PART VIII Systemic Disorders

Section 35 GASTROINTESTINAL DISORDERS

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Chapter 35.1
Anatomy and Physiology

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The gastrointestinal tract (GIT) constitutes the esophagus, the stomach and the small and large intestines. The esophagus serves as a passage for food from the mouth and pharynx to the stomach. The stomach is the site where the food is thoroughly mixed with gastric secretions. It aids emptying the contents into the duodenum. Absorption of digested food occurs mainly in the small intestine. The liver and pancreas form the major glands of the digestive system. They discharge their secretion into the duodenum. Fecal matter is formed in the descending and sigmoid colons and is collected in the rectum before defecation through the anal canal.

Gastrointestinal tract plays a prominent role in immune function. The low pH of the stomach, and the mucus secreted from it are lethal to microorganisms entering the gut. The enzymes in saliva and bile are other factors helping with immune function. *Helicobacter pylori* are the only bacteria found alive in the stomach. They are considered responsible for gastritis and gastric ulcers.

The microorganisms forming the beneficial flora of the gut prevent overgrowth of harmful bacteria by competing for space and food. A ratio of 4:1 between the beneficial and harmful bacteria is generally considered normal within the intestines. The *gut-associated lymphoid tissue* (GALT) plays a vital role in killing the organisms entering the gut.

DEVELOPMENT OF THE GUT

The development of gut occurs at the beginning of the 4th week of gestation. The trilaminar embryonic disc with the three germ layers is folded upon itself cranially, caudally and side-wise. As a result, the endodermal layer of the disc becomes tubular and forms the inner lining of the gut. During this process, most of the yolk sac communicating with the gut is incorporated into it and contributes to formation of gut. The remaining part of the yolk sac with the vitellointestinal (omphaloenteric) duct **(Fig. 1)** later disappears. Persistence of the vitellointestinal duct gives rise to the *Meckel's diverticulum*.

Following folding of the disc, two pits known as stomatodeum and proctodeum develop at the cranial and caudal ends of the gut respectively. Initially, the two ends of the gut are separated from these pits by the buccopharyngeal and the cloacal membranes, respectively **(Fig. 2)**. Later, these membranes rupture and the gut communicates with the exterior at these ends. Failure of rupture of the cloacal (anal) membrane results in *imperforate anus*.

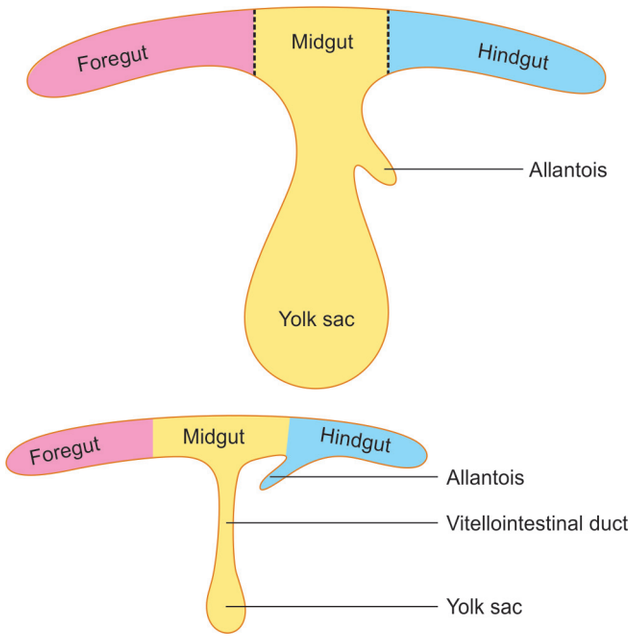

Figure 1 Formation of primitive gut following folding of the embryo

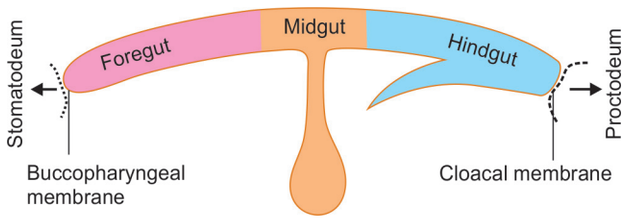

Figure 2 Formation of cranial and caudal pits (stomatodeum and proctodeum)

The foregut gives rise to the upper part of the alimentary canal from the floor of the mouth down to the level of upper part of duodenum marked by the major duodenal papilla. The midgut begins at this level and ends at the junction between the right two-thirds and left one-third of transverse colon. The remaining part of the gut down to the anal canal above the pectinate line is contributed by the hindgut. The lower part of anal canal develops from proctodeum.

The endoderm gives rise to the epithelial lining of the gut; the other layers of the gut are derived from the splanchnopleuric mesoderm surrounding the gut. The glands of the digestive tract and their duct system develop from the foregut as buds or diverticula. During early stage of development, the cells of the neural crest migrate into the wall of the gut and form the enteric nervous system (ENS). *Achalasia cardia and congenital megacolon* (Hirschsprung disease) are due to failure of migration of neural crest cells to form the nerve plexuses in the respective parts of the gut.

Rotation of Midgut Loop

In the initial stage, the abdominal cavity is largely occupied by the massive liver and kidneys. There is only little space within the peritoneal cavity to accommodate the rapidly elongating coils of intestines. As a result, during 6th week of development, the midgut loop herniates into the umbilical cord. This is known as *physiological umbilical herniation* and is a normal event in all embryos. Elongation of intestines occurs outside the body.

During 10th week of development, when the abdominal cavity becomes sufficiently larger, the whole of the herniated bowel is withdrawn into the abdominal cavity. During the process of herniation and withdrawal, the midgut loop undergoes 270° rotation in anticlockwise direction. This rotation of the midgut is essential to establish appropriate positions of parts of gut within the peritoneal cavity. Failure of return of the midgut results in *omphalocele* or *exomphalos*. Similarly, incomplete rotation (mixed rotation), rotation in the opposite direction (reversed rotation) or failure of rotation (nonrotation) gives rise to various anomalies associated with abnormal position of parts of the gut in the abdominal cavity (e.g., presence of cecum in the midline below the stomach). Such abnormal positions of the parts of gut are prone to intestinal obstruction due to *volvulus*.

Fixation of the Gut

Initially, the gut is suspended from the posterior abdominal wall by a fold of peritoneum known as the dorsal mesentery. Later, alternate parts of the gut lose their mesentery and become retroperitoneal. Fixation of the gut is essential to retain its appropriate position in the abdominopelvic cavity and to prevent intestinal obstruction due to volvulus. The parts of the gut that lose their mesentery include the duodenum except its first part, the ascending colon and descending colon, the rectum and the anal canal. The cecum is covered with peritoneum on all sides. However, it does not have a mesentery.

DEVELOPMENT OF LIVER AND GALLBLADDER

The liver develops as a diverticulum (hepatic bud) extending from the lower part of foregut. This diverticulum soon bifurcates into two parts: pars cystica and pars hepatica. The pars cystica expands to form the gallbladder and the pars hepatica expands to form the parenchyma of the liver **(Fig. 3)**. The proximal parts of the diverticulum remain narrow and form the biliary ducts. The stroma of the liver such as sinusoids, Kupffer cells and capsule develop from the *septum transversum,* a fibrous septum that forms part of the diaphragm.

DEVELOPMENT OF PANCREAS

The development of pancreas is marked by two pancreatic buds: ventral and dorsal extending from the lower part of the foregut close to the hepatic diverticulum. Due to rotation of the stomach and differential growth of the duodenum, the buds come closer and fuse to form the pancreas **(Fig. 4)**. Insulin secretion begins from 10th week of development. Variations in the formation

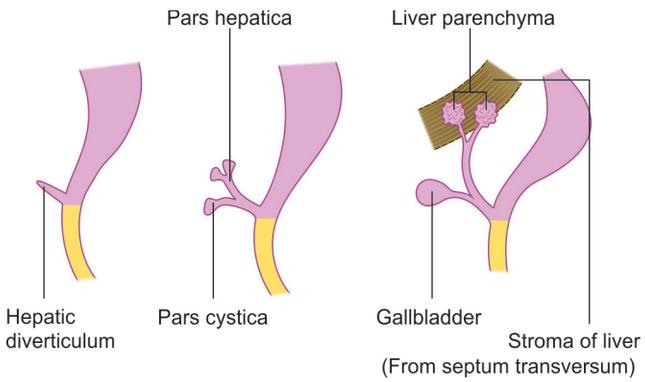

Figure 3 Development of hepatobiliary apparatus

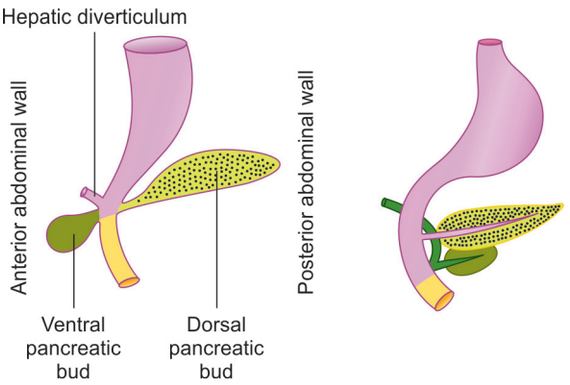

Figure 4 Development of pancreas

and mode of termination of the biliary and pancreatic ducts are common. In some cases, the bile duct and the pancreatic duct fail to unite and open independently into the duodenum. *Annular pancreas* is a developmental anomaly in which a ring of pancreatic tissue surrounds the second part of the duodenum. A bifid ventral pancreatic bud is attributed to be a cause of this anomaly.

BLOOD SUPPLY OF THE GUT

The aorta running behind the gut gives off several branches to the gut in the initial stage of development. Later, many of these branches disappear and only three arteries persist. The celiac trunk supplies the foregut from the lower part of esophagus, liver, gallbladder and pancreas, which are the derivatives of the foregut; the superior mesenteric artery (SMA) supplies the midgut and the inferior mesenteric artery (IMA) supplies the hindgut.

Since the duodenum develops from both the foregut and the midgut, it is supplied by the branches of celiac trunk and SMA. The branches of these arteries anastomose to form an arterial arcade around the head of the pancreas. This anastomosis provides an alternative source of blood to the foregut structures in case of occlusion of celiac trunk or its branches.

Since the transverse colon marks the junction between the midgut and the hindgut, it is supplied by both the midgut (SMA) and the hindgut (IMA) arteries. The branches of these arteries anastomose freely and form a circumferential artery known as the *Marginal artery of Drummond* along the inner margin of the colon. This artery supplies the entire colon. In cases of occlusion of the

SMA or IMA, this anastomosis helps to provide blood to the affected part of the colon. However, the area near the splenic flexure where the branches of the two gut arteries meet is least vascular and it becomes a common site of *ischemic necrosis* of colon.

The *jejunum and ileum* are supplied by 15–18 branches arising from the SMA. They unite to form loops or arches called *arterial arcades*, from which straight arteries known as *vasa rectae* arise to supply the jejunum and ileum. These arteries are end arteries to the jejunum and ileum. Therefore, occlusion of vasa rectae due to internal hernia or compression by a tumor can produce *gangrene* of the small bowel.

The appendicular artery supplying the appendix ends even before reaching its tip in most of the cases. Therefore, the tip becomes least vascular and suffers gangrenous changes first in *acute appendicitis.*

The veins draining the gut form the *portal venous system*. The superior and inferior mesenteric veins collect blood from the midgut and the hindgut respectively. The veins from the foregut, pancreas, spleen and most of the gallbladder empty their blood into the portal vein either directly or indirectly through the splenic vein. The portal vein carries blood to the liver through its hilum. This blood after undergoing metabolic changes and detoxification in the liver is emptied into the inferior vena cava through hepatic veins that emerge from the liver.

Unlike the systemic veins, the veins of the portal system are devoid of valves. Therefore, blood flow can occur in either direction depending on pressure changes. The veins of the portal system anastomose with systemic veins (portosystemic anastomosis) in five regions of the abdomen. In portal obstruction or hypertension due to cirrhosis of liver, the blood flow through the liver slows down and blood backs up throughout the portal system. The tributaries of the portal venous system are very much engorged at the sites of portosystemic anastomoses.

INNERVATION OF THE GUT

The GI tract is innervated by both intrinsic innervation through ENS, and extrinsic innervation through autonomic nervous system. ENS referred to as the *minibrain of the gut* organizes and coordinates the activity of musculature, glands, and blood vessels of the gut. Functionally, it consists of three types of neurons: motor, sensory and interneurons. Musculomotor neurons (excitatory and inhibitory) control the contraction and relaxation of musculature of the gut. Secretomotor neurons control the secretory activities of the glands; the sensory neurons receive information regarding the state of the gut, and the interneurons form information-processing networks through their synaptic interconnections. The neurons of the ganglia and their fibers form the two nerve plexuses of the ENS. *Myenteric (Auerbach's) plexus* is primarily concerned with initiation and control of smooth muscle contraction and relaxation such as peristalsis. *Submucosal (Meissner) plexus* coordinates reflexes associated with secretion and absorption, as well as motor control of smooth muscle. Both these plexuses communicate freely within the wall of the gut.

The *parasympathetic fibers* innervating the foregut and midgut originate from the dorsal vagal complex (cranial outflow) in the medulla. The parasympathetic fibers innervating the hindgut originate from the S_2, S_3, S_4 spinal segments (sacral outflow). They form the pelvic splanchnic nerves (nervi erigentes). The parasympathetic innervation exerts both excitatory and inhibitory effects on the gut. The efferent vagal fibers synapsing with neurons in the ENS activate circuits to the effecter systems. In the case of musculature, they exert reciprocal control over both inhibitory and excitatory musculomotor neurons. These neurons send signals to the musculature of gut both in anticipation of food intake and following a meal. In the case of glands, the secretomotor neurons are activated to stimulate secretion of the glands. The afferent vagal fibers (visceral afferents) send signals from the gut to the ENS in response to distension of the gut from food. These vagal afferent neurons are connected with a variety of sensory receptors (physical, chemical, and thermal) in the gut. They detect physical parameters such as brushing of mucosa with food, changes in muscle tension, and changes in chemical parameters such as pH, glucose concentration and osmolarity.

The *sympathetic fibers* innervating the gut innervate mainly the blood vessels to produce vasoconstriction, and also mucosa, and musculature of the gut. They suppress gut activity when stimulated. Sympathetic suppression of digestive functions, including motility and secretion, occurs secondary to reduced blood flow mediated by the *norepinephrine* released from sympathetic postganglionic neurons. It acts directly on sphincteric muscles (*lower esophageal sphincter* and *internal anal sphincter*) to keep them closed by increasing their tension.

MICROSCOPIC STRUCTURE OF THE GUT

The wall of the GIT consists of four major layers: mucosa, submucosa, muscularis propria, and serosa (if covered with peritoneum) or adventitia (if not covered with peritoneum). The mucosa, in turn, consists of a lining epithelium, lamina propria of loose connective tissue and muscularis mucosae, a thin layer of smooth muscle. The mucosa differs considerably from region to region based on functional changes in different parts of the gut.

Stomach

The tall columnar epithelium lining the stomach invaginates to form the gastric pits, into which the gastric glands secrete. The gastric glands are composed of four types of epithelial cells:

1. *Mucous neck cells* secrete mucus, which forms a thick lining of about 1 mm thickness on the luminal surface.
2. *Chief cells* produce pepsinogen, a precursor of the proteolytic enzyme pepsin.
3. *Parietal cells (or oxyntic cells)* secrete the gastric acid. In addition to activating the pepsinogen, the gastric acid effectively sterilizes the contents of the stomach. They also secrete *intrinsic factor*, which is necessary for the absorption of vitamin B_{12}.
4. *Argentaffin cells (unicellular endocrine glands)* are found scattered throughout the epithelium of the GIT. They include gastrin-producing cells (*G cells*) and somatostatin-producing cells (*D cells*). *G cells* stimulate the secretion of acid and pepsinogen. *D cells* are activated by acid in the lumen of the stomach and duodenum. They inhibit *G cells* and thereby acid production.

Other types of endocrine cells include vasoactive intestinal polypeptide (VIP)-producing cells (or *D1 cells*) and serotonin-containing cells (enterochromaffin cells). Endocrine cells in the GIT are alternatively named *amine precursor uptake and decarboxylation (APUD) cells.*

Small Intestine

The intestinal mucosa contains numerous *villi*. Each *enterocyte* or the lining epithelial cell forms several *microvilli (brush border)*. The simple tubular glands of intestine (*crypts of Lieberkühn)* open between the villi. Four types of cells are found throughout the mucosa of the intestinal villi. Some have absorptive function while others secrete digestive enzymes and mucus to protect the intestinal lining from digestive actions. The following are the cell types: (1) *simple columnar absorptive cells*; (2) *goblet cells producing protective mucus*; (3) *Paneth cells*, producing lysozyme

capable of digesting bacterial cell walls; and (4) *argentaffin* or enteroendocrine cells, which produce gut hormones like *cholecystokinin* and *secretin*. Cholecystokinin stimulates the secretion of digestive enzymes in the pancreas and the contraction of the gallbladder. Secretin stimulates the pancreas to release *pancreatic juice*. It also augments the effects of cholecystokinin.

The crypts of Lieberkühn secrete the *intestinal juice* (*succus entericus*). A few enzymes are found in the intestinal juice. These include the *amylase* and the *enteropeptidase* (enterokinase). The latter activates the pancreatic enzyme trypsin which in turn activates all proenzymes secreted by pancreas to their active forms. The lymphocytes in the lamina propria form solitary lymphoid nodules known as *Peyer's patches* in the ileum.

The duodenum is characterized by the presence of the *glands of Brunner* in the submucosa; their secretion protects the duodenal mucosa just like the mucus in the stomach.

The lacteals are the specialized lymphatic vessels found in the intestinal villi. They absorb the end-products of fat digestion. They empty their milk-like fluid into the lymphatic plexuses in the walls of the jejunum and ileum.

Large Intestine

Since the mucosa of large intestine is devoid of villi, the mucosal surface is flat with several deep intestinal glands. It contains numerous goblet cells that secrete mucus to lubricate fecal matter as it solidifies. It harbors several kinds of bacteria that help breaking down of molecules, which the gut is not able to break down itself. This is an example of symbiosis. Colon is sterile at birth; colonization of bacteria occurs within a few hours. This is essential for digestion and formation of vitamin K. Further, the intestinal flora helps in the synthesis of vitamin B complex. These bacteria also account for the production of gases.

Liver

The parenchyma of liver is composed of several *hepatic lobules*. Each hepatic lobule is a hexagonal structural unit with hepatocytes arranged in the form of sheets or cords radiating outward from a central vein like the spokes of a wheel. Located between the hepatic cords are the sinusoids, which receive blood at the periphery of the lobule from the portal vein and the hepatic artery and, after traversing the lobule, discharge the blood into the central vein at the center of the lobule. The sinusoids are lined with endothelial cells and contain the stellate cells of Von Kupffer. Bile capillaries (canaliculi) are formed between adjacent hepatic cells, which drain toward the periphery of the hepatic lobule into a bile ductule in the portal canal. This structural unit of the liver is repeated throughout the liver.

Another way of considering the function is a triangular or biliary unit known as *portal lobule*, the corners of which are formed of three central veins. This approach emphasizes the secretion of bile and the biliary system; bile from the canaliculi drain into bile ductules at the center of the triangular unit (portal lobule) **(Fig. 5)**.

The third unit of structure/function is the *hepatic acinus*. Each acinus is a diamond-shaped unit connecting the two adjacent hepatic lobules. The central veins are located at the diametrically opposite angles and portal triads are located at the other two diametrically opposite angles of the diamond. Each hepatic acinus is divided into three *zones*. There is an oxygen gradient (from high to low) between zones 1, 2 and 3. The cells of the zone 3, being least oxygenated are the first to undergo necrosis due to ischemia or drug reaction. After a meal, glycogen will be stored first in the zone 1, later in zone 2, and finally in zone 3. The reverse is true when glucose is needed: zone 3 is depleted of its glycogen first, followed by zones 2 and 1.

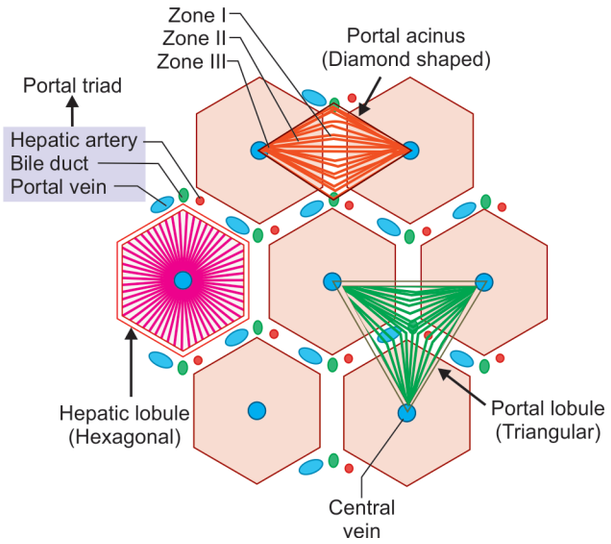

Figure 5 Anatomic and functional lobules of liver

Pancreas

Pancreas is subdivided into several lobules separated by connective tissue septae. Each lobule consists of several compound tubuloalveolar glands with purely serous alveoli. The glandular epithelium consists of pyramidal cells, which secrete zymogen granules into a system of ducts. The centroalveolar or centroacinar cells lie between the secretory cells and the lumen of the alveolus. Interspersed between the exocrine parts of the pancreas are the cells of islets of Langerhans. They are found in abundance near the tail end of the pancreas. Four types of cells constitute the islets: *alpha cells* secreting glucagon, *beta cells* secreting insulin, *delta cells* secreting somatostatin and *PP cells* secreting pancreatic peptide.

IN A NUTSHELL

1. In addition to digestion and absorption of food, the GIT plays significant role in immune function.
2. The liver, the gallbladder and the pancreas including the respiratory tract and the lungs develop as diverticula from the wall of the foregut.
3. Elongation of the intestines occurs outside the body of the embryo and the midgut loop undergoes 270° rotation in the anticlockwise direction during this process. Failure of return of the midgut to the abdominal cavity after elongation results in omphalocele or exomphalos.
4. During initial stage of development, the entire gut is suspended from the posterior abdominal wall by the dorsal mesentery and is therefore intraperitoneal in position. Later, alternate parts of the gut lose their mesentery and become retroperitoneal. The fixation of the gut in this manner is essential to retain their appropriate position in abdominal cavity and to prevent intestinal obstruction such as volvulus.
5. Besides the nerve plexuses of the ENS, the sympathetic innervation to the gut is provided by T5-T6 to L2-L3 spinal segments and the parasympathetic innervation is provided by the vagus and the pelvic splanchnic nerves (S2, S3, S4).
6. Pain impulses from the gut down to the middle of the sigmoid colon are conveyed through the sympathetic fibers and, caudal to this level by the parasympathetic fibers.
7. From within outward, the mucosa, submucosa, muscularis externa and serosa or adventitia are the four major layers forming the wall of the gut.

MORE ON THIS TOPIC

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Chapter 35.2
Common Symptoms of Gastrointestinal Diseases

Sarah Paul, John Matthai

Symptoms related to gastrointestinal (GI) system are common in children. In most cases, they are indicative of a mild disease, while in some, they are pointers to serious underlying disorders. Not infrequently, they are functional, psychogenic or stress-related. While systemic diseases may manifest with abdominal symptoms, GI diseases need not always have symptoms referable to the GI tract. A basic understanding of the pathophysiology of the common signs and symptoms will help avoid unnecessary investigations and parental anxiety.

DIARRHEA AND DYSENTERY

Increase in frequency, fluidity and volume of feces in relation to the age of the child is called diarrhea. In epidemiological studies, diarrhea is defined as the passage of three or more loose or watery stools during a 24-hour period, a loose stool being one that would take the shape of a container. The most common type is the acute watery diarrhea where the illness starts acutely, lasts less than 14 days (most episodes last less than 7 days), and involves the passage of frequent loose or watery stools without visible blood. Diarrhea with visible blood in the feces is called dysentery and signifies inflammation of the intestinal mucosa. Children appear sick and systemic signs like fever, anorexia and abdominal pain last much longer.

Watery stools are common in either osmotic or secretory diarrhea. Small bowel mucosa is a porous epithelium through which water and salts move across rapidly to maintain osmotic balance between the bowel contents and the blood. Diarrhea occurs when a poorly absorbed, osmotically active substance (usually a carbohydrate) is present in the gut lumen. The stooling stops on fasting, the stool pH is acidic and reducing substances are positive. Removal of the unabsorbed component of the diet is the only treatment. The unabsorbed substance is usually isosmotic and therefore dehydration and electrolyte disturbances are unlikely. Secretory diarrhea is caused by toxins [for example, cyclic AMP of cholera, cyclic GMP of enterotoxigenic *Escherichia coli* (ETEC)], which impair sodium absorption by the villus cells, while the chloride secretion by the crypt cells continues. The stooling continues despite fasting, the stool pH is alkaline and reducing substances are negative. Dehydration and electrolyte imbalances are common. Ion transport disorders (congenital chloride or sodium diarrhea) present with watery stools in the newborn period and result in failure to thrive and severe electrolyte disturbances. Increased gut motility from VIPoma, carcinoid or thyrotoxicosis are rare in children, but should be considered in chronic watery diarrhea when other causes are ruled out. Dysentery occurs from an inflammatory diarrhea and may be either infective (*Shigella, Salmonella*, amebiasis) or noninfective [inflammatory bowel disease (IBD), cow's milk protein allergy].

ABDOMINAL PAIN

Differentiating the varied types of functional abdominal pain from those with an organic pathology is a big challenge in practice. Pain-related functional GI disorders were categorized into five groups in the Rome III criteria of 2006: functional dyspepsia, irritable bowel syndrome, abdominal migraine, childhood functional abdominal pain, and childhood functional abdominal pain syndromes. It is important however to recognize signs and symptoms that are suggestive of an underlying organic disease **(Table 1)**.

Clinically, there are three patterns of abdominal pain in children: (1) Isolated per-umbilical pain, in which only 5% are organic causes (malrotation, renal stone, pelviureteric junction obstruction, food allergy); (2) upper abdominal pain with dyspepsia, in which 10% are organic [gastroesophageal reflux disease (GERD), *H. pylori*, pancreatitis, biliary disease and food intolerance] and (3) lower abdominal pain with altered bowel habits in which over 25% have an organic basis (constipation, IBD, lactose intolerance and gynecological). A careful history is important and helps avoid unnecessary investigations.

VOMITING

Vomiting, a complex protective reflex which helps rapid expulsion of any ingested toxins has three linked components: nausea, retching and emesis. It is a common symptom that occurs in many disease states, the cause of which is age-related. While congenital anomalies of the GI tract, necrotizing enterocolitis and inborn errors of metabolism are the most common causes in neonates, infections of the GI and hepatobiliary system, urinary tract and CNS as well as food allergy/intolerance predominate in infants and young children. In infants, it is important to distinguish reflux, which is the effortless passive bringing up of gastric contents, and involves no muscular activity. Gastroesophageal reflux is a physiological phenomenon that improves with age and most infants remain healthy. At any age, presence of any of the following features is very suggestive of an abdominal surgical cause: persistent vomiting with distended abdomen or constipation, bilious vomiting, absent bowel sounds, GI bleeding, point tenderness or diffuse guarding. Altered sensorium points to a CNS cause, electrolyte imbalance, liver/renal failure, diabetic ketoacidosis or poisoning.

In patients with recurrent episodes of vomiting, malrotation of gut, superior mesenteric artery syndrome, obstructive uropathy, chronic pancreatitis, diabetes, adrenal insufficiency, CNS lesions as well as inborn errors of metabolism should be considered. Cyclic vomiting syndrome is essentially a diagnosis of exclusion and is characterized by episodes of persistent vomiting without an identifiable cause, interspersed with complete symptom-free periods. The episodes may last up to 72 hours, cease spontaneously

Table 1 Features suggestive of an organic cause in chronic abdominal pain

• Localized or radiating pain	• Dysphagia
• Pain that wakes the child from sleep	• Persistent vomiting
• Gastrointestinal bleeding	• Malabsorption stool
• Growth deceleration or weight loss	• Unexplained fever
• Chronic GI disease in family	• Oral ulcer/perianal disease

and often result in dehydration and electrolyte disturbances. Some have a family history of migraine and respond to antimigraine prophylaxis. The routine use of antiemetics in infants and children without a clear understanding of the underlying disease should be discouraged.

CONSTIPATION

Constipation is defined as delay or difficulty in defecation that causes significant distress to the child. If it persists more than two weeks, it is referred to as chronic constipation. Acute constipation is easier to treat and usually caused by a change in feeds, addition of formula in infants, sudden change in diet or place of stay, low-fiber diet, anal fissure or drugs. Chronic constipation is generally diet- and habit-related and presents a challenge in management. Organic causes of chronic constipation are given in **Table 2**. While examination of the spine and the anal region is mandatory in all children with constipation, rectal examination should be avoided unless indicated. Associated urinary tract infection should be ruled out.

Encopresis is the involuntary passage of semiformed stool in a child's inner wear and is generally seen with functional constipation. Fecal incontinence is consistent fecal soiling and usually seen in association with an organic or anatomic lesion.

MALABSORPTION

Malabsorption is said to be present when there is a persistent disturbance of the digestive-absorptive process across the intestinal mucosa and is usually associated with growth faltering. The normal process of digestion involves three important steps: solubilization (fats by micelle formation), digestion (by specific digestive enzymes) and mucosal absorption (by diffusion or carrier-mediated transport). Maldigestion occurs when the amount of bile or pancreatic enzymes in the intestine is inadequate; for example, cholestasis and pancreatic insufficiency. Classical malabsorption occurs when there is a mucosal disease and defective absorption; for example, celiac disease, giardiasis and cow's milk protein allergy. The stools are pale, bulky with steatorrhea and foul smell in impaired fat digestion and explosive watery in defective carbohydrate digestion. In malabsorption, the child has flatulence and bloating; the stool contains both fat globules and fatty acid crystals, and there is associated anemia and hypoalbuminemia. In maldigestion, there is no bloating; the stool contains only fat globules and the child has no anemia or hypoalbuminemia.

GASTROINTESTINAL HEMORRHAGE

Upper GI bleeding defined as bleeding above the ligament of Treitz (esophagus, stomach and duodenum) presents with hematemesis. Only sudden massive bleeding causes bright red blood, since exposure to gastric juice quickly changes the color to coffee ground. While swallowed maternal blood and hemorrhagic disease are the most common cause in a well neonate, stress ulcer, coagulopathy and vascular anomaly should also be considered. In older children, esophagitis, gastric erosions and varices are relatively common, while prolapse gastropathy, Mallory-Weiss tear and vascular lesions are unusual causes. An upper GI endoscopy is the investigation of choice. A significant upper GI bleed can result in melena for three to five days.

Lower GI bleeding refers to bleeding beyond the ligament of Treitz and presents in two different ways:

1. Melena refers to black tarry stools, the black color being due to hematin, formed by the oxidation of haem by intestinal bacteria. Melena usually occurs when the bleeding is proximal to the ileocecal valve, but can occur in proximal colonic bleeds if the colonic transit time is slow.
2. Hematochezia is the presence of red blood in stool and is seen in colonic disease or in massive bleeds in the small intestine. Necrotizing enterocolitis, Hirschsprung enterocolitis and malrotation with volvulus are common causes in a neonate. While infectious enterocolitis, anal fissure and milk protein allergy are causes of mild bleeding in infants and young children, Meckel's diverticulum and intussusception can cause massive blood loss. In older children, infectious colitis, polyp, hemorrhoids, IBD and Henoch-Schönlein purpura require consideration. Hematochezia limited to spots or streaks on the outside of the stool suggest an anorectal source. However, if it is mixed through the stool, it suggests a local pathology above the rectum and if it is seen with mucous in a loose stool, it is characteristic of colitis. Maroon-colored blood suggests significant bleeding in the distal small bowel and currant jelly stools are indicative of ischemic bowel lesion as in intussusception or volvulus. In melena, the more proximal the bleed, the darker black will be the stool.

ABDOMINAL DISTENSION

Abdominal distension is either due to a lax abdominal wall, a mass in the abdomen or from accumulation of fluid or gas within or outside the intestine. Ascites in significant amount distends the abdomen both anteriorly and in the flanks. The ascitic fluid is usually a transudate with low protein concentration and commonly results from increased portal venous pressure and/or reduced oncotic pressure from hypoalbuminemia. Portal hypertension per se is unlikely to cause clinically apparent ascites, until serum albumin declines. Exudative ascitic fluid has a high protein concentration and indicates an inflammatory pathology. When fluid or gas distends the gut, a mechanical or functional obstruction of the gut should be suspected. While gas filled loops of intestine will yield a tympanitic resonance over the periumbilical area, gas in the peritoneal cavity will result in a tympanitic resonance even over the solid organs like the liver. Localized abdominal distension can occur from enlargement of liver, spleen and kidney, a tumor or a congenital or acquired cyst.

Table 2 Organic causes of chronic constipation

Surgical	*Medical*
Local anal pathology	Drugs
Hirschsprung disease	Hypothyroidism
Anterior anus	Mental retardation, hypotonia
Spina bifida	Tethered cord
Meningomyelocele	Hypokalemia, hypercalcemia

IN A NUTSHELL

1. Watery stools indicate small bowel pathology, commonly of viral etiology.
2. Dysentery is diarrhea with visible blood in the stool and implies a large bowel disease.
3. Periumbilical episodic abdominal pain is functional in most children.
4. In children with persistent vomiting, intestinal surgical causes and extraintestinal medical causes should be considered.
5. Chronic constipation in young infants has an organic basis, while in older children, it is functional.
6. Hematemesis indicates bleeding above the ligament of Treitz and requires upper GI endoscopy.
7. Hematochezia occurs in distal colonic disease while melena suggests bleeding proximal to the ileocecal valve.

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Chapter 35.3
Cleft Lip and Cleft Palate

VS Akbar Sherif, Sayed Mohammed Akbar

Cleft lip (CL) and cleft palate (CP) are the most frequently encountered congenital anomalies of the craniofacial region. In India, about 30,000 babies with a cleft are born every year. The main categories of cleft are CL, CP, or CL and CP. They can present as an isolated anomaly, as part of a syndrome or associated with other anomalies.

Children affected with cleft will have a range of esthetic and functional problems, which leads to poor feeding, repeated ear and chest infections, malnutrition and even death in some cases. This situation has improved in recent times after the NGO—Smile Train began participating in surgical repair programs all over India. In 2008, WHO included CL and CP in the noncommunicable disease category in the Global Burden of Disease Initiative.

EPIDEMIOLOGY

The global prevalence of orofacial cleft is 1 in 700 livebirths. Males are more affected than females. Isolated CP is seen more in females. For reasons not known, left side is more affected than right. 75% clefts are unilateral and 25% bilateral. The risk for the next sibling getting affected is as follows:

- *Normal parents with one cleft child* 4% risk for the next child to have CL/CP
- *Normal parents with two kids with CL/CP* 9% risk for the next sibling
- *One parent affected with CL/CP, no affected kid* 4% risk for the next child
- *One parent and one child with CL/CP* 17% risk for the next child.

Siblings of babies with severe forms of CL/CP carry a high-risk of acquiring clefts. By high resolution ultrasonography, orbicularis oris muscle discontinuity has been demonstrated in relatives of patients with nonsyndromic clefts.

ETIOLOGY

The exact etiology is not known but is believed to be multifactorial involving both genetic and environmental factors. Although facial clefts occur in a variety of genetic syndromes, identification of a single gene controlling lip and palate cleft has not yet been identified. About 15% of the clefts are syndromic and more than 170 syndromes have cleft as a feature. Certain specific chromosomal aberrations are consistently seen, like trisomy D syndrome with midline cleft, 22q11.2 in velocardiofacial syndrome (CATCH 22). Few environmental factors are known to increase the incidence of clefting. They include factors like drugs (phenytoin, retinoic acid), maternal smoking, alcohol, folate deficiency and rubella infection in early pregnancy.

EMBRYOPATHOGENESIS

Craniofacial region develops through active migration of cells and the rearrangement of facial prominences and pharyngeal arches. Hence, this area is more vulnerable to many congenital birth defects. The special cells which contribute for the majority of skeletal and connective tissue of the craniofacial region are the pluripotent neural crest cells. Upper lip develops by the 4th week of embryonic life as five prominences arranged around the future mouth, the stomodaeum. They are the single frontonasal process (FNP), paired maxillary and mandibular processes. The maxillary and mandibular processes originate from the 1st branchial arch. Fusion of maxillary and FNP completes the formation of upper lip **(Fig. 1)**. The lower lip and the lower jaw are formed by the fusion of the two mandibular processes in the midline. Fusion of maxillary and mandibular processes will complete the formation of cheek and angle of mouth **(Fig. 2)**.

The palate develops later around 7–8 weeks of intrauterine life. The two palatal process of maxilla meet with each other in the midline and also with the premaxilla anteriorly. Initially, the palatal processes are vertically oriented because of the presence of developing tongue in between it. As the oral cavity develops space, the tongue will fall back allowing the palatal process to move horizontally and fuse in the midline. Pathological states where the tongue is too big or the capacity of the oral cavity is small will result in a CP. Classical example is the Pierre-Robin syndrome **(Fig. 3)**.

Failure of fusion between maxillary and medial nasal process results in classical cleft lip **(Fig. 4)**. If the fusion defect is bilateral, it results in bilateral cleft lip **(Fig. 5)**. The lip and palate develop separately which means it is possible for a baby to be born with only CL, only CP or a combination of both.

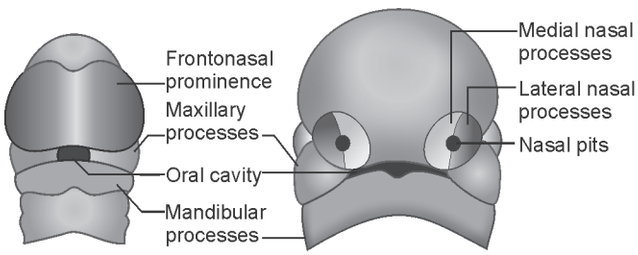

Figure 1 Formation of upper lip

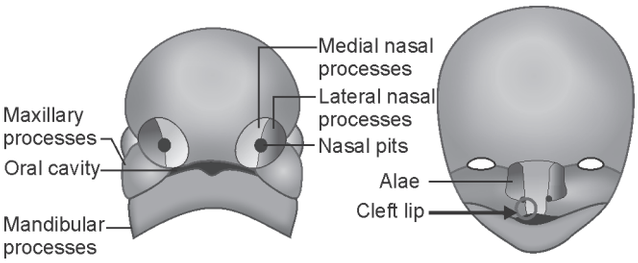

Figure 2 Formation of cheek and angle of mouth

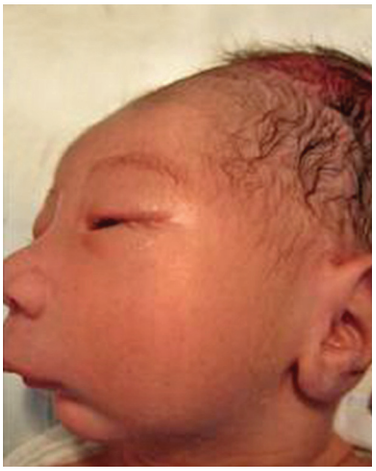

Figure 3 Pierre-Robin syndrome. Note small and receding chin

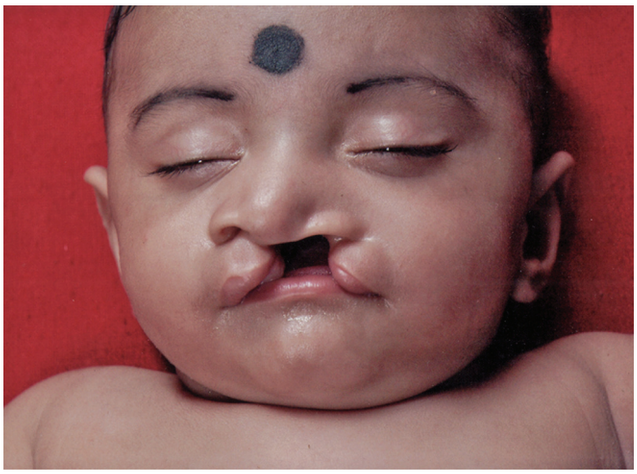

Figure 4 Unilateral cleft lip

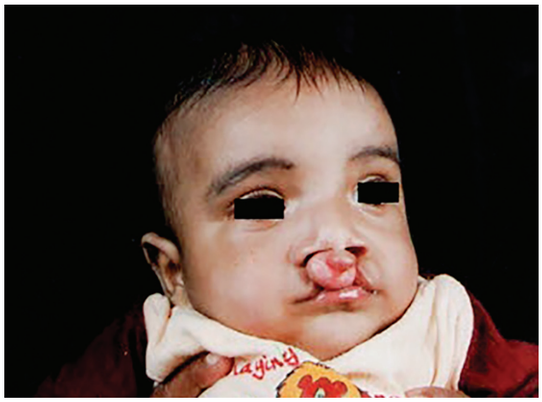

Figure 5 Bilateral cleft lip

CLASSIFICATION

Numerous methods have been developed for recording cleft deformities but none of them are accepted universally due to limitations, inadequate description of deformity and varying complexities. There are four basic structures involved in CL/CP. They are nose, lip, primary and secondary palate. These basic structures may be involved completely or incompletely in many combinations. The morphological classification given below helps the clinician to understand the severity, grading, communication and treatment planning.

- *Isolated CL/CP* Unilateral/bilateral: Complete/incomplete
- *Combined CL/CP* Unilateral/bilateral: Complete/incomplete
- Syndromic.

CLINICAL PROBLEMS

Besides the obvious facial deformity from an external cleft, immediate functional concerns are for airway patency and the ability to feed. Certain clefts like the Pierre-Robin sequence will have severe life-threatening respiratory distress which may require immediate attention.

Feeding Problems

Normal feeding requires the creation of suction by velopharyngeal closure and compression by the orbicularis oris muscle and tongue. Babies with CL/CP cannot create a negative pressure for suction or compression. So, they may be given expressed breastmilk using special feeding devices or breastfed using feeding obturators. The baby should be fed every 2 hours, in a calm and quite environment with the caregiver sitting in a comfortable chair. The teat should be kept on the uncleft side and gently squeezed after every 3–4 sucks. Feeding should not exceed to 20–30 minutes, since longer feeds are energy-consuming leading to poor weight gain. If bottle fed, the baby should be kept upright to prevent nasal regurgitation. Special teat or bottle which can be squeezed while the baby is sucking is now available. This will push the milk into baby's mouth and will compensate for suction.

Nasal Regurgitation and Aspiration

In babies with CL/CP sucking and swallowing mechanisms are defective, which leads to repeated aspiration pneumonia. Aggressive treatment may be needed to control the pneumonia. Feeding the baby with head-up position will decrease the problem until they learn adaptive techniques to overcome the handicap.

Middle Ear Infection

A majority of CP/CP patients develop middle ear infections, which if recurrent leads to conductive hearing loss. This predisposition may persist even after CP repair. The tensor palatini muscle is attached to the cartilaginous part of eustachian tube. Normally when this muscle contracts as in the act of swallowing or yawning, it will open up the eustachian tube equalizing the pressure in the middle ear and allowing drainage of any secretion. In babies with cleft palate, the action of this muscle is ineffective leading to fluid accumulation and infection. Also the eustachian tube is directly exposed in these babies, with regurgitation of milk feeds leading to edema and infection. Adenoid hypertrophy secondary to repeated infections also contributes to eustachian tube obstruction.

Speech Problems

The suction and compression of the breast during the normal feeding produces a coordination of these muscles, which is essential for normal speech development. This co-ordination is missing in children with cleft palate. The other factors which contribute to the poor speech development are velopharyngeal incompetence, palatal fistula, poor hearing, dental malocclusion and psychological factors. Hypernasality of speech is very common.

Psychosocial Problems

The facial appearance of babies with cleft interferes with early mother-child bonding. Patients with CL/CP show very low self-esteem and have difficulty in social interactions. Family environment is very important in rehabilitation of these children.

