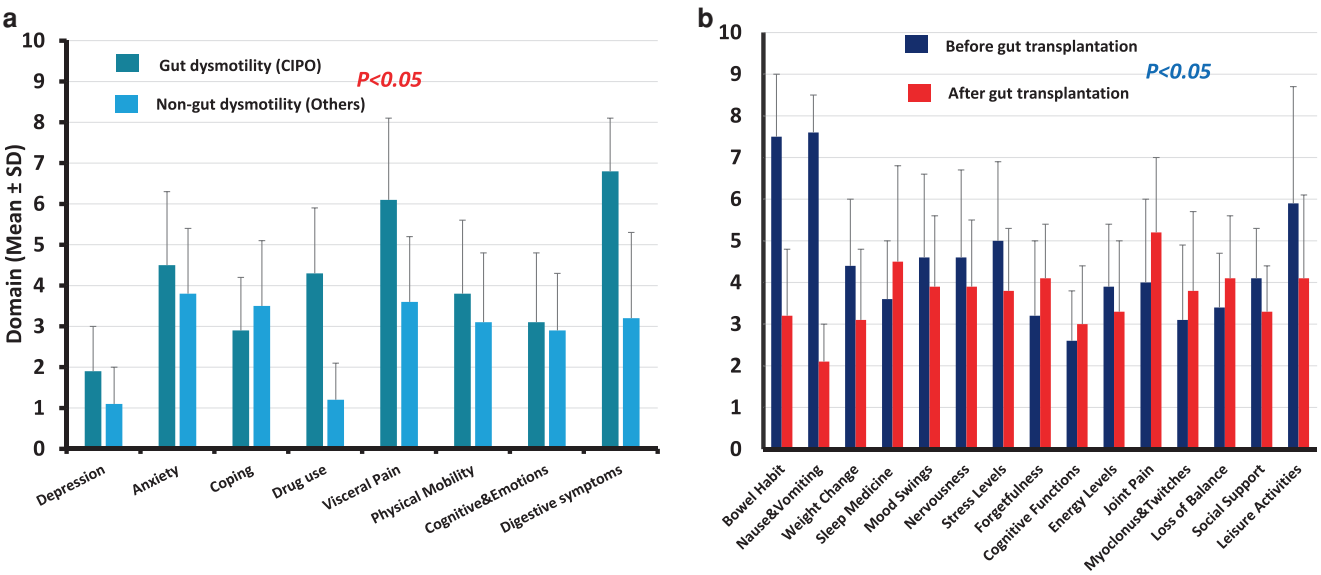

Fig. 51.10 A quality of life inventory (QOLI) survey was utilized to assess the health-related quality of life (HRQOL) issues in the adult gut failure patients. The self-assessment survey consists of 125 assorted questions addressing 25 domains with higher values indicating greater level of disturbance. (**a**) Most of the pretransplant QOLI domains were more depressed among the gut dysmotility compared to the non-gut dysmotility and gut failure patients with the difference reaching a higher level of significance in 7 of the 25 domains. (**b**) With a median follow-up of 4 years, the gut dysmotility patients showed significant improvement in nearly half of the domains after gut transplant. The data of both histograms were extrapolated from Sogawa et al with special focus on the domains with significant differences or changes, respectively (used from Ref. [8])

Surgical Integration and the Trifecta Procedure

The strategy of integrative management of GF with TPN dependence has been recently introduced with successful outcomes [10]. Neuromuscular disorders were the second leading cause of GF and were treated with surgical remodeling and GT. The newly introduced "Trifecta" procedure was the mainstay of the non-transplant surgery. With the intent to treat, the Trifecta (Fig. 51.11) was given to patients with preserved liver functions and intact gut. Most patients had clinical/radiologic evidences of preferentially advanced colonic inertia and partially preserved gastric motility. The procedure was also offered to patients who are not suitable candidates or

