15.15 Congenital abnormalities of the gastrointest

15.15 Congenital abnormalities of the gastrointestinal tract 2967

ESSENTIALS Congenital abnormalities of the gastrointestinal tract can be divided into macroscopic anatomical abnormalities and single gene high- penetrance functional defects that present either directly postnatally or during the first few months of life. On occasion, symptoms may be delayed for months or years even in patients with substantial ana- tomical defects. Anatomical and structural abnormalities can affect any part of the gut. These include oesophageal atresia and tracheo-oesophageal fis- tula, anterior abdominal wall defects, congenital pyloric stenosis, atresia and stenosis of the small intestine, duplication of the gastrointestinal tract, small intestinal malrotation with or without volvulus, small intes- tinal lymphangiectasia, Meckel's diverticulum, congenital short intes- tine syndrome, colonic atresia, Hirschsprung's disease, and imperforate anus. Meconium ileus is an intestinal obstruction that develops in utero, often associated with subsequent structural abnormalities. The widespread use of ultrasonography allows many abnormal- ities to be recognized prenatally. Presentation of structural congenital abnormalities of the gastrointestinal tract in adult life is uncommon, but small intestinal lymphangiectasia, Meckel's diverticulum, or small intestinal obstruction can present beyond childhood. Functional congenital abnormalities include multiple genetic defects that cause congenital diarrhoea due to malabsorption and maldigestion, defects in enterocyte and enterochromaffin cell de- velopment, and autoimmune enteropathies. In addition, there is a group of genetic defects that predispose to development of extreme early infantile onset of inflammatory bowel disease. An interdisciplinary approach is required for the optimal manage- ment of children with complex congenital abnormalities. Congenital structural abnormalities Oesophageal abnormalities Oesophageal atresia and tracheo-oesophageal fistula The incidence of this condition is approximately 1 in 2500 to 1 in

4500 live births. The occurrence is typically sporadic. In about 85% of cases, the upper oesophagus ends in a blind pouch and the lower oesophagus communicates with the trachea via a tracheo-oesophageal fistula. In addition, there are other anatomical vari- ations as indicated in Fig. 15.15.1.
Clinical features In some children, the combination of polyhydramnios and absent gastric bubble can suggest an oesophageal atresia during prenatal ultrasonographic scans. About 40% of infants with oesophageal atresia are born prematurely and some are small for gestational age. Shortly after birth, copious amounts of frothy saliva dribble from the mouth, associated with choking, dyspnoea, and cyanotic episodes. Frequent suction is required to keep the airway clear. The infant with a tracheo-oesophageal fistula without associated oesophageal atresia coughs, chokes, and becomes cyanosed during feeds. As air escapes through the fistula into the oesophagus, gaseous distension of the abdomen is frequently present. Aspiration of feed into the airway results in pulmonary collapse and consolidation. In children with lower tracheo-oesophageal fistulas, acidic stomach secretions can reach the lungs and contribute to complications. Over 80% of infants with oesophageal atresia have cardiac, ano- rectal, urogenital, or skeletal anomalies (or combinations such as VACTERL association). Cardiac anomalies occur in up to 60%, with ventricular septal defects and tetralogy of Fallot being most common. 15.15 Congenital abnormalities of the gastrointestinal tract Holm H. Uhlig 85% 2% <1% 8% 4% Fig. 15.15.1 Anatomical variations of oesophageal atresia and tracheo- oesophageal fistula with their relative frequencies indicated.

section 15 Gastroenterological disorders 2968 Survival of infants with oesophageal atresia is high (95%) but depends on specialized care and risk factors such as low birth weight, associated congenital abnormalities, and complications (pneumonia). Diagnosis When oesophageal atresia is suspected, a size 10 or 12 FG catheter is passed through the mouth and into the oesophagus. If the oe- sophagus is obstructed, the catheter meets a resistance 9 to 12 cm from the gum margin. A smaller catheter may curl up in the ob- structed oesophagus. Contrast studies of the oesophagus are rarely necessary. A chest and abdominal radiograph will show the position of a radio-opaque tube in the upper oesophagus. The presence of gas in the bowel despite an oesophageal atresia indicates a tracheo- oesophageal fistula. Complete absence of gas in the abdomen is diagnostic of an oesophageal atresia without a distal tracheo- oesophageal fistula. The radiograph will also reveal abnormalities of ribs or vertebrae, signs of pneumonia, and may provide evidence of an associated cardiac abnormality. In isolated tracheo-oesophageal fistula, very contrast studies of the oesophagus may demonstrate the fistula, but endoscopic exam- ination of the trachea and oesophagus is usually diagnostic. Management Early division of the tracheo-oesophageal fistula and anastomosis of the oesophagus are possible in most cases. A primary anastomosis may not be feasible in oesophageal atresia with a long gap, extreme prematurity, or where the infant’s general condition is poor. A gas- trostomy or a transanastomotic nasogastric tube is usually used for feeding after operation. In case of long-gap oesophageal atresia, sev- eral surgical and thoracoscopic procedures aim to elongate the oe- sophagus and adjust the ends of the atretic oesophagus to provide continuity. Postoperative complications include anastomotic leaks, gastro-oesophageal reflux, anastomotic strictures (30–40%), and oe- sophageal dysmotility. Anterior abdominal wall defects Exomphalos The incidence of exomphalos is approximately 1 in 5000 births. An exomphalos occurs when the abdominal contents, in particular liver and intestine, herniate through the umbilical ring into the base of the umbilical cord. Clinical features The herniated abdominal contents are covered by a translucent membrane composed of peritoneum and amnion. The diagnosis is often already made on a prenatal ultrasonographic scan. The le- sion will be obvious at birth. Occasionally, the membrane will rup- ture during, or shortly after delivery. In