Dental Problems

Children with cleft may have special problems related to missing, malformed, malpositioned teeth. The first orthodontic evaluation is done before dental eruption and helps assess the facial growth, especially the growth of the jaws.

DIAGNOSIS

Craniofacial clefts can be diagnosed by antenatal ultrasonography, as early as 18–20 weeks of gestation. Antenatal diagnosis gives the family time for prenatal education, prenatal psychological preparation and counseling. After birth, minor forms of clefts like the forme fruste cleft lip or the submucosal cleft palate may produce diagnostic confusion. Submucosal CP presents with nasal regurgitation, otitis media and poor speech. Examination will show a bifid uvula, midline of palate showing a pearly white line due to mucosal union alone. This will require treatment like any other CP.

MANAGEMENT

Considering the anatomical complexity of cleft, its effect on multiple orofacial functions, and its effect on orofacial growth and development, a multidisciplinary team approach is mandatory for optimal results. Prenatal diagnosis and parental interaction with the cleft team will lay the foundation for the subsequent surgical correction. After birth, attention should be given to ensuring the patency of airway, proper feeding advice and ruling out associated anomalies.

The goals of surgical treatment include repair of birth defect without affecting the growth of face, achieving normal speech, language and hearing, ensuring functional dental occlusion and dental health, optimizing psychological and developmental outcome, and facilitating ethically sound, family-centered sensitive care in a cost-effective manner. The currently recommended treatment schedule is as follows:

- *Birth* Initial assessment, presurgical evaluation and orthodontics
- *3–6 months* Primary lip repair
- *9–12 months* Palate repair (before speech develops)
- *2 years* Speech assessment
- *3–5 years* Lip revisions
- *8–9 years* Initial intervention orthodontics
- *10 years* Alveolar bone grafting
- *16 years* Nasal revision
- *17–20 years* Orthognathic surgery.

Surgical Repair

The many types of surgical repairs available emphasize the fact that each cleft is different. Every patient should be explained the number of surgeries they need including secondary corrections and alveolar bone grafting. CL is traditionally repaired before palate repair between 3 months and 6 months. The rule of 10 (10 g hemoglobin, 10 pounds weight and 10 weeks of age) is useful as an initial criteria for patient selection for surgery. Preoperative orthodontic care involves repositioning of the displaced dentoalveolar segments with various intraoral and extraoral orthodontic appliances, and this makes the surgical correction easier. The nasoalveolar molding device (NAM) is most commonly used.

The ideal technique for palatoplasty is the one which gives perfect speech without affecting maxillofacial growth and hearing. *The surgical steps are*: Closure of the defect, correction of abnormal position of muscle tensor palatini, reconstruction of muscle sling, push back of soft palate to improve velopharyngeal valve mechanism during speech, minimum raw area to be left either in the oral or nasal surface and tension-free suturing. Grafting of the tooth bearing portion of the maxilla completes the primary repair sequence of the original cleft deformities. This procedure is usually done around 10 years of age.

Despite optimal primary repair, most patients require secondary revision of lip, nose or both. Common secondary corrections include scar revision, vermilion realignment, philtral lengthening, nasal base rotation or nasal tip cartilage correction. Most of this scar revisions are done between 2 years and 4 years to allow scar maturation to occur before the child enters the school. Septorhinoplasty reconstructions are done once they pass the growth phase. Hypernasality of speech with velopharyngeal incompetence is a common sequel of palate repair. Corrective pharyngoplasty is done after confirmation by nasal endoscopy and video fluoroscopy. Some patients may also require orthognathic surgery at around 20 years to correct the midfacial hypoplasia of maxilla, malocclusion and cross bite.

IN A NUTSHELL

1. The global prevalence of orofacial cleft is 1 in 700 livebirths. Males are more affected. Left side is more affected; only 25% clefts are bilateral.
2. The exact etiology is not known but is believed to be multifactorial involving both genetic and environmental factors.
3. There are four basic structures involved in cleft lip and cleft palate. They are nose, lip, primary and secondary palate.
4. Besides the obvious facial deformity from an external cleft, immediate functional concerns are for airway patency and the ability to feed.
5. The goals of surgical treatment include repair of birth defect without affecting the growth of face, achieving normal speech, language and hearing, ensuring functional dental occlusion and dental health, optimizing psychological and developmental outcome, and facilitating ethically sound, family-centered sensitive care in a cost-effective manner.

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Chapter 35.4
Dental Caries

Madhu S

Dental caries is considered to be the single most common chronic childhood disease. It is found to be more common than asthma in children. The disease is neither self-limiting nor amenable to

treatment with antibiotics. Proper advice given at the right time often helps the child to remain caries free or at least limit the severity of the lesion. The pediatrician, often the first medical professional to see the child is in a unique position to influence the child and the parent. It is extremely important for the pediatrician to know the details regarding the causes and preventive strategies available for this very common childhood disease. The disease often regarded and neglected as dental disease has the potential to cause severe bacteremia leading to worsening of the existing systemic conditions.

EPIDEMIOLOGY

Dental caries is a disease that occurs in proportion to the state of civilization. The main factors implicated in increased dental caries are the production of sugar commercially and increased use of refined food. The incidence of caries is directly proportional to sugar intake. Studies in 20th century showed a high incidence of caries in USA and European countries, whereas it was low in developing countries in Africa. In developed countries, the incidence of caries is in the reversal phase at present due to the preventive strategies taken. However, it is actually increasing in the developing countries due to the increased use of refined food and poor oral hygiene. The incidence of caries is low in children whose parents have low incidence of caries. This could be due to lesser vertical transmission of cariogenic microorganisms or due to the resistant structure of enamel, and quantity and quality of salivary factors acquired from the parents. The role of dietary factors is well-known. A definite correlation is now established between soft drink usage and dental caries.

ETIOPATHOGENESIS

Currently, the term dental caries is used to describe the signs and symptoms of a localized chemical dissolution of the tooth surface caused by metabolic events taking place in the biofilm (dental plaque) covering the affected area. This occurs in an interplay between the tooth, saliva, diet, microorganism and time. The basic hydroxyapatite crystal is constantly modified during and after development of enamel. Two ions constantly involved in the replacement of lattice crystals are carbonate and fluoride. With carbonate ion inclusion, the crystal becomes weak and with fluoride ion, it becomes strong. Trace elements also decide the demineralization-remineralization potential **(Table 1)**. Higher the salivary clearance rate, better the caries protective effect. Increased dental caries is seen in conditions involving hyposalivation or xerostomia **(Table 2)**. Salivary enzymes, immunoglobulins and buffers contribute to its antibacterial property **(Table 3)**.

Role of Sucrose

Probably among all the etiological factors, diet is the main factor which can be controlled by the child and parent. Sucrose is considered to be the arch rival of tooth. In the presence of cariogenic microorganism, mutans are produced from sucrose, which help to form adherent plaque on tooth which help *Streptococcus mutans* to form the initial colony on tooth surface. The habit of snacking in between meals by children has a direct link to dental caries. This is because more time is available for the bacteria to act. Sticky chocolates and bakery items eaten frequently by the child also lead to increased food retention and caries. The main organisms associated with dental caries are *Streptococcus mutans* group, Lactobacilli species, filamentous bacteria, *Veillonella* species and *Streptococcus* other than mutans group **(Fig. 1)**.

Table 1 Trace elements in enamel and its effect on dental caries

Trace elements	*Effect*
Flourine, phosphorus	Cariostatic
Molybdenum, vanadium, copper, strontium, lithium, gold	Mildly cariostatic
Selenium, magnesium, cadminum, platinum, lead, silicon	Caries potentiating

Table 2 Medical conditions with xerostomia and medications increasing susceptibility to dental caries

Disease	*Use of medicine*
Sjögrens syndrome	Antihistaminics
Salivary gland malignancies	Narcotics
Diabetes mellitus	Antidepressants
Thyroid disorders	Antihypertensives

Table 3 Salivary antibacterial property

Enzymes	*Immunoglobulins*	*Buffers*
Lysozyme	SIgA	Bicarbonates
Lactoferrin	IgG	Saliavary proteins
Lactoperoxidase	IgM	Phosphates

TYPES OF DENTAL CARIES

Pit and fissure caries seen on the deep pits and fissures of occlusal surface of molars and premolars **(Fig. 2A)**, and smooth surface caries seen on the proximal surfaces **(Fig. 2B)** are the two main types of caries. In children, nursing caries warrants special attention. It is a unique pattern of tooth destruction seen exclusively in primary dentition. Different studies show prevalence as high as 45% in India. It is due to prolonged improper night feeding. Children fall asleep while bottle feeding, and there is prolonged pooling of milk in the oral cavity. The lower anterior teeth are somewhat protected due to the physical presence and cleansing action of tongue **(Fig. 3)**. Proper instruction to the parents can completely prevent or limit this condition **(Box 1)**. Rampant caries, another type of early childhood caries, can affect both primary as well as permanent dentition. The usual contributory factors are a reduced salivary flow due to any disease state of salivary glands, children treated with tranquilizers, Sjögren syndrome, and genetic factors. Night feeding with milk or sugar-containing juices, nutritional deficiency, improper diet and emotional disturbances can all be contributory to this condition **(Fig. 4)**.

BOX 1 Instructions to parents to prevent nursing caries

- Avoid feeding while sleeping after 1 year
- Oral cavity should be wiped clean with a cloth after each feed
- If child has the habit of sleeping with milk, discourage it
- Reduce the amount of sugar in the milk or juices gradually
- Encourage the child to drink warm water after each feed.

CLINICAL FEATURES

The common complaint with which the child is brought to a pediatric dentist is pain or swelling. Early sign detected is a white spot lesion. Here, the enamel surface is noncavitated but will become carious if demineralization continues. The child may have no pain in such lesions. Sensitivity and pain are features of

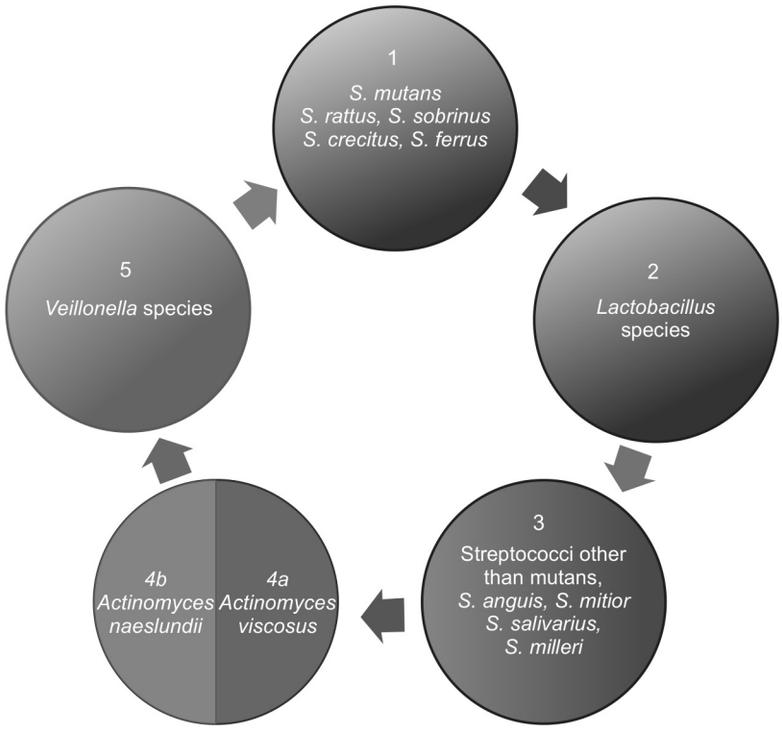
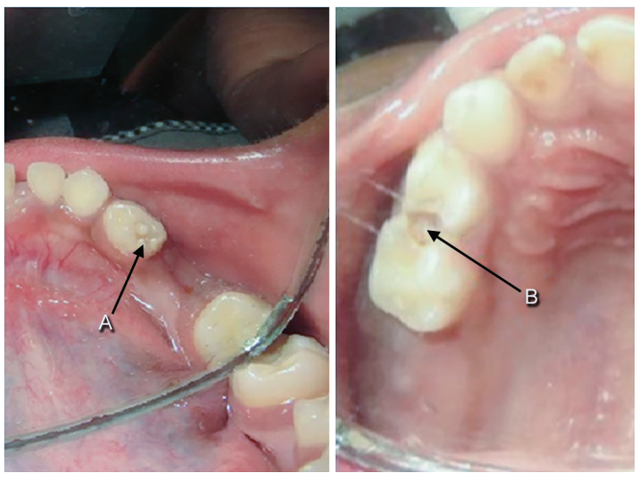


Figure 1 Microbiology of dental caries



Figures 2A and B (A) Pit and fissure caries; (B) Smooth surface caries

Figure 3 Nursing caries

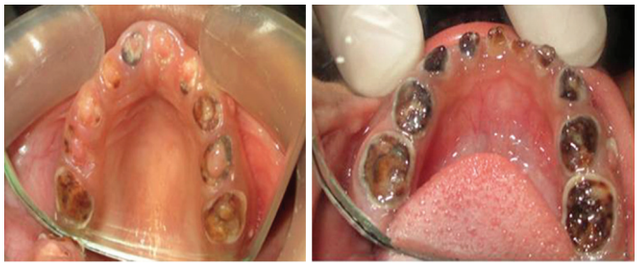


Figure 4 Rampant caries

the cavitated initial lesions. Deeper lesions show more pain and features of reversible pulpal damage. When infection progresses to affect the pulp, severe spontaneous and night pain will be present which suggests that pulp is irreversibly damaged. Infections crossing the root and spreading into bone can result in cellulitis and space infections **(Fig. 5)**.

APPROACH TO DIAGNOSIS

A major paradigm shift took place in the field of diagnosis of caries in 21st century. Earlier only cavitated lesions diagnosed with visual tactile examination were counted as decayed, whereas

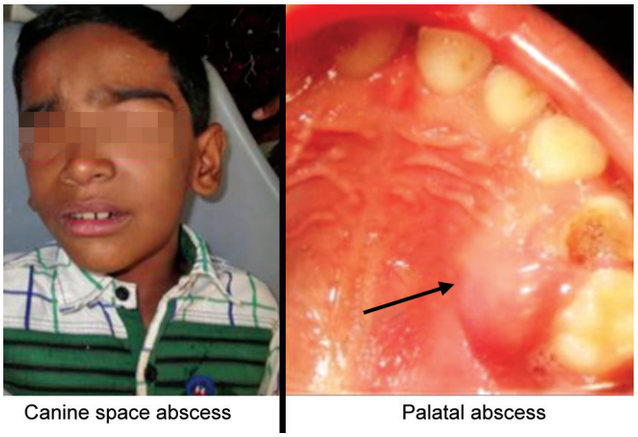


Figure 5 Space infection due to dental caries

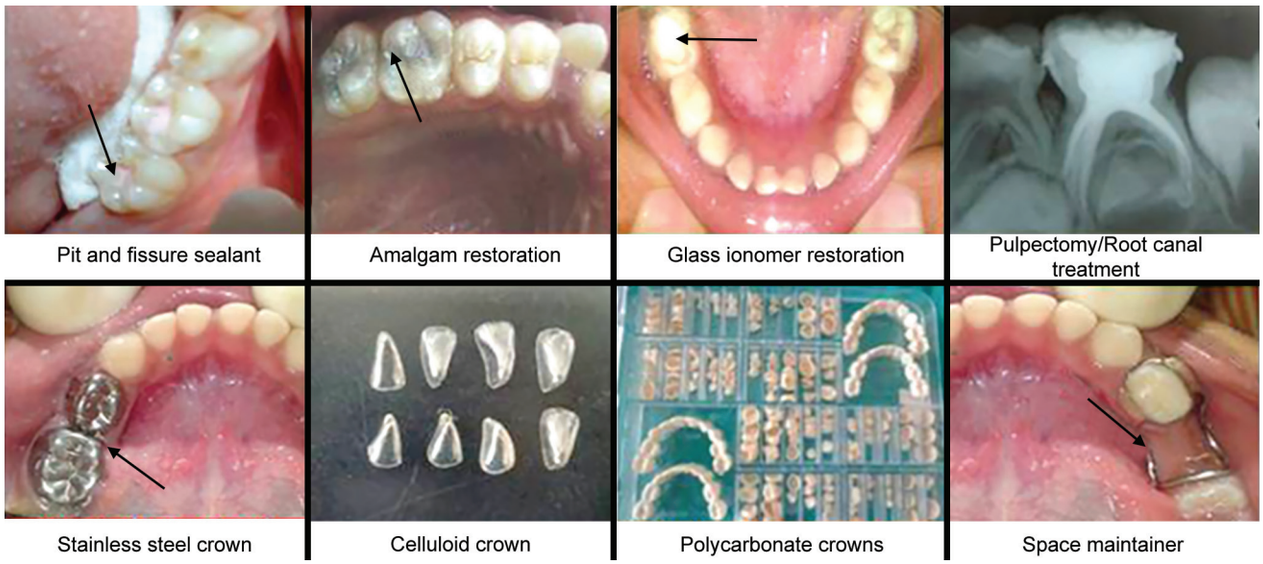


Figure 6 Operative treatment modalities for dental caries

at present, even minimally demineralized lesions like white spot lesions detected with advanced diagnostic methods are counted as decayed.

MANAGEMENT

Early diagnosis of caries has resulted in two modes of treatment: nonoperative and operative. Nonoperative management is done in cases of early white spot and noncavitated lesions. This is done basically to arrest the progress of the lesion and to shift the environmental equilibrium toward remineralization so that more invasive operative treatment is avoided. The methods involved are maintenance of proper oral hygiene, use of antimicrobials, fluorides, remineralization agents and dietary control. Probably, the most important preventive method in early childhood caries (nursing or rampant caries) is dietary restriction. Instructions regarding feeding can be given to the mother **(Box 1)**. Children's medicinal preparations for diseases like asthma, epilepsy, or fever are in syrup form with high sugar content. Vitamin supplements they regularly take at bedtime can be contributory to dental caries. Parents should be informed about the effect the medicines can cause to the child's teeth and sufficiently motivated for the maintenance of oral hygiene after taking such medicines. Operative management involves use of different restorative materials. A lesion causing pulpal damage may have to be treated with endodontic treatment followed with a crown. Grossly decayed teeth may have to be extracted and a space maintainer provided to prevent space loss **(Fig. 6)**.

CONCLUSION

A young child may often have a set of completely damaged teeth causing chronic severe pain so that he is unable to consume a proper diet resulting in malnutrition and even developmental delay due to lack of essential nutrients. Pediatricians, who are usually the first medical specialists to see such a child, are in a privileged position to give timely advice regarding feeding pattern and problems of night feeding (other than breastfeeding) which can go a long way in preventing debilitating childhood caries and associated problems.

IN A NUTSHELL

1. Dental caries is one of the most common chronic childhood diseases.
2. Dental caries, once established, always leaves a scar and can progress further leading to complications.
3. Many systemic diseases including cardiovascular diseases can get worse due to bacteremia from untreated lesions.
4. Night feeding (other than breastmilk) and its sequelae should be explained to the parents.
5. Pediatricians are often the first medical professionals to see a child, and in a position to give valuable suggestions to parents to prevent this dental disease.

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Chapter 35.5
Recurrent Parotitis

Prakash Agarwal

Recurrent parotitis is defined as recurrent inflammation of one or both parotid glands. It is usually associated with swelling, pain, fever and redness. It is also known as juvenile recurrent parotitis or recurrent sialectatic parotitis. Recurrent parotitis is differentiated from suppurative parotitis by the inability to express pus from the parotid duct in recurrent parotitis.

EPIDEMIOLOGY

Recurrent parotitis has a male preponderance, and the peak age of onset is between 4 years and 6 years. Although rare, it is the most common inflammatory salivary gland disease in childhood after mumps. It presents with episodes lasting 4–7 days, approximately every 3–4 months. The disease is self-limiting usually resolves by adolescence, but a few cases may continue into adulthood. Mainly, the symptoms are seen to resolve after puberty.

ETIOLOGY

In vast majority of cases, its etiology is not known. Recurrent infection, allergy, congenital defects and genetic factors may play a role. Recurrent parotitis may be associated with Sjögren's disease and immune deficiency. As the age of onset increases, the diagnosis of Sjögren's disease is most likely. Certain viral infection like Epstein-Barr virus, parainfluenza virus, adenovirus, enterovirus, human herpes virus 6, enterovirus and parvovirus are implicated in recurrent parotitis. HIV-infected children are more prone to have persistent parotitis as part of the lymphoid interstitial pneumonitis complex. Recurrent parotitis may be associated with hypogammaglobulinemia, isolated IgG3 deficiency, and IgA deficiency. *Streptococcus viridans*, a mouth commensal, has also been implicated.

PATHOGENESIS

Its pathogenesis is still unknown. Decreased salivary flow may lead to stasis and cause damage to the ductules. The ductules may be abnormal from birth leading to inflammation and infection. Unilateral disease may be supported by pre-existing abnormality before the onset of clinical symptoms. Many asymptomatic glands had similar though often milder lesions. Most commonly mumps and other viral infections has been implicated but not proven to cause recurrent parotitis. According to Maynard, recurrent parotitis may be the end result of a sequence of events:

Initially, there is a low-grade inflammation of the gland and duct epithelium, due to low salivary flow rate due to dehydration and debility. This results in distortion and stricturing of the distal ducts, and metaplasia of the duct epithelium. The metaplasia results in excessive mucus secretion.

The histological picture includes lymphocytic infiltration around the intralobular ducts leading to damage of the duct wall reticulum, allowing extravasation of secretions into the gland parenchyma, and thus aggravating the inflammation.

CLINICAL FEATURES

It is characterized by intermittent swelling **(Fig. 1)** and redness of one or both parotid glands associated with pain, which can be very distressing. Overall condition of the patient may be good. The child may have difficulty in mastication with coexisting fever. There may be signs of dehydration in severe parotitis. The saliva expressed from the Stensen's duct may be grainy and whitish compared to bacterial parotitis where it will be frank pus.

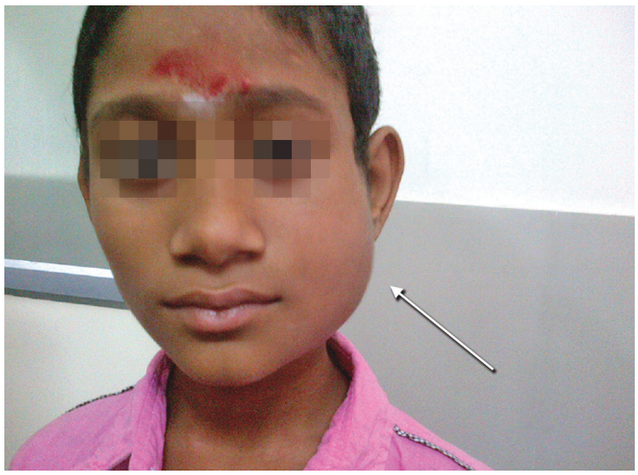

Figure 1 Parotid swelling

DIAGNOSIS

Suppurative bacterial parotitis, mumps, benign lymphoepithelial cysts and stone in the duct should be excluded. It is distinguished from suppurative bacterial parotitis by the absence of pus from the parotid duct.

Approach to Diagnosis

The diagnosis of recurrent parotitis is made on a clinical basis, and can often be confirmed by ultrasound, showing the classical features of sialectasis. Serum amylase may be elevated in acute parotitis. Sialogram may suggest multiple hypoechoic areas that correspond to the punctate pools. Histology may show periductal lymphocytic infiltration. Mutations of *SPINK-1* gene may predispose to juvenile parotitis. CT and MRI help to assess parotid tissue, along with MR sialography. Ultrasound scan has the advantage of being less invasive and can exclude stones, abscess and mass lesions. A normal ultrasound or sialogram does not exclude the condition. Sialendoscopy may be diagnostic and therapeutic. On scopy, the duct opening may be avascular and whitish compared to a normal opening, thereby confirming the diagnosis.

MANAGEMENT

Treatment may range from conservative measures to radiotherapy and total parotidectomy as in the past. As it is a relatively benign condition, conservative symptomatic treatment is recommended. Majority of the cases are viral in origin, and hence the role of antibiotics is doubtful. Nonsteroidal anti-inflammatory drugs (NSAIDs) are given to control pain and rarely fever. Sialagogic agents, warmth and massage and duct probing have been recommended. Ductal irrigation and dilatation may be possible by sialendoscopy. It gives a correct picture of the duct opening which is whitish and avascular compared to a normal duct. Intraductal irrigation with intraglandular hydrocortisone may give some relief. Surgical options are total parotidectomy in resistant cases, which is curative, but carries with it the inherent risks of nerve damage. Stensen's duct ligation with tympanic neurectomy may give some relief.

IN A NUTSHELL

1. Recurrent parotitis is presents with swelling, pain, fever and redness of parotid glands lasting 4–7 days, approximately every 3–4 months. It is also known as juvenile recurrent parotitis.
2. Recurrent parotitis is differentiated from suppurative parotitis by the inability to express pus from the parotid duct in recurrent parotitis.
3. Recurrent parotitis has a male preponderance, and the peak age of onset is between 4 years and 6 years.
4. Recurrent infection, allergy, congenital defects and genetic factors may play a role. Recurrent parotitis may be associated with Sjögren's disease and immune deficiency.
5. The disease is self-limiting, usually resolves by adolescence, but a few cases may continue into adulthood.

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Chapter 35.6
Vomiting

Sumathi Bavanandam

Vomiting is a common problem in children and can occur in diseases involving many organ systems. Causes of vomiting vary from respiratory tract infection to more serious conditions like inborn errors of metabolism, central nervous tumors apart from gastrointestinal (GI) disease. A good history and thorough physical examination are important in identifying the underlying etiology and tailoring the investigations. Any child with prolonged vomiting (> 12 hours in a neonate, > 24 hours in children younger than two years of age, or > 48 hours in older children) should undergo appropriate investigations.

DEFINITIONS

- *Vomiting:* Is an active process and involves the forceful expulsion of gastric contents through the mouth associated with contraction of the abdominal and chest wall musculature.
- *Regurgitation:* Is a passive process in which food from the stomach is brought back into the mouth without abdominal and diaphragmatic muscular activity.
- *Rumination:* This is a chewing and swallowing process of regurgitated food that has come back into the mouth which occurs within minutes of eating (or even during eating), through a voluntary increase in abdominal pressure.
- *Recurrent vomiting:* At least three episodes of vomiting in a three-month period which may be chronic or cyclical.
- *Acute vomiting:* Abrupt onset of short-term vomiting.
- *Cyclical vomiting syndrome (CVS):* Characterized by recurrent, discrete, self-limited episodes of vomiting and is defined by symptom-based criteria with negative laboratory, radiographic and endoscopic testing.
- *Psychogenic vomiting:* There is no underlying organic cause. It is often chronic and is due to cortical or psychological input. Stressful events precipitate an attack and many children require hospitalization.

PATHOPHYSIOLOGY

The act of vomiting is a complex, coordinated autonomic response triggered by peripheral and central stimuli and involves neural, hormonal, and muscular responses generated by the reticular formation of the medulla with its several scattered groups of neurons. The vomiting center is located in the lateral medullary reticular formation of the brainstem and is the final pathway. The center has predominantly muscarinic (M1), histamine 1 (H1), neurokinin 1, and serotonin receptors and receives input from four distinct centers, namely chemoreceptor trigger zone, vagal afferent system, vestibular system and high cortical centers. Area postrema situated in medulla contains predominant D2 dopamine receptors and is unprotected by blood-brain barrier. As a result of this sampling of peripheral blood and cerebrospinal fluid, various metabolic and hormonal disorders can cause vomiting. Luminal distension or irritation of GI mucosa from various causes result in activation of vagal afferent system (mediated by serotonin receptors) and cause vomiting. In motion sickness and labyrinthine disorders, the vestibular system mediated via M1- and H1-receptors is involved in pathogenesis of vomiting.

The phases of vomiting are pre-ejection phase, a retching phase, and ejection phase. There is gastric relaxation and retrograde peristalsis in pre-ejection phase. During the phase of retching, there is rhythmic contraction of respiratory, abdominal wall, intercostal, and diaphragm muscles against a closed glottis. In the final phase of ejection, there is intense contraction of the abdominal muscles along with relaxation of the pharyngoesophageal sphincter. These sequential events are not seen in projectile vomiting as in gastric outlet obstruction.

DIFFERENTIAL DIAGNOSIS

Vomiting is a symptom with a wide differential diagnosis, ranging from lesions of the GI tract to systemic illnesses, metabolic, endocrine, central nervous disorders to rare inborn errors of metabolism. Acute onset of vomiting with severe abdominal pain may suggest a surgical origin and is usually associated with localized or generalized abdominal tenderness, rigidity, absent or hyperactive bowel sounds. Causes of vomiting based on age are illustrated in **Table 1**. **Table 2** shows the *red flag signs* of vomiting.

EVALUATION

A detailed history, including diet, drug intake, family history, surgical history is important in the initial evaluation to identify a cause. History should include the following:

- Onset and type, whether acute, chronic or episodic
- Presence of nausea, headache, visual disturbances, photophobia, suggestive of migraine
- Previous history of surgery indicating adhesive obstruction
- Projectile vomiting without nausea suggestive of central nervous system (CNS) pathology
- Bilious vomiting to indicate a possible surgical cause (though it can occur in nonsurgical conditions)
- Presence of blood in the vomitus due to mucosal ulcerations, erosions or variceal bleed
- Feculent vomitus to indicate intestinal/colonic obstruction or gastrocolic fistula
- Presence of abdominal pain, food-related pain indicating peptic ulcer disease

Table 1 Common causes of vomiting depending on age

Neonate (< 1 month)	*Infant (> 1–12 months)*	*Toddler (> 1–4 years)*	*Child (4–12 years)*	*Teenager (13–19 years)*
GER and GERD Feeding intolerance, pyloric stenosis, meconium ileus, malrotation with midgut volvulus, necrotizing enterocolitis, congenital atresia/webs, metabolic disorders, Hirschsprung disease, protein intolerance infection (UTI/meningitis)	GER or GERD Acute otitis media, protein intolerance, UTI, acute gastroenteritis, malrotation, volvulus, meningitis, CNS tumors, intussusception, metabolic disorders	Urinary tract infection, pharyngitis, GERD, celiac disease, intracranial lesion, malrotation, poisoning	Gastroenteritis, pharyngitis, postinfectious appendicitis, celiac disease, pancreatitis, IBD, poisoning/toxic ingestion Eosinophilic esophagitis	Gastroenteritis, peptic ulcer disease, cyclic vomiting, eosinophilic esophagitis, pregnancy, poisoning/toxic ingestion, migraine, diabetic ketoacidosis, drug abuse, appendicitis, gallstone, pancreatitis, bulimia, IBD

Abbreviations: GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; UTI, urinary tract infection; IBD, inflammatory bowel disease; CNS, central nervous system.

Table 2 *Red flag signs* with probable causes of vomiting

S. No.	*Vomiting characteristics/associated features*	*Probable cause*
1.	Failure to thrive or weight loss	GERD, obstructive GI diseases, metabolic causes, urinary causes
2.	Projectile vomiting, presence of abnormal neurological signs	CNS tumors, meningitis
3.	*Localized abdominal pain:* Right upper quadrant pain—Localized epigastric pain	Gallbladder disease esophagitis, peptic ulcer
4.	Hematemesis/melena	Esophagitis, esophageal ulcer, peptic ulcer, portal hypertension
5.	Severe dehydration with dyselectrolytemia	Serious underlying conditions, such as obstruction, CAH
6.	Bilious vomiting	*Surgical causes* Intestinal obstruction
7.	Short stature, anemia	Inflammatory bowel disease, hypothyroidism, or celiac disease
8.	Nocturnal vomiting, recurrent wheeze	Gastroesophageal reflux disease or postnasal drainage
9.	Fever, toxemia in young	Sepsis, meningitis
10.	Episodic vomiting with symptom-free interval	Cyclical vomiting syndrome

Abbreviations: GERD, gastroesophageal reflux disease; CAH, congenital adrenal hyperplasia; GI, gastrointestinal; CNS, central nervous system.

- Stale food vomitus in gastric outlet obstruction
- Undigested food often seen in achalasia cardia, Zenker's diverticulum.

Physical Examination

Physical examination should focus on the following: Assessment of nutritional status, growth and development, assessment of hydration status, presence of anemia, icterus, abnormal odor, and abnormal neurological signs. Abdominal examination should include abdominal tenderness, absent or exaggerated bowel sounds, scars, hernia orifices. Presence of visible gastric peristalsis indicates gastric outlet obstruction. Complications of persistent vomiting include dehydration, electrolyte disturbances, acid-base imbalance and nutritional deficiency.

Investigations

These are indicated for: (1) bilious vomiting, abdominal tenderness and/or severe abdominal pain; (2) attacks precipitated by intercurrent illness, fasting, and/or high protein meal; (3) abnormalities on neurological examination including severe alteration of mental status, abnormal eye movements, papilledema, motor asymmetry, and/or gait abnormality (ataxia); and (4) progressively worsening episodes or conversion to a continuous or chronic pattern.

Tests include complete hemogram, liver function tests, renal functional tests, blood sugar, urine ketones to rule out diabetic ketosis, urine routine and culture, lactate, electrolytes, ammonia, ketones and arterial blood gas analysis for inborn errors of metabolism. A plain abdominal X-ray is useful to rule out intestinal obstruction **(Fig. 1)**; ultrasonography (USG) abdomen helps in diagnosis of hypertrophic pyloric stenosis, malrotation, intussusception, and obstructive uropathy. Barium contrast studies may be useful in gastroesophageal reflux disease (GERD), congenital esophageal stenosis **(Fig. 2)**, achalasia cardia **(Fig. 3)**, infantile hypertrophic pyloric stenosis (IHPS), duodenal web/atresia and intestinal narrowing. Upper GI endoscopy is useful in diagnosis of mucosal disease of upper GI tract **(Fig. 4)**, *H. pylori* gastritis, eosinophilic esophagitis, and obstructive causes like strictures. Esophageal manometry helps in achalasia cardia and motility disorders of esophagus. CT brain/MRI is useful for identifying CNS tumors.

TREATMENT

Treatment depends on the underlying cause. A course of proton pump inhibitor (PPI) or histamine 2 receptor antagonist (H2RA) will benefit children with GERD. Avoidance of cow milk, thickening of feeds, and positioning will be of benefit. Infants and young children outgrow the problem by 1–2 years. Treatment options for eosinophilic esophagitis include acid suppression, corticosteroids (topical and systemic), and dietary modifications like elimination diet, like milk, soy, egg, peanut, wheat and fish or complete elemental diet. Stricture of esophagus secondary to eosinophilic esophagitis needs cautious endoscopic dilatation. Swallowed fluticasone (44–220 mg per swallowed puff) given as two puffs two times a day has been effective. Endoscopic stricture dilatation may be needed for peptic, corrosive and anastomotic strictures. Surgical management is indicated in IHPS/malrotation/intestinal atresia/web and intestinal obstruction. The recommended indications

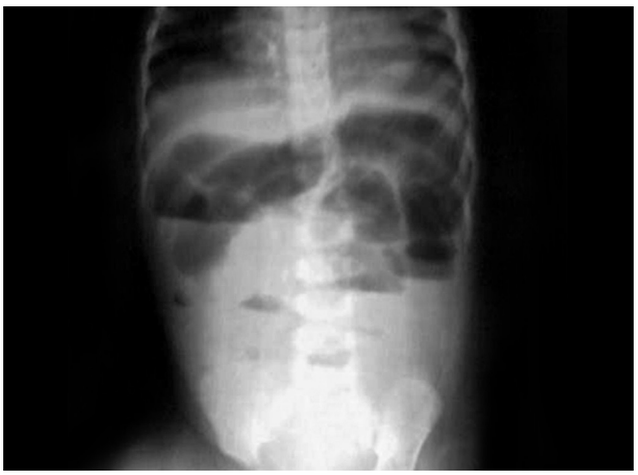

Figure 1 Plain abdominal X-ray with multiple air fluid level in intestinal obstruction

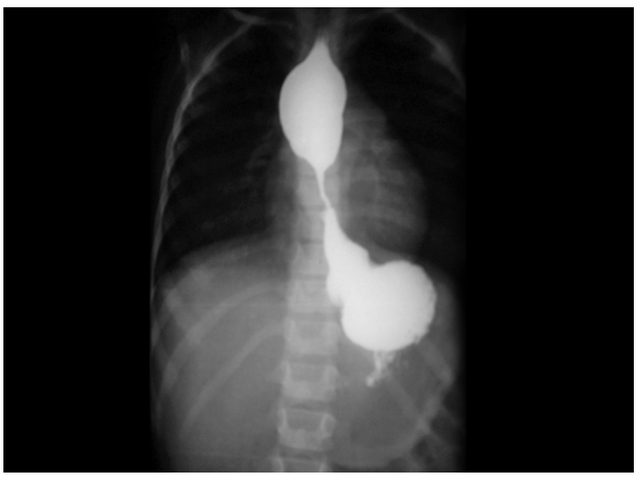

Figure 2 Barium swallow showing long segment narrowing—congenital esophageal stenosis

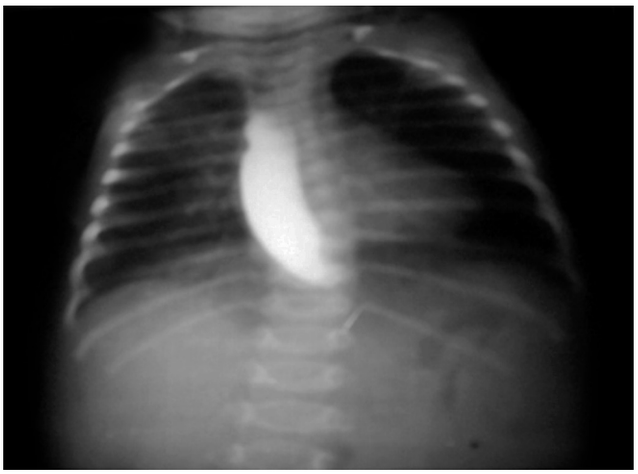

Figure 3 Barium swallow in an infant showing dilated esophagus with smooth distal tapering suggestive of achalasia cardia

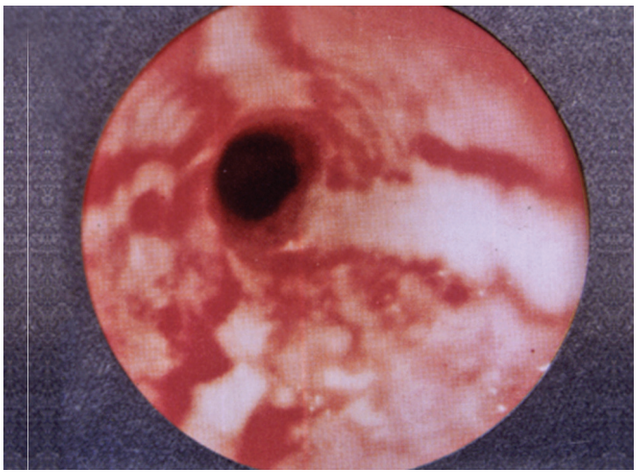

Figure 4 Upper gastrointestinal endoscopy showing severe esophagitis

of antiemetics are chemotherapy/radiation-induced vomiting, postoperative vomiting, cyclical vomiting and vomiting due to GI motility disorders.

CYCLICAL VOMITING SYNDROME

The exact etiology and pathogenesis of cyclical vomiting syndrome (CVS) still remain unclear. Girls are affected more than boys. Migraine variant, mitochondrial fatty acid oxidation disorders, GI motility disorder, disorder of the brain-gut axis, autonomic dysfunction, abdominal epilepsy, ion channel dysfunction, corticotropin-releasing factor in response to stress, altered psychodynamics, mitochondrial energy depletion due to mitochondrial mutation precipitated by stress/excitement are some of the proposed mechanisms that can trigger episodes of vomiting in children with CVS. The bilious vomiting is intense associated with disabling nausea and dehydration requiring hospitalization. Accompanying symptoms including pallor, listlessness, anorexia, nausea, retching, abdominal pain, headache and photophobia may make it difficult to distinguish episodes of CVS from other causes of acute abdomen and altered consciousness. Migraine, motion sickness, epilepsy, anxiety and depression are some of other observed associations of CVS. There are no specific laboratory markers to diagnose CVS. Since vomiting is often bilious and associated with pain, investigations need to be done to exclude organic causes.

Criteria for Diagnosis

- At least five attacks in any interval, or a minimum of three attacks during a 6-month period
- Episodic attacks of intense nausea and vomiting lasting 1 hour–10 days, occurring at least 1 week apart
- Stereotypical pattern and symptoms in the individual patient
- Vomiting during attacks occurs at least 4 times/hour for at least 1 hour
- Return to baseline health between episodes and not attributed to another disorder.

Treatment

During an acute attack, taking care of hydration and electrolytes is essential to prevent dehydration as well as in decreasing the duration of the acute illness. Ondansetron provides symptomatic relief. Sedation is usually beneficial during the episode. Avoidance

of triggers such as fasting, intake of caffeine, chocolates are essential to avoid an attack. If the attack is more than one per month, prophylactic drug therapy is advisable. Propranolol has been recommended as first-line prophylactic drug with good response in more than 85% of patients. Tricyclic antidepressants are effective in 68% of children with CVS. Phenobarbital, topiramate, and sumatriptan are other drugs that can be tried.

ABDOMINAL MIGRAINE

Abdominal migraine is defined as attacks of abdominal pain lasting for 1–72 hours, periumbilical or poorly localized, dull aching pain of varying intensity, usually accompanied with at least two of the following symptoms, namely anorexia, nausea, vomiting, and pallor. Thirty to forty percent of children can have associated headache. Family history of migraine can be documented in a subset of children. Vascular constriction causing ischemia of GI tract or CNS areas innervating the gut may be the cause. Clinical history, physical examination and investigations are essentially normal. Prophylactic use of propranolol can be useful.

IN A NUTSHELL

1. Vomiting is a symptom of a variety of disorders ranging from self-limited diseases to life-threatening diseases, and the treatment depends on the etiology apart from symptomatic therapy.
2. Good history and thorough physical examination are crucial to early identification of serious conditions.
3. Copious bilious emesis at any age is a sign of intestinal obstruction until proven otherwise.
4. Cyclical vomiting is not an uncommon cause of chronic recurrent episodic vomiting in older children and adolescents.
5. Presence of *red flag* signs and symptoms requires thorough evaluation and urgent attention.

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Chapter 35.7
Infantile Hypertrophic Pyloric Stenosis

Ketan Parikh

It is characterized by persistent nonbilious vomiting in a neonate and may lead to significant dehydration and metabolic disturbances if not diagnosed early enough. It was earlier believed that the condition is relatively rare in India; however, a relatively higher incidence is being reported in recent times. Most cases are sporadic but few cases may run in families. Boys (mostly first-born) are five times more commonly affected than girls.

PATHOLOGY

Musculature of the pyloric antrum is significantly hypertrophied, thus the pylorus is thickened and the pyloric canal is lengthened and narrowed. The hypertrophied pyloric muscle becomes olive-shaped and becomes hard to feel when contracted. This hypertrophied pylorus is clinically palpable as a pyloric tumor. The stomach proximal to the obstruction is dilated and is also secondarily hypertrophied.

Gastric mucosa in infancy produces a potent lipase which hydrolyses milk to free fatty acids. The hypertrophied pyloric muscle leads to a partial obstruction to the outflow from the pylorus. Thus there is stagnation of milk in the stomach. Rancidity of the curdled milk gradually causes progressive mucosal edema and precipitates complete obstruction of the narrowed and hypertrophied pyloric canal **(Fig. 1)** and thus symptoms are often delayed till 3–6 weeks.

CLINICAL FEATURES

Usually the child presents between 3 weeks and 6 weeks but the child may present anytime from 1 week to 4 months. Progressive, forcible, projectile and nonbilious vomiting is the most important presenting symptom. The vomitus may contain altered blood. The baby is usually very hungry after vomiting. There is associated weight loss or failure to gain weight. Constipation occurs due to poor intake. Jaundice is occasionally seen due to nutritional deficiencies. Facies is characteristic—alert, anxious and hungry look. These patients have a slow and shallow breathing due to the metabolic alkalosis secondary to persistent vomiting. Examination is characterized by visible gastric peristalsis on inspection (left to right) **(Fig. 2)**. Examination must be done with the child comfortably placed in the mother's lap and in good light. Palpation of the "tumor" (palpable in 70% cases) is the diagnostic sign. It should be sought for with the left hand, sitting on the patients' left palpating below the right costal margin, below the liver border.