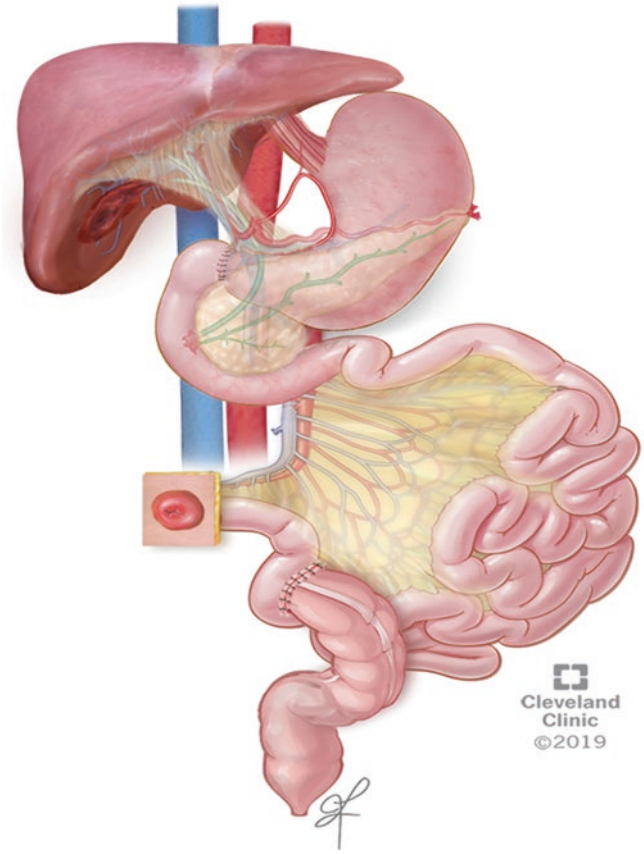

Fig. 51.11 The "**Trifecta"** procedure with the triad of subtotal colectomy, pyloroplasty, and chimney ileostomy that is designed for patients with gut dysmotility. The ileostomy is commonly taken down a few months after surgery particularly in patients with near complete resolution of the digestive symptoms and full restitution of the nutritional autonomy (Used from ref. [10])

unwilling to peruse transplantation. Patients with severe global dysmotility and advanced diffuse gut dilation were not suitable candidates for the Trifecta as shown in Fig. 51.6a.

The Trifecta Procedure

The procedure is designed to alleviate abdominal pain, restore oral tolerance and reduce risk of bacterial overgrowth [10]. It comprises subtotal colectomy, chimney ileostomy and pyloroplasty (Fig. 51.11). Accordingly, the intra-abdominal pressure is reduced and the gut transit time is modulated with significant improvement in intraluminal stasis. Although the procedure was initially implemented as a bridge to transplant, current results justify the increased utilization of the procedure with the intent to re-establish nutritional autonomy and improve quality of life.

Outcomes

In the recently published landmark paper of management of 500 patients with GF, autologous gut reconstruction (AGR) and surgical remodeling achieved better survival compared to long-term TPN therapy with an overall 5-year rate of 70% [10]. Interestingly, the neuromuscular cohort achieved better early survival compared to patients with surgical and mucosal GF with similar outcome at the 5-year landmark (Fig. 51.12a). This important observation may reflect the relative low operative risk associated with GD and disease progression with long-term follow-up.