about 30 to 50% of cases, other abnormalities are associated, particularly chromosomal tri- somy 18 (but also 13 and 21), cardiac anomalies, and the Beckwith– Wiedemann syndrome. The Beckwith–Wiedemann syndrome, also termed the exomphalos macroglossia gigantism syndrome, usually presents as a large-for-date infant with hemihypertrophy and exomphalos. It is due to defects in the epigenetic control of imprinted loci on chromosome 11 that control fetal and postnatal growth via genes such as H19, IGF2, KCNQ1OT1, and CDKN1C. The tongue is strikingly large, there are frequently ridges in the earlobes, and a prominent naevus flammeus on the forehead. Hypoglycaemia as a result of hyperinsulinism produced by islet cell hyperplasia is treated using standard neonatal hypoglycaemia protocols. In 20% of children, hypoglycaemia persists beyond the first week or even the neonatal period and might require sustained tube feeding, medication, or rarely subtotal pancreatectomy. In the long term, children with this syndrome have an increased incidence of solid tumours, particularly nephroblastoma (Wilms' tumour) and hepatoblastoma. Management The prenatal ultrasound examination is key to assess the extent of the anatomical problem, to differentiate exomphalos minor (<5 cm defect and no liver in sac) from exomphalos major (>5 cm defect or liver in sac), and to detect associated abnormalities. If a diaphrag- matic hernia is detected before birth, a fetal MRI scan may help to determine residual lung volume. A caesarean section can prevent birth trauma in children with exomphalos major. After birth, a nasogastric tube is passed to decompress the bowel. The sac can be very satisfactorily covered and supported by wrap- ping plastic film around the exomphalos and the baby's trunk. Preoperative plain radiographs of chest and abdomen may help to assess the intestinal gas pattern, and investigate a diaphragmatic hernia. Primary closure will be performed if the contents of the sac can be reduced into the peritoneal cavity. If closure of all layers of the abdominal wall is impossible, skin closure alone may be used, or a synthetic material is used to enclose the sac or to build a silo. Gradual reduction of the contents into the peritoneal cavity is then possible. If gradual closure is required, application of antiseptic so- lutions or silver-based solution or cream onto the membrane can produce a granulating surface that epithelializes. Postoperatively, ventilatory support may be necessary. Parenteral nutrition will be necessary if oral feeds cannot be given. Survival is related to the size of the lesion and the severity of any associated abnormalities. Gastroschisis The incidence of gastroschisis is approximately 1 in 2500 births. Incidence is increasing and young maternal age as well as primi- gravida status and low socioeconomic status are risk factors. In gastroschisis, there is a full-thickness defect in the anterior abdom- inal wall, usually to the right of the umbilical cord. The defect is small, but most of the gastrointestinal tract may be extruded through it. In contrast to exomphalos, other abdominal organs are rarely eviscer- ated and abnormalities outside the gastrointestinal tract are unusual. Prenatal diagnosis on an ultrasonographic scan is common. Labour is often induced at 37 weeks' gestation to reduce complications such as sepsis or bowel damage. Clinical features After delivery, hypothermia and hypoproteinaemia due to the ex- posed bowel are common problems. The small size of the defect in the anterior abdominal wall and the often narrow pedicle from which the bowel is suspended may impair the blood supply and result in infarction of the extruded intestine. Atresia may have oc- curred because of intrauterine impairment of the blood supply.

 Management A nasogastric tube is passed and the bowel decompressed. The bowel should be enclosed in plastic wrap (cling film) around the baby's trunk. This keeps the bowel moist and prevents excessive heat loss. Antibiotics are commenced preoperatively and management of hypoproteinaemia and hypovolaemia is important. At operation, primary abdominal wall closure is aimed for, but this is not possible in

some cases and a plastic sheet is used to form an artificial silo to enclose the intestine (often Silastic or Gor-Tex sheets, increas- ingly preformed manufactured silos). The size of the silo is gradually reduced over some days, squeezing the bowel back into the peri- toneal cavity until closure of the abdominal wall becomes feasible. Ventilatory support postoperatively is often necessary. Parenteral nutrition is essential and may need to continue until gastrointestinal motility and absorption are adequate. About one-fifth of children have complex gastroschisis with intes- tinal atresia or complications such as gangrene, closing gastroschisis, perforation, strictures or volvulus leading to sepsis, necrotizing en- terocolitis, prolonged parenteral nutrition, and short-gut syndrome. Abnormalities of the bowel Congenital pyloric stenosis Congenital hypertrophic pyloric stenosis is a disorder character- ized by hypertrophy of the circular muscle of the pylorus causing obstruction to the gastric outlet. The incidence is 2 per 1000 live births. The aetiology is unknown. Theories include primary muscle hypertrophy, abnormalities of the maturation of ganglion cells, ab- sence of a certain type of ganglion cell, or a response to abnormally high concentrations of circulating gastrin. Genetic and environ- mental factors play an important part. There is an increased inci- dence of pyloric stenosis in siblings of an affected child and in the offspring of a woman who has had the condition. Nonbreastfeeding also increases the risk. In any large series, the male-to-female ratio is 3 or 4:1. Clinical features The onset of symptoms is usually between 3 and 6 weeks of age, but may present shortly after birth. Vomiting of increasing severity is the cardinal symptom, eventually occurring after most feeds and becoming projectile. The vomitus is milk and mucus, and may con- tain altered blood suggesting an oesophagitis or gastritis, but bile is never present. The baby stops gaining weight and becomes consti- pated. Characteristically the baby is alert, anxious, and hungry. If diagnosis is delayed, severe malnutrition may develop. Due to the loss of gastric acid, a hypochloraemic, hypokalaemic metabolic al- kalosis might be found, but fluid loss can lead to subsequent meta- bolic acidosis. Examination reveals evidence of weight loss and in advanced cases, signs of dehydration will be present. After feeding, waves of peristalsis travelling from left to right in the epigastrium will be seen (visible peristalsis). The thickened pylorus is felt as an olive-sized tumour lying deep to the edge of the right rectus and is often most easily palpable when the stomach is empty. The diagnosis is largely supported by clinical symptoms, but ultra- sonography is the standard diagnostic technique with pyloric length more than 1.2 cm and pyloric wall thickness of more than 3 mm sup- porting the diagnosis. If ultrasonography is not available, a barium meal is diagnostic when the ‘string’ sign of the elongated pylorus and accumulation of contrast in the prepyloric antrum is demonstrated. Management Preoperative correction of water and electrolyte deficits is essential. The pyloromyotomy described by Ramstedt splits the hypertro- phied muscle longitudinally allowing the mucosa to bulge through the defect, thus enlarging the pyloric canal. The laparoscopic pyloromyotomy has increasingly replaced classical laparotomy. Postoperatively, various feeding regimens are advocated to achieve enteral feeding within 24 h. Ad libitum feeding is as safe as a regi- mented feeding protocol. The prognosis is excellent. Atresia and stenosis of the small intestine An intrinsic obstruction may produce either complete (atresia) or partial obliteration (stenosis) of the bowel lumen. Complete oblit- eration may be due to a gap between the two ends of the small in- testine, with or without a connecting band between these ends, or a complete mucosal diaphragm. Small intestinal atresia is a more common finding than is stenosis. The duodenum is most often af- fected, followed by jejunum, and ileum. Associated abnormalities of the gastrointestinal tract include malrotation, oesophageal atresia, imperforate anus, biliary atresia, and annular pancreas. Intrinsic ob- struction of the small intestine of congenital origin presents most often in the neonatal period. When the obstruction is partial, it may first present even in