DIAGNOSIS

Infantile hypertrophic pyloric stenosis (IHPS) need to be differentiated from other causes of nonbilious vomiting in young infants: gastroenteritis; septicemia, meningitis, intracranial hemorrhage; gastroesophageal reflux, and achalasia cardia. USG shows the thickened pylorus and may also show reverse peristalsis on the stomach. Contrast studies with Barium (only if necessary) reveal a large stomach, delayed emptying, string sign, and gastritis

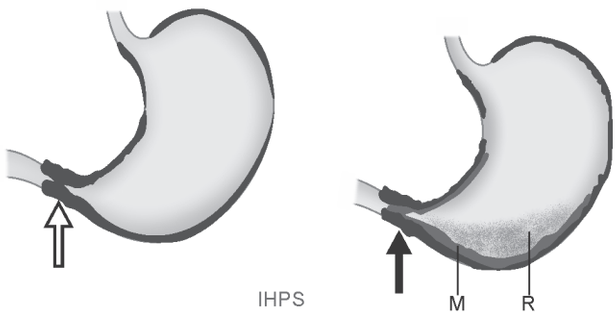

Figure 1 Pyloric muscle thickening (hollow arrow) causing partial obstruction and residue (R), causing mucosal edema (M) and resultant complete obstruction (block arrow)

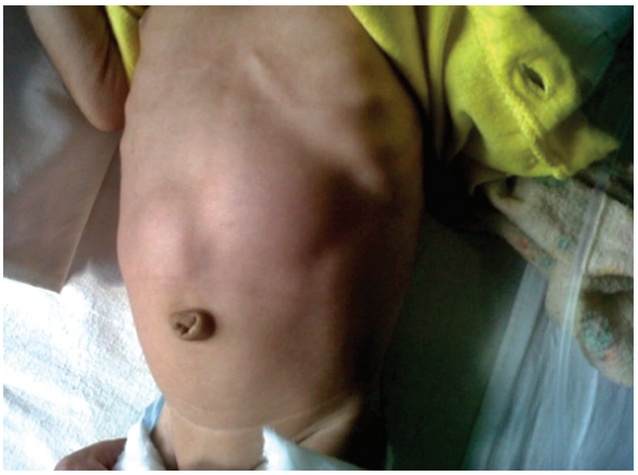

Figure 2 Visible peristalsis (L → R) seen in a quiet child after feeding

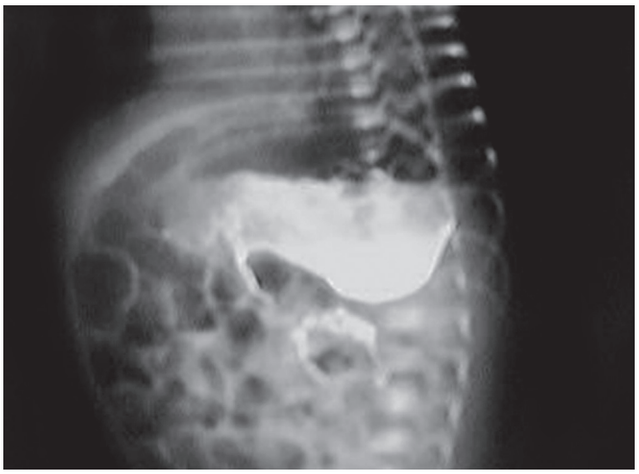

Figure 3 String sign on upper gastrointestinal (GI) series

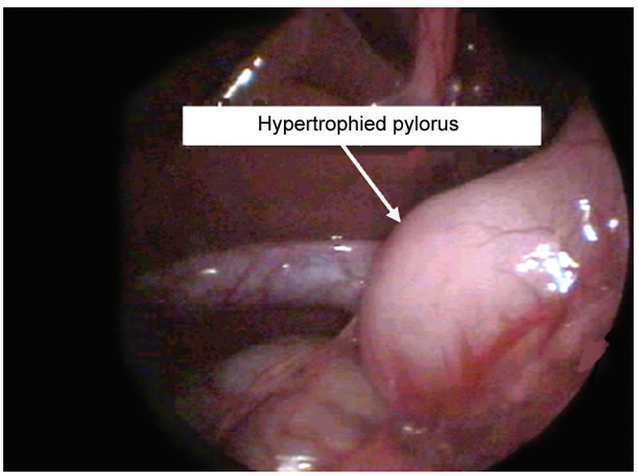

Figure 4 Laparoscopic view of hypertrophied pylorus, maybe palpable like an olive

(Fig. 3). Serum electrolytes and blood gas reveal hypokalemic hypochloremic alkalosis.

TREATMENT

Surgery is the treatment of choice. Nonsurgical treatment with prokinetics should be tried only in case of strong contraindication to surgery as the treatment has erratic results, is too prolonged and may lead to aspiration and malnutrition.

Preoperative correction of metabolic disturbances is an integral part of the surgical treatment and usually is achieved within 24 hours. Aggressive resuscitation can produce rapid fluid and electrolyte shifts, possibly leading to seizures. Correct dehydration and electrolyte imbalance. Aspiration of the gastric contents may help in reducing the gastric mucosal edema. If necessary a gastric lavage with normal saline would help. Oral rehydration with 0.33% or 0.5% dextrose saline with 20–40 mEq/L of potassium may help once the mucosal edema regresses within a few hours and this avoids the possible complications of rapid IV rehydration. Alternatively IV rehydration with 0.33% saline and appropriate potassium correction may be resorted to. Fredet-Ramstedt's pyloromyotomy is the desired procedure; which can be achieved by open or laparoscopic **(Fig. 4)** approach. The results are excellent with a low incidence of complications.

IN A NUTSHELL

1. IHPS should be suspected in any infant with persistent non-bilious vomiting.
2. Presence of visible gastric peristalsis (left to right) should increase this suspicion.
3. Ultrasonography is now the investigation of choice in the diagnosis of IHPS.
4. Serum electrolytes and blood gas reveal hypokalemic hypochloremic alkalosis.
5. Fredet-Ramstedt's pyloromyotomy is the desired treatment of choice.

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Chapter 35.8
Gastroesophageal Reflux

Elsie Jazmin Foglio, Dinesh S Pashankar

Gastroesophageal reflux (GER) is one of the most common disorders of the esophagus in the pediatric age group. It can be defined as spontaneous and effortless passage of gastric contents from the stomach into the esophagus. GER may be physiological as seen in infancy or pathological. Gastroesophageal reflux disease (GERD) usually implies the presence of significant clinical symptoms due to pathological reflux and complications.

EPIDEMIOLOGY

Gastroesophageal reflux is common in infancy worldwide and usually presents as vomiting or regurgitation. In a population-based study involving 602 infants from New Delhi, the prevalence of regurgitation was noted to be 55% in infants between 1 month and 6 months of age and the prevalence dropped to 15% in infants between 7 months and 12 months. The prevalence of GER decreases with age in children, but increases again in adolescence. In a study from USA, symptoms of reflux in the form of heartburn and regurgitation were reported in about 2% of 3–9-year-old children and about 5–8% of 10–17-year-old children.

There are certain groups of children who are at high-risk for severe reflux and GERD. These include children with neurological impairment such as cerebral palsy and children who have had surgery for esophageal atresia. Obesity, presence of hiatal hernia, and chronic respiratory disorders are also predisposing factors for severe GER in children.

PATHOPHYSIOLOGY

Transient relaxation of the lower esophageal sphincter (TRLES) is defined as abrupt, prolonged (> 10 sec) and complete relaxation of the lower esophageal sphincter (LES). It occurs independent of swallowing and is the most frequent mechanism causing GER in children and adults. This inappropriate relaxation of LES tone allows gastric contents to enter the esophagus, thus exposing the esophageal mucosa to the acidic gastric contents.

Recurrent acid reflux can injure the distal esophageal mucosa resulting in esophagitis. Chronic esophagitis may lead to complications such as stricture or Barrett's esophagus, which may subsequently result in adenocarcinoma of esophagus. Fortunately, this complication is very rare in children. GER can cause respiratory complications either due to aspiration or reflex bronchospasm. Reflux of acid into the larynx may cause irritation leading to laryngitis or apnea.

CLINICAL FEATURES

Gastroesophageal reflux in infancy is physiological and presents as regurgitation or spitting. Weight gain is excellent and there is no evidence of complications such as esophagitis or respiratory symptoms. These infants are aptly called "happy spitters". The physiological reflux of infancy generally begins in the first few weeks of life, peaks at about 6 months and usually resolves by 8–12 months of age.

As opposed to physiologic reflux of infancy, GER in older children can be significant and lead to GERD. **Table 1** shows symptoms and the spectrum of complications of GER. Esophagitis is one of the most common complications of GER in children and usually presents with epigastric pain or hematemesis. However, irritability with feeds or feeding refusal may be the only manifestation of esophagitis in younger children or neurologically impaired patients. Reflux esophagitis is being diagnosed more frequently in Indian children with the use of endoscopy. In a study from Lucknow, reflux esophagitis was diagnosed in 26 of 33 children who presented with symptoms suggestive of reflux. In the same study, other complications of reflux such as esophageal stricture, Barrett's esophagus and respiratory symptoms were also observed in Indian children.

There are a number of studies reporting an association between reflux and upper and lower respiratory symptoms in children. However, a clear etiologic role of reflux causing dental, ear, nose, throat and respiratory complications is not confirmed. The clinical association of bronchial asthma and GERD is well known although convincing causal relationship has not been established. *Waterbrash*, the sudden appearance of sour salty fluid in the mouth secondary to hypersecretion of the salivary glands in response to the presence of acid in the esophagus, may be seen in older children with GER. Some infants with severe GERD may present with failure to thrive secondary to frequent copious vomiting, and refusal of food due to the pain of esophagitis. Apnea in infants due to laryngospasm caused by nasopharyngeal microaspiration, and sudden infant death syndrome (SIDS) may be manifestations of GERD.

Sandifer syndrome is a rare complication of GERD. It is an unusual movement disorder characterized by spasmodic torsional dystonia with arching of the back and opisthotonic posturing. Hence, it may be mistaken for seizure disorder.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of chronic vomiting is wide and is discussed elsewhere in this book. In young infants with severe vomiting, pyloric stenosis and malrotation should be considered and ruled out. In older children, acid peptic diseases such as gastritis or ulcer can present with vomiting and epigastric pain. Eosinophilic esophagitis, a condition more common in the Western World, can present with vomiting, epigastric pain and dysphagia. Neurological causes should be considered in children presenting with chronic vomiting and headaches.

APPROACH TO DIAGNOSIS

The diagnosis of GER can be made in many children based on history and physical examination. Particularly, a detailed history is all that is necessary to diagnose physiological reflux of infancy. In a growing infant who is otherwise well, daily vomiting of small volume is suggestive of physiologic reflux and no further investigations are necessary. The diagnostic criteria of infant regurgitation according to Rome III classification include regurgitation of two or more times per day for 3 or more weeks in otherwise healthy infants (3 weeks to 12 months of age) without retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing. Infant questionnaire developed by Orenstein et al. has 11 questions which can be used to differentiate GER from GERD with high sensitivity and specificity (74% and 94%) in USA. However, when applied to Indian infants, this questionnaire had low sensitivity and specificity (43% and 79%) and has low diagnostic utility.

In older children, heartburn and regurgitation are the usual symptoms of GER. A careful history should be obtained to assess for GER and complications as shown in **Table 1**. It is important to determine the presence of predisposing risk factors, as mentioned

Table 1 Symptoms and complications of GER

Reflux	***Lower respiratory tract****
Vomiting	Bronchospasm, wheeze
Regurgitation	Chronic cough
Heartburn	Recurrent pneumonia
Esophagitis	***Upper respiratory tract ****
Feeding refusal, irritability	Laryngitis, hoarseness
Heartburn, epigastric pain	Obstructive apnea
Hematemesis	Dental erosions
Anemia	Sinusitis
Esophageal stricture	***Neurological***
Dysphagia	Sandifer's syndrome

* Possible association.

Table 2 Diagnostic studies for GER and complications

Tests	*Diagnostic utility*
Upper gastrointestinal series	• To assess anatomical abnormalities • To rule out malrotation, hiatal hernia, stricture
24-hour esophageal pH study	• To detect acid reflux in the esophagus • To correlate acid reflux and extraesophageal manifestations
Endoscopy with histology	• To diagnose esophagitis, Barrett's esophagus • To rule out gastritis, peptic ulcer, eosinophilic esophagitis • To dilate esophageal stricture
Impedance study	• To detect acid and nonacid reflux in the esophagus • To correlate acid and nonacid reflux and extraesophageal manifestations

above, as these children are likely to have severe reflux disease and require investigations and long-term therapy.

There are various diagnostic studies to assess reflux and complications and are shown in **Table 2**. There is no single test to assess GER in children and tests should be planned depending on the clinical presentation of the child. Upper gastrointestinal barium study is not a good test to diagnose reflux because of poor sensitivity and specificity, but it is useful to rule out anatomical abnormalities. Twenty-four hour esophageal pH study is useful to assess acid reflux in the esophagus. The test is performed by the transnasal placement of a standardized microelectrode into the lower esophagus, for continuous measurement and recording of intraesophageal pH for 24 hours. An episode of acid reflux is usually defined as an esophageal pH less than 4. Computerized analysis calculates the number, duration of reflux episodes and reflux index. The reflux index (percentage of time esophageal pH is less than 4) of more than 5% and 10% are suggestive of GER in children and infants respectively. The pH study is particularly useful to look for acid reflux in children with extraesophageal symptoms and to assess adequacy of acid suppression. Multichannel Intraluminal Impedance (MII) is a procedure that measures change in electrical resistance (impedance) between multiple electrodes located on an esophageal catheter. It is done with pH monitoring and can detect acid and nonacid reflux. MII can be useful for correlation of (acid and nonacid) reflux and symptoms such as apnea, cough and respiratory symptoms. However, the test is expensive and is not readily available.

Endoscopy with histology can determine the presence and severity of esophagitis, strictures and Barrett's esophagus. It is also useful to rule out other conditions such as eosinophilic esophagitis and acid peptic disease including gastritis or peptic ulcers which may present with similar symptoms as GERD. Therefore, endoscopy has become the test of choice for children with reflux symptoms in many centers in USA. At endoscopy, erosions or ulcers of distal esophagus indicate severe esophagitis. Histological criteria of reflux esophagitis include presence of eosinophils, basal zone hyperplasia and increased papillary length.

There are other tests to assess GER and complications, but are not used routinely. Gastric scintigraphy is a nuclear medicine scan used to assess gastric emptying and reflux of nonacidic gastric contents. A lack of standardized technique and absence of age specific normative data limit the value of this test. Bronchoscopy may show lipid-laden macrophages suggestive of pulmonary aspiration secondary to reflux.

In adults, an empiric trial of proton pump inhibitor (PPI) is routinely used. Although not well studied in children, empiric trial of PPI for up to 4 weeks is justified in older children with classical symptoms of GERD such as heartburn or regurgitation. However, a long-term PPI therapy without a specific diagnosis is not recommended.

MANAGEMENT

For physiologic reflux of infancy, reassurance to parents is the most important part of the management as reflux improves with time and without any intervention. Smaller and more frequent feeds are beneficial in infants with GER. Frequent burping during feeds as well as keeping infants in an upright position after feeding is recommended. Thickening of formula feeds with rice cereal can decrease the number of episodes of vomiting in infants. Acid suppression medications can be used, but are not recommended. Therapeutic strategies for the management of GER in older children are shown in **Table 3**.

General Measures

Elevation of the head of the bed is recommended for older children with nocturnal reflux symptoms. Children should be advised to avoid acidic fruit juices, caffeinated beverages, chocolate and fatty foods as these tend to make reflux symptoms worse. Exposure to smoking can also worsen reflux symptoms and therefore should be avoided. Weight loss is beneficial in obese children with reflux.

Acid Suppression Therapy

It is commonly used as first line therapy for significant reflux. Antacids directly buffer gastric acidic contents and reduce heartburn and reflux symptoms. They can be used on as needed basis, but regular long-term use is not recommended. Acid suppressants such as histamine 2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) act to decrease esophageal acid exposure by reducing the quantity of gastric acid secretion. H_2RAs block histamine receptors on the parietal cell while PPIs block the Na–K-ATPase enzyme (proton pump), which is the final common pathway of acid secretion. While both H_2RAs and PPIs are effective in the healing of esophagitis and symptomatic relief of reflux symptoms, PPIs are superior to H_2RAs. PPIs should be given 30 minutes before breakfast to get maximum efficacy. The duration of therapy should be 3–6 months and an attempt should be made to withdraw these medications after that time.

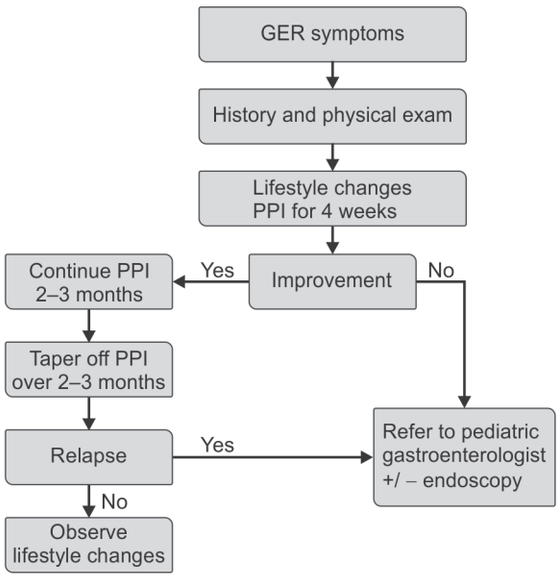
Flow chart 1 shows algorithm for treating children with GER symptoms who have no risk factors for chronic GERD. High-risk

Table 3 Therapeutic strategies for GER

Lifestyle changes	• Positioning • Avoidance of smoking exposure • Weight reduction in obese children • Dietary changes
Antacids	• Aluminum hydroxide/magnesium carbonate 10–20 mL as needed • Aluminum hydroxide/magnesium hydroxide 10–20 mL as needed
H_2RA	• Famotidine 1 mg/kg/day divided bid; Max 40 mg/day • Ranitidine 6-8 mg/kg/day divided bid; Max 300 mg/day
PPI	• Omeprazole 1–3 mg/kg/day, Max 40 mg daily • Lansoprazole 1–3 mg/kg/day, Max 60 mg daily • Pantoprazole 20–40 mg daily • Esomeprazole 10–40 mg daily • Rabeprazole 10–40 mg daily
Surgery	• Nissen fundoplication • Laparoscopic fundoplication

Abbreviations: H_2RAs, histamine 2 receptor antagonists; PPI, proton pump inhibitor.

Flow chart 1 Approach to GER in older children



Abbreviations: GER, gastroesophageal reflux; PPI, proton pump inhibitor.

group of children often require long-term therapy for months to years for ongoing severe GERD. In children with GERD and asthma, chronic cough can predispose to reflux and reflux can cause reflex bronchospasm. Therefore, it is prudent to treat both conditions simultaneously for symptomatic relief. Adverse effects related to H_2RA and PPIs are generally mild and rare. They include headache, diarrhea and constipation. Tachyphylaxis can develop with H_2RAs and therefore they should not be used for long-term therapy. PPIs are generally well tolerated over long-term (up to 11 years). Some patients taking them for prolonged periods may develop mild to moderate hypergastrinemia. Even though gastric carcinoids have been shown in some animal studies, they have not been shown in humans. The secretion of intrinsic factor of Castle is also inhibited along with that of acid. However, megaloblastic anemia due to vitamin B_{12}-deficiency is rare, which reflects the large stores of the vitamin in the body.

Prokinetic Agents

Metoclopramide (dopamine-2 and 5-HT_3 antagonist), domperidone (D2 receptor antagonist), cisapride, mosapride and renzapride (selective 5HT4 agonists) and erythromycin (motilin receptor agonist) are commonly used in adults with GERD to improve esophageal motility and gastric emptying. However, they cannot decrease TRLES which plays a key role in the pathogenesis of GER. Cisapride may cause QT prolongation, arrhythmia and Torsades de pointes, and has been withdrawn from many countries. Hence, prokinetic agents are not recommended currently in children due to their doubtful efficacy and risk of adverse effects.

Other Drugs

The selective GABA agonist *baclofen*, which is used in children with spasticity, inhibits TRLES, and is hence useful in GERD. It also reduces postprandial acid and nonacid reflux and its associated symptoms. However, it may cause fatigue, confusion and insomnia and there are only very few studies in children. Drugs like salbutamol, theophylline, diazepam and barbiturates, which can precipitate or aggravate reflux should be avoided in children with GER.

Surgical Therapy

It is indicated for intractable reflux despite medical management and life-threatening aspiration. The most common procedure is fundoplication in which a part of stomach is wrapped around the lower esophagus to prevent reflux. Nissen fundoplication is the most common operation performed. Fundoplication has a high success rate in the otherwise normal children with reflux. However, in a high-risk group of children with severe GERD, fundoplication is associated with a significant rate of failure and complications. In this group of children PPIs have been shown to be effective, even after failure of fundoplication. Recently laparoscopic fundoplication has been gaining popularity due to shorter postoperative stay. Overall, with the availability of proton pump inhibitors, necessity of fundoplication has decreased considerably.

PROGNOSIS

Physiologic reflux of infancy usually does not need any major therapeutic intervention and has excellent prognosis. Children with GERD respond well to dietary advice and PPI therapy. Children in high-risk group can develop severe GERD and complications and often require combination of long-term PPI therapy and surgery.

IN A NUTSHELL

1. Gastroesophageal reflux is common in infancy and disappears by 1 year of age in most cases.
2. Gastroesophageal reflux of infancy is diagnosed by history and does not require any tests or major therapeutic intervention.
3. Children with neurologic impairment, chronic respiratory disorders, obesity and history of repaired esophageal atresia are at high-risk for developing severe GERD.
4. Gastroesophageal reflux in older children presents as vomiting, regurgitation and heartburn.
5. Gastroesophageal reflux can lead to esophagitis and may be associated with asthma and other respiratory complications.
6. Esophageal pH study and impedance study can be helpful to assess correlation of GER and extraesophageal symptoms.
7. Endoscopy with histology is the best test to diagnose esophagitis.
8. Acid suppression with H_2RA and PPI are effective in healing esophagitis and providing symptomatic relief.
9. Children with high-risk for GERD require a long-term PPI therapy.
10. Surgery for GERD is reserved for severe aspiration or failure of medical therapy.

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Chapter 35.9
Umbilical Hernia

Prakash Agarwal

Umbilical hernia is herniation of the intestine through the umbilical ring **(Fig. 1)**. Umbilical hernia is commonly seen in infants, which may herald an underlying problem or in most of the cases may be just a routine finding and settles down on its own.

EPIDEMIOLOGY

Umbilical hernia in children has an equal frequency in boys and girls. A slightly higher incidence is reported in Africa and African-American infants. The incidence is around 75% in low birthweight infants, which will spontaneously close over time. The incidence is higher in patients with Down syndrome, Trisomy 18, Trisomy 13, mucopolysaccharidosis, and congenital hypothyroidism. It may also be a part of Beckwith-Wiedemann syndrome.

ETIOLOGY

Defect in the underlying fascia below the umbilical ring leads to an umbilical hernia.

PATHOGENESIS

During development of the fetus the umbilical cord passes into the abdomen through the umbilical ring. After birth, the opening in the abdominal muscles closes as the baby matures. Sometimes, these muscles do not meet and grow together completely, and there is still a small opening present. A loop of intestine can move into the opening between abdominal muscles and cause a hernia.

An umbilical hernia in children is surrounded by a dense layer of fascia through which a peritoneal sac attached to the overlying skin protrudes; this is known as direct umbilical hernia. Usually the umbilical ring continues to close over time and the fascia of the umbilical defect strengthens, which accounts for the spontaneous resolution of this defect in most children. An indirect umbilical hernia is one in which the peritoneal contents herniate superior to the umbilical ring. The hernia follows the umbilical canal along the umbilical vein, the linea alba anteriorly, and a thin layer of preperitoneal fascia in a posterior direction. This form of hernia is also known as proboscoid hernia **(Fig. 2)**. Hernia of the umbilical cord is one in which there is a defect in the peritoneum and the fascia leading to intestine herniating into the substance of the umbilical cord **(Fig. 3)**.

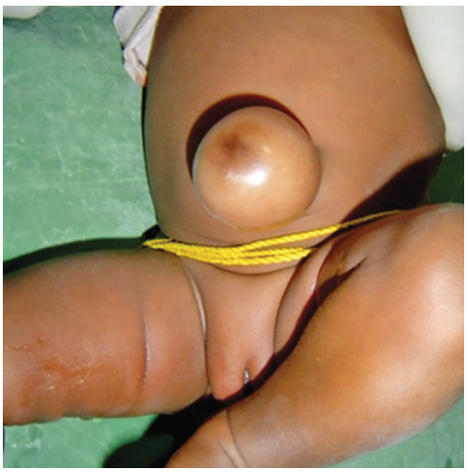

Figure 1 Typical presentation of an umbilical hernia

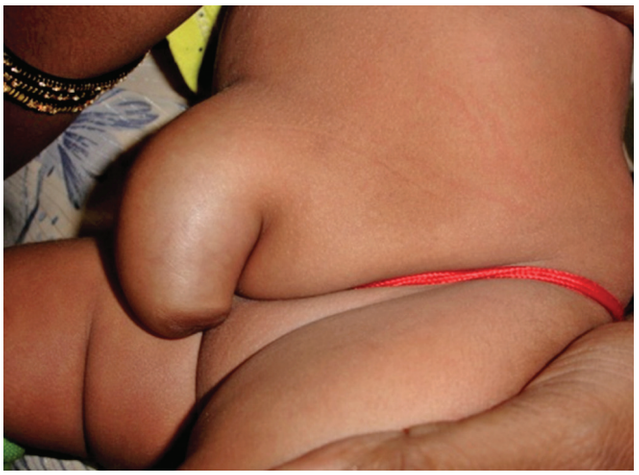

Figure 2 Proboscoid umbilical hernia

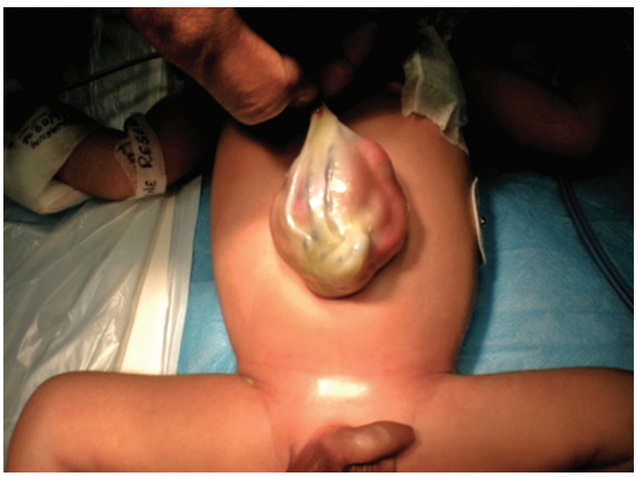

Figure 3 Hernia of the umbilical cord

CLINICAL FEATURES

Umbilical hernias do not usually cause pain. They are present at birth but may become more noticeable when the child is bearing down—crying, coughing, or straining to have a bowel movement. The bulge may seem to disappear when the child is quiet or resting. Umbilical hernia with a small ring diameter (< 1.0 cm) is more likely to close spontaneously and earlier than those with a ring diameter of more than 1.5 cm. Incarceration of intestine or omentum, strangulation, perforation, evisceration and pain are rare events in the natural history in the umbilical hernia of children.

MANAGEMENT

Umbilical hernia is a clinical diagnosis and usually does not require any investigations to confirm the diagnosis. Routine blood investigations are required before proceeding for surgery in order to rule out anemia and bleeding profile. A thyroid profile may be done to rule out congenital hypothyroidism. An ultrasound may be done to rule out intra-abdominal tumors or ascites.

Indications for surgery We usually observe umbilical hernia and manage conservatively till 2 years of age. Rare event of incarceration requiring reduction, strangulation, perforation, evisceration are absolute indications for surgery. Infant with giant proboscoid hernia in whom the umbilical ring does not narrow may be considered for repair before 2 years. Typical umbilical hernia should be observed until the age of 2 years. Sometimes the most difficult task is to convince the family that observation alone will be successful in most cases and that the hernia may resolve spontaneously by 2 years of age. If the child has an obstructed umbilical hernia it is reduced by milking the air out of the incarcerated loop of intestine and applying firm pressure on the mass. One episode of obstruction should prompt the surgeon to operate immediately. If reduction is not possible then emergency surgery is required. If an infant is having both inguinal and umbilical hernia, the umbilical hernia should be left alone as it may close spontaneously.

Surgery for umbilical hernia Standard procedure for umbilical hernia repair involves multilayer closure of the peritoneum and fascial layer. A small curved incision (resembling a smile) will be made under your child's belly button. Absorbable and nonabsorbable sutures are used in the repairs. The redundant skin may be left in place to resolve over a period of time. Usually repair of umbilical hernia is performed as a day care surgery after infiltrating the wound with local anesthesia. Complications of umbilical hernia repair may be infection of the repaired wound, recurrence of the hernia and rarely visceral injuries.

After surgery, the child's umbilicus may appear to be slightly swollen, but this will resolve over the next few weeks. The child should be advised not to participate in physical education or sports for 2–3 weeks after surgery.

IN A NUTSHELL

1. Umbilical hernia is herniation of the intestine through the umbilical ring.
2. Umbilical hernia may be of three types, an indirect umbilical hernia, proboscoid hernia and hernia of the umbilical cord.
3. Incarceration of intestine or omentum, strangulation, perforation, evisceration and pain are rare.
4. Umbilical hernia with a small ring diameter (< 1.0 cm) is more likely to close spontaneously and sooner than those with a ring diameter of more than 1.5 cm.
5. Umbilical hernia is a clinical diagnosis and usually doesn't require any investigations for confirmation of the diagnosis.
6. Indications for surgery in umbilical hernia are, umbilical hernia not resolving spontaneously by 2 years, proboscoid hernia and incarcerated umbilical hernia.

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Chapter 35.10
Constipation

Praveen Kumar, Preeti Singh

Constipation is a feeling of unsatisfactory defecation—hard stools, passage of too small stools or too difficult to expel. North American Society of Pediatric Gastroenterology, Hepatology and Nutrition has defined chronic constipation as *delay or difficulty in defecation present for 2 or more weeks which causes significant distress to the patient*. If inadequately treated, it may lead to chronic abdominal pain, loss of appetite, and fecal incontinence. In addition, it can also make the child under confident and socially secluded. Constipation is generally under-reported because of lack of lucid definition and embarrassment to seek medical advice. The reported prevalence varies from 0.3% to 30%, depending upon the definition used in the study.

NORMAL PHYSIOLOGY

There is a wide variation in stool according to age and diet. Some breastfed infants may defecate after each feed, while others may have infrequent soft bowel movements (2–14 days). In infants and young children defecation is a simple spinal reflex and social training brings control of the reflex by higher centers. Most children achieve voluntary control of stool by the age of 2–3 years. Bowel continence is primarily maintained by internal and external anal sphincters. The involuntary internal anal sphincter which is the thickened circular smooth muscle at the pelvirectal flexure, receives innervations from parasympathetic splanchnic nerves (inhibitory) and sympathetic (excitatory) nerves. Internal sphincter relaxes when the rectum gets distended. The external anal sphincter which is under voluntary control consists of somatic skeletal muscle innervated by the pudendal nerve. It is maintained in a state of tonic contraction unless the person has the desire and the place is conducive. Another important anatomical landmark is puborectalis muscle which makes a sling around the lower part of rectum. Puborectalis gets inserted into symphysis pubis and is responsible for maintaining the normal anorectal angle of 85–100 degree. During defecation, this angle becomes straight or obtuse in squatting position to ensure smooth passage of stool. Rectal distension with feces initiates reflex contractions of its musculature with initiation of the desire to defecate. Subsequently voluntary defecation is initiated by relaxation of the external anal sphincter with expulsion of the rectal contents. Difficulties with defecation result from dysfunction in any part of the normal anatomy or physiology of defecation.

PATHOPHYSIOLOGY

The desire to defecate is activated when stool comes into contact with lower rectal mucosa. In the absence of favorable environment to defecate, there is failure of relaxation of the external anal sphincter and feces keep getting accumulated higher in the rectal vault further abolishing the defecation reflex. With progressive stool accumulation over a period of time, the rectum dilates leading to loss of sensation and effective propulsive movements required for evacuation. The retained stools become harder and difficult to pass causing painful defecation and development of anal fissure. This further reinforces stool withholding behavior, thus leading to a vicious cycle. The retentive posture is an attempt to avoid defecation in which the infant typically screams with facial flushing, exhibit stiffening of the body with arching of back and contraction of gluteal muscles. Similarly toddlers and older

children stand straight and stiff, or hold onto furniture, cross their legs, walk on tiptoes to withhold stools till the defecation urge passes off. These signs are often misinterpreted by parents as straining to pass stools. If this persists for a long duration, watery stools may leak around the large fecal mass causing involuntary soiling or encopresis.

DEFINITIONS

Functional constipation The Rome III criteria for diagnosis of functional constipation depends on the age of the child and is given in **Box 1** and **2**.

Encopresis Encopresis is the involuntary passage of formed, semi-formed or liquid stool in the child's underwear after achieving age of continence. This may be a complication of chronic constipation.

Intractable constipation Constipation not responding to optimal conventional management given for 3 months.

ETIOLOGY

Organic causes accounts for only 5–10% cases, but there are a large number of conditions which can cause constipation **(Box 3)**. Constipation is labeled as functional or idiopathic when it cannot be explained by organic causes. Functional constipation is responsible for 90–95% of chronic constipation in children. The most common organic cause in young children is Hirschsprung disease (HD) accounting for 6% of all patients.

Functional constipation during childhood is a result of a complex interplay of developmental transitions, environmental factors and parental response. Retention of stools starts in response to a number of relatively innocent events like voluntary retention to avoid school toilets, protest against bowel training, diet lacking fiber or temporary illness, anal fissure, etc. If an acute episode of constipation is not managed appropriately, it leads to chronic constipation.

BOX 1 The Rome III criteria for functional constipation in neonates and toddlers*

- < 2 defecations per week
- > 1 episode per week of incontinence after the acquisition of toileting skills
- History of excessive stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large-diameter stools that may obstruct the toilet
- *For a child with a developmental age < 4 years, at least 2 of the above symptoms must occur for at least 1 month.*

* Hyman PE, Milla PJ, Benninga MA, et al. Gastroenterology. 2006;130: 1519-26.

BOX 2 The Rome III criteria for functional constipation in children and adolescents*

- Two or fewer defecations in the toilet per week
- At least one episode of fecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large diameter stools that may obstruct the toilet.

For a child with a developmental age > 4 years with insufficient criteria for irritable bowel syndrome, ≥ 2 criteria fulfilled at least once/week for at least 2 months before diagnosis.

* Rasquin A, Di Lorenzo C, Forbes D, et al. Gastroenterology. 2006;130:1527-37.

BOX 3 Etiology of constipation

- **Functional constipation** (85–95%)
- **Organic causes** (5–15%)
  - *Abnormalities of colon and rectum*
    - Chronic intestinal pseudo-obstruction
    - Pelvic or sacral mass
    - Anal stenosis
    - Anal or colonic stricture—post NEC or IBD
    - Postsurgical repair of imperforate anus
    - Anteriorly placed anus
  - *Neuropathic lesions of the gastrointestinal tract*
    - Hirschsprung disease
    - Intestinal neuronal dysplasia
  - *Spinal cord lesions*
    - Spina bifida
    - Meningomyelocele
    - Sacral agenesis
    - Diastematomyelia
    - Spinal cord tumors (lipomas, cysts)
  - *Metabolic causes*
    - Diabetes mellitus
    - Diabetes insipidus
    - Hypothyroidism
    - Hypercalcemia/hypocalcemia
  - *Neurologic causes*
    - Cerebral palsy, autism
  - *Drugs*
    - Analgesics, antacids, anticholinergics, lead toxicity
    - Bismuth, iron, cholestyramine, psychotropics
  - *Others*
    - Celiac disease, cystic fibrosis, cow milk protein allergy.

Abbreviations: NEC, neonatal necrotizing enterocolitis; IBD, inflammatory bowel disease.

CLINICAL PRESENTATION

Although many children are brought with difficulty in defecation or infrequent bowel movements, others present with a variety of symptoms like recurrent abdominal pain, vomiting, abdominal distension, abdominal mass, blood-streaked stools or excessive flatulence. Infants and toddlers may present with irritability. Mothers may sometimes give history of straining while passing stools, posturing (squeezing of buttocks, scissoring or crossing of their legs) with some children even having loose stools from encopresis.

EVALUATION

A thorough history and physical examination **(Table 1)** is essential for differentiating functional constipation from an organic cause. Examination of the perineum and perianal area is important. Abdominal examination may reveal a lump in the left iliac fossa or suprapubic area due to retention of fecal matter in the sigmoid and descending colon. Development and psychological history (interaction with siblings and peers, temperament, any disruption of family life) helps in identifying underlying cause. Family history of chronic gastrointestinal diseases like inflammatory bowel disease, irritable bowel syndrome should also be enquired.

The *Red Flags Signs* helpful in identifying an organic disease are given in **Table 2**. One of the most important organic causes of constipation during neonatal period is HD. Important clinical pointers in an affected infant include abdominal distension, pencil—thin hard pellet like stool and failure to thrive. While delayed passage of meconium beyond 48 hours is very suggestive, 50% of babies with HD do pass meconium within 48 hours of birth. Delay in treatment can lead to development of enterocolitis. Delayed

Table 1 Evaluation of constipation

History	*Physical examination*
Stooling habits • Frequency, amount, diameter, and consistency of stools • Age of onset of constipation • Character of stools in toilet and underwear • Stool withholding maneuvers • Fecal incontinence	*Anthropometry:* Weight, height *Abdominal examination:* Distension, palpable fecal mass
Any precipitating factors Change of diet, timing of/toilet training or some events such as infections, fissure, starting nursery/school, major change in family conditions	*Neurological examination* Tone, strength of lower limbs, deep tendon reflexes, cremasteric reflex, perianal sensation testing
Abdominal pain, vomiting and distension, poor appetite and irritability *Urinary complaints* Day wetting Bed wetting History of urinary tract infections *Dietary habits* Diet low in fiber, poor intake of fluids, high intake of dairy products *Drug history:* Antispasmodics, codeine containing cough preparations	*Anal size and location* Position, stool present around anus or on clothes Perianal erythema Skin tags Anal fissures *Digital rectal examination* Anal wink, anal tone, presence or absence of stool, consistency of stool, explosive stool on withdrawal of finger

Table 2 Red flag signs indicating organic causes

Clinical features	*Diseases*
Delayed passage of meconium (after 48 hours after birth), small-caliber stools, failure to thrive, tight anal sphincter, empty rectum with palpable abdominal fecal mass, gush of air and liquid stool may follow withdrawal of the examining finger	Hirschsprung disease
Abdominal distention, bilious vomiting, ileus	Pseudo-obstruction
Decreased lower extremity tone and/or strength Absence or delay in relaxation phase of lower extremity deep tendon reflexes, absence of anal wink and cremasteric reflex or presence of pilonidal dimple or hair tuft	Spinal cord abnormalities
Abnormal position or appearance of anus	Imperforate anus, anal stenosis, anteriorly displaced anus
History of delayed passage of meconium, fatigue, cold intolerance, bradycardia, poor growth	Hypothyroidism
Polyuria, polydipsia	Diabetes insipidus
History of delayed passage of stool, failure to thrive, fever, recurrent pneumonia	Cystic fibrosis
Chronic/recurrent diarrhea, pallor, abdominal distension	Celiac disease
Diarrhea, failure to thrive, occult blood positivity	Cow's milk protein intolerance

passage of stools is also seen in hypothyroidism and cystic fibrosis. While delayed passage of meconium, symptoms since first month of life and abdominal distension are more common in children with organic cause, fecal impaction is more in functional group.

Digital rectal examination (DRE) reveals hard fecal matter in acquired constipation while it is empty in HD. A typical finding seen in HD is gush of fecal matter on withdrawal of fingers. DRE requires expertise, privacy and informed consent. Present guidelines do not support the routine use of DRE to diagnose functional constipation.

Flow chart 1 presents an algorithm for evaluation of constipation.

INVESTIGATIONS

Most children with functional constipation with or without fecal incontinence do not require any laboratory work-up apart from a careful history and physical examination.

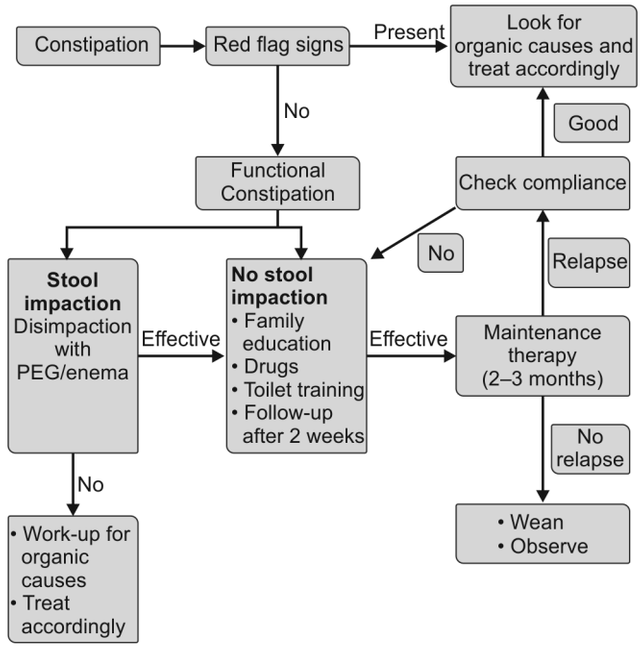
Rectal biopsy Rectal suction biopsy is the gold standard for the diagnosis of HD. It is performed around 3 cm above the anal verge, deep enough to include the submucosa. The aganglionic segment is recognized by absence of ganglion cells in submucosa and the presence of hyperplastic nerve trunks. There is absence of both ganglion cells and hypertrophied nerves in total colonic aganglionosis. Hyperganglionosis and/or ectopic ganglion cells are features of neuronal intestinal dysplasia.

Imaging Plain X-ray abdomen will help diagnose fecal impaction, the presence of which has implications in management. An unprepared barium enema will demonstrate a transition zone (more prominent in older children due to prolonged stool retention) separating dilated, stool-filled normally innervated ganglionic segment from an empty abnormal or aganglionic bowel segment. It is not a valid alternative to gold standard rectal biopsy.

Anorectal manometry When the above investigations are inconclusive, anorectal manometry helps in diagnosing abnormalities of defecation. Normal individuals will demonstrate relaxation of internal anal sphincter in response to rectal distension (rectoanal inhibitory reflex). This reflex gets abolished in HD and in patients with internal sphincter achalasia. In latter group, a rectal biopsy is normal despite a nonrelaxing internal anal sphincter. Other functional problems like pelvic floor dyssynergia and neurosensory rectal abnormalities can also be diagnosed using anorectal manometry.

Colonic transit study Dysfunctional (pan or segmental) colonic motility can be evaluated using radiopaque markers during

Flow chart 1 Algorithm for evaluation of constipation



colonic transit study. It is a precise tool for evaluation of colonic motor function and helps differentiate myopathy from neuropathic causes. Neuropathy is characterized by nonpropagating, disordered high amplitude contractions or an absence of the gastrocolic response while absent or weak colonic contractions is suggestive of myopathy.

MANAGEMENT

Acute constipation Identify any precipitating cause. Treat local causes like anal fissure, boil, dermatitis, etc., if any. Encourage use of high fiber diet-cereals, pulses, vegetables and fruits. Prescribe laxatives for short duration (7–10 days). Encourage toilet training if not already done.