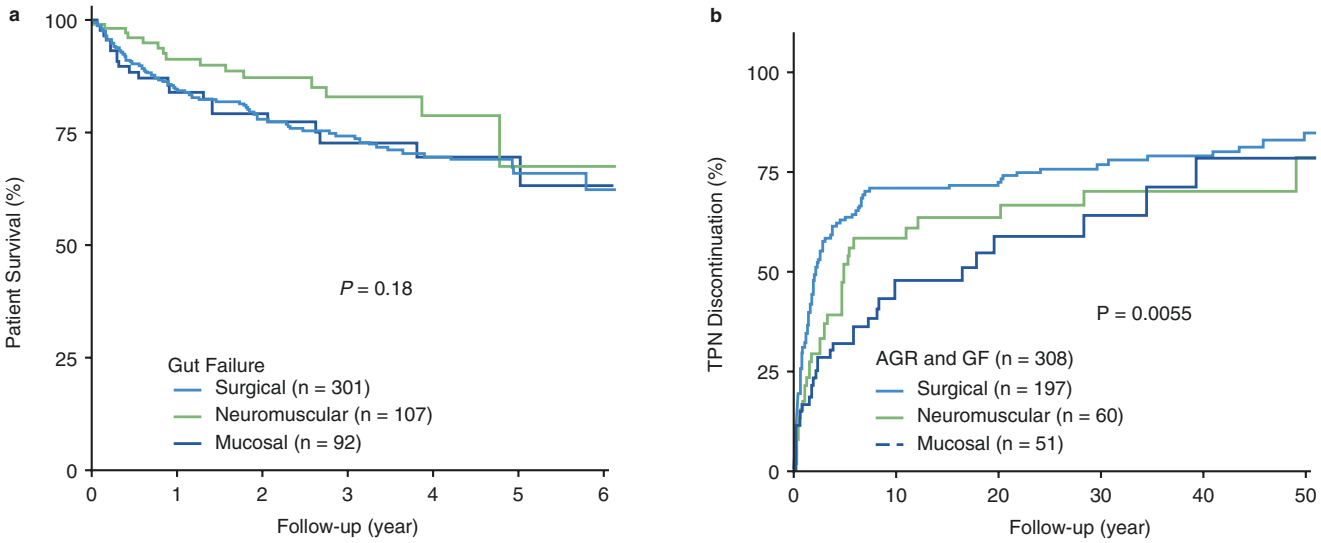

Fig. 51.12 Kaplan-Meier cumulative patient survival (**a**) and freedom from total parenteral nutrition (TPN) (**b**) after autologous gut reconstruction (AGR) and surgical remodeling. Note the higher survival rate and the lower incidence of restored nutritional autonomy (RNA) among patients with neuromuscular gut failure (GF) compared to those who had surgical or mucosal failure (used from Ref. [10])

The Trifecta was successful in restoring full nutritional autonomy among long-term survivors (Fig. 51.12b). Such an achievement was higher than that observed after single or combined reductive/decompressive interventions with a 3-year cumulative success rates of 71% and 55%, respectively [10]. Discontinuation of TPN therapy occurred at a slower rate during the first year among the neuromuscular compared to the surgical and mucosal GF patients (Fig. 51.12b). As such, the cause of GF was a significant predictor of achieving nutritional autonomy and was computed in our recently established predictive model [10].

It is our expectation that some of the neuromuscular GF patients may once more lose their oral tolerance with an attrition rate that could be driven by the underlying pathobiology of each individual disease entity. Patients with congenital and genetic disorders may continue to deteriorate overtime requiring organ replacement.

The Trifecta procedure achieved a better quality of life compared to transplantation with higher performance and fewer hospital re-admissions [10]. Comorbidities were also less with minimal daily oral medications. However, the primary disorder may continue to have some unwanted effects on the digestive health regardless of the nature of the offered treatment modality as observed with the new corrective surgery for congenital gut malrotation (Fig. 51.13).

Fig. 51.13 The impact of gut dysmotility (GD) on the clinical outcome of the gut malrotation correction surgery (GMS) "Kareem's procedure" in patients with digestive symptoms. Utilizing the National Institute of Health (NIH) patient-reported outcomes measurement information system (PROMIS) gastrointestinal symptom scales methodology, coexistence of GD depressed the procedure's therapeutic advantages Used from Ref. [21])

Allograft Motility Disorders

Gut Failure Patients

The coordinated interface between the gastrointestinal neuromuscular network, foregut digestive organs and midgut absorptive structures is essential to maintain gut homeostasis and total body energy equilibrium [56, 57]. Accordingly, re-establishment of such an intricate dynamic process across the transplanted and residual native organs is crucial to fully restore long-term nutritional autonomy. Of particular importance is a functioning neuromuscular system that conducts physiologic fasting and postprandial motor activities to maximize absorption with a healthy intraluminal milieu.

Study of the allograft motility was conducted, for the first time, among the early unprecedented Pittsburgh pediatric recipients [40, 51]. Interdigestive motor activities with preservation of normal manometric characteristics was seen in 62% of the transplanted intestine. However, the physiologic propagation of the migrating motor complexes (MMCs) across the anastomosis was disrupted during the early post-operative period with some qualitative abnormalities. There was an element of delayed gastric emptying and atypical post-prandial motility in the majority of recipients which could be partially responsible for the abnormal intestinal transit time with some impairment of digestive health.