infancy and childhood. Congenital intrinsic duodenal and jejunoileal obstruction Congenital intrinsic duodenal obstruction may be accompanied by an annular pancreas; this is a sign of failure of duodenal develop- ment rather than an obstructive lesion per se. Congenital intrinsic duodenal obstruction is not, in general, associated with multiple atresias in the remainder of the small intestine, but there may be obstruction at two levels in the duodenum. Associated abnormal- ities include Down's syndrome where duodenal lesions occur in 10% of cases. In patients with multiple intestinal atresia, recessive defects in the gene TTC7A have been described, causing a variable combination of severe intestinal epithelial cell polarization defects, multiple intes- tinal atresia, and severe combined immunodeficiency (SCID)-like immunodeficiency. Subsequent intestinal inflammation develops in some patients. The substantial epithelial component of the defect is illustrated by the finding that haematopoietic stem cell transplant- ation does not cure the intestinal defect. Clinical features When duodenal obstruction is complete, bilious vomiting usually occurs within a few hours of birth and is bile stained unless the ob- struction is proximal to the ampulla of Vater. Meconium may be passed normally and there may be obvious epigastric distension. When obstruction is incomplete, the symptoms may be intermittent and the diagnosis delayed. In jejunoileal obstruction, bile-stained vomiting and abdominal distension usually occur within the first 2 days of life. Meconium may or may not be passed. When obstruction is incomplete, the diagnosis may again be delayed and the child may present with intermittent vomiting, abdominal distension, and even with features of malabsorption.

section 15 Gastroenterological disorders 2970 Antenatal ultrasonography may guide diagnosis by showing di- lated proximal bowel loops associated with polyhydramnios. Plain radiographs of the abdomen are usually diagnostic in symptom- atic infants who present with a complete obstruction. In duodenal atresia, there is the characteristic 'double bubble' (Fig. 15.15.2) and in jejunal atresia a 'triple bubble' may be found. When duodenal ob- struction is incomplete, there may be small amounts of air in the lower bowel. A contrast study may be necessary to demonstrate the obstruction and may suggest an associated malrotation. When there is complete jejunoileal obstruction, there are usually multiple dilated loops of intestine. A contrast enema may reveal an unused microcolon. When obstruction is incomplete, a contrast follow- through may be needed to establish the diagnosis. Management A nasogastric tube is passed to empty the stomach and allow ac- curate measurement of gastric losses. Fluid and electrolyte disturb- ances should be corrected. In duodenal obstruction, the operation of choice is duodenoduodenostomy. In jejunoileal lesions, adequate re- section of the proximal dilated gut reduces the great discrepancy in size between the two blind ends and can facilitate end-to-end anas- tomosis, allowing better peristalsis of the nondilated prestenotic gut and preventing delay in establishing enteral feeds. Considerable loss of intestinal length may occur as a direct result of the atresia and surgical correction will result in further loss. Loss of considerable lengths of jejunum is well tolerated. Every effort is made to preserve some ileum and the ileocaecal valve to prevent sec- ondary complications caused by malabsorption and problems in the enterohepatic circulation. Duplication of gastrointestinal tract Duplications are cystic or tubular structures whose lumen is lined by a mucous membrane, usually supported by smooth muscle. They occur most often within the dorsal mesentery of the gut. Duplications may occur anywhere along the alimentary tract but they are found most often in relation to the small intestine, particu- larly the ileum. They may not communicate with the main lumen of the gastrointestinal tract. Duplications may be found in association with intestinal atresias. Small intestinal duplication may contain ec- topic gastric mucosa causing peptic ulceration of the adjacent small intestinal mucosa with bleeding and perforation. Clinical features

