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ESSENTIALS Immune homeostasis in the gut is the result of a delicate balance between peaceful coexistence with commensal microbiota, immu- nomodulatory effects of dietary antigens, and appropriate responses to pathogens. Immune disorders of the gut arise when defects in the integrity of these components lead to a dysregulated immune re- sponse to the commensal environment. Immunodeficiency disorders Primary immunodeficiency syndromes can present with intestinal inflammation but are commonly characterized by an increased sus- ceptibility to infections in childhood. This heterogeneous group of diseases arise from genetic defects in the development of a specific part of the immune system; most are related to an antibody defect (e.g. selective IgA deficiency or common variable immunodefi- ciency). Secondary immunodeficiency can occur in a protein-losing enteropathy where loss of immunoglobulins and lymphocytes in- crease susceptibility to infections, or as a result of metabolic diseases (e.g. diabetes or liver cirrhosis), infections (e.g. HIV), or drugs (e.g. chemotherapy). Therapy-associated and autoimmune-related gastrointestinal immune disorders Immunosuppressive medication can not only lead to secondary immunodeficiency but in the context of neutropenia, cytotoxic gastrointestinal mucosal injury can lead to neutropenic typhlitis. Graft-versus-host disease, which commonly affects the gut, arises from host antigen-presenting cells engaging with donor T cells and triggering an inflammatory cascade. Immunotherapy with check- point inhibitors can have significant gastrointestinal immune-related adverse effects, most notably enterocolitis. Autoimmune diseases can impact gastrointestinal function. Autoimmune dysautonomia can result in gastrointestinal-specific dysmotility and systemic IgG4-related disease can lead to auto- immune pancreatitis. Systemic autoimmune diseases (e.g. rheuma- toid arthritis, systemic lupus erythematosus) can have gastrointestinal manifestations related to the primary autoimmune process (e.g. mesenteric infarction) or as an adverse effect of treatment (e.g. non- steroidal anti-inflammatory-induced peptic ulceration). Food allergy and eosinophilic gastrointestinal disorders

Hypersensitivity reactions to dietary antigens (e.g. peanuts) result in food allergies and can be either IgE or non-IgE mediated. Food intolerance which is not immunologically mediated is the result of pharmacological (e.g. monosodium glutamate), enzyme-related (e.g. lactose intolerance), or noncoeliac gluten sensitivity. Eosinophilic gastrointestinal tract disorders are often associated with a food al- lergen: treatment is with steroids and avoidance of the allergen. The immune system of the gastrointestinal tract The gastrointestinal tract is the largest mucosal organ in the human immune system and indeed home to the greatest accumulation of im- mune cells within the body. It has a vast surface area that is continually exposed to compounds from the diet and microbial life (e.g. bacteria, viruses, and parasites), which altogether are foreign antigens from an immune system's perspective. The gastrointestinal tract contains an enormous density of microbial life (the intestinal microbiota), with the colonic lumen most densely populated, and hence is challenged with the formidable task of distinguishing potential pathogens from commensals. Indeed, crosstalk between the gut immune system and the commensal microbiota is a prerequisite for the normal devel- opment and function of the mucosal immune system. This delicate host—microbial balance can be disrupted, such as during infection, but also in the context of immune-related disorders that are charac- terized by mucosal inflammation and an inappropriate immune re- sponse involving the commensal flora. Gut immune homeostasis is hence key to the coexistence of commensal microbial communities in such close proximity to gut mucosal cells and is achieved through a combination of luminal barriers, the gut lymphoid system, and regu- lation by innate and adaptive immune cells (Fig. 15.5.1). Luminal barriers A single layer of intestinal epithelial cells (IECs) provides a phys- ical separation between mammalian hosts and the external environ- ment. IECs play an important role in dynamic barrier function and microbial sensing, and have emerged as key regulators of the mu- cosal immune system critically involved in maintaining intestinal 15.5 Immune disorders of
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 immune homeostasis. Although the majority of IECs are absorptive enterocytes adapted for metabolic and digestive functions, secretory IECs are specialized for maintaining the barrier function. Paneth cells are specialized secretory IECs that line the base of small in- testinal crypts that contribute to the intestinal gut barrier not only through their production of key factors that are crucial to help main- tain the stem cell niche thereby supporting the continual renewal of the epithelial surface, but also through the secretion of antimicro- bial peptides. Antimicrobial peptides function as endogenous anti- biotics that target and disrupt highly conserved features of bacterial proteins. Antimicrobial peptides such as regenerating islet-derived protein IIIγ (REGIIIγ) are produced by most enterocytes but Paneth cells are capable of secreting a wide range of antimicrobial peptides, including defensins, cathelicidins, and lysozyme. Paneth cells also play an important bona fide immune role by secreting cytokines such as tumour necrosis factor (TNF) and interleukin (IL)-17. Intestinal barrier function is further reinforced by goblet cells se- creting highly glycosylated mucins into the lumen, the most abun- dant of these being mucin 2 (MUC2). This provides an extensive and thick layer of protective mucus which together with luminal Fig. 15.5.1 Anatomy of the intestinal mucosa and its immune apparatus. Reprinted by permission from Springer Nature: Mowat AM, Agace WA (2014). Regional specialization within the intestinal immune system. Nat Rev Immunol, 14, 667–85, © 2014.