After decades of experience, less than half of the long-term GT survivors continued to experience variable degrees of motility disorders. Gastric emptying was delayed and intestinal transit was accelerated with minimal impact on the allograft absorptive capacity [10, 42]. The diagnosis was suspected clinically, demonstrated radiologically and documented in selected cases, with manometric studies identifying discoordinated myoelectric migrating motor complexes (MMCs). With overt clinical symptoms, a single or multiple prokinetic and antimotility agents with periodic treatment for bacterial overgrowth were effective in optimizing allograft functions. Full recovery of the allograft motility functions is anticipated with future efforts to overcome the technical, immunologic, and inflammatory perpetuating factors inherent with GT.

Gut Dysmotility Patients

Similar to other GT recipients, altered short- and long-term allograft functions has been observed among both children and adults [26, 28–33, 40, 41]. In our most recent published study, overt allograft dysfunction with the need to reinstitute intravenous nutritional support was observed in 13% of the long-term surviving allografts. In these morbid cases, the development of progressive oral intolerance dictated the need for a thorough evaluation including imaging studies with abdominal exploration, in selected cases, to exclude correctable mechanical pathology and perform full thickness biopsy of the intestinal allograft. In a few patients, the digestive dysfunction was primarily due to progression of the native rectosigmoid dysmotility (Fig. 51.14) that was successfully managed by a diverting chimney or end ileostomy.

Disease recurrence was suspected in 7% of the study patients [8]. The loss of enteral tolerance was gradual with the ultimate development of negative energy balance requiring reinstitution of TPN. Progression of allograft dysmotility in the absence of opiate dependency, mechanical obstruction and chronic rejection fostered the putative diagnosis of disease recurrence (Fig. 51.15). Interestingly, one of these patients was successfully re-transplanted to develop recurrent allograft dysmotility 2 years later (Fig. 51.16).

The potential clinicopathologic commonality of de novo and recurrent allograft dysmotility has been one of our major interests [8, 58]. Such a convoluted topic can only be addressed by conducting a large multicenter study that include a diverse population of gut failure and utilize multifaceted clinicopathologic and biologic diagnostic tools. In light of the ongoing scientific discoveries, the diagnosis of disease recurrence can be justified by persistence of the pre-transplant altered circulating neuropeptides and gut microbiota with disarray of the gut-brain-neuronal-circuit [54, 55]. The development of de novo allograft dysmotility could be rationalized by the long-term damaging effects of ischemia reperfusion injury (IRI), destructive alloimmunity and dysregulated adaptive immune responses on the myogenic/intrinsic neurogenic circuits including the interstitial cell of Cajal.

Pathogenesis

Better understanding of the pathobiology of impaired intestinal and multivisceral allografts motility is essential to achieve further improvement in long-term outcomes. Such a task is rather complex in patients with primary or secondary gut motility disorders. Of the incriminating factors are IRI, allograft rejection, altered adaptive response, extrinsic denervation, lymphatic disruption and dysbiosis (Fig. 51.17) [58]. The interplay between these harmful events has the potential to induce cumulative damage of the different components of the gut neuromuscular structures. Of utmost importance is IRI and allograft rejection.

Static cold storage (SCS) is currently the standard method of organ preservation including the intestinal allograft. The prolonged state of hypoxia-induced anaerobic metabolism provokes IRI with the subsequent development of allograft structural injuries and systemic inflammatory response. Accordingly, SCS-induced IRI has the potential to disrupt the structure and impair the function of the allograft neuromuscular system [58]. Great efforts have been recently made to advance organ preser-