Duplications often present in infancy as a small-bowel obstruction, or a small cystic duplication may form the lead point of an intus- susception. A palpable abdominal mass in infancy, as well as rectal bleeding and volvulus, may also be modes of presentation. The clin- ical diagnosis is often difficult, and although ultrasonography and MRI can be supportive, and a technetium scan may be helpful by demonstrating ectopic gastric mucosa, sometimes diagnostic lapar- oscopy or laparotomy is required. Initial presentation may be a posterior mediastinal cystic mass, possibly associated with cervical or upper thoracic vertebral abnor- malities. The mass is likely to communicate through the diaphragm with an intestinal duplication. Management Excision of a cystic duplication, with or without the adjacent intes- tine, is usually straightforward. Any associated thoracic cyst will also need excision. Short tubular duplications can be excised with the adjacent intestine. Long tubular duplications can be opened longi- tudinally and the mucosa stripped out, leaving the common muscle wall and preserving the intestinal length. Small intestinal malrotation with or without volvulus Malrotation of the small intestine is due to disordered movement of the intestine around the superior mesenteric artery during the course of intrauterine development. It affects up to 1 in 1200 births. Several genetic defects have been identified that cause malrotation, including mutations in the forkhead transcription factor gene FOXF1 and several genes that affect left–right pattern and cause complex intrauterine development defects including intestinal malrotation (CFC1, ZIC3, NKX2–5, ACVR2B, LEFTY2). There are two main abnormalities. First, there is a gross narrowing of the base of the mesentery, which may allow the midgut to twist around and cause a volvulus. This may occur acutely, causing com- plete obstruction, or it may occur intermittently, producing bouts of partial or complete obstruction. Secondly, there may be partial duo- denal obstruction from extrinsic compression of the small intestine by peritoneal bands (Ladd’s bands) that extend from the caecum to the subhepatic region. Clinical features Malrotation may be associated with intestinal atresia or stenosis. It is also found in association with diaphragmatic hernia, omphalocele, and gastroschisis. Malrotation may be asymptomatic and is some- times discovered only as an incidental finding on a barium study (Fig. 15.15.3). Most children who develop symptoms related to malrotation do so within the neonatal period, presenting with features of complete or incomplete intestinal obstruction. Obstruction to the blood supply
Fig. 15.15.2 Plain radiograph of the abdomen of an infant with duodenal atresia showing the characteristic ‘double bubble’.

 to the bowel will lead to extensive gangrene of the small bowel. Bloody stools may present as an early sign of this complication. Intermittent and incomplete obstruction may present later in childhood with episodes of (bile-stained) vomiting and abdominal pain, but also malabsorption. Intestinal stasis may cause bacterial overgrowth in the lumen of the small intestine and steatorrhoea may be caused by protein-losing enteropathy due to obstruction of the mesenteric lymphatics. Plain radiographs of the abdomen may reveal an air-filled stomach with some gas scattered through the lower part of the abdomen. A contrast study can reveal the presence of malrotation by failure of the duodenal passage to cross to the left of the vertebral bodies. Management Surgical intervention is indicated when a firm diagnosis is estab- lished. Ladd’s operation is usually the procedure of choice. This in- volves, in general, the placement of the colon on the left and the small intestine on the right, having divided any bands and adhesions between the duodenum and large bowel, and, by dissection, broad- ened the base of the mesentery as much as possible. Although bowel necrosis after a volvulus is untreatable, severe bowel ischaemia can be reversible and a ‘second-look’ laparotomy may allow necrotic tissue to be differentiated from ischaemic tissue and recovered intes- tinal tissue to be

preserved. Meckel’s diverticulum This diverticulum is the vestigial remnant of the vitellointestinal duct. Although most people who have such a diverticulum are asymp- tomatic, complications may arise due to the presence of ectopic gastric or pancreatic tissue in the diverticulum. The diverticulum is located antimesenterically in the distal ileum within 100 cm of the ileocaecal valve. Rectal bleeding is the main symptom. This is usually the passage of bright blood rather than tarry melaena stools. Typically, the stool is at first dark in colour but later bright red. Bleeding may be acute, with shock requiring urgent blood transfusion, or it may be chronic. In any child who has a massive, painless rectal bleed, a Meckel’s di- verticulum is a likely differential diagnosis. Most often bleeding from a Meckel’s diverticulum is associated with ulceration of the small bowel adjacent to ectopic gastric or pancreatic mucosa. Small intestinal obstruction may occur due to volvulus, or an intussuscep- tion with the diverticulum as the lead point. Acute diverticulitis may produce a picture indistinguishable from acute appendicitis. A technetium scan is usually the most important investigation. The radionuclide 99mTc concentrates in the gastric mucosa and ec- topic gastric mucosa appears as an abnormal abdominal localization on scintigraphy. This allows detection of a Meckel’s diverticulum with ectopic gastric mucosa, or indeed any duplication with such ectopic tissue. When rectal bleeding occurs, investigation includes colonoscopy to exclude polyps, intestinal vascular malformation, or ulceration. An upper gastrointestinal endoscopy may exclude peptic ulceration or oesophagitis, but upper gastrointestinal bleeding often presents with haematemesis. Angiography or red blood cell scintigraphy (Fig. 15.15.4) might be considered in cases of severe bleeding, but a diagnostic laparoscopy or laparotomy is typically required. Meconium ileus Meconium ileus affects about 10 to 20% of children with cystic fi- brosis during the neonatal period, and a similar syndrome in older children and young adults with cystic fibrosis may occur—the meconium ileus equivalent. The meconium of abnormally viscid consistency adheres to the mucosa and cannot be propelled along the bowel, causing small intestinal obstruction in the distal ileum. The abnormal consistency may result from several factors including the lack of pancreatic enzymes during fetal life and reduced secre- tion of water and electrolytes in such infants. Fig. 15.15.3 Intestinal malrotation. Barium examination of the small bowel shows the duodenum and small bowel on the right and the colon (arrows) on the left. The duodenum does not cross the midline and the ligament of Treitz is absent. From Levy AD, Mortele KJ, Yeh BM (eds) (2015). Gastrointestinal imaging. By permission of Oxford University Press. Fig. 15.15.4 Bleeding Meckel’s diverticulum. Fused images of a technetium red blood cell scan obtained by single-photon emission computed tomography show bleeding (arrows) in the right lower abdomen surgically proven to stem from within a Meckel’s diverticulum. From Levy AD, Mortele KJ, Yeh BM (eds) (2015). Gastrointestinal imaging. By permission of Oxford University Press.

section 15 Gastroenterological disorders 2972 Over 1000 mutations in the CFTR gene have been described in cystic fibrosis. The ΔF508 CFTR mutation is most common. Meconium ileus is enriched in patients with severe loss-of-function mutations in the CFTR gene (such as the ΔF508 mutation). Clinical features If not already suspected on antenatal ultrasonographic scans by white-appearing guts, the neonate with meconium ileus usually de- velops signs of intestinal obstruction within the first 24 to 48 h of life. Classical signs are bile-stained vomiting, progressive abdom- inal distension, and failure to pass meconium. In some cases, meco- nium may just cause obstruction, but meconium ileus may also be complicated by perforation of the gut. When this occurs in utero, intraperitoneal calcification may be observed on a plain radio- graph of the abdomen, providing evidence of meconium peritonitis. Perforation may also occur in the neonatal period. In simple meconium ileus, the plain radiograph of the abdomen may show dilated bowel but few fluid levels.