Chronic constipation Patients with an identifiable organic cause for constipation should be appropriately treated medically or surgically. Treatment of functional constipation requires multimodality approach and includes education of parents and counseling; disimpaction and bowel cleansing; maintenance therapy; and follow-up. These measures have already been discussed in the chapter on encopresis (see section 21).

The drugs used in management of constipation are listed in **Table 3**. The first line of management of a child who presents with constipation and fecal impaction is disimpaction using polyethylene glycol (PEG) orally at a dose of 1–1.5 g/kg/day for 3–6 days. PEG is not degraded by bacteria; is not readily absorbed and thus acts as an excellent osmotic agent. If PEG is not available then disimpaction may be achieved with once a day enema for 3–6 days. Phosphate enema is better than normal saline enema. Other

Table 3 Drugs used for the treatment of constipation in children

Oral laxatives	*Dose*	*Side effects*
A. *Osmotic laxatives*		
Lactulose	1–2 mL/kg body weight twice/day	Bloating and abdominal distension
PEG 3350 with electrolytes PEG 3350 without electrolytes	1–1.5 g/kg/day for 3–6 days (disimpaction) *Maintenance:* 0.2–0.8 g/kg/day	Nausea, bloating, cramps and vomiting
Milk of magnesia (magnesium hydroxide)	2 mL/kg body weight twice/day for 7 days (disimpaction) *2–5 years:* 0.4–1.2 g/day, once or divided *6–11 years:* 1.2–2.4 g/day, once or divided *12–18 years:* 2.4–4.8 g/day, once or divided	Abdominal distension, hypermagnesemia, metallic taste. Avoid in renal failure
B. *Fecal softeners*		
Mineral oil	3 mL/kg body weight twice/day for 7 days (disimpaction) *1–18 years:* 1–3 mL/ kg/day, once or divided, max 90 mL/day	Not for infants Lipoid pneumonia if aspirated
C. *Stimulant laxatives*		
Bisacodyl (Oral)	*3–10 years:* 5 mg/day *> 10 years:* 5–10 mg/day	Abdominal pain, diarrhea
Bisacodyl (Suppository)	*2–10 years:* 5 mg once/day *> 10 years:* 5–10 mg once/day	Abdominal pain, skin rash, fixed drug eruption rarely
Senna	*2–6 years:* 2.5–5 mg once or twice/day *6–12 years:* 7.5–10 mg/day	Abdominal cramps, diarrhea
Sodium picosulfate Tab 10 mg, syrups 5 mg/5 mL	*1 mo–4 years:* 2.5–10 mg once/day *4–18 years:* 2.5–20 mg once/day	
Rectal laxatives/enemas		
Sodium docusate (lubricant)	*< 6 years:* 60 mL, *> 6 years* 120 mL	Cramps, abdominal pain
Sodium phosphate enema	*1–18 years:* 2.5 mL/kg, max 133 mL/dose	Hyperphosphatemia, hypernatremia, hypokalemia, hypocalcemia and dehydration
NaCl	Neonate < 1 kg: 5 mL, > 1 kg: 10 mL *> 1 years:* 6 mL/kg once or twice/day	
Glycerin suppository	Infants and toddlers	No side effects

alternatives are glycerin suppositories in infants and bisacodyl suppositories in older children. Hospitalization may be required to treat children with severe disimpaction particularly when oral PEG is not tolerated. Such children are given nasogastric lavage and are closely monitored for abdominal distension and dyselectrolytemia during the disimpaction. Maintenance therapy (PEG 0.4 g/kg/day) is then started to maintain normal stool frequency of once or twice a day. It is important to ensure good therapeutic compliance otherwise recurrence of stool impaction can restart the constipation cycle. Maintenance therapy should be continued for at least 2 months and it should then be gradually weaned and discontinued after ensuring resolution of symptoms for at least 1 month. Parents are advised to ensure adequate water intake and daily servings of a variety of fiber-rich foods such as whole grain breads and cereals, fruits, vegetables, and legumes in diet to ensure adequate fiber (required: age in years + 5 g/day).

Follow-up Children and their parents are instructed to maintain a record of daily bowel movements, and medication use. After regular bowel habits are established the drug dosage is gradually decreased to ensure one soft bowel movement per day. Follow-up is recommended at 1 month, 3 months, 6 months and then 3–6 monthly intervals to ensure optimal response.

Patients with *refractory or recurrent constipation* in spite of good compliance to the prescribed therapy will require detailed work-up. Metabolic tests such as serum calcium, thyroxine or thyroid-stimulating hormone, and celiac disease should be carried out. MRI of the lumbosacral spine can exclude occult spinal cord abnormalities and colonic manometry will detect occult myopathy or neuropathy. Full-thickness rectal biopsies will reliably exclude HD or neuronal intestinal dysplasia.

PROGNOSIS

Conventional treatment with adequate fiber and laxatives, toilet training is successful in approximately in 60% of cases. Adequate dose and treatment adherence is more important than which laxative is used. Good prognostic indicators are better compliance, adequate intake of roughage diet and self-confidence. Poor prognostic indicators include severe motor disability, mental retardation, school time soiling and neurogenic causes.

IN A NUTSHELL

1. Constipation is a common problem in children which can present with infrequent and or painful defecation, fecal incontinence and abdominal pain.
2. Functional constipation is most common cause accounting for 90–95% of cases.
3. Most children with functional constipation with or without fecal incontinence do not require any laboratory work-up apart from a careful history and physical examination. Presence of red flags increases possibility of underlying organic cause.
4. The most common organic cause in young children is Hirschsprung disease accounting for 6% of all patients.
5. Treatment of functional constipation requires multimodality approach and includes education of parents and counseling; disimpaction and bowel cleansing; maintenance therapy; and follow-up.
6. The first line of management of a child who presents with constipation and fecal impaction is disimpaction using polyethylene glycol (PEG) orally at a dose of 1–1.5 g/kg/day for 3–6 days.
7. Maintenance therapy should be continued for at least 2 months and it should then be gradually weaned and discontinued after ensuring resolution of symptoms for at least 1 month.

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Chapter 35.11
Hirschsprung Disease

Ketan Parikh

Hirschsprung disease (HD) is characterized by a congenital aganglionosis of a variable length of the distal colon extending proximally from the anorectal junction. The incidence ranges from 1:4,000 to 1:700 newborns in various series. The disease is usually sporadic but occasionally runs in families. Male:female ratio is 4:1 however in females the length of the aganglionic bowel is often longer. HD usually presents with chronic constipation.

PATHOGENESIS

Normal peristaltic activity involves a wave of relaxation preceding a wave of contraction. Parasympathetic innervation is essential for this wave of relaxation. In HD, the parasympathetic ganglia are absent from the Meissner's and Auerbach's plexuses of the affected bowel. The aganglionic bowel is normal in caliber but because of the absence of the peristaltic activity, the wave of relaxation is absent thus leading to a functional obstruction. The chronic obstruction leads to massive dilatation and hypertrophy of the normally ganglionated proximal bowel. The junctional portion of the bowel often shows a section of hypoganglionosis with partial function. The mucosa in the proximal hypertrophied portion of the bowel may show ulceration and hyperplasia due to chronic inflammation due to stagnation.

CLASSIFICATION

Depending on the length of the segment of aganglionosis, the disease is categorized as *short segment* (aganglionosis restricted to either the rectum or the rectosigmoid); *long segment* (extending more proximally to colon); *total colon* (entire colon); *very long segment* (a portion of the small bowel is also aganglionic); *total bowel* the entire bowel (small and large) is aganglionic—almost incompatible with normal life) and *ultrashort segment* (aganglionosis restricted only to the terminal portion of the rectum).

CLINICAL FEATURES

At birth—there is failure to pass meconium for more than 48 hours after birth and gradual onset of intestinal obstruction. Even if the

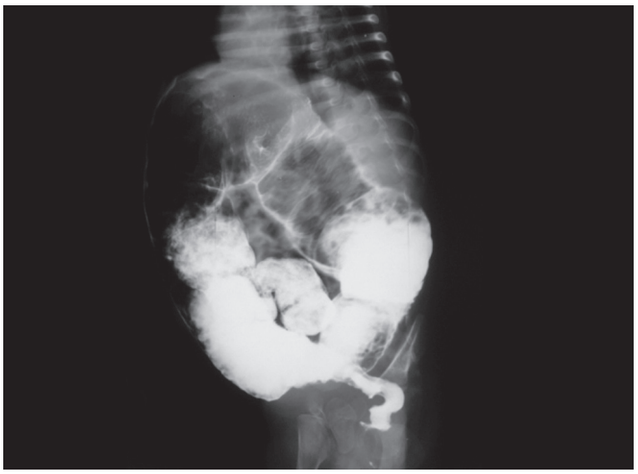

Figure 1 Barium enema showing narrow segment in classical Hirschsprung disease
Source: Dr Praveen Kumar, New Delhi.

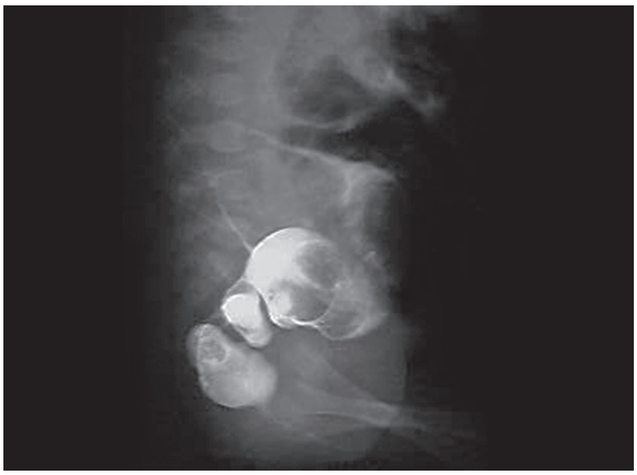

Figure 2 Barium enema of Hirschsprung disease showing the cone

baby passes meconium with some assistance, he again may get obstructed. There may be a persistent passage of meconium even until 1 week of life.

In case the disease does not manifest at birth, it presents later with constipation dating back to early infancy. Intestinal obstruction may manifest at any age which may be relieved by enemas. Rarely, attacks of foul smelling diarrhea interspersed with constipation may confuse the picture. In chronic cases—child fails to thrive and is malnourished. Abdominal distension is marked and the transverse colon is often visible. On rectal examination—the rectum is felt to be empty, and on withdrawal of the examining finger, there is an explosive passage of flatus and feces.

DIAGNOSIS

Most of the diagnostic techniques for HD have been described in the previous chapter on constipation. A plain X-ray of the abdomen may show features of intestinal obstruction-large dilated colon loops. It may also show absence of rectal gas shadow. Barium enema reveals a narrow aganglionic segment and a cone-shaped colon at the junction of the ganglionic and aganglionic segments **(Figs 1 and 2)**. Anorectal manometry may strongly suggest the diagnosis of HD. The final confirmation is only with a full thickness biopsy of the rectal wall which will show absence of ganglion cells.

TREATMENT

Conservative treatment involving repeated enemas/suppositories may help in overcoming an acute attack of intestinal obstruction and may help to postpone the surgery. However, many infants may not respond at all to conservative treatment and may need an emergency surgery. In such a case, an emergency colostomy may be the only option to save the child.

The principle of the surgery is the removal of the aganglionic segment of colon and ensuring that normal ganglionic bowel is anastomosed to the terminal rectum as closes as possible to the anal canal. Traditionally this surgery is done in stages but in recent years, single stage surgery is being done with variable success rates.

Various commonly performed surgeries include the modified Duhamel's procedure, Swenson's procedure and Soave's procedure. Either of these may be performed by regular laparotomy or by laparoscopic methods.

IN A NUTSHELL

1. Hirschsprung disease (HD) should be suspected in any apparently normal newborn who fails to pass meconium in the first 24 hours.
2. Hirschsprung disease should be suspected in any child who has repeated attacks of enterocolitis (profuse explosive diarrhea) interspersed with constipation.
3. Most patients with HD do not have soiling/encopresis.
4. A palpable fecaloma—low in the rectum is not likely to be due to HD.
5. Rectal biopsy is diagnostic.

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Chapter 35.12
Chronic Abdominal Pain

B Bhaskar Raju, Sumathi B

Abdominal pain is a common complaint in pediatric practice, with at least 15% of all outpatients suffering from it. *Recurrent abdominal pain* (RAP) which troubles the child periodically with pain-free intervals in between, is so common, that the term *RAP* was used as a specific diagnosis for several decades, to refer to a condition wherein, pain occurs at frequent intervals with no organic cause made out on examination or investigation. Today, the same is referred to as *chronic abdominal pain* (CAP). Functional abdominal pain, which is the most common form of

CAP seen in clinical pediatric practice, has been discussed here. There are many organic and nonorganic causes of abdominal pain in children within and outside the gastrointestinal tract (GIT); they will be touched upon, but not discussed in detail, since that would be beyond the scope of this chapter.

CHRONIC FUNCTIONAL ABDOMINAL PAIN

Even though functional abdominal pain is a benign disorder, it is something to be taken seriously since it troubles the child and the whole family. It has to be clearly differentiated from malingering, wherein the child feigns pain for some reward like avoiding school or homework, or just for the sake of sympathy. Functional abdominal pain is true pain that is actually felt by the child. Chronic functional abdominal pain (CFAP) may also present as *functional* dyspepsia; *irritable* bowel syndrome; *abdominal* migraine; or a combination of the above.

Chronic functional abdominal pain is a specific diagnosis to be made after ruling out all anatomic, infectious, inflammatory and metabolic causes of abdominal pain. Presence of red flag signs and symptoms should warn the physician to make every effort to rule out organic causes of CFAP. The final diagnosis of CFAP will always depend upon a good clinical history, and a thorough physical examination of the child, besides evaluation of precipitating and reinforcing factors in the family and immediate environment of the child.

DEFINITIONS

Any abdominal pain that exceeds 8 weeks in duration is said to be chronic. Previous definitions of RAP insisted on presence of pain-free intervals and number of bouts of pain are obsolete. Apley and Naish, who were the first to scientifically study children with abdominal pain syndrome as early as 1958, defined RAP as three or more episodes of abdominal pain that occurred over 3 months, that were severe enough to interfere with the child's daily activities. Rome III criteria, which clarifies and defines all functional disorders of GI system in adults, children and infants, has two pediatric categories based on age. It defines CAP as any pain recurrent or continuous, lasting beyond 8 weeks.

PREVALENCE

Functional gastrointestinal disorders (FGID) account for more than 50% of consults in pediatric gastroenterology practice and a significant proportion is CFAP. CFAP is diagnosed in 2–4% of all cases in general pediatric practice in the West. Epidemiological studies in Europe and America have shown prevalence rates of RAP/CAP varying between 0.5% and 19% among school going children. Apley and Naish found that the incidence of detectable pathology in RAP was less than 8%. Among growing children 10–15% experience RAP over 8 weeks, sometime in their life, with the highest prevalence in middle school girls. However, many Indian and Pakistani studies which screened children for CAP in schools that cater to poorer socioeconomic strata, found a disproportionately high incidence (84%) of minor organic pathology in their cohort of CAP children, giardiasis being the most common. Given the ubiquitous nature of giardiasis in poorer societies, this finding is understandable. Studies from India and Sri Lanka that looked at CAP in urban settings with more hygienic environments reflect Western numbers; 74–76% of CAP being nonorganic. In Malaysia, the prevalence of CAP in urban and rural population-based cohorts is 9.6% and 11%, respectively, most of it being functional. Abdominal migraine affects 1–4% of school going children in the West, with girls being affected more than boys; mean age of onset is 7 years, peaking at 10–12 years.

PATHOPHYSIOLOGY

Functional CAP is essentially a disorder of gut-brain neural cross talk. Gut has more neurons and complicated neural interconnections than even the brain in higher primates. The *enteric nervous system* (ENS) as it is called, consists of two major collections of neurons called (1) Auerbach's plexus which is essentially a myenteric system controlling GI motility and (2) the Meissner's plexus which is essentially a submucosal system that controls secretions and has sensory functions as well. The interstitial cells of Cajal which are interspersed between the nerve endings and smooth muscles of GIT, act as pace makers, regulating propagation of intestinal contractions. ENS is responsible for the motor, sensory and vascular responses of the entire GIT to intrinsic and extrinsic stimuli and it extensively interacts with the central nervous system (CNS) through the vagus nerve. The ENS and CNS profoundly influence each other and abnormalities in ENS and its response to the CNS inputs are the basis for the pain felt in CFAP.

Recent research on the pathophysiology of functional bowel disorders focuses on two disordered physiological functions in children with CFAP—(a) heightened response to visceral pain (visceral hyperalgesia); (b) disturbed bowel motility.

Visceral hyperalgesia This is otherwise known as augmented visceral perception or visceral hypersensitivity. This refers to the capacity of children with CFAP to feel events in the gut that are otherwise usually imperceptible to normal children. Signals from Meissner's plexus are generally filtered at the hypothalamus (hypothalamic gate) and very few signals make their way for perception by the cortex. This explains why most intestinal activity is not felt. Children with CFAP however, feel physiological events like peristalsis, postprandial and gaseous distension of gut, as pain, thanks to augmented visceral perception. Many studies have documented enhanced awareness and pain in response to balloon distension of the rectum in these children. Almost a third of them also have autonomic disturbances with pain episodes, like dizziness, headaches, vomiting, pallor, temperature intolerance, also indicating the role of the nervous system in CFAP. Mucosal inflammatory processes secondary to infections, allergy, and primary inflammatory diseases may also cause sensitization of afferent nerves and visceral hyperalgesia, resulting in augmented visceral pain perception. This explains the often elicited history that the CAP started with a bout of diarrhea and vomiting.

Altered intestinal motility Besides augmented visceral perception, children with CFAP have significantly increased amplitude of both peristaltic and nonperistaltic contractions of intestine. Levine's famous hypothesis tries to understand this phenomenon of increased cortical stimulation of gut musculature through his conceptual model of CFAP **(Fig. 1)**. This model suggests various external and intrinsic stimuli can trigger inappropriate contractions of the bowel, felt as pain by the child. The normal function of the CNS is to integrate all interoceptive inputs from gut and elsewhere in the body, and accordingly send back efferent neuronal signals to GIT which trigger myoactivity in the intestines. Aberrations in this integration and response from the CNS result in inappropriate and enhanced bowel contractions felt as pain by the child.

Levine's Hypothesis

Levine suggests CFAP is triggered and induced by several intrinsic and extrinsic inputs inducing pain in a susceptible child who has heightened sensitivity to visceral sensations and increased bowel activity secondary to CNS inputs **(Fig. 2)**.

Lifestyle and habits Regular eating habits, an active lifestyle including exercise and regular bowel habits improve CFAP symptoms, lack of them predispose to CFAP.

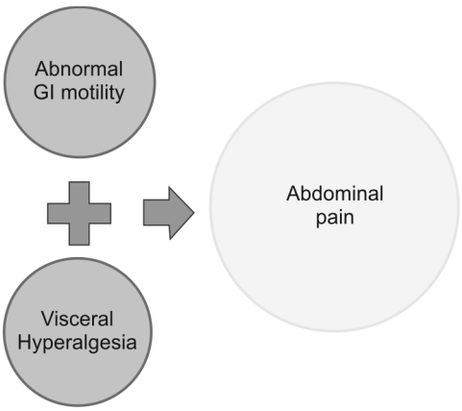

Figure 1 Schematic representation of pathophysiology of functional abdominal pain (FAP)

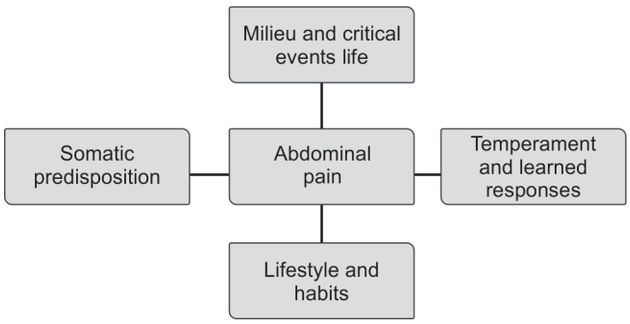

Figure 2 Environmental factors and cortical stimulation of increased gut activity

Temperament and learned responses Learned responses refer to children who respond poorly to discomfort and pain with exaggerated responses because of being petted and pampered. They do not take disappointment well. If secondary gain is involved, their expression of discomfort worsens. For example, allowing children to skip school on account of pain makes pain episodes worse and more frequent.

Somatic predisposition Chronic functional abdominal pain tends to run in families (Pain families). This may have a genetic predisposition, but it is more likely that there is modeling involved. Children mimic their parents' complaints and tendency to complain and grumble.

Milieu and critical events These refer to several events in a child's life, besides examinations, that can be stress triggers for pain. Loss of a friend, relocation to a new home and family discord can all precipitate pain episodes.

CLINICAL PRESENTATION

In the 80s, all RAPs were classified as organic (10%) or psychogenic (90%). Later psychogenic pain was split into dysfunctional abdominal pain (95%), and RAP due to psychiatric problems (5%). Dysfunctional abdominal pain is presently called CFAP. Given the complexity of presentation of FGID, attempts were made to streamline, define and clarify these disorders. The third committee on functional disorders of GIT (adults, children and infants) met in Rome and published the scholarly treatize on FGID, called Rome III criteria for FGIDs in 2006. As per Rome III criteria, all childhood functional abdominal pain disorders are one of four types:

1. *Functional dyspepsia:* This is characterized by rapid gastric emptying associated with slow bowel transit. Children with this disorder have poor appetite, dyspepsia and postprandial bloating as predominant symptoms, instead of pain.
2. *Irritable bowel syndrome (IBS):* Symptoms of IBS include altered stool frequency (four or more stools/day or two or less stools/week), abnormal stool form (lumpy/hard or loose/watery stool), abnormal stool passage (straining, urgency, or feeling of incomplete evacuation), passage of mucus and bloating or feeling of abdominal distension. Abdominal pain may or may not be a part of the syndrome.
3. *Abdominal migraine:* Defined as severe paroxysmal periumbilical pain, often intense, lasting 1 hour or more, interspersed with pain-free intervals, lasting weeks to months. Investigations fail to reveal any evidence of inflammatory, anatomic, metabolic, or neoplastic process attributable for subject's symptoms. Pain interferes with normal activities and pain episodes are associated with two or more of the following symptoms like anorexia, nausea, vomiting, headache, photophobia, or pallor.
4. *Childhood functional abdominal pain:* Characterized by episodic or continuous abdominal pain (mild to moderate) with insufficient criteria for other FGIDs, in the absence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms.

(*Criteria to be fulfilled at least once per week for at least 2 months before diagnosis*).

FUNCTIONAL ABDOMINAL PAIN SYNDROME (FAPS)

The term syndrome is used for functional abdominal pain, if at least 25% of pain episodes include, interference with daily activities, sleep disturbances, other somatic symptoms like headache and limb pains (*criteria to be fulfilled at least once per week for at least 2 months before diagnosis*).

Typical pain pattern in functional pain is characterized by paroxysmal nature of pain with variable severity; clustering of pain; gradual onset; usually periumbilical, occasionally epigastric location; poor relationship to food, defecation and inability to clearly describe nature or localize the pain. It may be associated with other symptoms like pallor/nausea/fatigue/anxiety in about 10% of the cases. It should be differentiated from the typical pain pattern in organic pain which is well defined and clearly localized, away from the umbilicus, and may be radiating. Burning, stabbing pain; pain awakening the child at night; pain with fever; pain with weight loss; tenderness/organomegaly; blood in stools (occult or obvious); altered bowel movements; anemia, urinary symptoms, increased erythrocyte sedimentation rate/C-reactive protein (ESR/CRP) and associated arthralgia/rash/purpura are the red flag signs that should immediately warn the physician that he could be dealing with an organic pathology, requiring diligent investigations to identify it.

EVALUATION

History, clinical examination and the presence or absence of red flag signs/alarm symptoms, help to differentiate between organic and nonorganic causes of pain in clinical practice. Many studies especially in India, have picked up conditions like constipation, gastroesophageal reflux disease (GERD) esophagitis, *Helicobacter pylori (H. pylori)* gastritis, lactase deficiency, and rarely inflammatory bowel disease (IBD) and celiac disease, in what was clinically diagnosed to be functional abdominal pain. As a general rule, if the pattern of abdominal pain appears functional, with a completely normal history and physical examination

without occult blood or parasites in stool and bowel movements are normal, a physician is justified in diagnosing CFAP without extensive investigations. But, he must follow-up the child closely, however, and whenever red flag signs appear or pain relief is not observed with time, he must order investigations to rule out organic causes.

Besides a detailed history and physical examination, all cases of suspected CFAP require evaluation of the child's interpersonal relationship with the rest of family especially parents, siblings, grand parents and friends; child's immediate emotional environment in school and home; child's personality; child's response to discomfort and pain; sociability and school performance/problems.

INVESTIGATIONS

Majority of cases of CFAP can be picked up on clinical examination and most do not require investigations other than stool microscopy and occult blood. Where pain in CFAP has been long-standing, and reassurance does not result in relief of pain, investigations are order of preference are listed in **Box 1**.

Before a child is finally labeled CFAP, it is wise to keep in mind some conditions that cause RAP, but may be easily missed by both clinical examination as well as by investigations. These include GERD (may be missed if not biopsied), *H. pylori* gastritis (requires biopsy), constipation, chronic appendicitis/appendicular colic, giardiasis/pinworms, leukemia (iliac bone pains), hernias (linea alba) and spinal lesions.

MANAGEMENT

Principles of management are summarized in **Box 2**. The goal of therapy does not include complete relief of pain which may not be possible in short-term. Reassurance of the parents and child that nothing is wrong with him/her is the cornerstone of therapy in CFAP. Most children with CFAP tolerate pain better, once reassured there is nothing seriously wrong and the parental anxiety about pain disappears. The aim should be to have normal school attendance and scholastic and sports activities to the child's potential. Counseling by the pediatrician usually achieves all these. Some severe cases that do not respond to reassurance and counseling may need additional modalities like:

- Cognitive behavioral therapy
- Psycho education
- Relaxation based therapy.

Dietary management includes reduction in sugary foods, sodas and irregular eating habits. Increase in fiber intake also helps. Food allergies are increasing in incidence and a good dietary history might unravel food allergies. If found, avoidance will help. Lactose intolerance, which is an important cause of RAP in Caucasian population, is, however, rare in India beyond infancy.

BOX 1 Investigations for chronic pain abdomen

Level I investigations

- Complete hemogram
- *Serum amylase*/lipase/liver and renal function tests
- Stool and urine analysis
- Screening for tuberculosis
- Ultrasonography (USG) of abdomen

In the absence of red flag signs, when the above set of investigations are normal, one can label the child as having CFAP. If the above investigations fail to pick up any pathology and the child presents with one or more red flag signs, additional investigations may be needed (*Level II investigations*). Pain with altered bowel movements, occult blood positive in stool, anemia, ↑ESR/CRP, fever, rash and recurrent aphthous ulcers, merit direct visualization of the bowel, both upper and lower.

Level II investigations

- Contrast studies of upper and lower GIT
- Upper and lower GI endoscopies, including appropriate biopsies

Inability to identify a cause with level II investigations, with persistence of pain occurred in less than 1% of cases in our series. They will need third level investigations to identify rarer causes of recurrent abdominal pain.

Level III investigations

- EEG to rule out abdominal epilepsy and cyclical vomiting disorder
- Screening for porphyrias/lead poisoning/collagen vascular disorders/lactose intolerance/food allergies/motility disorders.

Abbreviations: CFAP, chronic functional abdominal pain; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; EEG, electroencephalogram.

BOX 2 Principles of management of chronic abdominal pain

- Arriving at a positive diagnosis
- A detailed explanation of the pathophysiology and the cause of pain to parents and child
- Establishing goals of therapy and explaining that complete relief of pain is not one of them
- Identification and modification of triggers and physical or psychological stress
- Diet modification
- Drug therapy in selected cases
- Active psychological support
- Avoidance of hospitalization
- Avoidance of psychiatric consults, unless strong evidence for an underlying psychiatric disorder exists.

Medications

Drugs are uniformly useless in CFAP except in selected situations. Functional dyspepsia may respond to proton pump inhibitors (PPIs) and prokinetics and so does documented acid peptic disease including GERD. Antispasmodics are best avoided in CFAP, except in IBS with a significant pain component. They precipitate gastroesophageal reflux and constipation. Peppermint oil has been found useful in IBS and some cases of CFAP. Stool softeners benefit children with constipation. Abdominal migraine if suspected, would do well with pizotifen. Recently, many trials have looked at probiotics like *Lactobacillus* GG, *Bifidobacterium*, VSL#3, and have reported mixed results. Antimotility agents are best avoided, except in severe diarrheal forms of IBS. In endemic areas, empirical metronidazole therapy for giardiasis might help. Routine deworming has no role in CFAP therapy. Treatment of *H. pylori*, even when identified in biopsy has had only equivocal effect. Typical CFAP does not need antipsychotic medication. Psychiatric consult often scares the parents and child and worsens the pain and may be avoided, unless an underlying psychiatric disease is suspected. A multidisciplinary team including a psychiatrist will be needed in the following situations: conversion reaction; low self-esteem; anxiety, depression; maladaptive family; modeling/imitating family behavior; or poor response to conservative therapy.

PROGNOSIS

About 70% of CFAP children have complete relief of pain without any medication, with just a positive diagnosis and reassurance that there is nothing seriously wrong with them. Many do get recurrences, but they too remit well. About a third of them grow into adulthood with abdominal pains. An equal number develop new symptoms like headaches, back pains, etc. CFAP children, however, handle pains much better as they grow into adulthood.

CHRONIC ABDOMINAL PAIN: ORGANIC CAUSES

It is beyond the scope of this chapter to deal with all pathology that could present with CAP, but some guidelines are given as to what diseases to screen for depending on presentation of the pain.

Child presenting with isolated periumbilical paroxysmal pain (IPUPP) Screen for renal/biliary/pancreatic colic, malrotation, abdominal epilepsy, intussusception, vasculitis (Henoch-Schönlein purpura), porphyrias, less than 5% of children with IPUPP actually have an organic basis. Others are functional in origin.

Child presenting with CAP and significant dyspepsia GERD, peptic ulcer disease, *H. pylori* infection, giardiasis, pancreatitis and motility disorders.

Child presenting with CAP and altered bowel movements Simple constipation, IBDs, abdominal tuberculosis, immunodeficiency syndromes, intestinal lymphomas, eosinophilic enteritis, postoperative adhesions and congenital band obstructions.

Almost one-third of patients with CAP and significant altered bowel habits will have an organic basis for the pain, the rest will be functional.

IN A NUTSHELL

1. The term RAP is now replaced by CAP.
2. Chronic functional abdominal pain is a specific diagnosis, made after ruling out anatomic, infectious, inflammatory, or metabolic causes of abdominal pain.
3. Chronic functional abdominal pain includes functional dyspepsia, irritable bowel syndrome, abdominal migraine, and FAPS.
4. A clinical diagnosis of CFAP can be made in children between 4 years to 18 years of age when alarm symptoms/signs are absent and physical examination is normal, provided stool microscopy and occult blood test are negative.
5. Alarm symptoms requiring investigations include involuntary weight loss, linear growth deceleration, anemia due to GIT blood loss, significant vomiting, chronic diarrhea, persistent right upper or lower quadrant pain, unexplained fever and any family history of inflammatory bowel disease.
6. Alarm signs that require investigations include localized right upper or lower quadrant tenderness, localized fullness, mass, organomegaly, costovertebral angle tenderness, spine tenderness, and perianal abnormalities like fistula or abscess.
7. Investigations are indicated if pain significantly decreases quality of life and interferes with routine activities, even if alarm signs and symptoms are absent.
8. Psychological factors should be addressed during diagnostic evaluation and management and if found contributing to pain, should ideally be handled by counseling by pediatrician.
9. Time-limited use of medications, such as acid-reduction therapy, antispasmodic agents, smooth muscle relaxants, low doses of psychotropic agents, nonstimulant laxatives or antidiarrheals may be appropriate in selected cases to decrease symptom frequency or severity.
10. The role of antidepressants (tricyclics, selective serotonin reuptake inhibitors) in the treatment of FGIDs associated with abdominal pain needs to be assessed.

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Chapter 35.13
Acid Peptic Disease

R Bhanu Vikraman Pillai

Acid peptic disease is one of the important treatable causes of abdominal pain. The term encompasses esophagitis, gastritis, peptic ulcer disease and duodenitis. It is important to identify these causes and treat them appropriately for the resolution of symptoms as well as prevention of certain conditions with lifelong implications. Acid peptic diseases are relatively common causes of abdominal pain in children, but are less common than chronic constipation or irritable bowel syndrome. Peptic ulcer disease, either primary or secondary, is an important but uncommon cause of abdominal pain in children compared to adults. Since gastroesophageal reflux disease (GERD) as well as *Helicobacter pylori* (*H. pylori*) infection is described in detail elsewhere, we will restrict our discussion to the rest of the spectrum.

PATHOPHYSIOLOGY

It is important to recall the different types of cells in the stomach and their functions. In the body and fundus of the stomach, they include the chief cells producing pepsinogen, parietal cells producing acid and intrinsic factor, enterochromaffin-like cells producing histamine, enterochromaffin cells secreting serotonin and D-cells secreting somatostatin. The antrum contains mucus glands, gastrin secreting G-cells, some D-cells and enterochromaffin cells.

The pathophysiology of peptic disease involves the imbalance between the aggressive and protective factors of the gastric mucosa. Gastric acid and pepsin are the major aggressive factors. Acid secretion is an active process in the parietal cells by the enzyme H^+/K^+-ATPase, which is the proton pump. In term neonates, acidification of the gastric contents occurs soon after birth. The acid production gradually increases and reaches adult levels by 24 weeks. Gastric acid production is increased in duodenal ulcers but not in gastric ulcers. The bicarbonate-mucus barrier protects the mucosa from the acid-pepsin attack. The gastric epithelial cells secrete mucus continuously, and most importantly it is stimulated by the prostaglandins. The mucus barrier forms the *unstirred layer* and lies directly over the epithelial cell layer and protects the mucosa from the harmful effects of acid and pepsin. The mucin glycoprotein at the luminal side of the unstirred layer is broken down by pepsin, but is replaced by the continuous production of mucus by the epithelial cells. However, when there is a disruption of mucus production by infections, ischemia or noxious agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), it predisposes the mucosa to attack by the acid and pepsin that could result in peptic ulcer disease.

ETIOLOGY

There are several causes for gastritis in children. By strict definition, gastritis is a histologic diagnosis and should have inflammatory

cells; but in gastropathy, there is mucosal injury without significant inflammation. However, the terms gastritis and gastropathy are used together since the clinical symptoms are similar. The causes of gastritis or gastropathy in children are listed in **Box 1**; few important ones are discussed here.

Infection H. pylori is well known to cause of gastritis. It can cause nodular gastritis, erosions, as well as peptic ulcer disease. World Health Organization (WHO) has classified *H. pylori* as a group 1 carcinogen as it is associated with adenocarcinoma as well as lymphoma arising from mucosa-associated lymphoid tissue (MALToma) of the stomach. These are fortunately very rare in children. In addition to *H. pylori*, *H. heilmannii* infection has also been implicated in gastritis. *H. pylori* infection is discussed in detail elsewhere.

Drugs Nonsteroidal anti-inflammatory drugs are very frequently prescribed medications in rheumatologic conditions and can result in a spectrum of mucosal damage ranging from microscopic changes to frank ulceration and bleeding or even perforation. Cyclooxygenase (COX)-catalyzes conversion of arachidonic acid to prostaglandins. The beneficial and harmful effects of NSAIDs are due to their ability to inhibit this reaction. The most common site of NSAID-induced damage is the stomach, but it certainly can damage the small bowel, colon as well as esophagus. The prostaglandins produced by COX-1 pathway are responsible for hemostasis and mucosal integrity; while those produced in the COX-2 pathway are responsible for pain, fever and inflammation. The nonselective NSAIDs such as aspirin, ibuprofen, indomethacin, diclofenac, mefenamic acid and meloxicam inhibit both pathways, and are more likely to cause GI side effects. The COX-2 inhibitors such as celecoxib or rofecoxib are less likely to cause GI side effects, but are not totally safe. As NSAIDs are protein-bound, hypoalbuminemia increases the serum levels of free drugs which increase the risk for toxicity.

Allergy Food allergies can cause eosinophilic gastritis as well as eosinophilic esophagitis. It can be isolated or be part of eosinophilic gastroenteritis. In children, the proteins of cow's milk, soy, wheat and egg are the most commonly encountered allergens. Peripheral eosinophilia may or may not be seen. Ménétrier's disease is a rare disorder with giant, hypertrophied gastric folds with excessive mucus production and protein-losing gastropathy. This could be associated with cytomegalovirus (CMV) infection. In children, it is considered benign and self-resolving, whereas in adults it can be an acquired premalignant condition.

Graft versus host disease (GVHD) Acute GVHD which occurs between 21 days and 100 days after transplantation may present with nausea, vomiting, diarrhea and abdominal pain and GI bleed. GVHD usually occurs after allogenic bone marrow transplantation, but rarely after solid organ transplant also. They have characteristic histologic features. Chronic GVHD rarely involves the stomach. Pernicious anemia is associated with body-predominant atrophic gastritis, and results in loss of secretory function of acid, pepsinogen as well as intrinsic factor causing achlorhydria and anemia from vitamin B_{12} deficiency. These patients have antibodies against parietal cell components.

Crohn's disease may cause gastritis resulting in abdominal pain, hematemesis, melena and delayed gastric emptying. Up to 30% patients with Crohn's disease have histologic evidence of gastritis with granulomas. Granulomatous gastritis can also occur in chronic granulomatous disease of childhood.

Zollinger Ellison (ZE) syndrome is caused by gastrinomas and has fasting hypergastrinemia, usually greater than 125 pg/mL, resulting in hyperchlorhydria. ZE syndrome can be sporadic, or associated with multiple endocrine neoplasia type 1 (MEN1). Gastrinomas can occur in pancreas as well as stomach, duodenum, liver and kidney. In addition to refractory peptic ulcerations, ulcerations may occur in unusual locations such as jejunum. They present with abdominal pain, diarrhea, heartburn, weight loss as well as GI bleeding. ZE syndrome associated with MEN1 presents with nephrolithiasis in addition to abdominal pain, heartburn and GI bleeding. Pseudo-ZE syndrome or G-cell hyperplasia also causes hypergastrinemia, hyperchlorhydria as well as peptic ulcerations, but there is no response to gastrin stimulation, unlike in ZE syndrome.

BOX 1 Causes of gastritis in children

- Stress gastritis
- *Helicobacter pylori* gastritis
- Nonsteroidal anti-inflammatory drugs-induced gastritis
- Other drug-induced gastritis including iron
- Crohn's disease
- Eosinophilic gastritis
- Allergic gastritis
- Cytomegalovirus gastritis
- Corrosive-induced gastritis
- Graft versus host disease
- Gastritis associated with chronic granulomatous disease
- Bile gastropathy
- Gastritis associated with autoimmune disorders
- Pernicious anemia
- Radiation-induced gastritis
- Collagenous gastritis
- Gastric lymphoma (mucosa-associated lymphoid tissue lymphoma).

CLINICAL PRESENTATION

Epigastric pain is an important symptom of acid peptic disease in children. It may be associated with vomiting and nocturnal awakening. The temporal relationship with food is noted only in 50% of children with peptic ulcer disease. Some children may present with upper gastrointestinal (GI) bleed in the form of hematemesis or melena, while some may have associated heartburn, weight loss or iron deficiency anemia. Occult GI bleeding in a child with abdominal pain and vomiting needs to be investigated for possible peptic ulcer disease or other etiologies such as inflammatory bowel disease or eosinophilic disorders.

PRIMARY VERSUS SECONDARY PEPTIC ULCER DISEASE

Peptic ulcer disease can be classified as primary or secondary, based on whether or not there is an underlying systemic disease. Most primary peptic ulcers develop between 8 years and 17 years of age, whereas the secondary peptic ulcers can develop at any age. Even though *H. pylori* associated peptic ulcer is rare in children, it is the most common cause of primary peptic ulcer disease. Less commonly, ulcer can develop even if *H. pylori* is negative. Up to 29% of duodenal ulcers can be *H. pylori* negative. Hence, when *H. pylori* is ruled out by more than one test and there is no history of recent NSAIDs or antibiotics, ZE syndrome and G-cell hyperplasia, which can also cause primary peptic ulcer disease, should be excluded.

DIAGNOSIS

The definitive diagnosis of gastritis and peptic ulcer disease is by upper GI endoscopy **(Fig. 1)** and biopsy. The diagnosis of *H. pylori* is discussed elsewhere. Barium studies are not relevant currently given the high rates of false-negatives as well as false-positives. However, barium contrast studies are useful in identifying

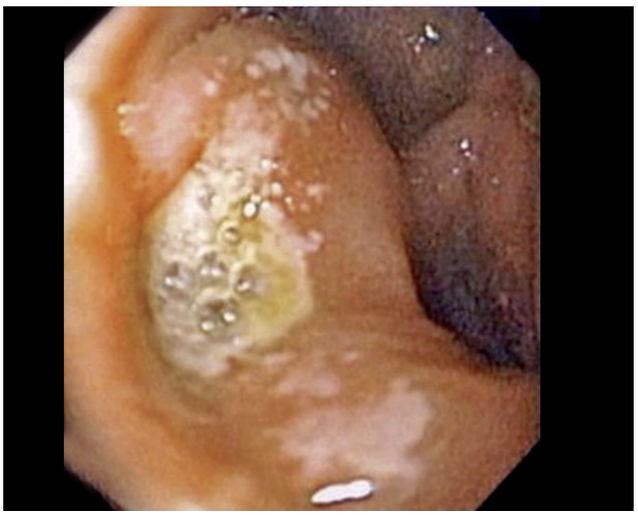

Figure 1 Duodenal ulcer

complications such as gastric outlet obstruction. If there is suspicion of ZE syndrome due to persistent peptic ulcers, further investigations like computed tomography, magnetic resonance imaging as well as radionucleide octreotide scanning and selective arterial secretin testing to locate the gastrinoma may be necessary.

TREATMENT

The treatment of *H. pylori* is discussed elsewhere. Acid suppression is the mainstay in the treatment of gastritis as well as peptic ulcer disease. In addition to acid suppression, treatment specific to the etiology such as avoiding NSAIDs when possible is essential. Ulcerations from Crohn's disease require immune modulator therapy. Eosinophilic gastritis would need avoidance of the allergic foods and at times corticosteroid therapy. Proton pump inhibitors (PPI) are very effective in acid suppression and are now the preferred drugs for acid suppression. There are sufficient data on the safety and efficacy of PPIs in children, even though most of the studies are done in patients with GERD. H_2-receptor antagonists such as ranitidine and famotidine may be used, but are less effective than PPIs and many patients develop tolerance or tachyphylaxis. Sucralfate may be used for short term, and in acid pH, the molecule dissociates and binds to damaged tissue. It contains aluminum and should be used with caution in renal failure.

Diet should be modified so as to avoid carbonated and caffeinated drinks that increase acid secretion. Every effort should be made to discourage and stop cigarette smoking which predisposes to ulcer formation and complications, probably by inhibition of prostaglandin synthesis.

Bleeding from the ulcer can usually be controlled endoscopically. However, at times one may need help from the interventional radiologist for hemostasis by coiling or embolization. Surgical treatment may be necessary for complications such as perforation, refractory bleeding and gastric outlet obstruction.

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IN A NUTSHELL

1. Acid peptic diseases are relatively common causes of abdominal pain in children, but less common than chronic constipation or irritable bowel syndrome. Peptic ulcer disease, either primary or secondary is important but uncommon cause of abdominal pain in children compared to adults.
2. The pathophysiology of peptic disease involves the imbalance of the gastric mucosal aggressive and protective factors.
3. The definitive diagnosis of gastritis as well as peptic ulcer disease is by upper GI endoscopy and biopsies.
4. Both the primary and secondary causes of gastritis require treatment of the underlying pathology as well as acid suppressive therapy.
5. Acid suppressive therapy is best achieved by PPI and is effective and safe in children.