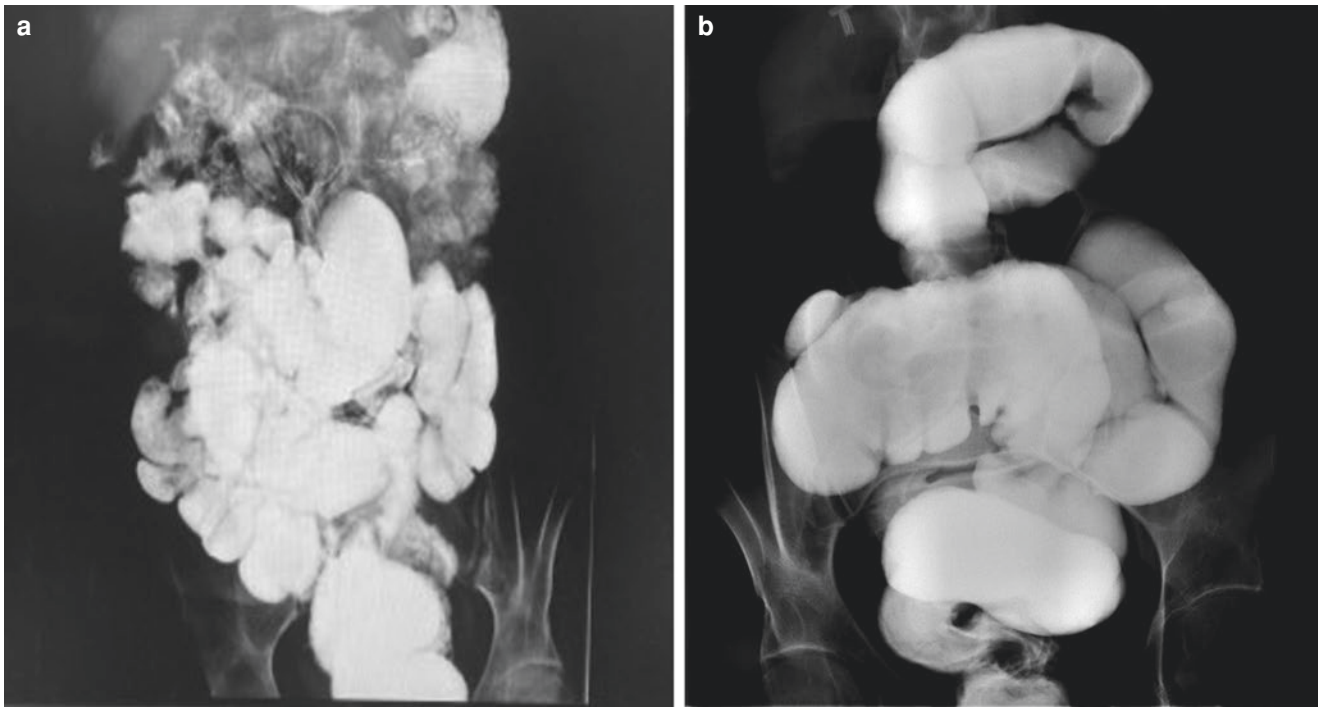

Fig. 51.14 Revelation of significant dysmotility of native rectum after stoma closure in an intestinal recipient with pre-transplant gut dysmotility (chronic intestinal pseudo-obstruction). (**a**) Gastrografin follow-through study showing dilatation of the allograft distal ileum with normal caliber proximal jejunum. (**b**) Gastrografin enema showing dilated native rectosigmoid and distal ileal allograft with no evidence of anastomotic stricture. The digestive tract was successfully decompressed with recreation of a chimney ileostomy