Sometimes there is the appearance of bubbly meconium in the right lower quadrant. Bowel loops may be palpable. If a contrast enema is performed, a microcolon, a consequence of disease, will be demonstrated. Atresia associated with meconium ileus is frequently indistinguishable radiologically from an atresia of ischaemic origin. Management Initial nasogastric tube decompression, application of antibiotics, and intravenous hydration will stabilize the child. Hyperosmolar enemas (such as Gastrografin, dilution 3:1) can resolve the meco- nium plug in about one-third of cases, but care is required to avoid them inducing dehydration. Enemas should not be used until a plain radiograph of the abdomen or ultrasonography has excluded the possibility of complicated meconium ileus with perforation. Additional application of N-acetylcysteine via nasogastric tube or enema to resolve the mucus plug has been suggested by some centres, but evidence of efficacy is not clear. When meconium ileus is complicated by atresia or perforation, gangrene, peritonitis, or associated volvulus, surgical intervention is essential. Surgical options include the formation of an ileostoma with decompression or resection with an immediate end-to-end anastomosis. The diagnosis of cystic fibrosis should be confirmed by sweat elec- trolyte estimations (concentrations of sweat sodium >60 mmol/litre are likely diagnostic) and genetic testing of the CFTR gene. Congenital short-bowel syndrome Congenital short-bowel syndrome is characterized by substantial reduction of small-bowel length due to mutations in the CLMP or FLNA genes. Compared to the 250 cm short-bowel length of a term baby, patients with congenital short-bowel syndrome present with approximately 50 cm length, associated with mal- or nonrotation of the intestine. Pyloric hypertrophy has been found in some patients. Patients present shortly after birth with bile-stained vomiting as well as diarrhoea and failure to thrive. They initially require parental nutrition and substitution of vitamins and trace elements. Although historically the prognosis is poor, the condition can be managed when sepsis episodes and liver failure can be avoided. Over time, there is some improvement in absorption capacity and food is often tolerated within 1 or 2 years of age. Colonic atresia Atresia of the large intestine affects approximately 1 child among 20 000 live births. The baby presents in the first 24 to 48 h with marked abdominal distension, vomiting, and failure to pass meco- nium. Abdominal radiographs reveal multiple dilated loops of bowel with fluid levels; the position of the loops may suggest a large-bowel obstruction. A contrast enema can help to define the position of the atresia/stenosis. Nasogastric suction and intravenous fluids are commenced pre- operatively. At laparotomy, the lesion may be an isolated atresia or associated with multiple atresias of the small and large bowel. If the atresia is solitary and right sided, it may be possible to perform a resection and primary anastomosis. Frequently a colocolic anasto- mosis and a covering enterostomy are required to allow the dilated proximal bowel to recover. Hirschsprung’s disease Intestinal innervation is key for autonomic bowel movement. The ganglion cells of the gut lie in the submucosa and intermyenteric plane. Ectodermal in origin, they migrate caudally along the length of the gut. Failure of migration of ganglionic cells down to the in- ternal sphincter of the anal canal results in an aganglionic seg- ment causing Hirschsprung’s disease. The distal rectum is always aganglionic and the aganglionosis extends proximally for a vari- able distance. In 70% of cases, the rectosigmoid is involved, in 20% the aganglionosis extends proximal to the sigmoid for a variable distance up the colon, and in 10% the aganglionosis extends into the small intestine. The aganglionic bowel is incapable of coordin- ated peristalsis and passively constricts, resulting in a mechanical obstruction. The incidence is approximately 1 in 5000 births. There is a clear male dominance (male-to-female ratio of approximately 4:1). Hirschsprung’s disease is a polygenic disorder, some patients carry mutations in the RET gene. Additional genes are implicated by the association with Down’s syndrome as well as other syndromal associations including Mowat–Wilson syndrome (ZEB2 gene), Waardenburg syndrome type 4 (EDNRB, EDN3, or

SOX10 gene), or Goldberg–Shprintzen syndrome (KIAA1279 gene). Clinical features Symptoms of Hirschsprung's disease are present in the first 2 days of life in almost all cases, although exceptionally a baby will have no symptoms during the early neonatal period. The major symptoms are failure to pass meconium within 24 h of birth, abdominal distension, vomiting, and poor feeding, which may occur singly or in combination. Frequently, a rectal examination will relieve the ob- struction by passively dilating the aganglionic segment. However, later presentation with constipation that dates back to the neonatal period and failure to thrive is not uncommon. Hirschsprung's enterocolitis is a serious complication presenting with abdominal distension, profuse diarrhoea, and circulatory collapse. The infant is gravely ill and the mortality is up to 20%. The incidence of enterocolitis can be reduced if the diagnosis of Hirschsprung's disease is made in the first week of life. In the neonatal period, a plain abdominal radiograph will reveal distension of small and large bowel. Water-soluble contrast enema may show the narrow aganglionic bowel with dilated proximal