Chapter 35.14
Pancreatitis

A Riyaz, Geeta M Govindaraj

35.14.1 ACUTE PANCREATITIS

Pancreatitis is inflammation of the parenchyma of the pancreas caused by the destructive effects of pancreatic enzymes, resulting in acinar cell injury. Traditionally considered a very rare disease in children, their numbers have increased over the past decade all over the world. This is possibly due to greater awareness of the disease among pediatricians. Ninety percent of children have acute pancreatitis and 10% chronic pancreatitis. However, pancreatitis being a mild disease in children unlike adults, the diagnosis may be easily missed, if the pediatrician is not aware of the problem.

CLASSIFICATION

Acute pancreatitis is a reversible process which does not cause any lasting effects on the pancreatic parenchyma or function. In contrast, *chronic pancreatitis* is a prolonged and frequently lifelong disorder secondary to fibrosis within the pancreas.

The *Atlanta classification* categorizes acute pancreatitis into mild and severe types. Mild acute pancreatitis has minimal organ dysfunction and has a self-limited course with an uneventful recovery. Severe acute pancreatitis consists of organ failure and/or local complications such as pseudocysts, necrotizing pancreatitis or abscess.

ETIOLOGY

The major causes of acute pancreatitis in children are infections, trauma, drugs and systemic diseases. This is in contrast to adults in

whom it is caused mainly by gallstones and alcohol abuse, and to some extent by hypercalcemia and hypertriglyceridemia.

Infections

Viral infections that cause pancreatitis include mumps, rubella, varicella, measles, influenza, infectious mononucleosis, etc. Serum amylase and lipase may be elevated in about 70% children with mumps, but pancreatitis rarely occurs. Viral hepatitis, especially hepatitis A and B may also cause pancreatitis. Human immunodeficiency virus (HIV) infection causes pancreatitis by several mechanisms. The virus may directly affect the gland. Opportunistic infections caused by cytomegalovirus, *Mycobacterium avium-intracellulare*, *Mycobacterium tuberculosis, Cryptococcus neoformans* (*Torula histolytica)*, *Cryptosporidium parvum*, *Toxoplasma gondii*, *Histoplasma capsulatum*, and *Candida* species may also cause pancreatitis. Pancreatic neoplasms like Kaposi's sarcoma and lymphoma seen in about 5% of patients with acquired immunodeficiency syndrome (AIDS) may also be responsible. Hydroxyurea as well as several antiretroviral drugs like stavudine and didanosine are notorious to cause pancreatitis. Hence, it is important to rule out HIV/AIDS in children with obscure pancreatitis.

Some bacteria like *Shigella*, *Campylobacter*, *Enterohemorrhagic Escherichia coli 0157*, *Legionella*, *Leptospira*, *Mycobacterium* and *Brucella* cause acute pancreatitis by releasing various toxins. There are several reports of severe pancreatitis complicating enteric fever. In developing countries like India, helminth infections caused by *Ascaris lumbricoides* (roundworms) may cause severe pancreatitis by blocking the main pancreatic duct and obstructing drainage of pancreatic secretions. It is difficult to diagnose and treat this condition. *Aspergillus fumigatus* and *Candida albicans* may also cause pancreatitis.

Systemic disorders The most important systemic disorder causing acute pancreatitis is hemolytic uremic syndrome, followed by sepsis, Kawasaki disease and Henoch-Schönlein vasculitis. Shock from any etiology may lead to pancreatitis by decreasing blood flow with resultant hypoxia. Reye's syndrome may be complicated by severe hemorrhagic pancreatitis. Children with collagen-vascular diseases including systemic lupus erythematosus (SLE), juvenile rheumatoid arthritis and polyarteritis nodosa, and inflammatory bowel disease like Crohn's disease and ulcerative colitis may also develop pancreatitis. However, many of these children may also be taking drugs known to cause pancreatitis, as part of the treatment of their primary disease.

Trauma The pancreas is not commonly damaged in blunt abdominal trauma as it is protected to some extent by its intraperitoneal location. Pancreatic damage is usually associated with injury to other organs, especially the liver and spleen. Bicycle handle-bar injury is an important cause of pancreatitis in children. It is important to rule out abuse in such cases. Traumatic pancreatitis should not be missed, as it may cause pancreatic duct transection, which may require surgical intervention.

Drugs are an uncommon but important cause of acute pancreatitis **(Box 1)**. Drug-induced pancreatitis can be diagnosed only after excluding other causes of pancreatitis. There is usually an interval of 4–8 weeks between the initiation of treatment and onset of pancreatitis. Some drugs cause pancreatitis by a clear mechanism like inducing hypertriglyceridemia, which in turn causes pancreatitis. Pancreatitis can be reproduced on re-challenge with the same drug. One of the most commonly implicated drugs in children is *valproic acid*. The incidence of valproic acid-induced pancreatitis, however, is quite low.

Gallstones which are the most common cause of pancreatitis in adults, may sometimes cause pancreatitis in children, particularly those with congenital hemolytic anemia like thalassemia, sickle cell anemia, hereditary spherocytosis, etc. This should not be overlooked since endoscopic retrograde cholangiopancreatography (ERCP) may be indicated in such children.

BOX 1 Drugs causing pancreatitis in children

- Valproic acid
- Prednisone
- Isoniazid
- Carbamazepine
- Erythromycin
- Sulfonamides: mesalamine, 5-aminosalicylates, sulfasalazine, trimethoprim/sulfamethoxazole
- Metronidazole
- Stavudine
- Pentamidine
- Didanosine
- 6-mercaptopurine
- L-asparaginase
- Azathioprine
- Methyldopa.

Metabolic causes The important metabolic causes of pancreatitis include cystic fibrosis and familial hyperlipidemia types I, IV and V. Both acute and chronic pancreatitis may be seen in these cases. In hyperlipidemia, serum amylase and lipase levels will be normal and serum triglyceride levels will be more than 1,000 mg%. In cystic fibrosis, pancreatic duct may be obstructed due to viscous secretions, resulting in pancreatitis. Pancreas divisum is a relatively common congenital anomaly of the pancreatic ducts. It is caused by the failure of the ducts of the dorsal and ventral anlagen to fuse during the 5th and 6th week of gestation. Here, a major part of the exocrine pancreatic secretion drains through the accessory pancreatic duct of Santorini and the accessory papilla into the duodenum. It is usually asymptomatic, but about 10% of these children may develop acute pancreatitis.

Idiopathic Almost 25% of children with pancreatitis do not have any underlying etiology. They are labeled as having *idiopathic acute pancreatitis*, which is a diagnosis of exclusion. These children may develop recurrent attacks of pancreatitis.

PATHOGENESIS

The following four basic changes occur in pancreatitis, regardless of whether it is acute or chronic disease:

- Proteolytic destruction of pancreatic tissue
- Necrosis of blood vessels resulting in hemorrhage
- Necrosis of fat by lipolytic enzymes
- Associated inflammatory reaction.

Mild disease is characterized by peripancreatic fat necrosis and interstitial edema and the more severe form by intrapancreatic fat necrosis, parenchymal necrosis and hemorrhage. It may derange both endocrine and exocrine functions of the gland. The pancreatic acinar cells synthesize and store digestive enzymes until they are stimulated to secrete them into the ducts. All pancreatic enzymes, except amylase and lipase, are synthesized as proenzymes. The duodenum secretes an enzyme called *enterokinase* which activates trypsinogen to trypsin. Trypsinogen also has the capacity to slowly autoactivate to trypsin. Trypsin plays a major role in the pathogenesis of pancreatitis. It activates most proenzymes that participate in the process of autodigestion. Trypsin also activates prekallikrein to kallikrein which directly activates the kinin system and indirectly causes abnormalities in clotting and the complement system.

CLINICAL FEATURES

Most children with acute pancreatitis present with upper abdominal pain and vomiting. The pain is sudden in onset, with gradual increase in severity and reaches maximal intensity in a few hours. It may radiate to the back. The most common site is the epigastrium, followed by right hypochondrium, periumbilical area, back and lower chest. Pain is aggravated by food intake. Some children may have fever, tachycardia, hypotension, jaundice and abdominal signs like guarding, rebound tenderness and decreased bowel sounds. Many children with severe systemic illnesses causing pancreatitis refuse feeds. Hence acute pancreatitis should be ruled out, if a sick hospitalized child has worsening of clinical status with feed intolerance. Jaundice or elevated transaminases should raise the possibility of biliary tract involvement. Rarely, patients present with ascites or an abdominal mass. Epigastric tenderness is a useful, but nonspecific and unreliable sign. There are two rare clinical signs of hemorrhagic pancreatitis due to extravasation of hemorrhagic pancreatic exudate: Grey-Turner's sign—ecchymoses in the flanks; Cullen's sign—ecchymoses in the periumbilical region. These signs are more commonly seen in adults than children, and indicate a poor prognosis. Clinical features are summarized in **Table 1**.

It is difficult to differentiate sterile from infected acute necrotizing pancreatitis as both may result in fever, leukocytosis and severe abdominal pain. However, the differentiation is vital as the mortality rate in infected acute necrotizing pancreatitis is nearly 100% without intervention. The organism can be identified and appropriate antibiotic started with the help of CT-guided fine-needle aspiration and culture of pancreatic and peripancreatic tissue fluid.

The most important factor that determines management of pancreatitis following trauma is whether or not the pancreatic duct has been disrupted. The child with blunt trauma usually presents with mild epigastric pain, which may become severe as the pancreatic fluid leaks into the surrounding tissues. A high index of suspicion is essential as the clinical presentation can be quite deceptive. Serum amylase and lipase will be elevated in most children. A CT scan, or MRI cholangiogram may be a valuable diagnostic tool at this stage. Most of these children respond to conservative management alone. Surgery is indicated if there is disruption of the main pancreatic duct.

Table 1 Clinical features of acute pancreatitis

	Common	*Rare*
Symptoms	• Abdominal pain • Irritability in infants • Anorexia • Nausea • Vomiting	• Jaundice • Fever • Feed intolerance • Respiratory distress
Signs	• Dehydration • Abdominal distension • Abdominal tenderness	• Ascites • Pleural effusion • Grey-Turner's sign • Cullen's sign

Complications

Acute pancreatitis is a self-limited disease and most children make an uneventful recovery. Mortality, if any, is due to complications of systemic illness. Major complications are summarized in **Table 2**. Pancreatic necrosis is a segmental pancreatic infarction which may result in serious complications. Fortunately, it is very rare, seen in less than 5% of adults and less than 1% of children. The risk of pancreatic necrosis increases with vascular leakage. The combination of hypovolemia, inflammation, and high hematocrit decreases pancreatic blood flow resulting in infarction. A contrast-enhanced CT reveals an area of under-perfused pancreatic gland. Pancreatic pseudocysts are rare in children compared to adults.

Table 2 Complications of acute pancreatitis

Systemic (in the 1st week)	*Local (after the 1st week)*
Cardiovascular • Shock—due to third spacing of fluids, peripheral vasodilatation, and depressed left ventricular function • Arrhythmias *Pulmonary* • Respiratory failure—due to ARDS and pleural effusion *Renal failure* Due to renal hypoperfusion, leading to acute tubular necrosis *Hematological* DIC *Metabolic* • Hypocalcemia • Hyperglycemia—caused by insulin deficiency due to islet cell necrosis and/or hyperglucagonemia • Hyperlipidemia *Gastrointestinal* • Ileus *Neurological* • Purtscher's retinopathy—sudden blindness due to occlusion of the posterior retinal artery by aggregated granulocytes • Encephalopathy *Miscellaneous* • Arthralgia • Subcutaneous fat necrosis—tender red nodules caused by elevated circulating lipase	• Sterile pancreatic necrosis • Infected pancreatic necrosis • Pancreatic abscess • Pseudocyst • Rupture of pancreatic duct • Pancreatic ascites • Pleural effusion • Sinistral (left sided) portal hypertension due to splenic vein thrombosis; presents as upper GI bleed due to ruptured gastric varices

Abbreviations: ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; GI, gastrointestinal.

They usually resolve spontaneously and drainage is usually not necessary.

APPROACH TO DIAGNOSIS

It is unfortunate that there is no gold standard for the diagnosis of pancreatitis. The diagnosis is based on a constellation of points in the history, clinical examination, supportive laboratory tests and imaging. Pancreatitis can be diagnosed based on the presence of two of the following:

- Abdominal pain suggestive of pancreatitis
- Serum amylase or lipase levels at least three times the upper limit of normal
- Radiologic evidence of acute pancreatitis.

Most children with acute pancreatitis will fulfill these criteria. However, infants and young children may not complain of abdominal pain. *Serum lipase* level is a very sensitive and specific marker of pancreatitis and considered as the first investigation of choice. Serum lipase will rise within 4–8 hour of onset, peak at 24 hour, and may remain elevated for 8–14 days before normalizing. In renal failure, renal excretion of lipase is decreased and hence it may increase up to twofold above normal. Lipase may leak from the intestine in perforation of the bowel and so it may increase up to threefold above normal.

Serum amylase level was the traditional, standard diagnostic test for pancreatitis. Levels will rise within 2–12 hours of onset, peak within the first 48 hours, and remain elevated for 3–5 days before returning to baseline. Even though it is a very sensitive test, its specificity is relatively low. Studies have shown that about 40% of cases of acute pancreatitis in children could be missed if diagnosis is based on amylase alone. Other causes of high amylase levels include intestinal obstruction, appendicitis, bowel perforation, acute cholecystitis and mesenteric ischemia, all of which come in the differential diagnosis of acute pancreatitis. In pancreatitis due to hypertriglyceridemia, serum amylase may be normal due to the dilutional effects of the lipemia. Serum amylase reaches adult levels only by adolescence whereas serum lipase reaches adult levels after 1 year of age. Hence, lipase is more useful than amylase to diagnose acute pancreatitis in young children **(Table 3)**.

The half life of amylase is relatively short (2 hours) and hence cleared rapidly from the circulation. If a child presents late in the course of the disease, the amylase peak may be missed and is one scenario where acute pancreatitis with a normal amylase occurs. Unlike amylase, serum lipase will be normal in diabetic ketoacidosis and in macroamylasemia. Many patients with pancreatitis have a selective elevation of either amylase or lipase at presentation. Hence, ideally, both amylase and lipase should be measured in patients with suspected acute pancreatitis. However, levels of amylase and lipase do not correlate with the severity of acute pancreatitis or its prognosis. Although not routinely available, serum trypsin level is the most accurate laboratory indicator of pancreatitis.

Table 3 Comparison between serum amylase and lipase for diagnosis of pancreatitis

	Amylase	*Lipase*
Sensitivity	Very high	Very high
Specificity	High	Very high
Time for elevation	2–12 hours of onset	4–8 hours of onset
Duration of elevation	3–5 days	8–14 days
Diabetic ketoacidosis and macroamylasemia	Increased	Normal
Utility in young children	Poor	Good

Complete blood count reveals leukocytosis. Hematocrit may be initially increased due to hemoconcentration. A low hematocrit may indicate hemorrhage or hemolysis. Serum electrolytes, blood urea nitrogen and creatinine help to determine the level of hydration especially in patients with intractable vomiting. Hyperglycemia may be caused by damage to the pancreas resulting in decreased insulin secretion and increased release of glycogen, catecholamines and glucocorticoids. High serum aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) are suggestive of tissue necrosis. Obstruction of the common bile duct may cause elevation of bilirubin and alkaline phosphatase. Hypoxemia may be caused by ARDS and pleural effusion and pH may be decreased due to lactic acidosis, respiratory acidosis and renal insufficiency.

It is essential to differentiate acute biliary pancreatitis which may require urgent ERCP with biliary sphincterotomy and stone extraction from nonbiliary conditions. If there is a threefold or more increase of alanine transaminase (ALT), biliary pancreatitis should be ruled out. The combination of elevated amylase/lipase and ALT may be more predictive of pancreatitis than elevated amylase or lipase alone. Fortunately, such cases are rare in children.

Role of imaging Plain erect abdominal radiograph may show nonspecific findings in pancreatitis like a generalized or local ileus (sentinel loop), or a colon cut-off sign. Rarely, calcified gallstones or pancreatic calcification may be seen. A chest radiograph may show pleural effusion and, in severe cases, a diffuse alveolar interstitial shadowing suggestive of acute respiratory distress syndrome (ARDS). Abdominal ultrasonography **(Box 2)** and CT scan help to document pancreatitis, determine the severity and detect complications like pseudocysts. They also identify any underlying chronic pancreatitis.

CT scan with intravenous and oral contrast helps to detect pancreatic necrosis which appears as nonperfused areas of pancreatic parenchyma. The presence of air within the pancreatic parenchyma suggests infection in the necrosed tissue. This should be confirmed with percutaneous needle aspiration and culture. MRI is useful in a pregnant adolescent (because of the radiation teratogenicity of CT), those who are allergic to the contrast used for CT, and those with renal failure which may be aggravated by the iodinated contrast. It is superior to CT in the characterization of pancreatic fluid collections. Magnetic resonance cholangiopancreatography (MRCP) delineates the bile and pancreatic ducts better than CT and has a higher sensitivity in detecting choledocholithiasis and pancreas divisum.

MANAGEMENT

Medical Management

Treatment is essentially supportive, with the aim of alleviation of symptoms and prevention of complications. If an etiologic factor is identified, treatment should be directed at it. If the initial assessment is suggestive of mild pancreatitis, a conservative approach is indicated with intravenous fluids and frequent, but noninvasive, observation. No drugs (including antibiotics) are

BOX 2 Ultrasonography (USG) findings in acute pancreatitis

- Enlargement and altered echogenicity of the pancreas
- Dilated main pancreatic duct; common and intrahepatic bile ducts
- Gallstones
- Biliary sludge
- Pancreatic calcification
- Choledochal cysts
- Fluid collections—peripancreatic or cystic.

BOX 3 Early management of severe acute pancreatitis

- Meperidine—1–2 mg/kg IM/IV
- Aggressive IV fluid therapy
- Oxygen
- Frequent monitoring of vital signs, CVP, fluid intake output, blood gases
- Frequent monitoring of blood glucose, calcium, ALT, creatinine
- CT scan—indicated in clinical deterioration/septicemia/organ failure
- Early nasogastric feeding.

Abbreviations: IM, intramuscular; IV, intravenous; CVP, central venous pressure; ALT, alanine transaminase.

necessary, apart from analgesics. CT scanning is unnecessary unless there is evidence of deterioration. Early management steps are summarized in **Box 3**.

The most important cause of death is shock. Hence, the child's vital signs, urine output and central venous pressure should be monitored and corrected. They should be carefully observed for any signs of early organ failure like hypotension and pulmonary or renal insufficiency. Blood gas measurements and oxygen supplementation are mandatory if child has tachypnea. Children with signs of early organ dysfunction may deteriorate rapidly, and need to be cared for in an intensive care setting. Proper analgesia and intravenous fluids are the mainstay of management. Traditionally, opiates are used because of their potency. As morphine may increase the pressure in the sphincter of Oddi, meperidine 1–2 mg/kg IM/IV is preferred.

Capillary leak syndrome is common in children with severe acute pancreatitis. Hence, they may lose fluids from the vascular compartment. The situation may be aggravated if the stomach is decompressed by nasogastric aspiration. Unfortunately, in some centers, children with pancreatitis are kept fasting even today. Volume expansion is vital, as it provides cardiovascular stability, and also helps to prevent development of pancreatic necrosis. Recent studies have clearly shown that early feeding of patients with pancreatitis is beneficial. Enteral nutrition should commence within 24 hours of admission after fluid resuscitation and pain control. Several studies show that adult patients with acute pancreatitis tolerate jejunal feedings with fewer complications than those given parenteral nutrition. Antibiotics are usually unnecessary unless the child has developed pancreatic necrosis. There is no role for surgery during the initial period of resuscitation and stabilization; it is indicated only if the patient deteriorates due to local complications.

Hyperglycemia may complicate severe pancreatitis. However, it usually normalizes as the inflammatory process subsides, and blood sugar levels fluctuate widely. Hypoalbuminemia may lead to hypocalcemia which is usually asymptomatic and does not require any specific therapy. However, reduction in levels of ionized calcium may cause tetany. *Gabexate mesilate* is a trypsin inhibitor used to prevent or treat acute pancreatitis in adults. Gabexate infusion may be useful in children also.

Surgical Management

Surgery is usually not required and is limited to debridement of infected necrosed pancreatic tissue. Necrosectomy, if necessary for severe pancreatitis, is usually deferred for at least 2 weeks. In the rare instance of mild gallstone pancreatitis, cholecystectomy should be performed as soon as the child has recovered, but before the child is sent home. Abscess can be managed with intravenous antibiotics and external drainage. Surgery or endoscopic stenting may be necessary for traumatic rupture of the pancreatic duct.

35.14.2 CHRONIC PANCREATITIS

Chronic pancreatitis is a painful, destructive, inflammatory disease characterized by progressive fibrosis that leads to irreversible destruction of pancreatic tissue, culminating in exocrine and endocrine insufficiency. Histologic changes include irregular fibrosis, acinar cell loss, islet cell loss and inflammatory cell infiltrates.

ETIOLOGY

In children, chronic pancreatitis is usually caused by genetic diseases such as cystic fibrosis, hereditary pancreatitis or may be idiopathic **(Table 4)**. This is in contrast to adults, in whom it is usually due to chronic alcoholism or is idiopathic.

Chronic pancreatitis may be secondary to mutations of several genes. Hereditary pancreatitis is an autosomal dominant disease due to mutations in the trypsinogen gene *PRSS1* that cause premature conversion of trypsinogen to trypsin. These children become symptomatic at a very young age and there is a high-risk of developing pancreatic cancer. *SPINK1* mutations are a common cause of tropical pancreatitis (TP). Severe homozygote mutations of the *CFTR* gene cause cystic fibrosis.

CLINICAL PRESENTATION

The most common presenting symptom of chronic pancreatitis is abdominal pain. A characteristic feature is the almost instantaneous aggravation of pain by food. Although food may also aggravate the pain of peptic ulcer, there is usually a much longer interval between the meal and the pain.

Nausea, vomiting, anorexia and weight loss are common in chronic pancreatitis. Weight loss is secondary to decreased caloric intake due to the fear of exacerbating the abdominal pain. Malabsorption, which occurs if enzyme secretion is reduced to less than 10% of normal, and uncontrolled diabetes may also contribute to weight loss. Such severe weight loss never occurs in other painful abdominal conditions like peptic ulcer. The combination of chronic upper abdominal pain and severe loss of weight should always alert the clinician to the possibility of an underlying chronic pancreatic disease.

Table 4 Causes of chronic pancreatitis

Hereditary pancreatitis
• *CFTR* mutations
• *SPINK1* mutations
• Shwachman-Diamond syndrome
Metabolic causes
• Types I, IV and V hyperlipidemia
• Hypercalcemia
• Chronic renal failure
Autoimmune
• Inflammatory bowel disease
• Autoimmune chronic pancreatitis
• Sjögren syndrome–associated chronic pancreatitis
Obstructive
• Pancreas divisum
• Duct obstruction due to tumors
Miscellaneous
• Tropical pancreatitis
• Fibrocalculous pancreatic diabetes
• Postirradiation
• Idiopathic.

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; *SPINK1*, serine protease inhibitor Kazal type 1.

DIAGNOSIS

Chronic pancreatitis can be diagnosed by histologic or morphologic criteria alone or by a conglomeration of morphologic, functional and clinical findings. Functional abnormalities alone are not diagnostic of chronic pancreatitis because these tests do not differentiate chronic pancreatitis from pancreatic insufficiency without pancreatitis. Fecal elastase 1 (< 200 µg/g of stool) and MRCP are two noninvasive pancreatic function tests useful in this condition.

TREATMENT

Treatment depends upon the stage and etiology of chronic pancreatitis. It is similar to that of acute pancreatitis during the early phases characterized by discrete episodes. Intractable abdominal pain is the most distressing feature of CP. Treatment may be initiated with paracetamol, but most patients will ultimately require narcotics, resulting in the risk of narcotic addiction. Endoscopic, surgical and nerve block therapies have been tried in children with intractable pain.

Pancreatic enzyme supplementation helps restore digestive function as much as possible. Being proteins in nature, pancreatic enzymes may be destroyed by gastric HCl. This may be prevented to some extent by prescribing a proton pump inhibitor (PPI). Prolonged use of mega doses of pancreatic enzymes (> 6,000 units lipase/kg/meal) may culminate in a rare complication called *fibrosing colonopathy* resulting in formation of strictures in the ascending colon. Even though free radicals may play an important role in the pathophysiology of pancreatitis, the role of antioxidant therapy is still not clear. Another major problem is the development of diabetes as a sequel to destruction of the pancreatic islet cells.

TROPICAL PANCREATITIS

Tropical pancreatitis is a juvenile form of chronic calcific nonalcoholic pancreatitis prevalent almost exclusively in the developing countries of the tropics. In India, the highest prevalence is in the southeastern part of Kerala state. TP is almost exclusively seen in under-privileged children with severe PEM, associated with high levels of circulating free radicals which can damage the pancreas. The staple diet of these patients is cassava (tapioca/*Manihot esculenta*), a tuber rich in carbohydrates but very poor in proteins (0.4 g%) especially the sulfur containing amino acids methionine and cysteine. It contains toxic cyanogenic glycosides like linamarin and methyl linamarin (lotaustralin), which have been implicated in the pathogenesis of TP. Many recent studies have identified genetic markers especially mutations of *SPINK1* and *N34S*.

Chronic severe abdominal pain in childhood, followed by diabetes in an emaciated teenager is the classic presentation. The radiologic demonstration of extensive pancreatic calcification clinches the diagnosis. Management includes control of diabetes with oral hypoglycemic agents and/or insulin. Long-term analgesics and surgery may be required for intractable pain.

IN A NUTSHELL

1. Acute pancreatitis is relatively rare in children, but early diagnosis depends on strong clinical suspicion.
2. Infections, trauma and drugs are the most important predisposing factors.
3. Always exclude accidental/nonaccidental trauma in children with idiopathic recurrent pancreatitis.
4. Rule out HIV infection in children with unexplained pancreatitis as the disease as well as its treatment may result in pancreatitis.
5. There is no gold standard for the diagnosis of pancreatitis, but lipase and amylase are still useful laboratory markers.
6. In the diagnosis of pancreatitis, serum lipase is as sensitive but more specific than amylase.
7. Antimicrobials have no role unless patient has infected necrosis.
8. In recurrent pancreatitis, family history is important, since hereditary pancreatitis has an inherent propensity to lead onto carcinoma of the pancreas.
9. Early enteral feeding is of great importance; children should not be kept fasting for prolonged periods and nasogastric aspiration should be avoided.

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Chapter 35.15
Practical Approach to Malabsorption

VS Sankaranarayanan

Maldigestion often occurs due to defect in the luminal phase of digestion of ingested food (defective hydrolysis of nutrients) secondary to insufficiency of exocrine pancreatic enzymes such as pancreatic amylase, lipase and bile salts, pancreatic trypsin and chymotrypsin, and small intestinal bacterial overgrowth (SIBO) due to surgical causes resulting in failure of mixed micelle formation for fat digestion.

Malabsorption occurs most often due to defective mucosal absorption like celiac disease, cow's milk protein allergy (CMPA), tropical sprue, etc. It is characterized by relatively less fat in stool

(absence of grease/oil) and presence of abdominal bloating/flatulence, anemia and hypoalbuminemia. A good history and physical examination of the patient will give clue to the etiology and clinical diagnosis of malabsorption.

HISTORY

Consanguinity Abetalipoproteinemia, cystic fibrosis, congenital intestinal defects.

Age of onset Diseases causing malabsorption can present insidiously at different age groups (e.g., congenital disorders like cystic fibrosis, primary lactase deficiency at birth, acrodermatitis enteropathica and celiac disease by weaning age). Family history of similar illness has a role in cystic fibrosis, Crohn's disease, abetalipoproteinemia and food allergy.

Stool history Duration of chronic diarrhea, character, frequency, volume, consistency of stools, presence or absence of blood, mucus [inflammatory bowel disease (IBD)], oily or greasy, soft, bulky, pale and rancid stools (exocrine pancreatic insufficiency, biliary disease) or explosive with sore bottom (lactose malabsorption); diarrhea after gluten containing diet (celiac disease) or cow's milk (CMPA); associated symptoms like abdominal pain (Crohn's disease, pancreatic or biliary disease) failure to thrive and (fat, protein or carbohydrate malabsorption) nutrient deficiency like pallor and anemia (iron deficiency) glossitis and cheilitis (vitamin B complex especially, folic and B_{12} deficiency) angular stomatitis and cheilitis (riboflavin deficiency), edema (protein deficiency), stunting of growth with bony abnormalities (rickets), bleeding gums (vitamin C deficiency) epistaxis and petechiae (vitamin K deficiency) perioral and perianogenital ulcerations with alopecia (zinc deficiency—acrodermatitis enteropathica).

Abdominal surgery will suggest small bowel bacterial overgrowth or short gut syndrome or adhesive obstruction.

Immune deficiency History of contact with human immunodeficiency virus (HIV), or history of organ transplantation, chronic recurrent infections (tuberculosis, congenital immune deficiency) and drugs causing malabsorption (anticonvulsants).

Dietetic history Early introduction of cow's milk in CMPA, cereals in weaning food—wheat, rye, barley, oats in celiac disease. Appetite is often increased in exocrine pancreatic insufficiency and decreased in celiac disease.

PHYSICAL EXAMINATION

Physical examination includes a systematic general examination and systemic examination with assessment and recording of growth of the child. Any drop in growth centiles clinically will manifest as malnutrition and growth stunting (an indicator of chronic malabsorption). The attending physician is expected to look for hydration status; nutritional status [grade of protein energy malnutrition (PEM), stunting, vitamin, trace elements and mineral deficiencies]; presence/absence of peripheral edema (protein deficiency); constitutional symptoms such as fever (infection or inflammation); extra gut manifestations in eyes like Bitot spots; skin (infection, dermatosis, rash, edema, surgical scar, joint swelling in autoimmune diseases, and oral cavity (stomato glossitis); perianal area for excoriation, fistulae, fissures (Crohn's disease); persistent thrush in HIV; and abdominal examination for distension, scar, masses, organomegaly and ascites.

In summary, the physician at this stage should approach any child with malabsorption with high degree of clinical suspicion and try to answer the following questions: whether the patient is having chronic diarrhea of small bowel or large bowel; if small bowel, whether secretory or osmotic or mixed; if large bowel, whether it is inflammatory or infective or infiltrative; whether the child has maldigestion or malabsorption. What are the consequences of the disorder and how serious? And also determine the attitude of the caretaker and affordability for battery of laboratory diagnostic investigations to assess the specific cause. Only then a long-term management, counseling, and follow-up can be planned in an effective manner.

INVESTIGATIONS

Confirmation of malabsorption is based on the relevant laboratory tests **(Table 1)**. Various laboratory investigations intended for

Table 1 Clinical and laboratory findings in malabsorption

Signs and symptoms	*Laboratory findings*	*Malabsorbed nutrient*
Diarrhea	Stool weight ↑, serum potassium ↓	Water, electrolytes
Steatorrhea	Fecal fat ↑, serum cholesterol ↓	Dietary lipids, bile acids
Weight loss	Fecal fat ↑, fecal chymotrypsin or elastase ↓, xylose test ↓	Fat, carbohydrates, protein
Anemia	Serum iron ↓, hypochromic, microcytic, RDW ↑	Iron
Pernicious anemia, glossitis, Knuckle pigmentation	Macrocytic blood picture, megaloblastic marrow, Schilling's test abnormal	Vitamin B_{12}, folic acid
Pain in limbs and bones, pathologic bone fractures, Chvostek sign	Serum calcium ↓, alkaline phosphatase ↑	Potassium, magnesium, calcium, vitamin D_3, protein, amino acids
Signs of bleeding, easy bruising, petechial hemorrhage	Prothrombin time ↑	Vitamin K, vitamin C
Edema	Total protein ↓, serum albumin ↓, fecal α1-antitrypsin clearance ↑	Protein
Abdominal distension, gas	Abdominal X-ray, sonography, glucose H_2-breath test	Carbohydrates
Lactose intolerance (explosive diarrhea)	Lactose H_2-breath test ↑ intestinal mucosal lactase ↓	Lactose
Peripheral neuropathy		Vitamins B_1, B_6, B_{12}
Hyperkeratosis, parakeratosis, acrodermatitis	Retinol, zinc serum levels ↓	Vitamin A, zinc
Night blindness	Serum retinol ↓	Vitamin A
Malabsorption-clinical	Lymphocytopenia	Lymphangiectasia
Younger age, chronic diarrhea, Abetalipoproteinemia	Acanthocytes in blood smear	Calorie deficiency, deficiency of essential nutrients
Suspected Crohn's disease, tuberculosis	ESR ↑	Essential nutrients, calorie deficiency

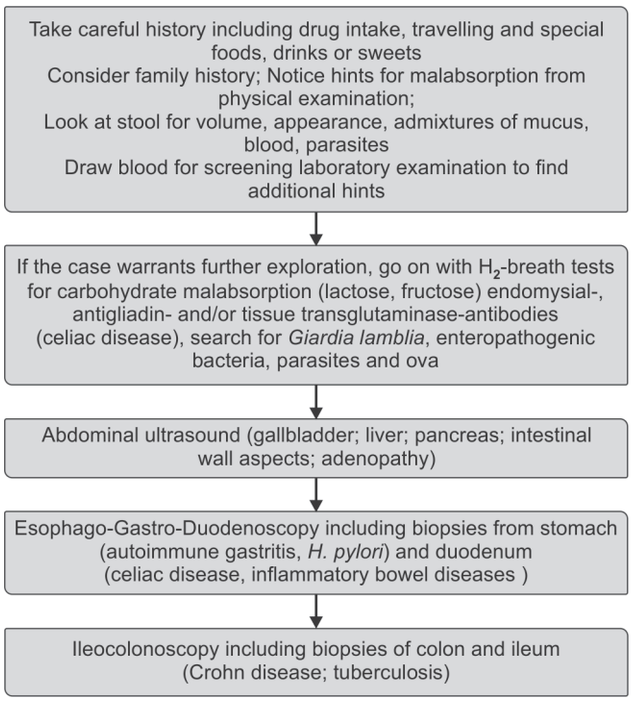
Abbreviations: RDW, red cell distribution width; ESR, erythrocyte sedimentation rate.

Table 2 Diagnostic significance of small bowel mucosal biopsy

Always positive	*Diagnostic and patchy*	*Diagnostic but nonspecific (abnormal villus atrophy)*
• Abetalipoproteinemia (intraepithelial fat) • Whipple disease (acid fast organism) • Agammaglobulinemia (absent plasma cells in LP)	• Lymphangiectasia (dilated lacteals in LP) • Giardiasis • Strongyloidiasis • Lymphoma • Eosinophilic gastroenteritis (> 15 eosinophils/hpf) • Crohn's disease (noncaseating granuloma), etc.	• Celiac disease • Tropical sprue • Cow's milk protein allergy • Severe PEM • Prolonged iron and folate deficiency

Abbreviations: LP, lamina propria; PEM, protein energy malnutrition.

Flow chart 1 An algorithm for diagnosis of malabsorption syndrome



chronic diarrhea hold good for malabsorption with chronic diarrhea also. These will be discussed in detail in the next section on diarrheal disorders.

The cause for malabsorption can be determined by the following tests: endoscopy (scalloping for atopy, white plaques in lymphagiectasia, eosinophilic abscesses, duplication cysts, aphthoid ulcers in Crohn's disease); small intestinal biopsy for villi/crypt study, parasites, eosinophil count (> 15/HPF); colonoscopy and biopsy (for tuberculosis, IBD, CMPA) and CT scan. The specific diagnostic tests for etiology of malabsorption include celiac serology [endomysial antibody, immunoglobulin A (IgA) tissue transglutaminase]; sweat chloride test and mutation analysis (cystic fibrosis); cow's milk specific IgE antibody (IgE specific CMPA), among others. Upper gastrointestinal endoscopy and duodenal biopsy are the mainstay of confirmatory diagnosis of malabsorption **(Table 2)**.

If pancreatic disease with secretory insufficiency is suspected, consider tests for secretory function, e.g., elastase or chymotrypsin in stool; and CT/MRI of pancreatic duct-systems or ERCP. The gold standard still is the secretin-pancreozymin test; this test is not really necessary for routine examination but may be helpful in individual cases; likewise the quantitative determination of 72 hour fecal fat excretion is cumbersome and not done now. When in doubt a therapeutic trial with pancreatic enzyme supplementation may be considered. If small bowel disease is still within the differential diagnostic scope, consider: Schilling-test (Vitamin B_{12} malabsorption), Glucose-H_2 breath test (bacterial overgrowth), α1-antitrypsin clearance (protein losing enteropathy), small bowel X-ray (fistulae, diverticula, blind loops, short bowel, etc.), and angiography of celiac and mesenteric arteries (ischemic bowel damage).

Flow chart 1 presents an algorithm for diagnosis of malabsorption syndrome.

IN A NUTSHELL

1. Maldigestion and malabsorption describe insufficient nutrient uptake and utilization by the gastrointestinal tract.
2. The etiology is varied with wide spectrum of clinical signs, symptoms and biochemical findings including vitamin and nutrient deficiency syndromes.
3. Chronic diarrhea and failure to thrive are the most common presenting symptom, yet there are several other presentations.
4. It is emphasized that the attending physician should focus on the underlying disease entity to provide appropriate counseling and treatment after making the diagnosis of a malabsorption syndrome.

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Chapter 35.16
Specific Malabsorption Syndromes

Srinivas S

Malabsorption syndromes refer to disorders in the intestinal processes of digestion and/or transport one or more nutrients—*carbohydrate, fat, protein or micronutrients* across the intestinal mucosa into the systemic circulation. This could be either due to a congenital disorder or a secondarily acquired disorder. **Table 1** enlists the common causes of malabsorption syndrome in India. In this chapter we will discuss some causes of malabsorption which are not discussed elsewhere in this book. Readers are also advised to refer to the chapters on chronic diarrhea, celiac disease, inflammatory bowel diseases (IBD), cystic fibrosis and alpha-1-antitrypsin deficiency.

SHORT BOWEL SYNDROME

Most patients with short bowel syndrome (SBS) have undergone bowel resection for one of the following:

- A congenital anomaly such as an omphalocele, gastroschisis, or intestinal atresia
- Necrotizing enterocolitis associated with prematurity
- Intestinal ischemia from malrotation and volvulus
- Crohn's disease (infrequent with current treatment)
- Total colonic aganglionosis.

Pathogenesis In general, virtually all digestion and absorption are completed within the first 100–150 cm of jejunum in a healthy individual. In the absence of an intact colon, the minimum length of healthy bowel necessary to avoid parenteral nutrition is approximately 100 cm. Patients who have less than 100 cm of jejunum exhibit significant malabsorption.

Table 1 Etiology of malabsorption in India

Pathology	*Specific diseases*
• Short gut syndrome	*Due to surgical intestinal resection for bowel gangrene as in* • Neonatal necrotizing enterocolitis • Intussusception • Malrotation and volvulus
• Damage to mucosal villi	• Celiac disease • Rotaviral diarrhea • Food protein enterocolitis, e.g., CMPA • Persistent diarrhea • Crohn's disease • Tuberculosis • Immunodeficiency state—with recurrent infections including giardiasis/strongyloidiasis • Radiation/chemotherapy/GVHD
• Pancreatic insufficiency	• Chronic pancreatitis • Cystic fibrosis
• Reduced intraduodenal bile causing fat malabsorption	• Cholestatic liver disorders
• Lymphatic disorders/disorders to lymph flow often manifesting as protein losing enteropathy	• Lymphangiectasia • Constrictive pericarditis

Abbreviations: CMPA, Cows' milk protein allergy; GVHD, graft-versus-host disease.

Clinical features Children with SBS may present with various medical issues, depending on the extent of their bowel resection, presence/absence of ileocecal valve and the level of medical complexity like total parenteral nutrition (TPN) dependency. These may include failure to thrive (FTT), nutritional deficiencies, malabsorptive diarrhea, recurrent dehydration, need for specialized enteral formula, catheter-related infections or sepsis.

Malabsorption of various nutrients also is likely to occur depending upon the area of bowel resected. For example, extensive jejunal resection leads to carbohydrate malabsorption. The undigested foods produce an osmotic diarrhea typical of most patients with SBS. The proximal small bowel is also important in the absorption of proteins, fat, and certain micronutrients, including copper. Semi-elemental or pre-digested formula is hence better tolerated than normal formula in short gut syndrome. Extensive terminal ileal resection would result in vitamin B_{12} deficiency and bile salt malabsorption causing cholestatic diarrhea.

Management The management of SBS requires an aggressive multidisciplinary approach. Since loss of intestinal mucosal absorptive surface remains the major hurdle, the main issues during the initial months following resection would be loss of fluid and electrolytes causing dyselectrolytemia and dehydration. The institution of early and aggressive enteral therapy is the most important stimulus for intestinal adaptation and the eventual discontinuation of parenteral therapy. Aggressive resuscitation with fluids, parenteral nutrition, or both is often required in the 1st week after intestinal resection. The hypersecretion of HCl noted within the first 12 months postresection is usually treated with H_2 blockers or proton pump inhibitors. Cholestyramine has been used to bind bile salts in patients with cholestatic diarrhea.

Prognosis Over a period time (months to years) intestinal adaptation occurs and diarrhea is no longer a problem in children with SBS; though some children with extensive bowel resections remain partially/completely TPN dependent for life. The ileum has greater adaptive function as far as improving its absorptive function in the presence of SBS. Small-bowel transplantation is used only if absolutely necessary in patients with associated severe advanced liver disease and those with major vascular access problems.

LACTOSE INTOLERANCE

Lactose intolerance is a syndrome characterized by impaired digestion of a disaccharide-lactose. This could be a congenital (primary lactose intolerance) or acquired (secondary lactose intolerance). The congenital variety is extremely rare.

Primary lactose intolerance due to congenital lactase deficiency is an extremely rare condition which presents with diarrhea since birth. The diarrhea typically is profuse while breastfed and stops while the child is put on a nonlactose containing formula. This is a permanent deficiency of lactase enzyme and does not improve with time.

In contrast secondary lactose intolerance is much more common and is often transient. Virtually any condition which causes intestinal mucosal damage can cause secondary lactose intolerance. This is because the *lactase* is present in the tips of the intestinal villi and is often the first among the intestinal disaccharidases to be lost in the event of mucosal injury.

Etiology The most common cause of transient secondary lactose intolerance is a viral gastroenteritis—like rotaviral diarrhea. Other causes include celiac disease, CMPA, Crohn's disease, radiation enteritis, GVHD, etc. Secondary lactase deficiency due to intestinal mucosal injury can appear at any age. However, children below 2 years are more susceptible because of many factors, including a high sensitivity of the gut to infectious agents, low reserve because of the small intestinal surface area, and high reliance on milk-based

products for nutrition. Adult-onset lactase deficiency is more of a genetically determined condition. Asians are known to be more prone for lactase deficiency than Caucasians.

Clinical features Symptoms are more severe in infants and younger children because of many factors, including a high sensitivity of the gut to infectious agents, low reserve because of the small intestinal surface area, and high reliance on milk-based products for nutrition. These include abdominal distension, borborygmi and a profuse watery diarrhea following ingestion of milk often causing perianal excoriation in infants and young children. Stool pH less than 5.5 along with the presence of stool reducing substance greater than or equal to 2+ (yellow) aids in the diagnosis. It is important to test the liquid component of stool for reducing substance. The clinical features in older children are less severe and restricted to flatulence, abdominal discomfort/crampy pain and the occasional diarrhea. A lactose hydrogen breath test is used for the diagnosis of lactose intolerance in older children.

Management Lactose intolerance is easily managed by reducing or completely avoiding lactose containing foods. Alternative non-lactose milk formula like soymilk is well tolerated. The secondary lactose intolerance improves within a few weeks once the primary disease causing intestinal damage is treated adequately and the intestinal villi recover.