 secretion of antimicrobial peptides provides a physical and bio- chemical barrier. Central to their role in barrier function is the cap-

acity of IECs for microbial sensing and the translation of microbial signals to immune cells. IECs express pattern recognition receptors such as toll ligand receptors (TLRs) and NOD-like receptors (NLRs) that can directly sense specific bacterial ligands and provide distinct immunoregulatory response pathways. Polarized expression of pat- tern recognition receptors on apical and basolateral surfaces of IECs may help distinguish between commensal and pathogen signals. Commensal-derived signals are also responsible for IECs producing immunoregulatory factors that promote development of tolerogenic immune cells. The lymphoid system The commensal microbiota is instrumental in the maturation of gut- associated lymphoid tissue (GALT); GALT and the draining lymph nodes serve as important immunosurveillance posts in the intes- tinal epithelium. Tissues of the GALT include Peyer's patches, their equivalents in the cecum and colon, and isolated lymphoid follicles. The GALT is comprised of subepithelial lymphoid aggregates with an overlying follicle-associated epithelium that contains microfold (M) cells. M cells are specialized epithelial cells that sample luminal contents and phagocytose and transcytose particulate antigens across the epithelium to the subepithelial dome, a dendritic cell-rich region. Subsequent antigen presentation by dendritic cells is not only instru- mental in T-cell priming but also in the production of secretory IgA against specific mucosal antigens. Secretory IgA is the most abun- dant isotype antibody found in the intestinal lumen of humans. In contrast to serum IgA, secretory IgA is mainly dimeric and chiefly derived from local synthesis. Secretory IgA is thought to prevent en- teric toxins and pathogens gaining access to the intestinal epithelium by receptor blockade, steric hindrance, and/or agglutination followed by mucous entrapment and clearance through peristalsis. Innate and adaptive immune cells Within the intestinal mucosa there are two main compartments har- bouring bona fide immune cells. The intraepithelial layer consists mainly of T cells while the lamina propria contains B cells, T cells, and innate immune cell populations. Intraepithelial lymphocytes (IELs) consist mainly of T cells and in contrast to conventional naïve T cells are antigen experienced and on activation release cytokines or mediate killing of infected target cells. IELs constitutively express CD103 (also known as αE integrin) which binds to E-cadherin expressed on intestinal entero- cytes. These T cells belong to T-cell receptor (TCR) γδ+ and TCR αβ+ lineages. IELs are more abundant in the small intestine and are predominantly of the TCR γδ+ lineage and most express CD8αα in their activated phenotype. There are two subsets of IELs: 'natural' IELs (previously known as 'type b' IELs) which acquire their acti- vated phenotype during thymic development in the presence of self-antigens and 'induced' IELs (previously known as 'type a' IELs) which are derived from conventional T cells that are activated in response to exogenous antigens encountered in the periphery. Both subsets have protective roles in immune regulation, epithelial homeostasis, antimicrobial response, and tolerance to intestinal antigens. T cells in the lamina propria are of TCR αβ+ lineage and play an important role in oral tolerance and protective microbial responses. They display an effector memory phenotype and there are twice as many CD4+ T cells as CD8+ T cells. The CD4+ population is highly varied and include forkhead box P3 (FOXP3)+ T-regulatory (Treg) cells and FOXP3− Treg cells subsets as well as IL-2+, IL-2+IFN- γ+, IL-2−IFN-γ−, IFN-γ+, and IL-17+ T cells. The most abun- dant leucocyte population in the lamina propria are macrophages which produce IL-10. IL-10 is not only important for maintaining immune homeostasis by blocking proinflammatory responses to TLR stimulation but also in promoting the function of FOXP3+ Treg cells. Intestinal dendritic cells are also found predominantly in the lamina propria. They can be classified based on expression on CD103 (also known as αE integrin) and CD11b. These distinct sub- sets are thought to have differing roles in intestinal immunity. Other immune cells in the lamina propria include plasma cells that pri- marily secrete IgA and members of the innate immune system such as innate lymphoid cells (ILCs), T cells with invariant TCR chains, eosinophils, and