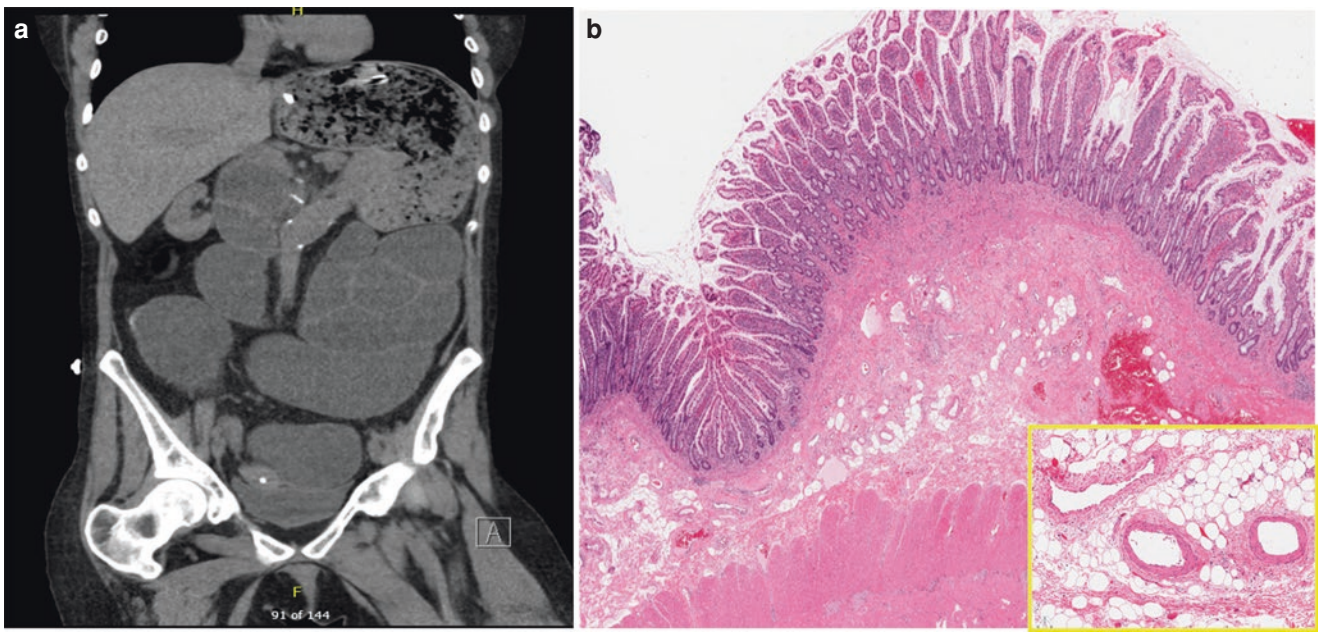

Fig. 51.15 Development of progressive motility dysfunction of a modified multivisceral graft in a female patient with pre-transplant gut dysmotility. (**a**) Abdominal CT showing retained food in the transplanted stomach with dilatation of the entire small bowel allograft. There was no evidence of mechanical obstruction. The recipient developed irreversible oral intolerance with loss of the nutritional autonomy and underwent allograft replacement 10 years after the first transplant. (**b**) The full thickness biopsy of the removed allograft showed no histopathologic evidence of chronic rejection; mucosa is intact with no mesenteric sclerosis or obliterative arteriopathy (insert)