 bowel (Fig. 15.15.5), but a normal contrast enema does not exclude Hirschsprung's disease. If the sigmoid diameter is larger than the rectum diameter, Hirschsprung's disease should be suspected in a symptomatic child. The definitive diagnostic procedure is a suction or full-thickness rectal biopsy. Endoscopic biopsies are not suffi- ciently deep to capture the intermyenteric plexus. Suction biopsy that can be taken at the bedside enable the pathologist to assess ganglion cells in the submucosal plexus with high sensitivity and specificity. Full-thickness biopsy provides the intermyenteric plexus as well. In Hirschsprung's disease, ganglion cells are absent, hyper- trophic nerve trunks are present, and histochemical stain for acetyl- cholinesterase activity reveals increased staining in the bowel wall. Anorectal manometry shows failure of relaxation of the internal sphincter in response to rectal distension in Hirschsprung's disease, but this method is unreliable in the neonatal period and is not part of the routine diagnostic method. Management Following diagnosis, either definitive surgery is carried out or a col- ostomy is fashioned in ganglionic bowel and definitive surgery de- ferred for a period of time. Definitive surgery consists of excision of aganglionic bowel with a 'pull-through' procedure, enabling an anastomosis to be made between the anus and ganglionic colon. The three operations most often performed are those described by Swenson, Duhamel, and Soave. Increasingly, laparoscopic tech- niques are used. Compared with transabdominal approaches, the transanal technique decreases operative times, length of hospital- ization, and offers improved continence and reduced constipation. Provided that the surgery is uncomplicated, the long-term compli- cations, which include faecal and urinary incontinence, and impo- tence, should be low. Bowel control is likely to be imperfect for a number of years, with soiling as a major problem, but good bowel control will be achieved in most patients treated by experienced surgeons. Imperforate anus The incidence is approximately 1 in 5000 births. The basic clas- sification differentiates between high and low abnormalities. In high anomalies, the bowel terminates above the pelvic floor and the bowel often communicates with the urethra in the male (a rectourethral fistula) and the vagina or vestibule in the fe- male (a rectovaginal/vestibular fistula). In low anomalies, the bowel passes through the pelvic floor and either opens onto the perineum in an ectopic position, or lies just beneath the skin-covered anus. More boys than girls present with an imper- forate anus. Associated anomalies of the urogenital tract, oe- sophagus, heart, and skeletal system are common (VACTERL association). Clinical features Examination of the perineum will establish the presence of an anorectal anomaly. In boys, the presence of meconium on the perineum usually indicates a low anomaly. In girls, careful inspec- tion is necessary to differentiate

meconium being passed per vag- inum, indicating a high anomaly, from meconium emerging from a perineal site, suggesting a low anomaly. If in doubt, the precise anatomy of the anomaly may be resolved by contrast studies. In boys, a cystourethrogram can demonstrate a rectourethral fistula in a high proportion of cases, but is rarely necessary as an ini- tial diagnostic procedure. Having defined the nature of the ano- rectal anomaly, evidence of any associated abnormality should be sought by careful clinical examination and radiographs of chest, abdomen, and the vertebral column. Management In case of a low anomaly, dilatation of the opening alone may suffice, but in most cases an anoplasty produces a sufficient re- sult. A high anomaly necessitates a defunctioning colostomy in the neonatal period. Definitive surgery involves division of any fistula and positioning the bowel accurately within the pelvic floor and sphincter muscles. Delay in achieving bowel control is common and a number of secondary operations designed to improve control have been advocated. A permanent colostomy should rarely be necessary. The high incidence of associated genitourinary abnormalities makes it mandatory to investigate carefully the urinary tract at an early stage. Functional congenital abnormalities Small intestinal lymphangiectasia Primary intestinal lymphangiectasia is a rare disorder that pre- sents with protein-losing enteropathy, lymphopenia, hypo gammaglobulinaemia, hypoalbuminaemia, or chylous ascites as a consequence of dilated intestinal lacteals and submucosal or subserosal lymphatic vessels resulting in lymph leakage. Small intestinal lymphangiectasia (Waldmann’s disease) is a primary congenital abnormality that needs to be differenti- ated from secondary manifestations of other disease processes such as constrictive pericarditis, Crohn’s disease, or intestinal tuberculosis. Several syndromic forms and lymphangiectasia-causing genes have been identified. These include Hennekam’s syndrome char- acterized by the association of lymphoedema, intestinal lym phangiectasia, intellectual deficit, and facial dysmorphism caused Fig. 15.15.5 Barium enema in Hirschsprung’s disease illustrating a narrow aganglionic rectum with dilation proximally.

section 15 Gastroenterological disorders 2974 by mutations in CCBE1 and FAT4. Intestinal lymphangiectasia has also been found in a patient with HOIP deficiency and patients with von Recklinghausen’s, Turner’s, Noonan’s, or Klippel–Trenaunay syndrome. The condition can present throughout life, but most often in the first 2 years with diarrhoea and failure to thrive as well as oe- dema with hypoproteinaemia (serum albumin and serum IgG). There is lymphopenia in the presence of normal bone marrow lymphopoiesis. Malabsorption may cause steatorrhoea, fat- soluble vitamin deficiency, as well as hypocalcaemia. Diagnosis is made by endoscopy and capsule endoscopy showing the characteristic lymphatic abnormality with multiple, white, swollen lymphatic lacteals. Single- or double-balloon enteroscopy might be required to assess distal jejunal or ileal lesions. As a noninvasive laboratory method, increased faecal α-1-antitrypsin levels suggest intestinal lymphatic protein loss. Lymphangiectasia is rarely localized enough to allow surgical excision of a segment and offer a permanent cure. Dietetic inter- vention to reduce the amount of long-chain fatty acids in the diet and adding medium-chain triglycerides can be helpful. A formula containing medium-chain triglyceride may be used, and medium- chain triglyceride oil may be added during cooking. Dietary inter- vention leads to sustained improvement of oedema and growth rates. Fat-soluble vitamin and electrolyte supplements might be required. Albumin infusions are of little value in management as their benefit is transitory. Congenital diarrhoeal disorders: noninflammatory enteropathies Congenital diarrhoea is a group of disorders caused by multiple monogenic defects that lead to osmotic or secretory diarrhoea. Several mechanisms contribute to the pathogenesis, including de- fects in absorption, transport of nutrients and electrolytes due to defective enzymes and membrane carriers or absent pancre- atic enzymes,