PANCREATIC EXOCRINE INSUFFICIENCY

This is infrequently seen in chronic pancreatitis and invariably seen in cystic fibrosis in children. The classical clinical manifestation is steatorrhea described as the passage of large volume, foul smelling and greasy stools. This is seldom confused with chronic diarrhea and almost never needs intravenous fluid rehydration. The classical history is that of a hungry child who eats a lot and still does not grow well due to passage of large volume stools—occasionally oily. Traditionally the confirmation of pancreatic exocrine insufficiency requires a 72 hours fecal fat estimation. This is very cumbersome and is not routinely used except in select laboratories in the world. Early pancreatic exocrine insufficiency may manifest only as failure to thrive and estimating fecal elastase is useful method to confirm the same. In general as the conventional Indian diet tends to be low in fat when compared to the Western diet, clinically apparent steatorrhea does not manifest until later.

Management of pancreatic steatorrhea includes supplementing the patient's diet with oral pancreatic lipase enzyme as capsules. Pancreatic lipase capsules have to given along with every meal with higher doses being needed for fat rich meals. Doses as high as 2,500 lipase units/kg/day are used in infants with cystic fibrosis without any complications.

MALABSORPTION IN CHOLESTATIC DISORDERS

The classical example of this syndrome is a child with neonatal cholestasis syndrome presenting with an intracranial bleed secondary to late hemorrhagic disease of newborn, i.e., secondary to vitamin K malabsorption.

The fat soluble vitamins A, D, E and K depend on bile acids for their absorption. Hence, the lack of intraduodenal bile in neonatal cholestatic disorders predisposes to fat soluble vitamin deficiency. Malabsorption of fat soluble vitamins increases with severity of cholestasis. Infants with prolonged cholestasis of infancy like Watson Alagille syndrome or progressive familial intrahepatic cholestasis are likely to develop Bitot's spots unless given regular parenteral vitamin A supplements. Children with cholestatic disorders should be given vitamin K, A and D injections regularly.

Dietary fat is broken down by pancreatic lipase into predominantly long-chain fatty acids and they are dependent on bile acids for micelle formation and absorption. In cholestasis, due to the lack of intraduodenal bile acids, fat is malabsorbed and this results in the passage of greasy/oily stools (steatorrhea). Unlike in pancreatic steatorrhea, exocrine pancreatic lipase enzyme supplementation will not improve the malabsorption. Substitution of medium-chain triglycerides (MCT) in the diet in place of long-chain fatty acids improves steatorrhea and weight gain as MCT does not require bile acids/micelle formation for its absorption. This forms the basis for prescribing a formula rich in median chain triglycerides for young infants with cholestasis. Coconut oil is a naturally rich source of MCT and should be used in their diet.

PROTEIN LOSING ENTEROPATHY: INTESTINAL LYMPHANGIECTASIA

Protein losing enteropathy is a general term used to describe all conditions that cause loss of proteins through the gastrointestinal tract. For practical purposes the diseases causing protein losing enteropathy can be grouped into the following categories:

- Bad mucosal disease with ulcerations and erosions causing loss of protein, e.g., IBD, intestinal tuberculosis, GVHD, CMPA or
- Conditions causing lymphatic block, e.g., primary intestinal lymphangiectasia (PIL), constrictive pericarditis, post-Fontan procedure.

Primary intestinal lymphangiectasia This is a unique condition manifesting as a protein losing enteropathy where the lymphatic channels in the intestines are congenitally and abnormally dilated (ectatic).

Pathophysiology These abnormally dilated lymph channels have some form of functional block to lymph flow. A fat rich meal is often the best stimulus for lymph flow as this causes the ectatic channels to swell up and burst open thus discharging/leaking lymph into the intestines. As lymph is a rich source of proteins and immunoglobulins, this results in protein losing enteropathy.

Clinical manifestations Patients with primary intestinal lymphangiectasia usually present in childhood with edema and diarrhea (malabsorption and steatorrhea). Edema may be unilateral or bilateral, depending on the site of the lesion. Edema in primary intestinal lymphangiectasia is usually bilateral, while the secondary type often manifests as unilateral edema and is caused by various neoplastic, infiltrative, and inflammatory lesions affecting one side of the body. Frequently, lymphocytopenia and hypogammaglobulinemia are present, though the absence of these does not exclude intestinal lymphangiectasia.

Upper gastrointestinal (GI) endoscopy may occasionally reveal a starry sky pattern of the duodenal mucosa due to dilated intestinal lacteals and biopsies may reveal dilated intestinal lacteals consistent with the diagnosis of PIL.

Complications Despite hypogammaglobulinemia, opportunistic infections rarely occur, although lymphocytopenia predisposes patients to abnormal cellular immunities, including homograft rejection and cutaneous anergy. In patients with early onset PIL, growth retardation is common. The risk of lymphoma is increased in PIL. Fibrotic entrapment of the small bowel is reported in patients with congenital intestinal lymphangiectasia. Oral manifestations include gingivitis caused by poor lymphocytic function and enamel defects caused by poor calcium absorption.

Management Dietary modifications include a low-fat diet and substitution of long-chain fatty acids with MCT. MCTs do not stimulate lymph flow and are directly absorbed into the circulation without micelle formation. This strategy thus reduces the lymph leak/protein loss into the intestines.

Clinical course and response are highly variable depending upon the extent and severity of intestinal lymphangiectasia and whether it is part of a syndrome involving abnormal lymphatics

throughout the body; e.g., Hennekam syndrome carries a poor prognosis. Medications are not usually useful in intestinal lymphangiectasia. Treatment of secondary causes of lymphangiectasia targets the underlying disease. Octreotide is found to be effective in refractory cases.

IN A NUTSHELL

1. Calcium, vitamin D, iron and folic acid are absorbed in proximal small intestine while bile acids and vitamin B_{12} are absorbed in terminal ileum.
2. Virtually any disease process causing intestinal mucosal villi damage can cause a secondary lactose intolerance which improves with intestinal villi recovery.
3. Patients with a short bowel and an intact ileum and colon rarely need long-term enteral or parenteral nutrition.
4. Celiac disease needs to be treated with lifelong adherence to gluten-free diet.
5. Pancreatic steatorrhea can be effectively treated with exocrine pancreatic enzyme supplementation.
6. Children with neonatal cholestasis are prone for fat soluble vitamin deficiency—which if not treated in time can result in intracranial bleed/night blindness.
7. Intestinal lymphangiectasia is a congenital cause of protein losing enteropathy which is managed with diet rich in MCT.

MORE ON THIS TOPIC

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Chapter 35.17
Inflammatory Bowel Disease

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The term *inflammatory bowel disease (IBD)* denotes a group of disorders characterized by chronic intestinal inflammation. It includes Crohn's disease (CD), ulcerative colitis (UC) and inflammatory bowel disease unclassified (IBDU).

Ulcerative colitis, the first to be described in 1859, is localized to the colon and spares the rest of the gastrointestinal (GI) tract. The disease begins in the rectum and extends proximally for a variable distance and is limited to the colonic mucosa. CD, which was first described as *regional ileitis* in 1932, can involve any region of the alimentary tract from the mouth to the anus and leads to transmural inflammation. Although there is an overlap between the two disorders, they differ significantly in their clinical course, management and outcome. Around 10% of patients with isolated colonic involvement have some features of both UC and CD, and are labeled as IBDU at diagnosis. These cases may show typical UC or CD features on follow-up. The term *indeterminate colitis* is used when the diagnosis of CD or UC cannot be made even on the histology of a colectomy sample.

EPIDEMIOLOGY

Inflammatory bowel disease has been most prevalent in North America, Northern Europe and the United Kingdom. The prevalence varies not only by the geographic location, but also by race and ethnicity. Pediatric IBD accounts for about 20–25% of all cases of IBD in the west and 7% of all cases in the available data from India. Overall, CD is more common than UC with a slightly higher prevalence in boys than girls. Most cases present between 10 years and 14 years of age. About 10% of all pediatric IBD occurs in children less than 6 years of age and 1% in infants. Children with UC have a more extensive colonic involvement at presentation and a higher propensity for extension of the disease compared to adults. In CD, children have more colonic and perianal disease and less of isolated small bowel involvement in comparison to adults.

The risk of IBD in family members of an affected person is around 7–30% and a child in whom both parents have IBD has a 33% chance of developing the disease. Although it is more common to have the same type (UC/CD) of IBD in family members, both CD and UC have been reported in the same family. A concordance rate of approximately 50% has been observed amongst monozygotic twins for all types of IBD.

ETIOPATHOGENESIS AND GENETICS

The etiopathogenesis of IBD is multifactorial. There is a complex interplay of genetic factors, environmental triggers and gut microflora which initiates an abnormal mucosal immune response and leads to intestinal inflammation. When the normal body mechanisms that keep *physiologic* inflammation in check fail, then pathologic inflammation ensues. But whether this represents an abnormal response to normal enteric antigens or a normal response to an as-yet-unidentified microbe is not known. Inflammatory mediators (cytokines, arachidonic acid metabolites, reactive oxygen metabolites and growth factors) are involved, with overproduction of proinflammatory cytokines and underproduction of anti-inflammatory or regulatory cytokines, leading to destruction of the tissue and remodeling with fibrosis.

Ulcerative colitis A number of environmental factors have been postulated to be important and may influence the development of UC. Appendicectomy, a diet low in refined sugars, breastfeeding and smoking are considered protective. Psychological stress and nonsteroidal anti-inflammatory drugs (NSAIDs) are potential triggers. The intestinal microbiome of IBD patients (both UC and CD) differs from that of healthy controls. Genome wide association study has shown that IBD is a complex disorder, with some shared and many unique predisposing genes between CD and UC. About 47 susceptibility loci/genes for UC alone and another 28 for both UC and CD are known. Linkage studies have shown that there are susceptibility genes for UC on chromosome 1, 2, 3, 5, 6, 7, 10, 12 and 17. The *IBD2* locus on chromosome 12 is the most common.

Crohn's disease A number of environmental factors such as gut microflora, *westernized* diet [rich in refined sugars and n-6 polyunsaturated fatty acids (PUFAs)], lack of breastfeeding and presence of infectious agents such as *measles* and *Mycobacterium paratuberculosis* have been implicated. Smoking and oral contraceptives appears to predispose to CD. Genome wide association study has shown 71 susceptibility loci/genes for CD. Mutations in *NOD2/CARD15* gene, located in pericentromeric region of chromosome 16, significantly increase the risk of CD and this is particularly associated with ileal location, younger age of disease onset and penetrating disease phenotype. Recently two new pathways have been implicated, which includes T-cell

regulation by the IL-23 pathway and the process of autophagy which controls intracellular bacteria by the *ATGI6L1* and *IRGM* gene. Mutations in IL-10 and IL-10R pathway have also been identified, especially in children with infantile onset of the disease. This subgroup of infantile IBD is characterized by severe disease, lack of response to the standard IBD therapy and poor outcome.

In CD, the main abnormality is in defective recognition and processing of intracellular bacteria whereas in UC it is of intestinal barrier integrity and function. However, it is important to remember that genetic factors provide no direct bearing on therapy.

CLINICAL PRESENTATION

Ulcerative colitis Passage of loose stools with blood and mucus accompanied by tenesmus and urgency is the most common presentation in children. In majority of cases, symptoms have a slow and insidious onset. Systemic symptoms such as anorexia, weight loss, fever and abdominal pain are present in those with extensive disease. The abdominal pain is crampy in nature and occurs before passage of stools. Fecal incontinence may be seen in patients with severe proctitis. A small percentage of children have an initial fulminant presentation with greater than five bloody stools/day, fever, tachycardia, anemia and abdominal tenderness and known as acute severe colitis. These children are at risk of developing the complication of toxic megacolon (presence of dilated colonic loop greater than 5.5 cm on abdominal X-ray) and perforation.

Crohn's disease The various sites of disease (small bowel, colon and gastroduodenal), discontinuous lesions and progression to involve other bowel segments with time lead to varied clinical manifestations in CD. This is also responsible for the delay in diagnosis of these subjects. Diarrhea, abdominal pain and weight loss are the classical triad of CD, but only 25% of affected children have this typical presentation. Abdominal pain is the most common presenting symptom (72%), followed by diarrhea (56%), weight loss (58%), lethargy (25%), anorexia (27%) and poor growth. Patients with predominant colonic disease present as diarrhea with blood and mucus, while those with small bowel involvement manifest as abdominal pain, watery diarrhea or with features of subacute intestinal obstruction. Some children may present with perianal disease in the form of fissures, fistulas and abscesses **(Fig. 1)**. Growth failure in CD may precede the abdominal complaints by few months and is characterized by delayed skeletal maturation, reduced lean body mass and delayed puberty. Early satiety, nausea, vomiting and epigastric pain may be seen in patients with gastroduodenal CD. Esophageal involvement is very uncommon and leads to dysphagia and odynophagia.

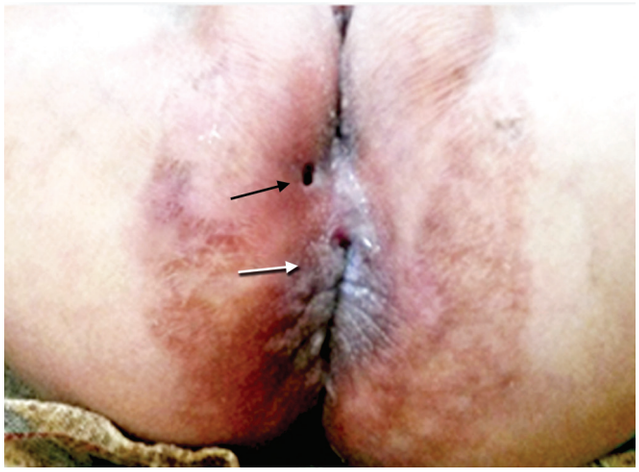


Figure 1 Perianal fistula (marked with black arrow) and fissure (short white arrow) along with rash in a child with Crohn's disease

Extraintestinal Manifestations

Extraintestinal manifestations (EIM) of IBD are present at diagnosis in 6–28% cases. Musculoskeletal (arthralgia, arthritis, and sacroiliitis) complaints are the most common EIM seen in 20–25% cases. Other EIM include aphthous stomatitis, pyoderma gangrenosum, erythema nodosum (EN), uveitis, scleritis, primary sclerosing cholangitis (PSC), fatty liver, autoimmune hepatitis and autoimmune hemolytic anemia. They may be present before, during or after the development of intestinal symptoms. EIM are more frequent in subjects with moderate to severe disease as compared to those with mild disease. Amongst the various EIM, PSC is more common in UC while ankylosing spondylitis (AS) and EN are more often seen in CD than UC cases.

Some EIMs, such as peripheral arthritis and EN correlate with disease activity whereas PSC, AS, and sacroiliitis do not. Arthritis in IBD is of two types: (1) peripheral arthritis involving primarily large joints, which may be further subclassified as pauciarticular (< five joints) or polyarticular (≥ five joints), and (2) axial arthropathy which includes AS and sacroiliitis.

Examination Complete physical examination with weight and height monitoring at each visit to detect growth faltering is essential in all children with IBD. Anemia, clubbing and pedal edema due to hypoalbuminemia may be present in patients with moderate to severe disease. Abdominal distension, loss of bowel sounds and rebound tenderness suggest presence of toxic megacolon. Patients with ileocolonic CD may have a mass palpable in right iliac fossa. Perianal examination may show presence of fleshy anal tags, deep fissures, abscesses and fistulae in children with CD. Presence of hepatosplenomegaly with or without jaundice points towards liver disease like sclerosing cholangitis.

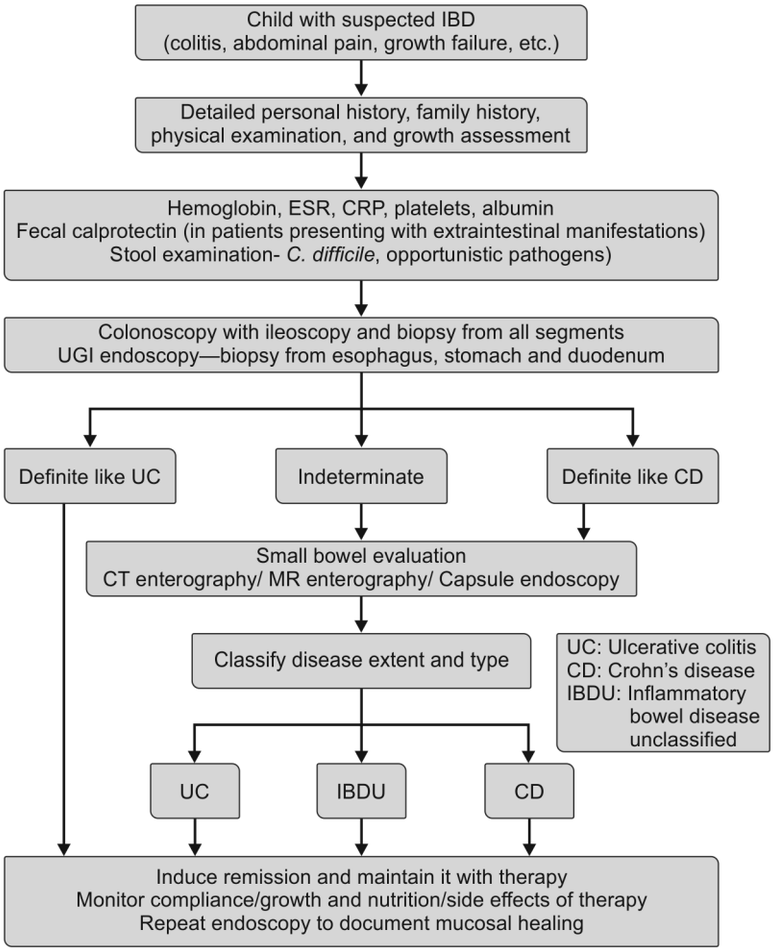
DIAGNOSIS

As a result of its varied presentation, diagnosis of IBD is often delayed by 5–15 months, with UC being diagnosed earlier than CD due to the alarming symptom of blood in the stools. The IBD working group of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), published *The Porto Criteria* for the diagnosis of childhood IBD. These criteria require that diagnosis of IBD should be based on a combination of history, physical examination, laboratory evaluation, esophagogastroduodenoscopy (EGD) and ileocolonoscopy with histology and imaging of the small bowel.

The stepwise evaluation of a child with suspected IBD is shown in **Flow chart 1**. Initial blood tests should include complete blood count, inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), serum albumin, transaminases and gamma-glutamyl transpeptidase (GGT). In a patient with active disease, there is anemia, hypoalbuminemia, thrombocytosis with raised ESR and CRP. However, normal values may be seen in patients with mild or inactive disease and thus do not exclude IBD.

Calprotectin is a protein, accounting for 30–40% of a neutrophil's cytosol. For the detection of intestinal inflammation fecal calprotectin (FC) is superior to any blood test. However, it is a nonspecific marker of inflammation and elevated FC levels cannot distinguish between the different causes of inflammation (e.g., IBD vs infection) or location of the disease (small vs large bowel). It is useful to discriminate between abdominal pain of functional origin and that due to inflammatory lesion of CD. Extraintestinal disease such as uveitis and PSC should be screened for by an ophthalmic examination and liver function tests (transaminases and GGT).

Flow chart 1 Algorithm for diagnosis of pediatric IBD



Various serological tests like antisaccharomyces cerevisiae antibody (ASCA) and perinuclear-antineutrophil antibody (p-ANCA) have been used for diagnosis and subtyping of IBD. ASCA is found more often in CD (50–70%) than in UC (10–15%) and p-ANCA is more common in UC (60–70%) than in CD (20–25%). However, they have a poor sensitivity and specificity and thus not very useful in clinical practice. Presence of ASCA also does not help in differentiating CD from colonic tuberculosis (TB).

Ileocolonoscopy and EGD should be done as the initial work-up for all children with suspected IBD. It is important that multiple biopsies are obtained from all areas of the visualized GI tract, even when macroscopic lesions are absent. The findings on endoscopy should be well documented. The typical macroscopic features of UC include erythema, granularity, friability, and superficial small ulcers which start from the rectum and extend proximally to various levels **(Fig. 2)**. As per the Paris Classification, UC is labeled as proctitis (rectum only), left-sided (distal to splenic flexure), extensive (distal to hepatic flexure) and pancolitis, depending upon the extent of colonic involvement. Pancolitis is the most common type in children, seen in 43–90% cases of UC. At times, the distal 5–10 cm of the terminal ileum may show erythema and/or edema without any ulceration and stricture in patients with pancolitis and this is known as *backwash ileitis*. Colonic histology shows cryptitis and crypt abscess along with signs of chronicity, i.e., alteration of the crypt architecture (crypt loss, branching), basal plasmacytosis and paneth cell metaplasia **(Fig. 3)**.

Crohn's disease is characterized by the presence of noncontiguous aphthous or linear deep ulcers involving single or multiple segments of the colon **(Fig. 4)**. The terminal ileum may show aphthous or linear ulcers with or without luminal narrowing. Histologically the disease is characterized by chronic focal inflammation, signs of activity (crypt abscess/cryptitis) and noncaseating granulomas **(Fig. 5)**. The Paris classification is used for defining the disease extent and nature. It gives an account of the age of onset, disease location (ileal alone, colonic, ileocolonic, isolated upper GI), behavior (stricturing/penetrating/inflammatory) and effect on growth at a glance. Ileocolonic disease is most commonly seen in children with CD. The differentiating features between CD and UC have been summed up in **Table 1**. In some cases, despite all efforts, it may not be possible to confidently diagnose patients as UC or CD so they are best labeled as IBDU.

Except when clinical, laboratory and endoscopic findings are suggestive of typical UC, an evaluation of the small bowel by imaging is mandatory at diagnosis. Magnetic resonance enterography (MRE) is the recommended imaging modality and is preferred over CT largely due to high diagnostic accuracy and lack of radiation exposure. It can help to define disease activity, distinguish between inflammatory, stricturing and penetrating disease and can demonstrate both mural and extramural complications. However, CT enterography may be used to delineate small bowel disease **(Fig. 6)** in places where MR facilities/expertise is not available.

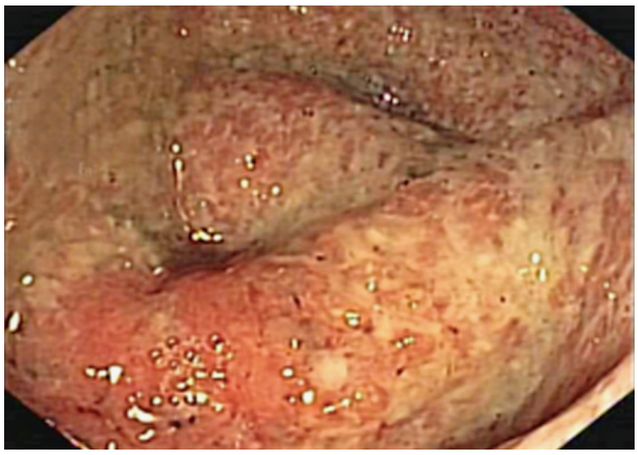


Figure 2 Colonoscopy showing diffuse ulceration, erythema, loss of vascular pattern and edema in a patient with ulcerative colitis

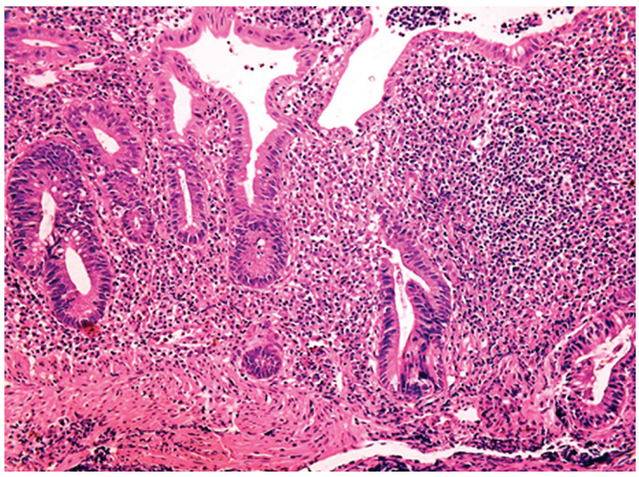


Figure 3 Rectal biopsy section from a case of active ulcerative colitis shows crypt distortion, crypt loss, crypt branching and mucodepletion and dense mixed inflammatory cell infiltrate in lamina propria. HE X 200 original magnification

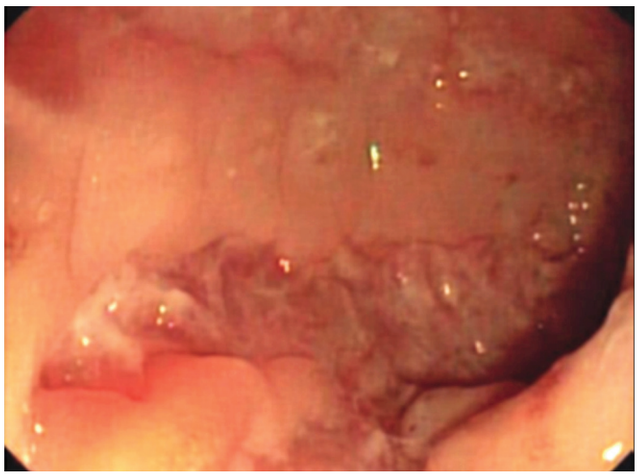


Figure 4 Colonoscopy showing deep longitudinal ulcers in a patient with Crohn's disease

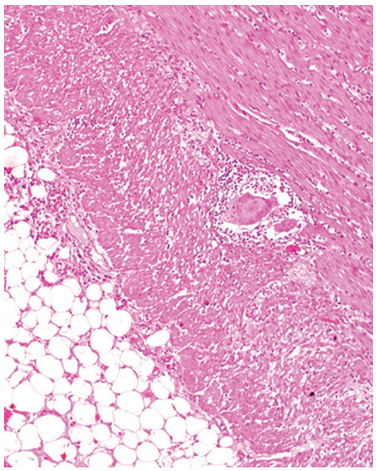


Figure 5 Sections from right-sided colectomy specimen shows granuloma in muscularis propria near adventitial adipose tissue from a case of Crohn's disease. HE X 100 original magnification

To assess the severity of UC or CD, various scoring systems have been devised which take into consideration clinical (stool frequency, nocturnal stools, general activity, abdominal pain and presence of blood in stools) and laboratory (hemoglobin, albumin, ESR) parameters. The pediatric Crohn's disease activity index (PCDAI) is used for CD, while the pediatric ulcerative colitis activity index (PUCAI) is used for UC. They are useful for assessing response to therapy and comparing outcomes across studies.

DIFFERENTIAL DIAGNOSIS

Inflammatory bowel disease has to be differentiated from other causes of colitis like infective colitis, allergic colitis, pseudomembranous colitis, immunodeficiency and TB. The important points that help in differentiating between these conditions and IBD are as follows:

- *Infective colitis, i.e., dysentery:* The most common cause of colitis in children; seen at all ages; acute onset often with fever and occasionally with vomiting; short duration of illness of 5–7 days, rarely last for more than 2 weeks and good response to treatment with antibiotics.
- *Cow's milk protein allergy:* Onset less than 3 years of age; temporal association with introduction of bovine milk; features of eczema, wheezing; family history of atopy; definite response to milk withdrawal and reappearance with a challenge; peripheral eosinophilia; and aphthous ulcers in rectum on proctosigmoidoscopy.
- *Pseudomembranous [Clostridium difficile (C. difficile)] colitis:* Seen at all ages; history of antibiotic intake; *C. difficile* toxin assay positive in stool; presence of pseudomembranes (yellowish gray plaques of 2–5 mm or larger) on colonoscopy are pathognomonic of *C. difficile* colitis. *C. difficile* colitis may occur in patients with IBD and should always be excluded in patients presenting with severe acute colitis.
- *Immunodeficiency:* Presents at an early age usually in infants or young children; family history of similar illness; history of infection at other sites, e.g., multiple episodes of respiratory or skin infections and liver abscesses. Chronic granulomatous disease may present with enterocolitis and perianal disease just like CD. Acquired immunodeficiency syndrome (AIDS) may present with colitis secondary to opportunistic infections

Table 1 Differences between Crohn's disease and ulcerative colitis

	Crohn's disease	*Ulcerative colitis*
Abdominal pain	+++	±
Bleed per rectum	++	++++
Growth failure	++	±
Weight loss	++	±
Perianal disease	+++	–
Rectal sparing	++	Rare
Small bowel disease	Common	None except backwash ileitis
Strictures	++	Rare
Fistulas	++	–
Colonoscopy	Aphthous, deep linear or serpiginous ulcers which are asymmetrical in distribution	Diffuse, small, superficial with erythema, edema, loss of vascular pattern and friability
Discontinuous (skip) lesions	Yes	No
Bowel involvement	Transmural	Mucosal
Granulomas on histology	Yes	No

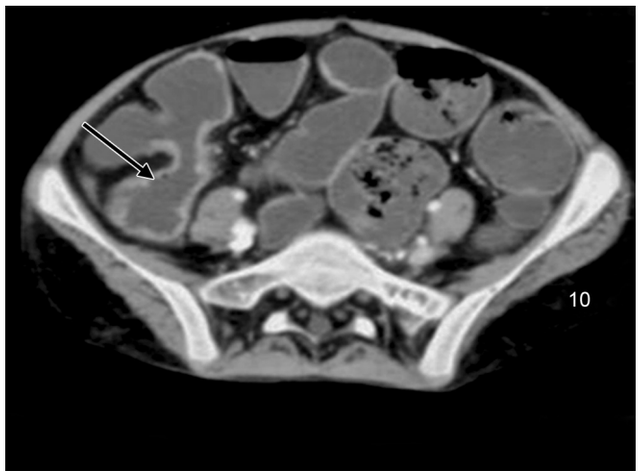


Figure 6 CT enterography showing thickening of ileum in a patient with Crohn's disease

like cytomegalovirus (CMV) colitis. Immunodeficiency work-up is required in few cases with immunoglobulin profile, test of phagocytic function and retrovirus serology.

- *Intestinal tuberculosis:* Intestinal TB often masquerades as CD in its clinical features. Colonic ulcers are circular in TB and longitudinal (along the long axis of colon) in CD. Cecum and ileocecal valve involvement is more common in TB. Ascites and necrotic abdominal lymph nodes are seen in TB. Granulomas are larger and show caseation in TB. Presence of acid fast bacilli on histology confirms the diagnosis of TB. It is essential to diagnose CD or TB correctly as the treatment for these two conditions is different and immunosuppression in a patient with intestinal TB may lead to disease flare and poor outcome.

TREATMENT

Medical Management

Inflammatory bowel disease is a disease of remissions and relapses. The goal of medical therapy is to induce and maintain remission **(Table 2)** and prevent disease complications with the minimum possible medications. Apart from the control of disease activity, maintenance of nutrition and bone health and prevention of infections by appropriate immunization is important. The main drugs used for treatment of children with IBD are as follows **(Table 3)**.

Steroids They have a central role as an induction agent in CD and moderate to severe UC. Prednisolone, in a dose of 2 mg/kg/day (maximum 40 mg/day) for 2–4 weeks followed by gradual tapering over 6–8 weeks achieves clinical remission in majority of cases. They are not used as maintenance therapy. The principles of steroid use in IBD are as follows—use an effective dose, do not overdose, do not treat for excessively short periods, do not treat for excessively long periods and anticipate side effects. Adequate dietary supplementation with calcium and vitamin D is essential to prevent bone disease.

5-aminosalicylic acid (ASA) agents They act by modifying neutrophil mediated tissue damage, by inhibition of leukotriene biosynthesis via the lipoxygenase pathway and scavenging of reactive oxygen species. Oral 5-ASA compound are recommended as first-line induction therapy for mild to moderately active UC and also for maintenance therapy in patients with UC. In CD its use is limited as an adjunctive role in isolated colonic CD as an induction agent. Combining oral 5-ASA with topical 5-ASA (enema, suppository) is more effective than oral alone. Sulfasalazine consists of 5-ASA in aza bond linkage with sulfapyridine. The sulfa moiety here acts as a carrier delivering the pharmacological active ASA moiety to the colon.

Immunomodulators These include drugs like azathioprine, 6-mercaptopurine (6-MP) and methotrexate. Thiopurines (AZA, 6-MP) take about 3 months to be fully effective and therefore cannot be used to induce remission. They have a role in steroid refractory [defined as active disease despite an adequate dose

Table 2 Induction and maintenance therapy in patients with Crohn's disease and ulcerative colitis

Therapy	*Crohn's disease*	*Ulcerative colitis*
Induction	Mild or moderate disease • Oral prednisolone or • Exclusive enteral nutrition *Severe disease* • Intravenous steroids or • Infliximab 5-ASA may be effective in mild disease Antibiotics [metronidazole (7.5 mg/kg/dose TDS)/ ciprofloxacin (5 mg/kg/ dose BD)] in perianal disease	*Mild disease* • Oral 5-ASA ± Topical mesalamine *Moderate or severe* • Oral prednisolone *Acute severe colitis* • Intravenous steroids (1st line) • Infliximab or IV cyclosporine (2nd line) • Surgery (failure of medical therapy)
Maintenance	Immunomodulators (Azathioprine/6-MP/or methotrexate) or Infliximab and other biologicals (severe disease)	5-ASA preparation or Azathioprine/6-MP (in frequent relapsers)

Abbreviations: ASA, aminosalicylic acid; IV, intravenous; MP, mercaptopurine.

Table 3 Dosage and side effects of medication used for treatment of inflammatory bowel disease (IBD)

Medication and dose	*Side effects*	*Monitor*
Steroids • Oral prednisolone (1–2 mg/kg/day) • IV methyl prednisolone (2 mg/kg/day)	*Common*: Acne, moon facies, hirsutism, cutaneous striae *Uncommon*: Steroid psychosis, hypertension proximal myopathy, growth impairment, osteoporosis, cataract and raised intraocular pressure	• Blood pressure • Ophthalmic evaluation
Aminosalicylate • Mesalamine (50–100 mg/kg/day) • Sulfasalazine (40–60 mg/kg/day)	• Vomiting, headache, diarrhea • Stevens-Johnson syndrome, pulmonary fibrosis, hepatotoxicity, agranulocytosis and mild hemolysis	• CBC • LFT • Creatinine
Immune modulator • Azathioprine (2–2.5 mg/kg/day PO) • 6-mercaptopurine (1–1.25 mg/kg/day PO) • Methotrexate (15 mg/m^2/week—PO/SC)	• Bone marrow suppression, pancreatitis and increased risk of infections • Hepatotoxicity	• CBC • Amylase • LFT
Biologicals IV infliximab (5 mg/kg/dose at 0, 2 and 6 weeks and 4–8 weekly thereafter for maintenance)	Infusion reactions, flare of infections (TB, hepatitis B), demyelinating diseases, psoriatic rash	Screen for sepsis/TB before therapy

Abbreviations: CBC, complete blood count; LFT, liver function tests; TB, tuberculosis; IV, intravenous; PO, per oral; SC, subcutaneous.

(1–2 mg/kg or minimum 20 mg/day) and duration (2 weeks) of steroids] and steroid dependent [relapse when steroids are tapered to 10 mg/day/frequently relapsing (≥ 2 relapses/year)] cases as a steroid sparing agent. Some centers add azathioprine from the beginning in severe cases to prevent subsequent relapses and repeated use of steroid.

Biologicals These include various antitumor necrosis factor alpha (anti-TNF-α) agents like infliximab, adalimumab and anti-α-integrin agents like natalizumab. These are potent and expensive medications indicated for induction and maintenance of severe luminal or fistulizing CD or induction of severe active UC refractory to steroid treatment. Infliximab is administered as an infusion at a dose of 5 mg/kg/dose at weeks 0, 2 and 6 and thereafter at 8-week intervals for maintenance.

Exclusive enteral nutrition (EEN) Exclusive enteral nutrition, in which a specific liquid formula (elemental, semi-elemental, or polymeric) is given without any other food item for 6–8 weeks, has been used for inducing remission in pediatric CD. Postulated mechanisms of action have included elimination of dietary antigens, overall nutritional repletion, correction of intestinal permeability, diminution of intestinal synthesis of inflammatory mediators via reduction in dietary fat, and provision of important micronutrients. EEN is as effective as steroids in inducing remission in newly diagnosed and active CD. EEN promotes mucosal healing and has beneficial effect on linear growth. The disadvantages of EEN include the high cost of the formula and the fact that the child cannot eat anything else for 6–8 weeks.

Surgery

Ulcerative colitis Surgery with restorative proctocolectomy (ileoanal pouch anastomosis) is curative and the surgical procedure of choice. The indications for surgery in UC patients are: acute severe colitis refractory to medical therapy; toxic megacolon; colonic perforation; uncontrolled GI hemorrhage; chronic ongoing disease with steroid dependence and colonic dysplasia or carcinoma.

Crohn's disease In CD surgery is not curative and management is directed at minimizing the impact of disease. At least 30% of patients require surgery in the first 10 years of disease and approximately 70–80% will have surgery in their lifetime. Surgery is indicated for bowel obstruction, drainage of abscesses, nonhealing fistulae, perforation or GI bleeding. Surgery should be considered for those in whom medical treatment has failed. In view of the chronic disease, attempts should be made to minimize intestinal resection and prevent short gut.

A close collaboration between gastroenterologist and surgeon experienced in pediatric IBD is essential for a good outcome.

Supportive Therapy

Nutritional therapy Recognition and correction of malnutrition by provision of adequate calories and proteins is important. The details of growth, pubertal status, disease mapping (site, extent and resections) and drugs administered should be noted. Anemia is seen commonly and is multifactorial due to iron deficiency (blood loss), vitamin B_{12} deficiency (terminal ileal disease/resection), folate deficiency (use of methotrexate, sulfasalazine) and chronic disease. Recognition of the type of anemia and appropriate supplementation of iron, B_{12} or folate should be done. *High-risk* children with IBD, i.e., those with growth failure, pubertal delay, vertebral fractures and prolonged steroid therapy should have a dual X-ray absorptiometry (DXA) scan for assessment of bone mineral density. Appropriate supplementation of vitamin D and calcium is essential.

Immunization Inflammatory bowel disease patients are treated with immunosuppressant medications which increase the risk of developing infections, several of which can be prevented by appropriate vaccination. A detailed history of prior immunization and illnesses suffered should be taken in all patients. Ideally, an effort should be made to immunize pediatric patients with IBD with age appropriate live viral vaccines [e.g., *varicella* and measles, mumps and rubella (MMR)] before starting immunosuppressive therapy. Treatment with high-dose systemic corticosteroids (≥ 2 mg/kg/day of prednisone or ≥ 20 mg/day of prednisone or its equivalent for ≥ 14 days), cyclosporine or tacrolimus, thiopurines, methotrexate or biological is defined as immunosuppressive therapy. It is recommended that patients wait at least 1 month after discontinuing corticosteroids before immunization with *varicella* vaccine. However, inactivated vaccines can be safely given even along with immunosuppressant therapy.

COMPLICATIONS AND PROGNOSIS

The disease course is characterized by remissions and exacerbations. The complications depend upon the disease extent and severity of IBD. Patients with severe disease are more likely to require prolonged immunosuppressive therapy and surgical interventions, which increases the risk of short bowel and adhesive intestinal obstruction. The risk of colon cancer is increased in patients with UC and CD (with colonic involvement) and they should undergo screening colonoscopy with surveillance biopsies every 1–2 years, beginning approximately 7–10 years after their initial diagnosis. Patients who require therapy with

immunomodulators and biologicals also have an increased risk of non-Hodgkin lymphoma. Children with IBD are at increased risk of having depression, social isolation, poor self-esteem and poor scholastic achievement due to chronic illness and school absences. Appropriate screening and attention to these psychosocial issues can improve the clinical outcome and health-related quality of life of these children.

PREVENTION

Efforts towards prevention of IBD by manipulation of gut microflora, exposure to helminths in childhood and dietary alterations (e.g., intake of polyunsaturated fatty acids, curcumin) are still in experimental stages. Prevention in IBD is therefore largely limited to preventing side effects related to disease management. Children with IBD, specifically CD, are at risk of exposure to ionizing radiation secondary to repeated medical imaging. Radiation has increased risk of cancer in children and therefore it is important to limit radiation exposure by using appropriate imaging modalities like ultrasonography, MRI and endoscopy. The combination of immunosuppressive medications places children with IBD at increased risk of opportunistic infections. Population studies suggest that there is an increased risk of thromboembolism in children with IBD (UC more than CD) compared to controls. Good control of disease activity and mucosal healing are paramount to achieve adequate growth, timely puberty and bone health. Meta-analysis of patients requiring surgery has shown that ileal pouch-anal anastomosis (IPAA) increases the risk of infertility compared to medical management alone and this should always be considered and discussed with the family.

IN A NUTSHELL

1. Inflammatory bowel disease includes Crohn's disease (CD), ulcerative colitis (UC) and inflammatory bowel disease unclassified (IBDU).
2. Nearly, 20–25% of all IBD has onset in childhood (< 18 years) with most children being diagnosed at 10–14 years of age.
3. The etiopathogenesis of IBD involves interplay between genetic factors, environmental triggers and gut microflora which initiates an abnormal mucosal immune response and leads to intestinal inflammation.
4. Crohn's disease can involve any part of the GI tract from mouth to rectum whereas UC is limited to the colon. Correct diagnosis of IBD and its subtype, i.e., UC or CD is essential as the management and outcome differs.
5. Loose stools with blood and mucus, i.e., features of colitis are the most common presentation. In addition, CD may present with abdominal pain, growth failure or small bowel type of diarrhea.
6. Extraintestinal manifestations (arthralgia, arthritis, EN, pyoderma gangrenosum, sclerosing cholangitis, uveitis, etc.) are seen in 6–28% children with IBD.
7. Diagnosis of IBD should be based on a combination of history, physical examination, laboratory evaluation, EGD with biopsy, ileo-colonoscopy with biopsy and small bowel imaging.
8. Treatment comprises of an induction phase (5-ASA, steroids, enteral nutrition, biological), followed by a maintenance phase (5-ASA, immunomodulators and biological).
9. Surgery is reserved for patients refractory to medical therapy or those with complications like toxic megacolon, perforation or hemorrhage.
10. Achieving optimal growth, timely puberty and prevention of bone disease is a very important aspect of management of children with IBD.

MORE ON THIS TOPIC

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Chapter 35.18
Celiac Disease

Lalit Bharadia

Celiac disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals. It is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, human leukocyte antigen (*HLA)-DQ2* or *HLA-DQ8* haplotypes, and enteropathy. CD has a prevalence of 0.8–2.67% in the Western world. In one of the large population studies in Northern India, the prevalence was 15.44% by serology and 1.04% by histology. In India the disease is not only under-diagnosed because of varied and nonspecific clinical symptoms, but also delayed due to lack of awareness.

The prevalence of CD, as well as other autoimmune disorders like type 1 diabetes, has greatly increased in recent years, for reasons that are currently unclear but are likely related to environmental changes. Samuel Gee, in 1888, published the first complete modern description of the clinical picture of CD and stressed the importance of diet in its control. By 1952, Willem Dicke recognized that the disease is caused by the ingestion of wheat proteins, and not carbohydrates.

PATHOGENESIS

Celiac disease is a disease of genes and grains. HLA class II genes play an important role in the disease pathogenesis. Most patients with CD carry a variant of *HLA-DQ2* (DQ2.5; DQA1*05/DQB1*02), whereas the remaining patients carry *HLA-DQ8* (DQA1*03/DQB1*0302). The *HLA* genes present gluten peptide to T-cells which function as central effecter cells of inflammation by releasing different cytokines, notably, interferon (IFN)γ, a key marker of the inflammatory Th1 response. The release of these cytokines precipitates a cascade of immune, mesenchymal, and epithelial cell activation in the small intestine, resulting in the hallmark lesions of crypt hyperplasia, villus atrophy and increased intraepithelial lymphocytes (IELs) **(Fig. 1)**.