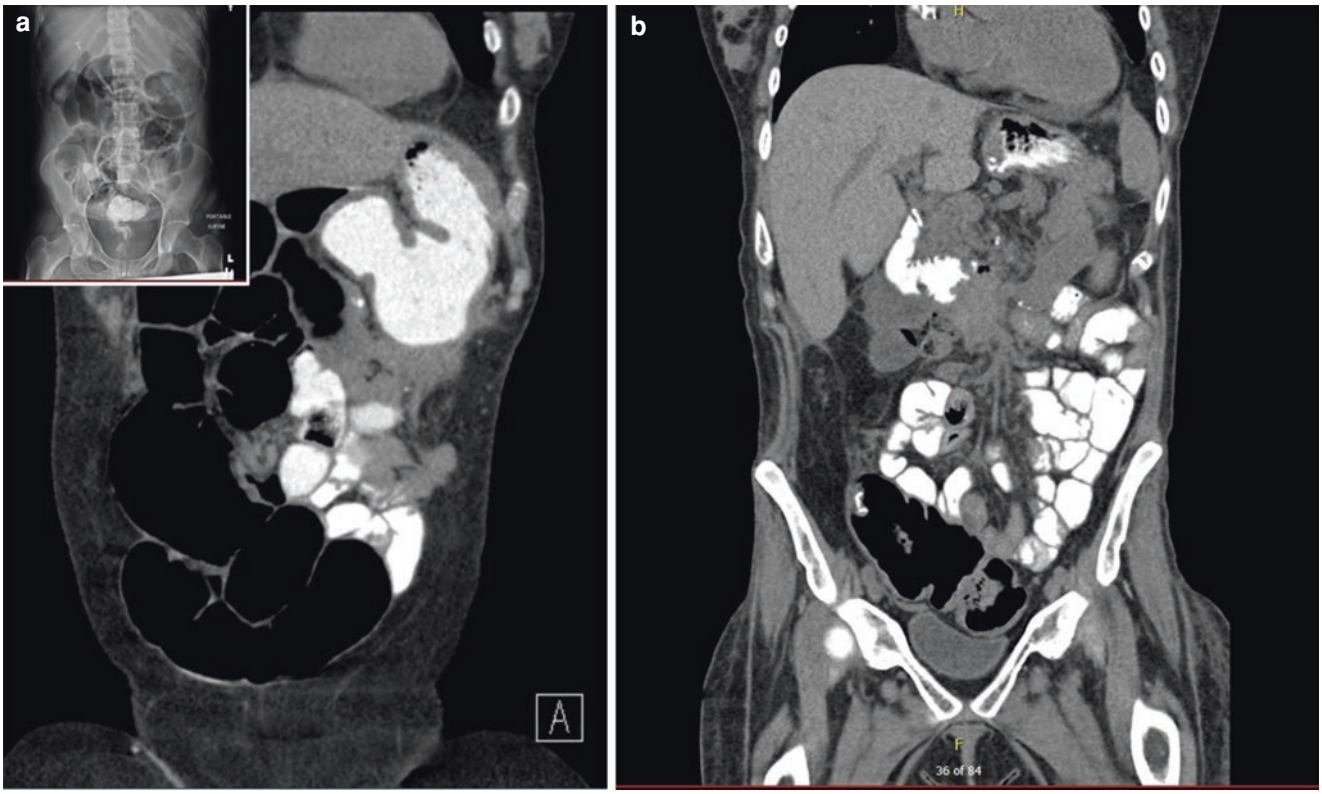

Fig. 51.16 Recurrence of allograft dysmotility two years after modified multivisceral re-transplant. (**a**) CT abdomen with a coronal section showing air filled dilated bowel loops with no radiologic evidence of mechanical obstruction. Note the absence of transition zone with gastrografin enema (insert) showing free passage of the contrast to the distal ileal allograft. (**b**) Abdominal CT with a coronal section showing significant improvement in the allograft gastric and intestinal distension after recreation of a chimney ileostomy with near complete restoration of oral tolerance

vation with the clinical introduction of the physiologic normothermic ex-vivo perfusion technology [59, 60].

The high immunogenicity of the intestine has the potential to induce acute and chronic rejection particularly of the liver-free intestinal allograft [61]. With recurrent episodes of severe acute rejection and progressive chronic rejection, the neuromuscular system can be irreversibly damaged due to the subsequent development of graft fibrosis, mesenteric sclerosis, and chronic ischemia due to obliterative arteriopathy [9, 39, 62]. These sinister problems are expected to be ameliorated with the future development of protocols to achieve allograft tolerance.

Local inflammatory responses are also reported to be responsible for damage of the neuronal network of the allograft intrinsic nervous system. Dysregulation of the adaptive immune system due to disruption of the normal ecology of gut microbiota and subsequent activation of the Toll-like receptors induces a state of local inflammatory responses in the intestinal submucosa and muscularis propria. Another harmful technical elements inherent with transplantation are extrinsic gut denervation and lymphatic disruptions with subsequent unwanted chronic changes in the intrinsic nervous system and interstitial compartments of the engrafted organs.

Fig. 51.17 Pathogenesis of intestinal and multivisceral allograft dysmotility. Note the complex and dynamic nature of the process (Modified from Von Websky MW, Kalff JC, and Nico Schafer. Current knowledge on regulation and impairment of motility after intestinal transplantation. Current Opinion. 20; 9(3) 2015)

Summary

The developmental and physiological aspects of the gut neuromuscular system are very intricate and have yet to be fully explored. Equally puzzling is the pathobiology of the associated gut motility disorders. With the current lack of effective pharmacologic and biologic therapy as well as pacing technology, it is our current practice to selectively use the optimal individualized surgical options. The commonly utilized modalities are the recently evolved remodeling procedures and transplant surgery. With the proper indication, both modalities are proven to be effective in restoring digestive health and nutritional autonomy. The diversified nature of the disorder merits an integrated care path to optimize the care of this complex population.

The proposed herein unprecedented algorithmic management is guided primarily by the different entities and associated morbidities of the disorder (Fig. 51.18). From the outset, the Trifecta procedure should be offered to patients with progressive oral intolerance and impaired quality of life particularly those with enteric dysmotility. It is also a valid option for the gut failure patients who are not candidates or unwilling to peruse transplantation. Gut transplantation is indicated for patients with end-stage pseudo-obstruction syndrome and irreversible gut failure. It should also be considered for those who failed or are not candidates for the Trifecta. The extent of foregut involvement and status of native liver largely determine the type of the required allograft. Further advances in the algorithmic management of these complex patients is foreseen with new discoveries in molecular genetics, gut biology and transplant tolerance.