enterocyte differentiation and polarization, and enteroendocrine cells differentiation. In addition to those dis- orders that primarily affect absorption and digestion, autoimmune enteropathies that cause destruction of enterocyte, Paneth cell, or enterochromaffin cell function can present in this group. A sum- mary of multiple mechanisms, diseases, and related gene defects is provided in Table 15.15.1. A systematic approach is required to differentiate underlying defects. Response to fasting allows differentiation between os- motic (stop after fasting) and secretory forms of diarrhoea (persist despite fasting). Clues to particular diagnoses can come from a range of blood, urine, and stool tests that include measurement of faecal ion concentrations (sodium and chloride-losing diarrhoea), faecal reducing substances (carbo- hydrate malabsorption), blood gas, blood glucose, albumin (protein-losing enteropathy), triglycerides and cholesterol (abetalipoproteinaemia), aminoaciduria (lysinuric diarrhoea), stool pancreatic elastase (pancreatic insufficiency), and sweat test (cystic fibrosis). Structural enterocyte defects (such as tufting enteropathy, microvillus inclusion disease, and pri- mary or autoimmune polyglandular syndrome-associated loss of enterochromaffin cells) and the presence of intestinal inflam- mation can be discerned by gastroduodenoscopy and biopsy evaluation using routine microscopy (haematoxylin and eosin stain, periodic acid–Schiff reagent, immunostaining) and electron microscopy. Autoantibodies towards enterocytes can be found in immunodysregulation polyendocrinopathy enter- opathy X-linked syndrome (IPEX), and autoantibodies against other intestinal antigens (antiparietal cell H+/K+-ATPase anti- bodies, anti-intrinsic factor, antitryptophan hydroxylase) are found in autoimmune polyglandular syndrome 1. Treatment depends on the underlying condition. Nutritional therapy, in particular exclusion diets and special formulae, will overcome osmotic diarrhoea and improve the condition in some absorption defects (such as lactose-free feeding in patients with lactase deficiency or fructose-based formulas in patients with Table 15.15.1 Causes of congenital noninflammatory diarrhoea Disease group/disease Gene Defects in absorption and transport of nutrients and electrolytes Abetalipoproteinaemia MTTP Acrodermatitis enteropathica SLC39A4 Chylomicron retention disease SAR1B Congenital chloride diarrhoea SLC26A3 Congenital lactase deficiency LCT Congenital sodium diarrhoea SPINT2, SLC9A3 Diarrhoea-associated DGAT1 mutation DGAT1 Enterokinase deficiency TMPRSS15 Familial diarrhoea syndrome GLUCY2C Fanconi–Bickel syndrome SLC2A2 Glucose–galactose malabsorption SLC5A1 Abetalipoproteinaemia APOB Lysinuric protein intolerance SLC7A7 Maltase–glucoamylase deficiency MGAM Primary bile acid diarrhoea SLC10A2 Sucrase–isomaltase deficiency SI Defects in enterocyte structure Congenital tufting enteropathy EPCAM, SPINT2 Microvillous inclusion disease MYO5B, STX3 Trichohepatoenteric syndrome
(syndromic diarrhoea) TTC37, SKIV2L Defects in enteroendocrine cell differentiation Enteric anendocrinosis NEUROG3 Mitchell–Riley syndrome RFX6 Proprotein convertase 1/3 deficiency PCSK1 X-linked lissencephaly with abnormal genitalia ARX Autoimmune enteropathy Autoimmune polyglandular syndrome 1 AIRE IPEX syndrome FOXP3 IPEX-like enteropathy IL2RA, STAT5B, STAT1, ITCH Adapted by permission from Springer Nature: Canani RB, Castaldo G, Bacchetta R, Martin MG, Goulet O (2015). Congenital diarrhoeal disorders: advances in this evolving web of inherited enteropathies. Nat Rev Gastroenterol Hepatol, 12, 293–302.

 glucose–galactose malabsorption). Nutritional deficits need to be compensated for by oral or parenteral substitution of nutri- ents. Defects that cause enterocyte structure defects might require total parenteral nutrition and intestinal transplantation. Immune- mediated disorders require a range of immunosuppressive and immunomodulatory medications. Monogenic forms of inflammatory bowel disease Among the

functional defects that can present with very early- onset and even infantile inflammatory bowel disease, there is a spectrum of more than 50 monogenic disorders. IL-10 signalling defects due to loss-of-function mutations in IL10 or its re- ceptor (IL10RA and IL10RB genes) present with infantile onset of intestinal inflammation. There is a large group of diseases that present as immunodeficiency, such as defects in bacterial handling as well as immune dysregulation. Immunodeficiencies and immune dysregulation defects should be considered in par- ticular in children under 2 years of age at onset of inflammatory bowel disease. The age of onset in monogenic conditions is sig- nificantly younger compared to polygenic inflammatory bowel disease, which has a peak incidence between 20 and 40 years of age. Monogenic diseases are associated with increased morbidity and mortality. Children often present with diarrhoea, in particular bloody diarrhoea and failure to thrive. Endoscopy shows frequently a pancolitis. Common causes of intestinal inflammation such as cow's milk protein allergy, coeliac disease, or uncomplicated in- fections need to be excluded. Twelve features that should raise sus- picion of a monogenic cause include (1) very Young Age of onset, (2) Multiple family members and consanguinity, (3) Autoimmunity, (4) failure to Thrive, (5) Treatment with conventional medication fails, (6) Endocrine concerns, (7) Recurrent infections or unex- plained fever, (8) Severe perianal disease, (9) Macrophage activa- tion syndrome and haemophagocytic lymphohistiocytosis, (10) Obstruction and atresia of intestine, (11) Skin lesions and dental and hair abnormalities, and (12) Tumours that can be summar- ized as 'YOUNG AGE MATTERS MOST'. Monogenic disorders that can present with very early-onset intestinal inflammation are shown in Table 15.15.2. Careful phenotyping can often suggest a genetic candidate de- fect. The introduction of multiplex sequencing technologies such as targeted gene panel sequencing, whole-exome sequencing, or whole-genome sequencing has already revolutionized the diag- nostic approach of such disorders since it allows the diagnosis to be established in patients with atypical presentations or before the full phenotypic characteristics have emerged. Many established anti-inflammatory and immunosuppressive therapy options are used in both monogenic and conventional in- flammatory bowel disease. However, it is important to establish a genetic diagnosis since some disorders require very specific treat- ments. Haematopoietic stem cell transplantation is the established curative approach in a number of defects that affect haematopoietic cell lineages (such as IL-10 signalling defects). The establishment of an early genetic diagnosis and appropriate curative approach via such transplantation can avoid repeated surgery, including colec- tomy in some patients. Anti-IL-1 targeting treatments can resolve Table 15.15.2 Monogenic disorders that can present with very early-onset intestinal inflammation Disease group/disease Gene Epithelial barrier Dystrophic epidermolysis bullosa COL7A1 Kindler syndrome FERMT1 X-linked ectodermal dysplasia and immunodeficiency IKBKG TTC7A deficiency TTC7A ADAM17 deficiency ADAM17 Familial diarrhoea GUCY2C Phagocyte defects Chronic granulomatous disease CYBB, CYBA, NCF1, NCF2, NCF4 Glycogen storage disease type 1b SLC37A4 Congenital neutropenia G6PC3 Leucocyte adhesion deficiency 1 ITGB2 hyper- and autoinflammatory Mevalonate kinase deficiency MVK Phospholipase Cγ2 defects PLCG2 NLRC4 NLRC4 Familial Mediterranean fever MEFV Familial haemophagocytic lymphohistiocytosis type 5 STXBP2 X-linked lymphoproliferative syndrome 2 (XLP2) XIAP X-linked lymphoproliferative syndrome 1 (XLP1) SH2D1A Hermansky–Pudlak syndrome HPS1, HPS4, HPS6 T- and B-cell selection and differentiation defects Combined variable immunodeficiency ICOS, LRBA IL-21 deficiency IL21 CTLA4 deficiency CTLA4 Agammaglobulinaemia BTK, PIK3R1 Hyper-IgM syndrome CD40LG, AICDA Wiskott–Aldrich syndrome WAS Atypical SCID/Omenn syndrome DCLRE1C, ZAP70, RAG1, RAG2, IL2RG, LIG4, ADA, CD3γ Hoyeraal–Hreidarsson syndrome DKC1, RTEL1 Loeys–Dietz syndrome TGFBR1, TGFBR2 PI3K hyperactivation PIK3R1, PTEN FOXP3