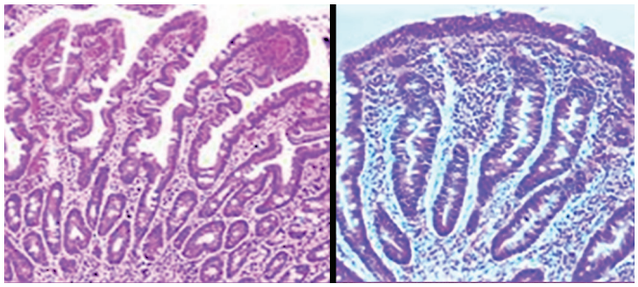


Figure 1 Normal histology (left) and total villus atrophy (right) in celiac disease

BOX 1 Extraintestinal manifestation of celiac disease

- Dermatitis herpetiformis
- Permanent enamel hypoplasia
- Iron-deficient anemia resistant to oral iron supplements
- Short stature, delayed puberty
- Chronic hepatitis
- Arthritis
- Osteopenia/osteoporosis
- Epilepsy with occipital calcifications
- Primary ataxia, white matter-focal lesions
- Psychiatric disorders.

In addition to genetics, grains play an important role in the pathogenesis of CD. Gluten is the most significant identified factor. Dietary gluten contains several distinct T-cell epitopes rich in proline and glutamine residues. The high-proline content of dietary gluten leads to peptides that are not easily degraded by gastrointestinal (GI) proteases, leading to an elevated concentration of potentially immunogenic epitopes in the small intestine. IgA-transglutaminase 2 (TG2), a ubiquitous intracellular and facultative extracellular enzyme that can associate with the extracellular matrix, plays a central role in CD. TG2 targets certain glutamine residues found in dietary gluten and deamidates them to negatively charged glutamic acid residues. The negatively charged gluten peptides are able to bind with greater affinity to *HLA-DQ2* or *HLA-DQ8*, leading to enhanced gluten-specific CD41 Th1 cell activation.

CLINICAL FEATURES

There are four different clinical presentations of CD as shown in **Table 1**. On the basis of clinical presentation, symptomatic CD is broadly divided into typical and atypical CD. Because of its varied manifestations, atypical CD runs the risk of delayed diagnosis. With the use of serologic markers, the spectrum of CD has further widened to include potential and latent CD. **Box 1** shows the common extraintestinal manifestations of CD. In a recent study from North America, up to 55% children with CD did not have chronic diarrhea. A similar Indian study reported a figure of 36%.

Recent Oslo definitions have discouraged use of the terms typical, atypical, silent and latent celiac and suggested the use of classical, nonclassical, asymptomatic and latent CD respectively. Those asymptomatic patients who improve after gluten-free diet (GLD) in any manner (e.g., improvement in fatigue) are labeled as subclinical CD. Groups that are at risk of having silent CD are listed in **Table 2**. National Institute for Health and Clinical Excellence (NICE) Clinical Guidelines 2009 on CD recommend offering serological test to those mentioned in **Table 3** and considering offering the same to those in **Table 4**.

Table 2 Groups that are at risk of having silent celiac disease

Condition	*Approximate prevalence of celiac disease (%)*
Type 1 diabetes mellitus	8–10
Thyroiditis	3–5
Sjögren syndrome and other connective tissue disorder	3–4
Down syndrome	10–12
William syndrome	5
Turner syndrome	5
First degree relative of celiac patient	8–10

DIAGNOSIS OF CELIAC DISEASE

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Guidelines of 2012 for are the current standard for management of CD. This guideline describes two algorithms—one for symptomatic and another for high-risk asymptomatic groups.

The *symptomatic group* should first be offered serology **(Flow chart 1)**, as against the previous guidelines which insisted on duodenal biopsies for the diagnosis of CD. If serology is more than 10 times the upper limit of normal, duodenal biopsies may be omitted, provided an additional serologic test and HLA are both positive. In all other children, a duodenal biopsy must be done to confirm CD. Symptomatic children who are negative for serology may require, further testing if they are less than 2 years of age, have immunoglobulin A (IgA) deficiency, have severe symptoms or have been on a low gluten diet at presentation.

Table 1 Presentations of celiac disease

Type	*Presentation*
Typical	• Predominant gastrointestinal signs/symptoms • Vomiting • Anorexia • Constipation • Diarrhea • Failure to thrive • Recurrent abdominal pain
Atypical or extraintestinal	Gastrointestinal signs/symptoms are minimal or absent. Most common extraintestinal manifestations described in **Box 1**.
Silent	No signs/symptoms. Gluten dependent duodenal mucosa are typical of celiac disease
Latent	Signs, symptoms may or may not be present. Duodenal mucosa normal. Gluten dependent changes with or without symptoms appear later in time

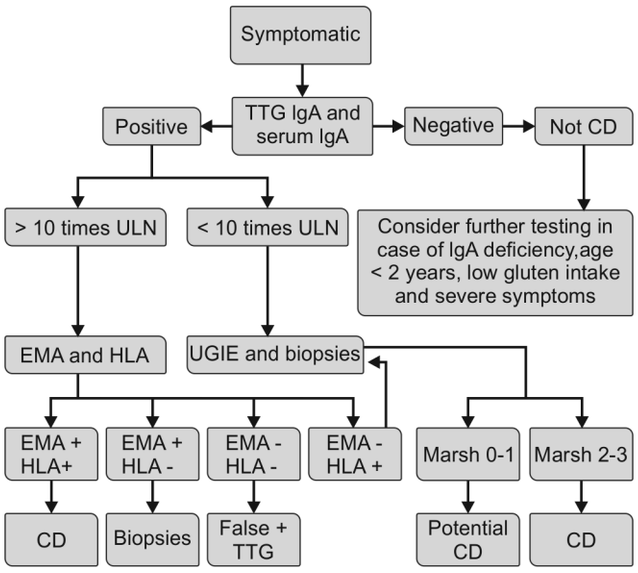
Table 3 Situations which warrant serologic testing for celiac disease (CD)

Signs and symptoms	*Conditions*
Chronic or intermittent diarrhea	Autoimmune thyroid disease
Failure to thrive	Dermatitis herpetiformis
Persistent or unexplained GI symptoms including nausea and vomiting	Irritable Bowel syndrome
Prolonged fatigue	Type 1 diabetes
Recurrent abdominal pain, cramping or abdominal distension	First degree relative with celiac disease
Sudden or unexpected weight loss	
Unexplained iron deficiency anemia or unspecified anemia	

Table 4 Consider offering serological testing to children and adults with any of the following

Addison disease	Microscopic colitis
Amenorrhea	Persistent or unexplained constipation
Aphthous stomatitis (mouth ulcers)	Persistently raised liver enzymes with no cause
Autoimmune liver disease	Polyneuropathy
Autoimmune myocarditis	Recurrent miscarriages
Chronic thrombocytopenic purpura	Reduced bone mineral density
Dental enamel defects	Sarcoidosis
Depression or bipolar disorder	Sjögren syndrome
Down syndrome	Turner syndrome
Epilepsy	Unexplained alopecia
Low trauma fracture	Unexplained subfertility
Lymphoma	
Metabolic bone disease	

Flow chart 1 Guideline for diagnosis of symptomatic patient



Abbreviations: TTG, tissue transglutaminase; CD, celiac disease; EMA, endomysial antibodies; F/u, follow-up; GFD, gluten-free diet; HLA, human leukocyte antigen; IgA, immunoglobulin A; IgG, immunoglobulin G; UGIE, upper gastrointestinal endoscopy; ULN, upper limit of normal.

The *asymptomatic group* who are investigated because of their increased risk for the disease should first be offered HLA test **(Flow chart 2)**. Those positive for *HLA-DQ2* or *-DQ8* should be tested for serology and offered duodenal biopsy if serology is more than three times upper limit normal. If serology is less than three times upper limit of normal, a repeat serology should be done after 3–6 months.

Which Serological Test

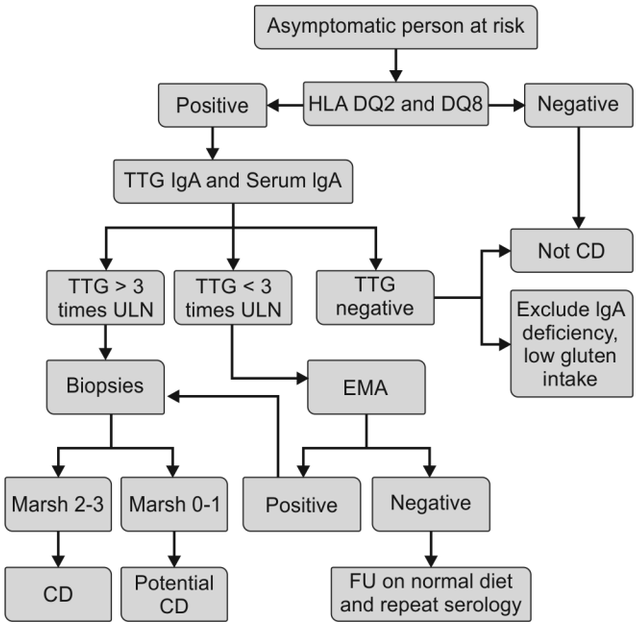
- Immunoglobulin A tissue transglutaminase (tTGA) is the first screening test.
- Immunoglobulin A endomysial antibodies (EMA) testing if the result of the tTGA test is equivocal.
- Check for IgA deficiency if the serology is negative.
- Immunoglobulin G tTGA and/or IgG EMA serological tests are for people with confirmed IgA deficiency.
- In children less than 2 years of age, deamidated gliadin peptide (DGP) IgG is better than other tests.

Upper GI Endoscopy

While performing the upper GI endoscopy, biopsies should be taken preferably from the duodenal bulb (at least one biopsy) and from the second or third portion of duodenum (at least four biopsies). The various endoscopic duodenal appearances which suggest CD include mosaic pattern (in 100%), scalloped folds of duodenum (70%) **(Figs 2A and B)**, visible vasculature (15%) and reduced folds of duodenum (6%). The pathology report should include a description of the orientation, the presence or not of normal villi or degree of atrophy and crypt elongation, the villus-crypt ratio, the number of IELs), and grading according to the Marsh-Oberhuber classification.

The enteropathy in CD is of variable severity and may be patchy, with changes present only in the duodenal bulb in some patients. The histological appearance is not specific for CD and may be

Flow chart 2 Diagnosis of celiac disease in asymptomatic patient



Abbreviations: TTG, tissue transglutaminase; CD, celiac disease; EMA, endomysial antibodies; F/u, follow-up; GFD, gluten-free diet; HLA, human leukocyte antigen; IgA, immunoglobulin A; IgG, immunoglobulin G; UGIE, upper gastrointestinal endoscopy; ULN, upper limit of normal.

found in other enteropathies as well. The characteristic histological changes in CD are increased IELs (> 25/100 enterocytes), increased crypt length, partial to total villus atrophy, decreased villus crypt ratio and infiltration of plasma cells and lymphocytes in the lamina propria. The histological changes are graded according to modified Marsh criteria as follows:

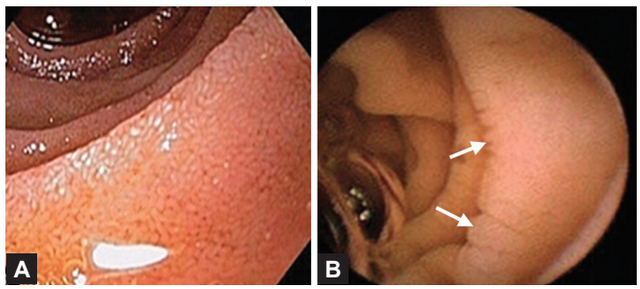
- Grade 0—Normal
- Grade 1—Infiltrative (increased IEL)
- Grade 2—Hyperplastic (grade 1 + hyperplastic crypt)
- Grade 3a—Partial villus atrophy
  - 3b—Subtotal villus atrophy
  - 3c—Total villus atrophy (23)
- Grade 4—Hypoplastics (total villus atrophy + hypoplastic crypts).

Marsh 3 and 4 are characteristic of CD. Marsh 2 is compatible with CD but needs serological positivity for definite diagnosis while Marsh 1 is not specific for CD in children.

Human Leukocyte Antigen Testing

The principal determinants of genetic susceptibility for CD are the major histocompatibility class II *HLA* class II *DQA* and *DQB* genes coded by the major histocompatibility region in the short arm of chromosome 6. More than 95% of patients with CD share the *HLA-DQ2* heterodimer and most of the remaining have the *HLA-DQ8* heterodimer. CD is a multigenetic disorder, which means that the expression of these *HLA-DQ2* or *HLA-DQ8* molecules is necessary but not sufficient to cause disease. Approximately 30–40% of the white population holds the *HLA-DQ2* haplotype, while only 1% of them develop CD.

Human leukocyte antigen testing should be performed in patients with an uncertain diagnosis of CD, for example, in patients with negative CD-specific antibodies and mild infiltrative changes in proximal small intestinal biopsy specimens. HLA testing may be offered to asymptomatic individuals with CD-associated conditions (group 2) to select them for further CD-specific antibody testing.



Figures 2A and B (A) Normal endoscopic appearance of duodenum; (B) Characteristic scalloped folds of duodenum in celiac disease

TREATMENT

All children with proven CD must be started on GFD. An unequivocal response to GFD within few weeks to months confirms the diagnosis of CD. A strict GFD for life is the cornerstone of treatment. Patients need to be counseled in local language on the specific cereals to be avoided. In India, wheat and barley (*Jaun*) are the most commonly used grains which contain gluten. *Rye* is another gluten containing cereal used to make breads in some parts of Europe, but is not available in India. In India, mustard (*Rai, Sarson*) is often wrongly excluded from diet, since it sounds similar to *Rye*. Sorghum (*Jowar*) is also wrongly excluded due to confusion with barley (*Jaun*). Pure oats (*Jaee*) does not contain gluten, but often gets contaminated with gluten during milling and harvesting. If purity is ensured, oats can be allowed. Patients and families need to be educated about sources of accidental contamination of gluten (e.g., common grinding machine or common cooking place for gluten and gluten-free food) and also about reading the ingredients of any ready to eat food. While no mention of *wheat* or *barley* in the contents is reassuring, a reliable label of *gluten free* is ideal. Supportive nutritional care to prevent vitamin, iron and calcium deficiency is required.

Although a *zero tolerance* policy is recommended, it is known that sensitivity to ingested gluten varies greatly amongst patients. A recent meta-analysis estimated, that gluten in amounts less than 10 mg/day may be safe to consume, while more than 100 mg/day are likely to result in the majority of patients exhibiting some signs of immune reactivation and/or symptoms. A typical western diet contains an average of 156 g of wheat (i.e., 40 g of gluten) a day. On a strict GFD, GI symptoms resolve within a few weeks, followed by normalization of biochemical parameters and finally increase in weight and height. Treatment with GFD also reverses the decrease in bone mineralization as well as risk for fractures. There is also marked improvement in their sense of physical and psychological well-being, as documented by a recent quality of life study.

REFRACTORY CELIAC DISEASE

Refractory celiac sprue is defined as symptomatic severe enteritis that does not respond to a strict GFD even after 6 months, without any other causes of enteropathy or overt intestinal lymphoma. It is rare in children and usually seen in elderly patients with poor nutritional status because of chronic malabsorption and protein losing enteropathy. Such patients require treatment with corticosteroids and immunosuppressants, like azathioprine or cyclosporin as well as total parenteral nutrition.

FOLLOW-UP AND MONITORING

If the diagnosis of CD is made according to the diagnostic criteria mentioned above, the family should receive professional dietary counseling for a GFD. They should be followed up regularly for

Table 5 Newer therapies for celiac disease

Target	*Approach*
Gluten modification	Modified grain, pretreated flour, oral glutenase
Intraluminal therapies	Gluten sequestering polymers, gluten neutralizing antibodies
Immune modification	Gluten vaccination
Modification of intestinal permeability	Zonulin receptor antagonist
Immune cell targeted therapies	Immunosuppressant

growth monitoring as well as for re-emphasizing the need for lifelong GFD. The CD specific antibody titers fall to below normal within 12 months after starting therapy. If there is no clinical response to a GFD in symptomatic patients, a careful dietary re-assessment should be done to exclude lack of compliance. If none is found, further investigations are required to look for coexisting food intolerances.

Gluten challenge is considered necessary in situations where there is doubt about the initial diagnosis. Gluten challenge should be preceded by HLA typing and assessment of mucosal histology and should be performed under medical supervision. Gluten challenge should be discouraged in children below 5 years of age and during the pubertal growth spurt, unless the child is *HLA-DQ2* and *HLA-DQ8* negative or has been placed on a GFD without proper testing. The daily gluten intake during gluten challenge should contain at least the normal amount of gluten intake for children (approximately 15 g/day). IgA anti-TG2 antibody (IgG in low levels of serum IgA) should be measured during the challenge period. A patient should be considered to have relapsed (and hence the diagnosis of CD confirmed) if CD-specific antibodies become positive and a clinical and/or histological relapse is observed. In the absence of positive antibodies or clinical symptoms, the challenge should be considered completed after 2 years. However, additional biopsies on a normal diet are recommended because delayed relapse may occur later in life.

PROGNOSIS

Gluten-free diet usually results in clinical, serologic, and histologic remission. In the long-term, it not only reduces the risk of malignancies, but also protects against developing autoimmune diseases such as IDDM, hematologic disorders, and inflammatory bowel disease. In western countries, adherence to a GFD in the general population is reported to be less than 50%, but may be as high as 81% in children. Studies from the developing world have reported a GFD adherence of 45–100%. Those who start a GFD below 10 years of age are 1.3–2 times more compliant. Maintaining a strict long-term GFD is a challenge, especially in children and adolescents. Noncompliance is due to several factors including ignorance about the diet, social/peer pressure, nonavailability of commercially available GFD, dislike of the taste of alternative food, increased outdoor activities, increased risk-taking behavior, and conflicts with parents. Adherence to a GFD is lower in asymptomatic patients who are diagnosed through a mass screening program, than in those referred because of clinical suspicion. In addition, more than 30% of those who think that they are adhering to a GFD are consuming gluten-contaminated food daily. The benefits of adherence to a GFD have been well documented in even in developing countries. Demir and colleagues reported improvement in growth rate in Turkish children with CD adhering to a GFD. Moreover, diabetic children with CD adhering to a GFD have fewer hypoglycemic episodes and better diabetic control. Zamani and colleagues found that Iranian patients with CD with IDA who are on a GFD had spontaneous recovery of their anemia even without iron supplementation.

Problems with therapy Currently, the only available therapy for CD is strict lifelong adherence to a GFD. Although the GFD is a safe and effective therapy, there are practical problems in enforcing it. Guidelines for permissible gluten content in gluten free products vary across the globe and monitoring is lacking in most developing countries. GFD is expensive, not readily available in many countries, and may be lower in its nutritional value, which can significantly impact patient adherence and quality of life. In addition there are issues related to social stigma in communities where awareness about the disease is poor. Alternatives to GFD is desirable and future possible therapies are shown in **Table 5**.

IN A NUTSHELL

1. Celiac disease (CD) is prevalent in 1% of general population in north India.
2. Due to its varied presentation, it runs the risk of remaining undiagnosed and delayed diagnosis in significant number.
3. Except in a minority of symptomatic children with two serologies and HLA DQ2/DQ8 positive, all other need duodenal biopsies for confirmation of CD.
4. Lifelong strict gluten free diet remains the only treatment for CD currently.

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Chapter 35.19
Abdominal Tuberculosis

Yogesh Waikar

Abdomen is a common site of extrapulmonary tuberculosis (TB) in children. It can involve the gastrointestinal (GI) tract, mesenteric lymph nodes or peritoneum. The diagnosis is difficult, since clinical features are varied as well as nonspecific. About 10% of all cases of abdominal TB occur under the age of 10 years.

PATHOGENESIS

The tubercle bacillus reaches the GI system by hematogenous spread from the primary lung focus, ingestion of bacilli from the sputum from an active pulmonary focus, direct spread from adjacent organs or through lymph channels from infected abdominal nodes. Ileocecal region is commonly involved. Mesenteric and peritoneal TB are seen in approximately one-third of patients. The initial infection is localized to the *Peyer's patches* leading to local ulcers followed by mesenteric lymphadenitis and peritonitis.

Intestinal TB is commonly classified as ulcerative, ulcero-hyperplastic and hyperplastic forms. Liver and spleen also can get involved by the tubercle bacillus leading to formation of tuberculoma. Peritoneal TB can be wet type with ascites or loculated ascites or fibrotic/plastic type with abdominal masses and omental thickening.

Esophageal TB is rare. It occurs mainly by extension of disease from adjacent intrathoracic lymph nodes. Duodenal TB is also rare, presenting as stricture. Abdominal TB can also present as malabsorption. Involvement of colon, rectum and anal canal in TB is rare.

CLINICAL FEATURES

Childhood abdominal TB is commonly seen in age group 7–15 years old. Fever, abdominal pain and/or discomfort and weight loss are common presenting symptoms. One of the most common differential diagnoses is Crohn's disease. The features of hematochezia, intestinal obstruction, fistula, oral ulcers, longitudinal ulcers, cobblestone appearance and pseudopolyps are more common in Crohn's disease than in intestinal TB. Hepatic TB presents with hepatomegaly. Tuberculoma and tuberculous liver abscesses are uncommon manifestations of hepatic TB. In miliary TB tubercles are seen near the hepatic veins. In localized forms of hepatic TB the portal vein appears to be the route of spread. TB can also involve pancreas and can present as acute or chronic pancreatitis.

APPROACH TO DIAGNOSIS

The following points are important in history: contact with an open case of TB; past treatment for pulmonary or extrapulmonary TB and features suggestive of an immunocompromised state. The following should be looked for on examination: peripheral stigmata of TB like lupus vulgaris, TB verrucosa cutis, cold abscess in neck, multiple ear drum perforations, scrofuloderma, lymphadenopathy, phlyctenular conjunctivitis, or spinal swelling. Associated involvement of other organs leading to respective manifestations should be screened, e.g., soft neurological signs of neurotuberculoma. Also obtain detailed anthropometry to determine the nutritional status. Examination of the abdomen should focus on the right iliac fossa. Subtle signs of subacute intestinal obstruction should not be missed. Peritoneal TB commonly present as ascites which should be carefully looked for.

DIAGNOSIS

Imaging studies Chest X-ray needs to be done to rule out associated pulmonary TB, which may be seen in about 25% of cases. X-ray of the abdomen may show evidence of intestinal obstruction or surgical complications of the disease. Small bowel contrast meal follow through imaging may reveal involvement of terminal ileum and ileocecal junction. The most common abnormality is short-segment strictures with symmetrical concentric mural thickening and homogeneous mural enhancement. Lymphadenopathy, ascites, enteroliths, peritoneal thickening, and enhancement can also be made out. *Barium enema* may reveal the following findings:

- *Fleischner or inverted umbrella sign* suggestive of early involvement of ileocecal valve.
- *Conical cecum:* Cecum pulled out of iliac fossa due to contraction or fibrosis of mesocolon.
- *Purse string stenosis:* Localized stenosis opposite the ileocecal valve with a rounded off smooth cecum and a dilated terminal ileum.
- *Stierlin's sign:* Narrowing of the terminal ileum with rapid emptying into a shortened, rigid or obliterated cecum.
- *String sign:* Persistent narrow stream of barium suggest stenosis.

Cross-sectional imaging is useful in detecting abdominal lymph nodes. Mesenteric and periportal lymph nodes are involved more often in patients with abdominal tuberculous, while iliac and inguinal lymph nodes are more with lymphoma. While peripheral enhancement is seen more often in tuberculous lymphadenopathy, homogeneous enhancement suggests lymphoma. Ultrasonography of abdomen may reveal ascites, loculated ascites, interloop ascites, mesenteric lymph nodes, bowel thickening, or pseudokidney sign (pulled up cecum).

Endoscopy On colonoscopy, mucosal nodules of variable sizes and ulcers in a discrete segment of colon, ulcer between nodules, and deformed ileocecal valve, are characteristic. Biopsies should be taken from the edge of the ulcers. The characteristic caseous granulomas are seen only in about one-third of cases. While acid fast bacilli (AFB) staining has a variable yield, cultures are rarely positive. Balloon-assisted and spiral enteroscopy with biopsy can be used for evaluating the small bowel. Upper GI endoscopy has limited role.

Others Ascitic fluid analysis shows a predominance of mononuclear cells. Ascitic fluid ADA (adenosine deaminase) greater than 39 IU/L can be used as adjunct test in diagnosis. Serum ascites albumin gradient (SAAG) is less than 1.1 g/dL in peritoneal TB. Ascitic fluid mycobacterial culture (after centrifugation) is positive in only 50% of cases. Laparoscopy with histology and culture of peritoneal biopsies has better sensitivity. Gastric lavage for AFB and positive *Mantoux test* are useful supportive investigations. Serological tests and nucleic acid amplification [e.g., polymerase chain reaction (PCR)] are not useful.

DIFFERENTIATING TB FROM CROHN'S DISEASE

Increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be seen in both TB and inflammatory bowel disease. Anti-*Saccharomyces cerevisiae* antibody (ASCA) is not useful in differentiating between Crohn's disease and TB. In one-third of cases tubercle bacilli can be cultured from mucosal biopsies. Ascites, transverse ulcers, patulous ileocecal valve and granulomas are more common in intestinal TB than in Crohn's disease. Granulomas exceeding 300 μm in maximal diameter,

more than five granulomas per section, and confluent granulomas are more frequently identified in intestinal TB than in Crohn's disease. Demonstration of caseating granuloma in the biopsy specimen is definitive. Granulomas of TB and Crohn's disease can be differentiated by CD73. Mesenchymal cells surface marker expression CD73 is expressed around the granulomas of TB alone and is absent in the Crohn's disease.

The sensitivity, specificity, positive predictive value and negative predictive value of T-SPOT-TB (interferon-γ release assay) are around 80–90%. Quantiferon-TB Gold test has many limitations and therefore not very useful. PCR using *Mycobacterium tuberculosis* complex–specific primers for IS6110 to differentiate TB and Crohn's disease is not sensitive enough. Correlation between PCR positivity and histological lesions such as caseation and granulomas is yet to be established. Immunohistochemical staining of biopsy specimens with anti-VP-M660 has high specificity but low sensitivity in differentiation.

MANAGEMENT

Abdominal TB comes in category of extrapulmonary TB and should be treated as $2H_3R_3Z_3E_3$ in intensive phase followed by $4H_3R_3$ in continuation phase as per the updated Revised National Tuberculosis Control Program with the Indian Academy of Pediatrics (RNTCP-IAP) guidelines. Previously incompletely treated abdominal TB may be considered to have in intensive phase regimen as $2S_3H_3R_3Z_3E_3 + 1H_3R_3Z_3E_3$. Follow-up therapy is recommended with $5H_3R_3E_3$. Abdominal TB in immunosuppressed patients and those with multidrug resistant TB are challenges which require specialist help. Strict drug compliance needs to be ensured to avoid emergence of multidrug resistant strains. Role of corticosteroids is controversial. Complications of abdominal TB depend on the site of involvement. They include ulcer, perforation, adhesion, obstruction, bleeding, fistulae formation and stenosis.

IN A NUTSHELL

1. The risk factors for abdominal TB are household contact with a newly diagnosed smear-positive case, age less than 5 years, human immunodeficiency virus (HIV) infection and severe malnutrition.
2. In wet type, peritoneal TB calculation of SAAG and ADA helps in diagnosing peritoneal TB.
3. The diagnosis of abdominal TB is based on clinical features, imaging of the abdomen and histology of the affected tissue. There is no role of serology to diagnose abdominal TB.
4. Abdominal TB in immunosuppressed patients or multidrug resistant TB should be managed with the help of pediatric infectious disease specialist and clinical microbiologist.

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Chapter 35.20
Ascites

Malathi Sathiyasekeran, R Ganesh

Ascites, defined as the pathologic accumulation of fluid (more than 25 mL in adults) within the peritoneal cavity. Ascites can occur at any age with varying etiological spectrum in the different groups.

INCIDENCE

In liver disease, the incidence of ascites depends on the underlying pathology. In cirrhosis, ascites is seen in 44%, in presinusoidal portal hypertension (PHT) in 10–12% and in more than 80% in postsinusoidal PHT. In acute liver failure and AVH it is seen in about 50% and 10% of patients, respectively.

ETIOPATHOGENESIS

The causes of ascites are shown in **Table 1**. Ascites can be broadly classified into cirrhotic and noncirrhotic ascites.

Noncirrhotic Ascites

Hepatic causes (a) *Acute viral hepatitis (AVH)*: Transient PHT due to sinusoidal collapse, spontaneous bacterial peritonitis (SBP)and hypoalbuminemia are possible explanations; (b) *Postsinusoidal PHT*: Ascites occurs when the hydrostatic and osmotic pressures within hepatic capillaries produce a shift of fluid from blood to the lymphatics at a rate which exceeds its drainage capacity; (c) *Presinusoidal PHT*: Ascites is uncommon in presinusoidal PHT but may occur following hemorrhage or surgery due to depressed hepatocellular function.

Pancreatic ascites Fluid initially accumulates due to leakage of pancreatic juice from a disrupted pancreatic duct or a pseudocyst. Further formation occurs secondary to *chemical burn* of the peritoneum.

Biliary ascites Bile may leak into the peritoneal cavity due to spontaneous or iatrogenic perforation of the bile duct.

Malignant ascites The malignant cells on the peritoneum produce fluid that is rich in protein which causes a rapid shift of fluid into the peritoneal cavity secondary to the osmotic drag.

Chylous ascites Rupture of obstructed or distorted abdominal lymphatics as occurs in congenital lymphangiectasia or other acquired conditions.

Tuberculous ascites Peritoneal tubercles secrete proteinaceous material causing an osmotic drag of fluid and present as either diffuse or loculated ascites.

Eosinophilic ascites In eosinophilic gastroenteritis (EGE), the eosinophils infiltrate the Peyer's patches and if the serosa is infiltrated it results in eosinophilic ascites.

Table 1 Causes of ascites in children

Organ involved	*Condition*
Hepatic	*Chronic liver disease*: Portal hypertension(PHT)—Common *Postsinusoidal PHT*: Hepatic venous outflow tract obstruction (HVOTO): Sinusoidal Obstruction syndrome, Budd-Chiari syndrome, IVC obstruction *Sinusoidal PHT*: All causes of cirrhosis, e.g., HBV, HCV, Wilson's disease, tyrosinemia, autoimmune, biliary, malignancy *Presinusoidal PHT*: • *Intrahepatic presinusoidal*: Congenital hepatic fibrosis, noncirrhotic portal fibrosis (10%) • *Extrahepatic*: Extrahepatic portal venous obstruction (EHPVO): 5–10% *Acute liver disease*: Acute hepatitis, acute liver failure *Traumatic*: Liver injury secondary to accidents, liver biopsy
Biliary	Perforation of bile duct: Spontaneous, iatrogenic
Pancreas	Anterior disruption of pancreatic duct, rupture of pseudocyst
Luminal GI	Intestinal perforation, appendicitis, eosinophilic gastroenteritis (EGE)
Peritoneal	Tuberculosis
Renal	Nephrotic syndrome, peritoneal dialysis
Hematological	Hemolysis, tumors
Lymphatic	Primary intestinal lymphangiectasia, Hennekam syndrome
Cardiac	Complex cyanotic heart disease, CCF, arrhythmia
Vasculitis	Henoch-Schönlein purpura, connective tissue disorder, SLE
Infections	Dengue fever, salmonellosis, leptospirosis, scrub typhus
Malignancy	Wilms tumor, germ cell and ovarian tumors, metastasis
Pseudo ascites	Omental cyst, retroperitoneal lymphangioma

Infections Transient ascites may occur in several febrile illnesses. Third spacing of fluid in dengue shock may cause ascites. In leptospirosis and typhoid fever the ascites is due to serositis.

Cirrhotic Ascites

Sinusoidal PHT is the initial mechanism that determines leakage of fluid into the peritoneal cavity. Sinusoidal PHT with increase in portal pressure is an essential component in the pathogenesis and ascites rarely develops unless the threshold pressure is more than 12 mm Hg. Hypoalbuminemia may predispose to fluid accumulation, but is not an essential component. Sodium and water retention causes increase in intravascular volume leading to ascites formation. The pathophysiology of cirrhotic ascites is shown in **Figure 1**.

A. *Underfill theory:* Portal hypertension results in decreased blood volume leading to decreased renal perfusion. This activates the plasma renin-aldosterone pathway and the sympathetic nervous system resulting in renal sodium and water retention and promotes ascites formation.

B. *Overflow theory:* An unknown hepatorenal reflex causes inappropriate sodium and water retention followed by increasing blood volume which together with PHT, leads to ascites.

C. *Peripheral arterial vasodilation theory:* The first step is vasodilation of the peripheral vessels leading to systemic hypotension and a decrease in cardiac output. This is followed by renal retention of sodium and water, plasma volume expansion and ascites. This theory has been modified and termed as *forward theory of ascites formation* and combines arterial underfilling with a forward increase in splanchnic capillary pressure and filtration with increased lymph formation. In cirrhosis, several vasodilators such as the potent nitric oxide, calcitonin gene-related peptide, substance P, carbon monoxide and endogenous cannabinoids are produced which augment the ascites formation.

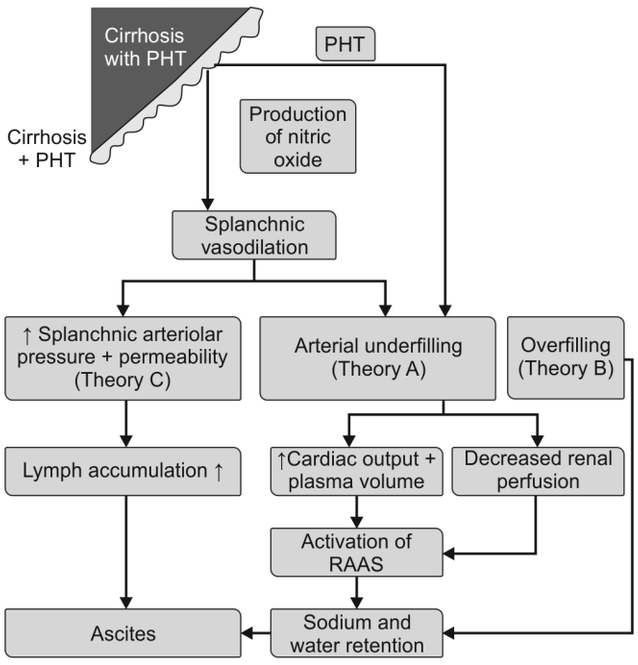


Figure 1 Pathophysiology of cirrhotic ascites

CLINICAL PRESENTATION

The child may be asymptomatic or have mild abdominal discomfort if the fluid is minimal. An increase in abdominal girth and weight gain may be early symptoms. Anorexia, nausea and growth failure are indicators of increasing ascites. When the ascites is massive and tense, the child presents with breathlessness and respiratory distress **(Fig. 2)**. Pain is not present unless there is an infection such as spontaneous/secondary bacterial peritonitis or

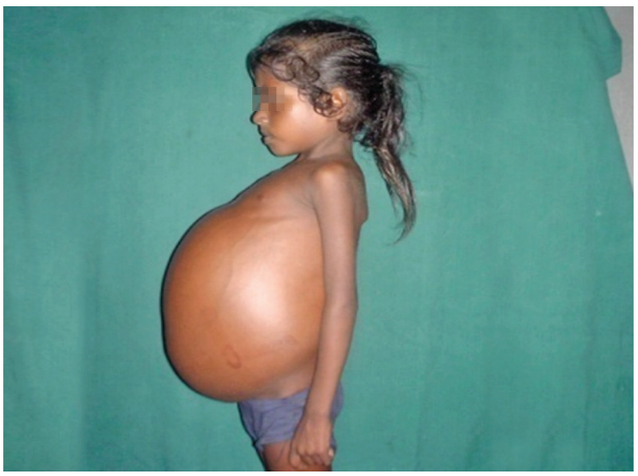
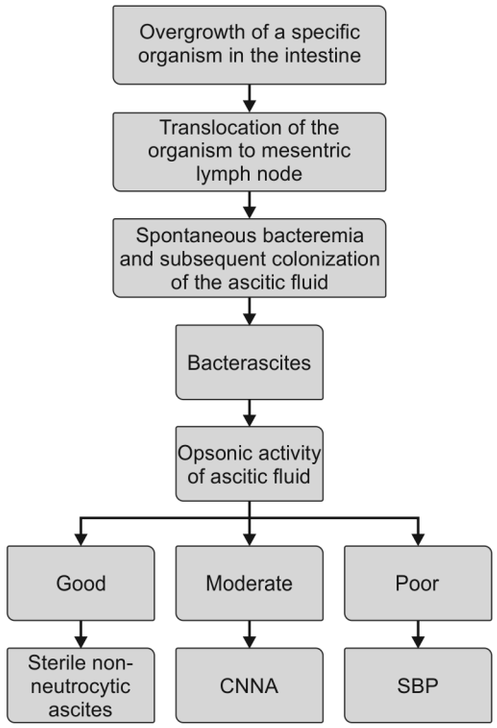


Figure 2 Child with tense ascites

malignancy. Depending upon the etiology there may be additional features such as jaundice, gastrointestinal (GI) bleed and altered sensorium in cirrhotic ascites. Fever and contact with tuberculosis (TB) may be suggestive of TB ascites.

The physical findings are a protuberant abdomen, fullness of the flanks, formation of hernias (umbilical, inguinal or femoral) and smiling/inverted umbilicus. The presence of splenomegaly and prominent abdominal veins suggest sinusoidal PHT. Splenomegaly with minimal free fluid in the abdomen and absence of abdominal veins indicates presinusoidal PHT whereas massive ascites and back veins suggest postsinusoidal PHT. Tender hepatomegaly with distended jugular veins and elevated jugular venous pressure suggests cardiac ascites.

Flow chart 1 Pathophysiology of spontaneous bacterial peritonitis



Abbreviations: CNNA, culture negative neutrocytic ascites; SBP, spontaneous bacterial peritonitis.

Complications

Mechanical Massive or tense ascites may cause respiratory distress, compression of great vessels, abdominal wall hernias (umbilical, inguinal or femoral), gastroesophageal reflux disease, delayed gastric emptying and obstructive sleep apnea syndrome. Pleural effusion or hepatic hydrothorax is a common finding in cirrhotic ascites.

Metabolic complications Dyselectrolytemia may occur secondary to diuretic use.

Infection Spontaneous bacterial peritonitis (SBP) is an important complication of cirrhotic ascites seen in 10–30% of patients and is associated with a high mortality. SBP denotes infection of ascitic fluid without evidence of an abdominal source and is usually due to gram-negative bacilli (*E. coli, Klebsiella*) and gram-positive cocci (*Streptococcus pneumonia*e, enterococci). The pathogenesis of bacterial peritonitis is shown in **Flow chart 1**.

Hepatorenal syndrome (HRS) Hepatorenal syndrome is the functional renal failure that occurs in patients with decompensated liver disease, in the absence of an identifiable renal cause.

Differential diagnosis Pseudoascites caused by retroperitoneal lymphangioma, ovarian tumor, large mesenteric cyst can mimic true ascites.

APPROACH TO A CHILD WITH ASCITES

Demonstration of Ascitic Fluid

Clinical Signs

Puddle or Lawson's sign This test detects a minimal amount (120 mL) of fluid and is beneficial in small children.

Shifting dullness This finding is based on the alteration of the percussion note in the flanks when the position is changed and the air filled loops are displaced by the fluid. In children at least greater than 500 mL is necessary for demonstration.

Fluid thrill Demonstration of a fluid wave indicates large amount greater than 1,000 mL of fluid in the peritoneal cavity. Ascites is graded according to the International club of ascites as Grade 0 if there is no demonstrable ascites, Grade 1 if mild ascites detected only by ultrasound, Grade 2 if moderate ascites without fluid thrill and Grade 3 if large/tense ascites with marked distension of abdomen and fluid thrill.

Imaging Studies

Plain abdomen skiagram reveals ground glass appearance, obliteration of the hepatic angle (Hellmer' sign), flank stripe sign and *mickey mouse sign*. On ultrasound (US) of the abdomen: Minimal peritoneal fluid (10–20 mL) has been detected in 7% of asymptomatic children. Limitations to ultrasound include obesity and complex, loculated ascites since fat and air are poor conductors of sonic waves. US also helps in the etiological diagnosis and guiding paracentesis. CT and MRI are as sensitive as US of abdomen in detecting fluid but cost is a limiting factor.

Diagnostic Abdominal Paracentesis

Diagnostic paracentesis is an essential part of the first evaluation. It is a simple, safe method for confirming diagnosis and identifying etiology. It is performed under local anesthesia following aseptic precautions and using the standard technique. Prophylactic platelet or fresh frozen plasma is not recommended prior to paracentesis.

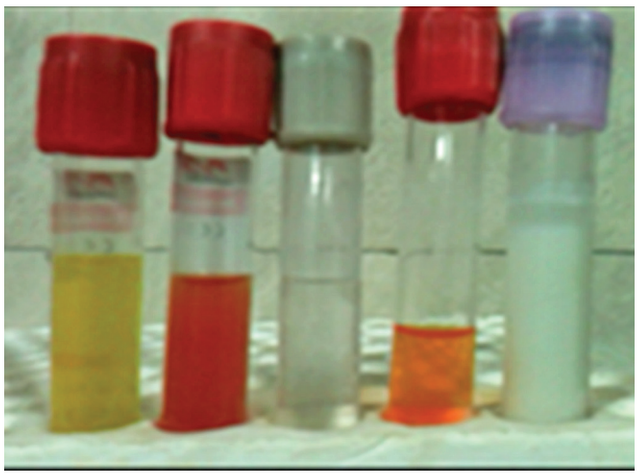


Figure 3 Color of ascitic fluid: straw, hemorrhagic, watery, xanthochromic and milky (from Left to right)

Color The fluid may be watery or transparent in cirrhosis with hypoproteinemia, straw colored in TB and cirrhosis, bloody or hemorrhagic in pancreatic ascites and malignancy, deep yellow or dark brown in biliary ascites, milky or chylous in TB, cirrhosis and intestinal lymphangiectasia **(Fig. 3)**.

Cell count Normally the total leukocyte count is less than 500 cells/mm^3 with less than 250 polymorphs/mm^3. A polymorphonuclear (PMN) count greater than 250 cells/mm^3 is suggestive of bacterial peritonitis.

Gram stain and acid-fast bacillus (AFB) stain In SBP, Gram's stain is not routinely required since the infection is paucibacillary with a yield rate of only 10%. However, in secondary bacterial peritonitis, neutrophils and multiple organisms are seen. AFB staining for TB rarely yields positive results.

Culture 10 mL of ascitic fluid directly innoculated into the blood culture bottles increases the positive yield of neutrocytic ascites to 80%. Polymicrobial infection is seen in secondary bacterial peritonitis while mono-microbial infection denotes SBP. There are five subtypes of bacterial ascites of which SBP, Mono-microbial non-neutrocytic bacterascites (MNB) and culture negative neutrocytic ascites (CNNA) are spontaneous bacterial infections. Secondary bacterial peritonitis and polymicrobial bacterascites occur due to an underlying pathological or procedural cause.

Serum ascites albumin gradient (SAAG) This gradient is calculated by subtracting the value of ascitic fluid albumin from the serum albumin estimated concurrently. SAAG is classified as high gradient ascites (> 1.1) and low gradient ascites (< 1.1). High gradient ascites is seen in PHT with a diagnostic accuracy of 97%. Other conditions where high SAAG is seen are Budd-Chiari syndrome, portal vein thrombosis, acute liver failure and hypothyroidism. Low-gradient ascites is seen in TB peritonitis, pancreatic ascites, biliary ascites, nephrotic syndrome and serositis. SAAG may be falsely high in chylous ascites since lipid interferes with albumin estimation.

Special additional tests High amylase in ascitic fluid [(AF)/serum ratio > 0.4] indicates pancreatic ascites, urea and creatinine in AF more than the serum indicates uroascites, AF bilirubin greater than 6 mg/dL indicates biliary ascites and AF triglyceride greater than 200 mg/dL indicates chylous ascites. GeneXpert MTB/RIF test is a new molecular test for TB that detects the DNA in TB bacteria.

Complications Paracentesis is generally considered a safe procedure when performed cautiously. Complications are uncommon though infection, dyselectrolytemia, bowel and bladder perforation and large intra-abdominal hemorrhage have been reported.