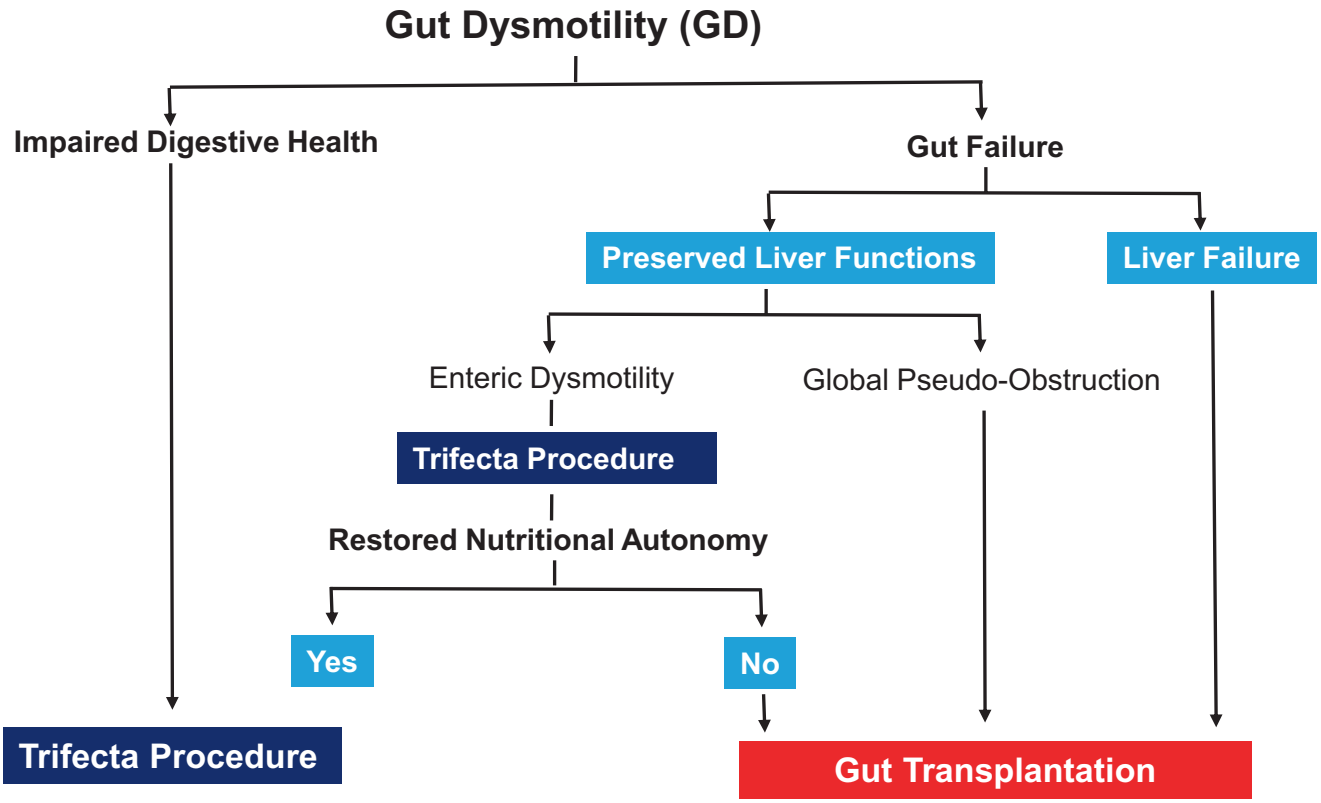

Fig. 51.18 The algorithmic surgical management of patients with gut dysmotility. Impaired digestive health indicates distressing digestive symptoms with food digestion and absorption. Enteric dysmotility is an entity of GD without bowel dilation. Global pseudo-obstruction indicates massive diffuse dilation of the gut

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This book was inadvertently published with incorrect dedication of the editor Dr. Nikhil Thapar which is corrected as follows:

"To my beloved parents, Baldev and Brijender Thapar—so blessed by your unending love. You will forever be my guiding light and inspiration."

The affiliation of the editor has also been corrected as given below:

Department of Gastroenterology, Hepatology and Liver Transplant,
Queensland Children's Hospital,
School of Medicine,
University of Queensland,
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