regulatory T-cell immundysregulation, autoimmune enteropathy IPEX syndrome FOXP3 IPEX-like syndrome IL2RA, STAT1, STAT3 IL-10 signalling defects IL-10 and receptor defects IL10RA, IL10RB, IL10 Other MASP2-deficiency MASP2 Trichohepatoenteric syndrome SKIV2L, TTC37 Adapted from Gastroenterology, Vol. 147, Uhlig HH, et al., The diagnostic approach to monogenic very early onset inflammatory bowel disease, pp. 990–1007, Copyright © 2014, with permission from Elsevier.

section 15 Gastroenterological disorders 2976 intestinal inflammation in autoinflammatory disorders such as mevalonate kinase defects. FURTHER READING Congenital structural abnormalities Burkardt DD, et al. (2014). Advances in Hirschsprung disease genetics and treatment strategies: an update for the primary care pediatri- cian. Clin Pediatr (Phila), 53, 71–81. Celli J (2014). Genetics of gastrointestinal atresias. Eur J Med Genet, 57, 424–39. Gamba P, Midrio P (2014). Abdominal wall defects: prenatal diagnosis, newborn management, and long-term outcomes. Semin Pediatr Surg, 23, 283–90. Herman RS, Teitelbaum DH (2012). Anorectal malformations. Clin Perinatol, 39, 403–22. Lakshminarayanan B, Lakhoo K (2014). Abdominal wall defects. Early Hum Dev, 90, 917–20. Martin V, Shaw-Smith C (2010). Review of genetic factors in intestinal malrotation. Pediatr Surg Int, 26, 769–81. Peters B, et al. (2014). Advances in infantile hypertrophic pyloric sten- osis. Expert Rev Gastroenterol Hepatol, 8, 533–41. Peeters B, Benninga MA, Hennekam RC (2012). Infantile hypertrophic pyloric stenosis--genetics and syndromes. Nat Rev Gastroenterol Hepatol, 9, 646–60. van der Werf CS, et al. (2015). Congenital short bowel syndrome: from clinical and genetic diagnosis to the molecular mechanisms involved in intestinal elongation. Biochim Biophys Acta, 1852, 2352–61. Functional congenital abnormalities Boisson B, et al. (2015). Human HOIP and LUBAC deficiency under- lies autoinflammation, immunodeficiency, amylopectinosis, and lymphangiectasia. J Exp Med, 212, 939–51. Canani RB, et al. (2015). Congenital diarrhoeal disorders: advances in this evolving web of inherited enteropathies. Nat Rev Gastroenterol Hepatol, 12, 293–302. Ingle SB, Hinge Ingle CR (2014). Primary intestinal lymphangiectasia: minireview. World J Clin Cases, 2, 528–33. Pazmandi J, Kalinichenko A, Ardy RC, Boztug K (2019). Early-onset in- flammatory bowel disease as a model disease to identify key regulators of immune homeostasis mechanisms. Immunol Rev, 287(1), 162–85. Sullivan KE, Conrad M, Kelsen JR (2018). Very early-onset inflamma- tory bowel disease: an integrated approach. Curr Opin Allergy Clin Immunol, 18(6), 459–69. Terrin G, et al. (2012). Congenital diarrheal disorders: an updated diagnostic approach. Int J Mol Sci, 13, 4168–85. Thiagarajah JR, et al. (2018). Advances in Evaluation of Chronic Diarrhea in Infants. Gastroenterology, 154(8), 2045–59. Uhlig HH (2013). Monogenic diseases associated with intestinal in- flammation: implications for the understanding of inflammatory bowel disease. Gut, 62, 1795–805. Uhlig HH, et al. (2014). The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology, 147, 990–1007. Uhlig HH, Muise AM (2017). Clinical Genomics in Inflammatory Bowel Disease. Trends Genet, 33(9), 629–41. Vignes S, Bellanger J (2008). Primary intestinal lymphangiectasia (Waldmann’s disease). Orphanet J Rare Dis, 3, 5.

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