Specific Investigations

Apart from basic investigations such as complete blood count, blood sugar, biochemical tests of the liver and renal function tests, additional investigations to confirm the etiology are done in children presenting with ascites. In children with short duration ascites serology for leptospirosis, dengue, *Salmonella* and markers for HAV and HEV should be done. In cirrhotic ascites, viral markers for HBV, HCV, Wilson disease work-up, auto antibodies should be included. Upper GI endoscopy is done to document varices and to perform duodenal mucosal biopsy.

MANAGEMENT

In children with non-cirrhotic ascites, definitive interventions and treatment of the underlying disease helps in the resolution of ascites. Management of cirrhotic ascites is detailed here:

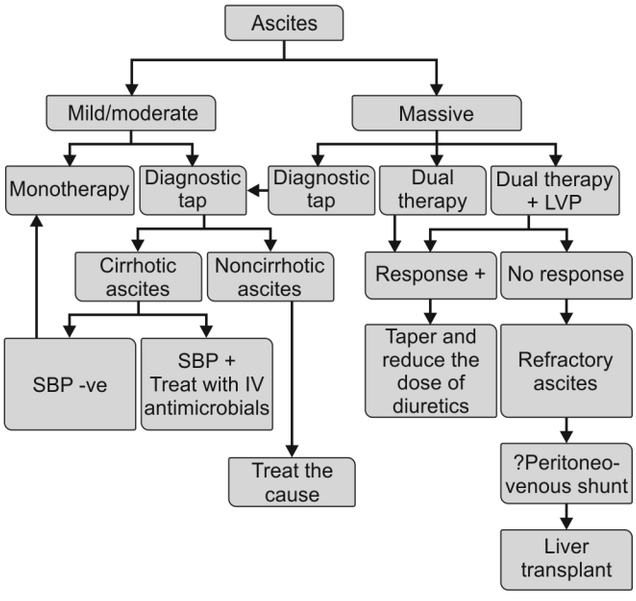
Cirrhotic Ascites

Asymptomatic children with minimal ascites may not require any intervention. The weight of the child and a proper fluid intake and output chart should be monitored and recorded daily. The two components of therapy are sodium restriction and diuretics. The aim is to achieve a negative sodium balance so that the ascites decreases and then maintain a sodium balance to prevent recurrence. The management of cirrhotic ascites is shown in **Flow chart 2**.

Restriction of sodium and fluids In infants and children sodium is restricted to a maximum of 1–2 mEq/kg/day and 1–2 g/day (44–88 mEq) in adolescents. Water restriction is necessary only if serum sodium is less than 125 mEq/L.

Diuretics In cirrhotic ascites renal sodium retention is due to hyperaldosteronism. Aldosterone antagonist spironolactone is the diuretic of choice being more effective than loop diuretics in the management of ascites. The metabolites of spironolactone act on the cortical and medullary collecting tubule thereby inhibiting the binding of aldosterone.

Flow chart 2 Management of cirrhotic ascites



Spironolactone is started at 2–3 mg/kg/day (max: 100 mg) given as a single dose in the morning and if necessary, increased by 2 mg/kg once in 5–7 days till the maximum dose of 4–6 mg/kg (up to 400 mg/day) is reached. The goal of therapy is to reduce body weight by 300–500 g/day until ascites resolves.

A combination of aldosterone antagonist and a loop diuretic (dual therapy) may be beneficial when there is no response with spironolactone as monotherapy, quicker response is required or recurrent ascites. Furosemide at 1 mg/kg/day (max: 40 mg) may be added to spironolactone.

Supplemental albumin When serum albumin is less than 2.5 g/dL it may be advisable to replace serum albumin since low albumin may worsen ascites.

Large volume paracentesis (LVP) Large volume paracentesis is the treatment of choice for diuretic resistant severe ascites or those with respiratory compromise. LVP is defined as removal of ascitic fluid 50 mL/kg or more of dry body weight. Studies have shown that a mean volume of 118 ± 56 mL/kg can be safely removed over one time. This is the first line treatment for tense ascites and second line treatment for refractory ascites. LVP should be done under cover of 0.5–1 g of albumin/kg or 8 g/L of AF drained.

Refractory ascites Diuretic-resistant ascites (DRA) is present if it is unresponsive to 1 week of maximum dosage of dual therapy. Diuretic-intractable ascites (DRI) is the term used when there are diuretic-induced complications that preclude the usage of an effective diuretic dosage. The various modalities of managing refractory ascites include LVP with albumin administration, continuing diuretic therapy, transjugular intrahepatic porto systemic shunt (TIPSS) and liver transplantation.

Transjugular intrahepatic porto systemic shunt Children with refractory ascites and in those awaiting liver transplantation, TIPSS acts as a bridge therapy. TIPSS lowers portal pressure and is therefore effective in decreasing ascites. Contraindications for TIPSS include severe liver failure, renal failure, sepsis and severe cardiopulmonary disease.

Peritoneovenous shunting (Leveen and Denver shunts) A conduit is created within the peritoneum for the fluid to drain into the superior vena cava via the right internal jugular vein in those with intractable ascites.

Liver transplantation This modality is the only definitive therapy for children with end stage liver disease and refractory ascites. The outcome is good if transplant is performed before the development of hepatorenal syndrome.

Newer modalities This includes atrial natriuretic peptide (ANP), terlipressin, docarpamine (an orally active prodrug), V2 receptor antagonist (OPC-3126), k-opioid antagonist (niravoline) and adenosine-1-receptor antagonist (FK352).

Prevention of SBP Since the occurrence of SBP is associated with increased morality it is necessary to prevent SBP. Long-term oral norfloxacin at a dose of 5–7.5 mg/kg once a day is recommended.

IN A NUTSHELL

1. Ascites is the pathologic accumulation of fluid in the peritoneal cavity.
2. The most important cause of ascites is cirrhosis.
3. Noncirrhotic causes should be considered and identified for definitive therapy.
4. Ultrasound of abdomen is an excellent noninvasive modality for diagnosis.
5. Paracentesis is a safe diagnostic and therapeutic procedure.
6. Spontaneous bacterial peritonitis should be recognized and appropriately treated.
7. Diuretics should be administered at the proper dosage and duration for effective results.
8. Liver transplant is indicated in refractory ascites and end stage liver disease.

PROGNOSIS

Persisting ascites in a child with cirrhosis is a marker of decompensation. Refractory ascites and SBP are also indicators of a poor prognosis in cirrhosis.

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Chapter 35.21
Intestinal Obstruction

Ketan Parikh

Intestinal obstruction is defined as failure of effective aboral progression of the gastrointestinal contents. The initial clinical presentation is similar to various other medical conditions in children and a very high index of suspicion is therefore required. Early and effective management will help to reduce the morbidity and complications which may otherwise follow. Most cases of intestinal obstruction in children are due to congenital anomalies. However, in our country abdominal tuberculosis continues to form a recognizable cause, whereas meconium ileus and Crohn disease which are relatively common in the west are less common.

ETIOLOGY

The failure of the aboral progression may be either due to a mechanical obstruction of the GI tract (dynamic) or the ineffective propulsive peristalsis (adynamic). The mechanical obstruction may be due to pathology of the wall of the intestinal tract, external compression of the intestinal tract; an intraluminal occlusion of the passage; or a combination of two of the above acute on chronic obstruction. Common cases are listed in **Box 1**.

PATHOPHYSIOLOGY

Once mechanical obstruction sets in, the bowel proximal to the obstruction undergoes dilatation due to the accumulated contents. There is hyper-peristalsis in an attempt to overcome the obstruction and this leads to colicky pain. If the obstruction is gradual or

BOX 1 Common causes of intestinal obstruction in children

- Intestinal atresias—duodenal, ileal, jejunal and colonic in that order of frequency
- Volvulus neonatorum due to intestinal malrotation
- Hirschsprung disease
- Anorectal malformations—not classically described as intestinal obstruction
- Intussusception
- Strangulated hernias—(external–inguinal/umbilical); Internal due to bands like persistent vitellointestinal bands, Ladd bands or other various unnamed bands and mesenteric defects
- Meconium ileus
- Inflammatory or postoperative adhesions
- Ascariasis bolus
- Tuberculous adhesions, cocoon formation, strictures
- Intestinal duplication cysts or mesenteric cysts.

chronic, then this proximal bowel also undergoes hypertrophy. The persistence of obstruction and dilatation may initiate reverse peristalsis in the proximal bowel and this may cause vomiting. The dilatation of the obstructed bowel also increases the quantity of the intestinal secretions. While the pylorus normally prevents the reverse egress of the duodenal (bilious) contents into the stomach, the dilatation and reverse peristalsis of this portion of the bowel leads to bilious vomiting or gastric aspirates. The stagnant intestinal contents provide a potent medium for the overgrowth of intestinal commensals. This leads to mucosal inflammation, increased intestinal secretions and formation of increased amounts of gas.

Occasionally, the dilated proximal loop of bowel may twist or kink on itself thus creating a secondary obstruction more proximally—*closed loop syndrome*. This sequestrated section which is obstructed both proximally and distally gradually dilates due to accumulated gas and intestinal secretions with potential chances of perforation. Prior to perforation, the bowel undergoes massive dilatation with resultant ischemia of its wall. At this stage the pain is severe and usually unresponsive to most antispasmodics. Once the bowel perforates, the dilatation settles due to leakage of the contents into the peritoneal cavity and the pain settles giving a false sense of recovery. Gradually the leaked bowel contents lead to localized or generalized peritonitis and progressive deterioration of the general condition. The high gastric aspirates or the sequestrated fluid in the dilated bowel lumen and the edema of the bowel wall collectively contribute to massive fluid losses (overt and covert) and electrolyte disturbances. Before perforation, infected foci may develop in the ischemic areas of the bowel wall leading to portal pyemia and rapid deterioration.

Adynamic obstruction is usually secondary to a pre-existing condition. Electrolyte disturbances, sepsis, metabolic disturbances and drugs are the few common causes. Perforation may occur secondary to a closed loop obstruction but severe fluid and electrolyte disturbances are common complications.

CLINICAL FEATURES

Children present with a variable combination of the following features: vomiting—initially nonbilious but gradually becoming bilious; abdominal distension; constipation; and abdominal pain. The mode of presentation depends on the following factors:

- *The type of obstruction:* Adynamic obstruction usually has an underlying primary pathology. Abdominal distension is a prominent feature and pain is a late symptom. Constipation may not be absolute and the patient may pass intermittent mucoid discharge with or without fecal matter.
- *The age of the patient:* In an infant, pain may manifest only as excessive crying and thus may be missed for some time.
- *The level of obstruction:* In high obstructions, the primary presentation is vomiting whereas abdominal distension may never be seen or is restricted to the upper abdomen. Additionally, the patient (even a newborn) may pass some stools but a careful history reveals that these are generally pale (mucoid). However, the patient tends to lose excessive fluids in vomiting and gastric aspirates. In lower intestinal obstructions, vomiting is a late sign whereas constipation is the primary symptom.
- *The stage of intestinal obstruction:* In patients, who present late, pain may reduce after perforation of the bowel and features of sepsis and metabolic disturbances may predominate rather than abdominal signs.

DIAGNOSIS

Bilious vomiting is the strongest clinical indicator of an intestinal obstruction. Passage of pure mucoid discharge per rectally is also a strong indicator. Abdominal colics unresponsive to oral medications and passage of blood stained mucus per rectum are warning signs of compromised bowel vascularity. Sudden fall in platelet count in a sick child may be the earliest indicator of bowel gangrene.

IMAGING

A plain vertical or lateral decubitus film of the abdomen is the most informative.

- The presence of fluid levels is indicative of obstruction; the number of fluid levels suggests the level of obstruction **(Fig. 1)**.
- If the colon is also dilated, it indicates either a low obstruction or adynamic obstruction.
- A supine film (although may not show fluid levels), shows the bowel pattern better and if showing an isolated massively small bowel loop may suggest a closed loop obstruction and thus an indication for early intervention.
- If the dilated bowel loops are seen in a relatively white background, it may indicate excessive peritoneal fluid/thickened (edematous) bowel wall due to peritonitis **(Fig. 2)**.
- Pneumoperitoneum is a rare finding even in the presence of bowel perforation thus its absence has negligible relevance. A large pneumoperitoneum is seen only in gastric or duodenal perforations or in colonic perforations.
- Intramural air or air in the portal vein is indicative of bowel wall necrosis with gas forming bacteria.

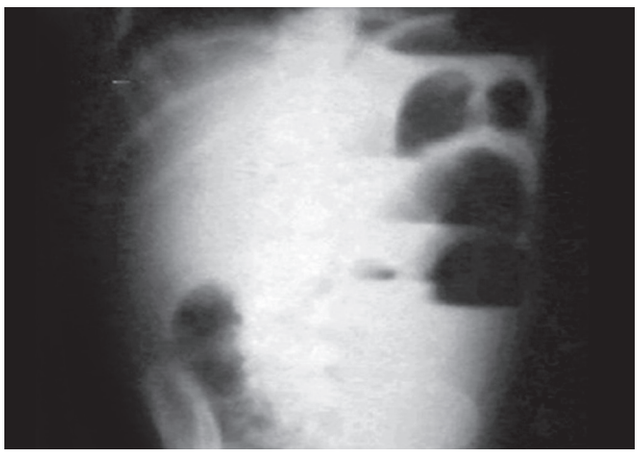

Figure 1 Fluid levels in a child with intestinal obstruction

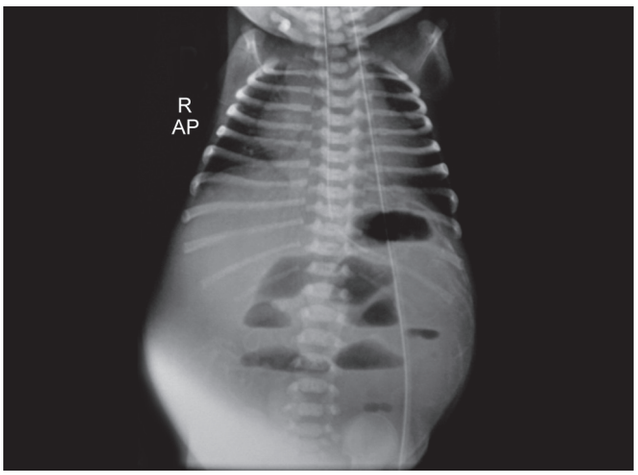

Figure 2 Fluid levels surrounded by ground glass appearance—peritonitis

- Air in the rectum in a case of multiple fluid levels suggests an adynamic obstruction.

Ultrasonography

Ultrasonography of the abdomen may additionally confirm the presence of fluid in the peritoneal cavity and the nature of the fluid (thick fluid suggesting pus). Identify pathologies like intussusception; and may identify an adynamic bowel loop. A concomitant Doppler study may indicate its vascularity. CT imaging of the abdomen is rarely done in children. It may yield information on localized inflammatory pathologies of the bowel and also help identify internal hernia.

MANAGEMENT

Most children with intestinal obstruction are given a trial of conservative management, traditionally referred to as *drip and suck*. This involves keeping the patient nil orally and intravenous supplementation along with a regular deflation of the proximal GI tract with regular aspiration through a nasogastric tube. It decreases the pressure on the bowel wall, reducing the edema and may result in opening out the narrowed portion of the bowel. Supplementation of electrolytes and judicious use of antibiotics are necessary in most cases. The indications for surgery are listed in **Box 2**.

OUTCOME

The outcome depends primarily on the nature of the obstruction and the associated complications, if any. In most cases of pure obstruction with negligible complications, the outcome is excellent even if surgical correction is required. Presence of sepsis and associated comorbidities may affect the final outcome.

BOX 2 Indications of surgery in intestinal obstruction

- Suspicion of closed loop obstruction (fear of perforation)
- Volvulus neonatorum
- Suggestion of strangulated hernia
- Any suggestion of perforation
- Suggestion of peritonitis
- Any suggestion of vascular compromise of section of bowel
- Associated peritonitis
- Failure of conservative treatment.

IN A NUTSHELL

1. In children with bilious vomiting intestinal obstruction should be suspected.
2. Abdominal pain which is not relieved with antispasmodics should raise a suspicion of compromised bowel vascularity.
3. Non-feculent passage of blood or mucus per rectum should raise the possibility of intestinal obstruction in a child with acute abdomen.
4. A vertical plain film of the abdomen is the single most helpful imaging modality.

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Chapter 35.22
Intussusception

Ketan Parikh

Intussusception is characterized by the telescoping of one part of the intestine into another **(Fig. 1)**. Even though it may occur at any age, the most common age of presentation is 8–10 months. Hence, rotavirus infection may play a role.

ETIOLOGY

- *Idiopathic* This is the most common variety of intussusception and occurs in the infant. It is usually linked with the period of weaning.
- *Secondary intussusceptions* Occur due to an intraluminal pathology or growths like polyps, submucosal masses, etc. **(Fig. 2)** which act as lead points. Submucosal hematomas seen in Henoch-Schönlein purpura may also contribute.

PATHOGENESIS

The most common site of the idiopathic variety is the ileocecal region, and the most common lead point is a hypertrophied Peyer's patch. This hypertrophy occurs due to a change in the bacterial flora during weaning or gastrointestinal infection or following ingestion of infected respiratory secretions. The telescoped bowel

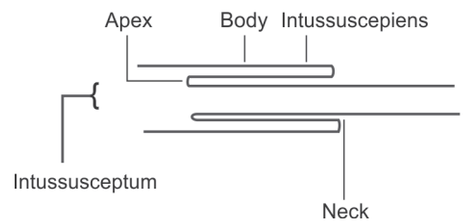

Figure 1 Diagrammatic representation of parts of intussusception

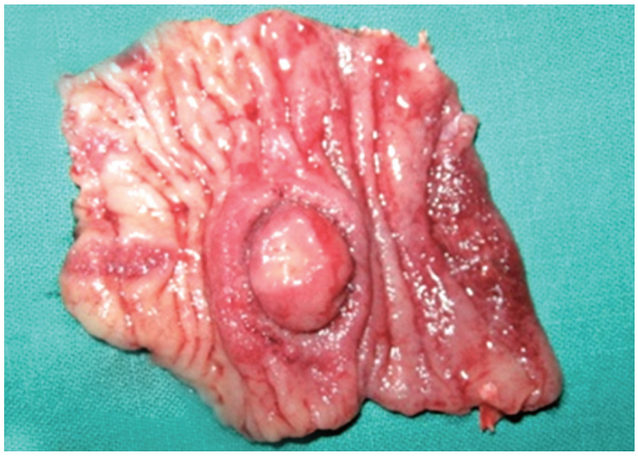

Figure 2 Luminal sessile polyp, a lead point for a secondary intussusception

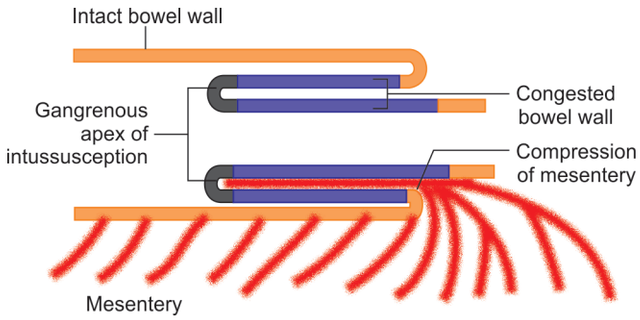

Figure 3 Diagrammatic representation showing the compression of the mesentery and resultant mucosal ischemia

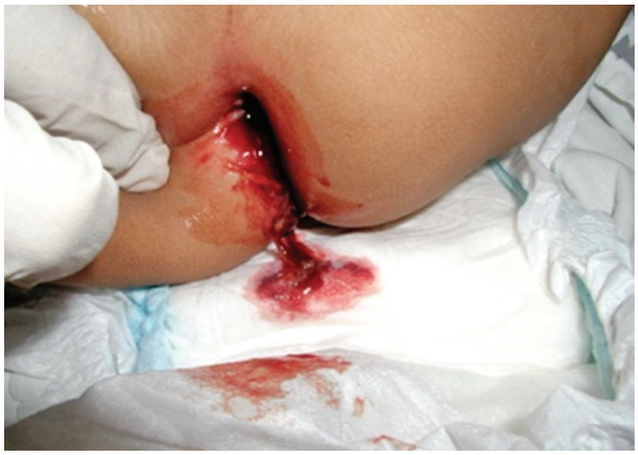

Figure 4 Rectal bleeding without fecal matter

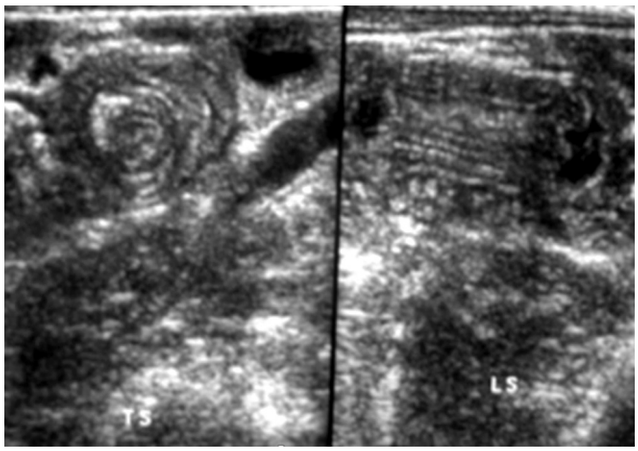

Figure 5 Ultrasonographic picture of intussusception

carries with it its attached mesentery. The resultant compression of the mesentery progressively leads to lymphatic and venous congestion of the involved segment of the bowel and finally arterial compression. The congested and hyperemic mucosa of the innermost layer of intussusception causes secretion of blood and mucus, characteristically labeled as *red currant jelly stool*. Further vascular compromise may then lead to gangrene of a portion of the bowel **(Fig. 3)**.

CLINICAL FEATURES

Disease usually occurs in a classically healthy, well-nourished child, less than one year of age. There may be a prior history of an upper respiratory tract infection. Colicky pain occurs in short bursts with intermittent periods of remission. Vomiting is bilious only in late cases. The hallmark of diagnosis is red currant jelly stools—usually with no fecal matter (a differentiating feature from dysentery) **(Fig. 4)**. On abdominal palpation, intussusception may be felt as a banana-shaped mass with the concavity towards the umbilicus. Occasionally, the mass can be felt per rectally. In late cases, features of septicemia and peritonitis may be seen.

DIFFERENTIAL DIAGNOSES

Intussusception is very commonly mistaken for dysentery and hence the diagnosis may be delayed. In intussusception, the stool contains mainly blood and mucus without fecal matter. Intestinal obstruction (fluid levels) and peritonitis are very late signs and one should never wait for them to appear.

APPROACH TO DIAGNOSIS

Clinically, a palpable (banana shaped) bowel mass is suggestive. Ultrasound of the abdomen can be diagnostic **(Fig. 5)**. It shows the *pseudo-kidney* sign or the *bowel-in-bowel* sign. A Doppler study performed simultaneously may indicate the blood flow to the portion. Alternatively, a barium enema may show the *coiled spring sign* or the *claw sign* **(Fig. 6)**. Laboratory studies may show evidence of blood loss, dehydration and electrolyte imbalance. A CT scan is rarely indicated, except in cases where there is excessive gas in the bowel loops which precludes a good sonographic assessment.

MANAGEMENT

Once suspected, the patient should be kept nil orally and a nasogastric decompression initiated as soon as possible. Correction of metabolic disturbances, including intravenous supplementation of fluid should be started before attempting any hydrostatic reduction. If necessary, blood transfusion may be started along with broad-spectrum and antianaerobic antibiotics.

Definitive Treatment

If diagnosed within 24 hours of onset, hydrostatic reduction (under sonographic or radiological control) may be attempted

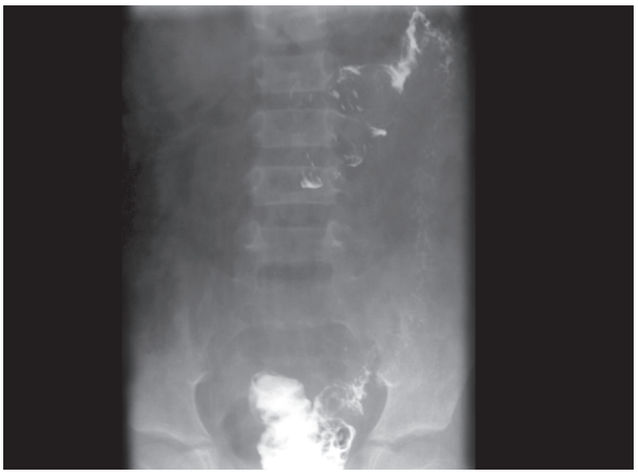

Figure 6 Barium enema showing *coiled spring sign*

by a pediatric surgeon, with facilities for immediate surgery kept ready in case of complications. It is important that any patient taken up for hydrostatic reduction should be ready to be taken to the operation theater immediately in case of a leak or perforation. Therefore, such a procedure must be undertaken only in the presence of a surgeon after initial resuscitation of the patient. Reduction may be attempted under laparoscopic monitoring in those patients where bowel vascularity is suspect. If hydrostatic reduction fails or is contraindicated, exploratory laparotomy with operative reduction or if necessary, resection and anastomosis may have to be undertaken.

IN A NUTSHELL

1. Intussusception is one of the most common abdominal emergencies in infants with disastrous consequences, if not treated in time.
2. In any infant with severe colicky pain or bleeding per rectum, intussusception should be ruled out.
3. A good ultrasonographic evaluation is reasonably reliable to diagnose intussusception.
4. Hydrostatic reduction should not be initiated on an out patient basis without intravenous resuscitation.

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Chapter 35.23
Appendicitis

Prakash Agarwal

Appendicitis is a medical emergency that requires prompt surgery. It is one of the most common acute surgical problems in children and is most commonly misdiagnosed. Left untreated, an inflamed appendix will eventually perforate leading to peritonitis. The incidence of appendicitis varies worldwide. In India more than 2,70,000 cases are reported annually. Although it can strike at any age, appendicitis is rare under age 2 and most common between ages 10 and 30.

ETIOLOGY

Appendicitis may be a result of luminal obstruction followed by infection due to *Yersinia, Salmonell*a and *Shigella*. The cause of luminal obstruction may be an inspissated and calcified fecal mater (fecalith). Appendiceal lymphoid hyperplasia may cause luminal obstruction leading to appendicitis. Parasitic infection such as *Entamoeba, Strongyloides, Enterobius vermicularis, Schistosoma* or *Ascaris* can cause appendicitis. Enteric and systemic viral infection can also lead to appendicitis.

PATHOGENESIS

Spectrum of appendicitis evolves from a simple infection to perforation. The varying stages of appendicitis include acute appendicitis, suppurative appendicitis, gangrenous appendicitis and perforated appendicitis.

CLINICAL FEATURES

The child may complain of vague gastrointestinal symptoms before classical presentation sets in. There may be anorexia, indigestion or change in bowel habits. Initially the child may complain of pain around the umbilicus which gets localized to the right iliac fossa. The continuous inflammation of the appendix will cause distention of the appendiceal wall leading to nausea and vomiting. After a few hours of nausea and vomiting, pain sets in. As the pressure inside the inflamed appendix increases, the lymphatics get obstructed, leading to further edema and swelling. Further increase in pressure leads to venous congestion resulting in ischemia, infarction and gangrene. This leads to bacterial transmigration of the wall of appendix. As a result of mediators released by ischemic tissue, white blood cells and bacteria, child develops fever, tachycardia and leukocytosis.

An inflamed appendix coming in contact with the parietal wall triggers off pain localized in the right iliac fossa or the McBurney's point. Further increase in intraluminal pressure will lead to perforation, localized abscess formation, if omentum conceals the perforation or it may lead to generalized peritonitis. Signs of acute appendicitis are fever more than 101°F, high leukocyte count and tachycardia with tenderness in the McBurney's point. A pelvic abscess due to perforated appendix may lead to diarrhea, or tenesmus.

Younger children usually present with a complicated appendicitis because of inability to give proper history and low index of suspicion by the clinician. The most common presenting symptoms for these children will be vomiting, followed by fever and abdominal pain.

DIAGNOSIS

Appendicitis can mimic a variety of intra-abdominal conditions **(Table 1)**. The clinical diagnosis of appendicitis is challenging and may be mistaken for acute gastroenteritis, viral mesenteric adenitis, Meckel diverticulitis and Crohn's disease. Extra-abdominal causes like pleurisy and pneumonia can mimic acute appendicitis.

Physical Examination

Clinically, a child with appendicitis will be quite and lie in bed with minimal movement. An older child may limp while walking with a grumpy face. They will give history of pain with every jerk while walking or coughing. If the child is asked to show the area of pain, they will usually point to the McBurney's point.

Table 1 Differential diagnosis of acute appendicitis

Gastrointestinal system	Acute gastroenteritis Acute viral mesenteric adenitis Constipation Meckel diverticulitis Crohn disease Typhoid Appendiceal tumor, carcinoid tumor
Hepatobiliary	Hepatitis Cholecystitis
Urinary system	Hydronephrosis Pyelonephritis Ureteral or renal calculus
Uterus, ovary	Ovarian torsion Ruptured ovarian cyst
Others	Primary peritonitis Henoch-Schönlein purpura Pancreatitis Pleuritis Pneumonia Psoas abscess Torsion of appendix epiploica

Palpation should be started away from the site of tenderness and progressed towards the site of pain. This will help in eliciting the Rovsing sign which indicates peritoneal irritation due to referred pain. A classical McBurney's point tenderness is diagnostic of acute appendicitis in conjunction with an elevated total leukocyte count, tachycardia and fever. Tenderness may be mild during the initial stages and can be elicited by palpation or percussion. The pain of retrocecal appendix may be elicited midway between the 12th rib and posterior superior iliac spine. Rectal tenderness will suggest a pelvic appendicitis.

A perforated appendicitis may present in the form of local or generalized guarding and rigidity, depending on the severity of the disease. Rebound tenderness may indicate localized peritonitis. If the diagnosis is in doubt, serial abdominal examination at intervals of 6–12 hours can be helpful.

Imaging

A plain X-ray may suggest fecaliths in 10–20% of cases but is rarely done. A chest X-ray to rule out pneumonia may be needed. An ultrasound may suggest a noncompressible appendix with an AP diameter of more than 7 mm. Presence of an appendicolith, with periappendiceal fluid may be confirmatory in the hands of a skilled radiologist. CT scan may show an enlarged appendix with thickening of the appendiceal wall, periappendiceal fat stranding and enhancement of appendiceal wall. It may help in the diagnosis due to anatomical abnormality such as malrotation or situs inversus. The sensitivity of CT scan is over 90% and its specificity is over 80%. Serial examination by the same examiner is the safest and the most accurate diagnostic tool.

Hematology

Leukocytosis with neutrophilia and increased CRP may be seen but are not diagnostic.

MANAGEMENT

In early noncomplicated appendicitis only perioperative antibiotics are required.

The gold standard treatment for appendicitis is prompt surgery. Majority of the appendicitis today are operated by laparoscopic methods **(Fig. 1)**. Open appendicectomy is becoming rarer in surgical practice though the trainee should be aware of it if having problems in performing laparoscopic appendicectomy. The advantages of laparoscopic appendicectomy are many fold including shorter hospitalizations, better scar, decreased postoperative pain, decreased wound complications, increased ability to diagnose coexisting conditions or other pathological conditions, surgical ease in obese patients and faster postoperative recovery. Laparoscopic appendicectomy for complicated appendicitis is becoming popular.

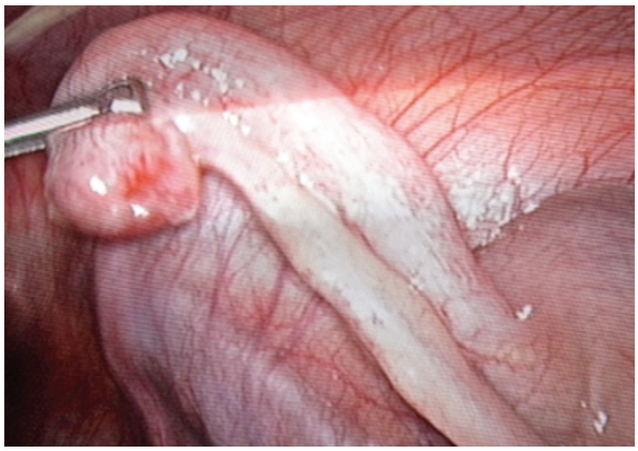

Figure 1 Laparoscopic view of a case of acute appendicitis

If not treated in time acute appendicitis may lead to complications like perforation and peritonitis. With the advent of higher antibiotics and awareness there is a decline in the incidence of complications. Complications of appendicitis include wound infection, intra-abdominal abscess formation, postoperative intestinal obstruction, prolonged ileus and enterocutaneous fistula. Acute appendicitis in females should be treated with a low threshold for surgery as complicated appendicitis may lead to fertility problems in the future.

In recent years due to broad spectrum antibiotics the mortality due to complicated appendicitis is almost nil. Antibiotics have markedly decreased the incidence of various complications listed above. Although the length of hospitalization and morbidity due to complicated appendicitis still far exceeds those with simple appendicitis, the overall morbidity in children with complicated appendicitis is less than 10%.

IN A NUTSHELL

1. Appendicitis remains the most common acute surgical condition of the abdomen in children.
2. Luminal obstruction due to fecalith remains the most common cause of acute appendicitis.
3. Salient clinical features of acute appendicitis are—right iliac fossa pain, nausea and vomiting, fever associated with tachycardia and elevated leukocyte count.
4. The gold standard treatment for appendicitis is laparoscopic appendicectomy.

MORE ON THIS TOPIC

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Chapter 35.24
Testicular Torsion

Prakash Agarwal

Torsion of the testis is a surgical emergency which results in occlusion of the gonadal blood supply. If unrelieved within hours it may lead to necrosis. It occurs usually in fully descended testis but maybe seen in undescended testis as well. Previously the incidence of torsion in an undescended testis was very high. However due to the present practice of earlier surgical intervention torsion in an undescended testis is now rare.

PATHOGENESIS

Torsion may be intravaginal or extravaginal. Intravaginal torsion is more common due to high investment of the spermatic cord by the tunica vaginalis. Extravaginal torsion is less common and confined to the perinatal period.

In *intravaginal torsion*, the long narrow mesorchium allows the testis to lie horizontally rather than fixed vertically as in the normal testis. The pendulous testis with a high investment of the cord has a horizontal lie and allows the testis to be readily twisted by cremasteric contractions or by a jerky movement. This phenomenon is seen more commonly in undescended testis.

In *extravaginal torsion* there is a loose areolar plane around the moving gubernaculums and testis into the scrotum, which allows the entire testis and spermatic cord to twist. Beyond the newborn period testicular torsion is almost always associated with the bell clapper deformity. Cremasteric contraction may be either the cause or the effect of torsion. The high incidence of testicular torsion in puberty is due to the increased levels of testosterone making the testis bulky and more prone for torsion. The most common age for torsion of the testicular appendix is around 11 years. This peak, just before the onset of puberty may be related to early pubertal stimulation by estrogen. Chances of necrosis of the testis are less, if the number of twists is less or there are chances of spontaneous untwisting. In adolescent boys necrosis may occur after as early as 2 hours and very likely after 24 hours. The testis has four testicular appendages of which the hydatid of Morgagni is the most frequently twisted.

CLINICAL FEATURES

Torsion of the testis is commonly seen in the adolescent age group but the testicular appendage torsion is seen before puberty. Usually there are two peaks of torsion of the testis: in the early neonatal period and in adolescent boys aged 13–16 years. Usually testicular torsion is heralded by the sudden onset of pain in the testis, lower abdomen or groin, associated with nausea and vomiting. The hemiscrotum looks red and edematous **(Fig. 1)** and if untreated leads to a bluish discoloration of the scrotum. In torsion of a testicular appendage, a bluish black spot (blue-dot) may be seen through the skin at the upper pole of the testis. This is more prominent in the white population compared to dark skin people. Palpation of this area causes extreme pain, whereas the rest of the testis is not so painful. Once secondary inflammation and edema of the scrotum occur, it may be impossible to distinguish between testicular torsion and torsion of a testicular appendage.

DIAGNOSIS

Inflammatory conditions of the scrotum like epididymo-orchitis, epididymitis may mimic torsion testis. Idiopathic scrotal edema, fat necrosis and mumps orchitis are the other differential diagnoses. Radioisotope scan and Doppler ultrasound has been used to determine whether there is blood flow to the testis or not. These tests may be more useful after puberty as the testicular volume is greater after puberty. However, exploration is recommended for all doubtful cases of acute scrotum.

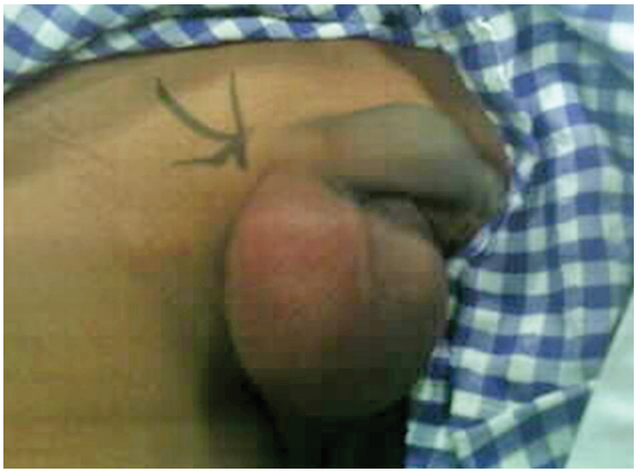

Figure 1 Red and edematous hemiscrotum in torsion testis

MANAGEMENT

Treatment of torsion of the testis is immediate operative exploration of the scrotum. The hemiscrotum is opened in the midline with a diathermy. The testis is delivered through the incision, and inspected. If the testis is twisted it is untwisted and the viability is assessed. If the torsion is early the circulation may return within few minutes. If there is congestion, then it may be better to observe the testis for several minutes by giving warm packs and asking the anesthetist to give 100% oxygen. If there is no improvement in the viability of the testis then an orchidectomy is done by double ligation of the testicular vessels. If the testis appears viable, no further treatment is required. The appendage testis is inspected and excised, if there is torsion. In case of epididymo-orchitis removal of the edematous fluid leads to relief of symptoms. Exploration of the contralateral testis is usually done since the anomaly is bilateral and the testis is fixed in all cases which required orchidectomy.

OUTCOME

The management of a testis of doubtful viability on operation is controversial. Leaving behind such a testis is to see if they will recover any hormonal function. However it has recently been reported that children older than 10 years of age are at risk of developing antisperm antibodies. It has been seen that men who underwent fixation of ischemic testes at adolescence had poor spermatogenesis later in life. Some authors therefore recommend preservation of a doubtful testis if the boy is below 10 years and orchidectomy for those above that age.

PREVENTION

Adolescents should be made to report sudden acute or recurrent testicular pain. Prophylactic bilateral orchidopexy may be justified, especially if there is a horizontal lie of the testes on clinical examination.

IN A NUTSHELL

1. Torsion testis is a surgical emergency with a high incidence of gonadal necrosis if not treated early.
2. Torsion of the appendage of testis, epididymo-orchitis and acute scrotal edema are differential diagnosis.
3. Doppler ultrasound may suggest a reduced flow in cases of torsion but is not reliable in prepubertal children, since their testicular volume is less.
4. Diagnosis is clinical and treatment is immediate exploration. All doubtful cases also require exploration.

MORE ON THIS TOPIC

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Chapter 35.25
Inguinal Hernia

Prakash Agarwal

Protrusion of abdominal viscus through the patent processus vaginalis in children is termed as hernia. It is one of the most common elective surgeries performed in children. The highest incidence is in premature infants (16–25%). Inguinal hernia is commonly seen during the first year of life, with a peak incidence in the first few months. Male to female ratio is between 3:1, and 60% of the hernias are right sided. In males, this is possibly the result of the later descent of the right testicle than the left. Bilateral hernias occur in 10% of cases **(Fig. 1)**. Approximately 11.5% of patients have a family history of hernia.

PATHOGENESIS

Indirect inguinal hernia is the result of failure of the processus vaginalis to close. The processus vaginalis is an invagination of the peritoneum through the internal ring through which the testis passes from the 7th month to 9th month of gestation. In females the canal of Nuck corresponds to the processus vaginalis and communicates with the labia majora. Reduced release of calcitonin gene-related peptide (CGRP) has been implicated in the formation of hernia and hydrocele.

Incarcerated hernias result from entrapment of intestine, appendix, tubes and ovaries in females or other viscera within the hernia sac. If the hernia is not reduced, strangulation may occur, and blood supply to the incarcerated organ may be reduced to the point of gangrene. The patient may present with signs of peritonitis. Incarceration is seen commonly in infants below 6 months.

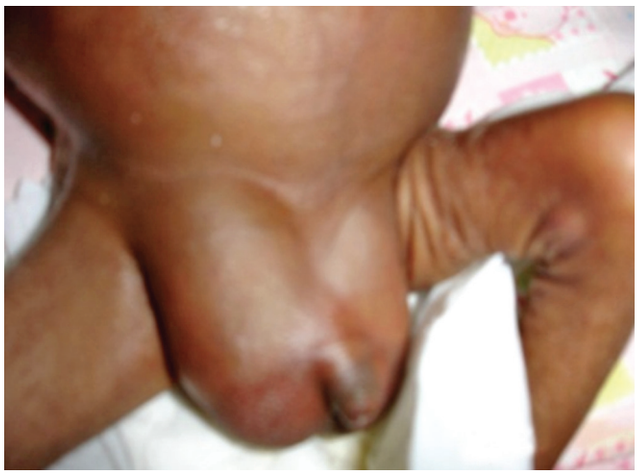

Figure 1 Bilateral inguinal hernia in a boy

CLINICAL FEATURES

Parents complain of noticing a bulge in the groin, labia or scrotum. Hernias may be seen at birth or even months after birth. They are usually asymptomatic and appear during crying, coughing or conditions due to raised intra-abdominal pressure. On examination a bulge may be seen and palpated in the inguinal region over the spermatic cord. If it is not present, the spermatic cord may be palpated to determine thickening-silk string sign. A positive sign indicates thicker cord structures within the inguinal canal compared with the normal side. If a hernia is not seen on physical examination, the history given by parents can be taken as a strong evidence for operating on the child. Obstructed hernia may lead to intermittent pain and irritability, abdominal distention, vomiting and obstipation.

DIAGNOSIS

Inguinal hernia is a clinical diagnosis made by history and physical examination. Plain X-ray abdomen if done, may show bowl loops in the scrotum. Ultrasound of the inguinal region can demonstrate herniation of omentum or bowl loops intermittently. It has gained popularity as an adjunct to physical examination. It is noninvasive and has an accuracy of 97%.

SURGERY

Herniotomy is advised at the earliest, since it will not resolve spontaneously. In young infants it should be performed immediately as the chances of obstruction are very high. Most children are operated under general anesthesia as day care surgery except premature infants who are prone for apneic spells. The repair is done with absorbable sutures which do not need removal later.

Laparoscopic repair in children has been controversial. Advantages include minimal handling of the vas, less pain, earlier return to school, repair of bilateral hernias through the same ports and easier repair of recurrent hernias. Disadvantages include longer operating time and a prolonged learning curve for the surgeons and increased cost. Laparoscopy involves insertion of 3 X 5 mm ports, correct identification of the side of hernia, excising the hernial sac and purse string intracorporeal suturing and closing the hernial sac.

Since patients presenting with left sided hernias are more likely to have bilateral hernias. Many surgeons recommend routine exploration of the opposite side. In such situations laparoscopy has the advantage of allowing direct visualization of the contralateral internal ring and repairing it at the same time.

Postoperative complications Some children may develop scrotal swelling in the postoperative period, which resolves spontaneously. Acquired undescended testis after hernia repair is an uncommon complication. Recurrence after hernia repair is reported in less than 1% of children with uncomplicated hernia, but may be as high as 15% in premature infants and 20% in incarcerated hernias. Accidental transection of the vas during surgery should be repaired immediately.

IN A NUTSHELL

1. Inguinal hernia is commonly in the first year of life, with higher incidence in premature infants.
2. The most common cause of indirect inguinal hernia in children is a patent processus vaginalis.
3. Inguinal hernia is a clinical diagnosis and surgical repair is recommended at the earliest.
4. Surgery is a day care procedure except in premature infants who are prone for apneic spells.

MORE ON THIS TOPIC

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