mast cells. ILCs are a recently described subset of the innate immune system. They are classified into three distinct groups identified by their dif- ferential expression of transcription factors, cytokine production, and cell surface markers. They are enriched in mucosal tissue and play an important role in maintaining intestinal immune homeo- stasis. Type 3 ILCs are an important source of IL-22, important in maintaining intestinal barrier integrity. The IL-22 receptor is exclu- sively expressed by the gut epithelium and activation leads to epithe- lial proliferation, repair, and the production of protective molecules, including antimicrobial peptides and mucins. Impact of dietary compounds and gut microbiota on gastrointestinal immune function There is regional variation in the distribution of immune cells in the gastrointestinal tract thought to at least partly reflect differing ex- posure to environmental influences. Immunomodulatory effects of dietary constituents are most evident in the small intestine. Dietary vitamin A is found in higher concentrations in the small intestine compared to the colon and is metabolized by gut epithelial cells to generate the vitamin A metabolite all-trans retinoic acid. Retinoic acid plays an important role in the migration and differentiation of immune cell subsets. Dendritic cells in the small intestine receive enhanced retinoic acid signals and are primed to expressed CD103 and eventually become imprinted with the ability to produce ret- inoic acid. This in turn induces the expression of gut homing recep- tors, α4β7 integrin and CCR9 chemokine receptor, on T cells, which in the presence of transforming growth factor (TGF)-β can amplify the development of FOXP3+ Treg cells. Retinoic acid also affects the relative populations of subsets of ILCs. There are two dominant tissue resident ILCs. ILC2s express the transcription factor GATA3 and constitute the majority of the ILCs present in the lungs and skin while ILC3s express the transcription factor RORγt and are the dominant subset in the gut. The presence of RA supports the expan- sion and maintenance of IL-17- and IL-22-producing ILC3s, while suppressing the maturation of IL-13-producing ILC2. Another regulator of the ILC population is the aryl hydrocarbon receptor (AhR). AhR is a highly conserved transcription factor whose ac- tivity is regulated by environmental and dietary small molecule lig- ands, particularly the phytochemical indole-3-carbinol found in the Brassicaceae vegetable family. ILC3s express the AhR and signalling via this receptor promotes development of ILC3s and postnatal lymphoid follicle development.

SECTION 15 Gastroenterological disorders 2786 AhR and RORγt-dependent expression of IL-22 limits coloniza- tion by segmented filamentous bacteria. segmented filamentous bac- teria are commensal bacteria that preferentially colonize the terminal ileum, where they drive enhanced IgA production and via the presen- tation of segmented filamentous bacteria antigens by dendritic cells can increase T-helper (Th)-17 cell numbers. Similar to segmented filamentous bacteria, various other microorganisms can impact im- mune cell distribution along the intestine. Lactobacillus spp. can in- fluence secretion of IL-22 by Th17 cells through generation of AhR ligand indole-3-aldehyde from tryptophan metabolism. In the colon, enhanced generation of Treg cells may be the result of a TGFβ-rich environment promoted by certain anaerobic Clostridia spp. Short- chain fatty acids that are produced by colonic bacteria can influence immune function by driving the expansion of FOXP3+Treg cells. Monogenic immune disorders and the gastrointestinal tract The importance of these interrelated components of the mucosal immune system, which form an integrated, physiological, complex barrier that functionally extends vastly beyond being just an ana- tomical boundary, is most visibly revealed by a whole range of monogenic defects that are associated with intestinal inflamma- tion. The majority of these defects manifest in the gastrointestinal tract very early in life, and some of them are classified as ‘very early-onset inflammatory bowel disease’ (VEOIBD). These defects affect genes involved in epithelial barrier function (e.g. X-linked

ectodermal dysplasia and immunodeficiency, IKBKG gene) and in phagocytic killing (e.g. chronic granulomatous disease, CYBB gene), defects leading to autoinflammation (e.g. mevalonate kinase deficiency (also known as hyper-IgD syndrome), MVK gene; fa- milial Mediterranean fever, MEFV gene; X-linked lymphopro- liferative syndrome 2, XIAP gene), T- and B-cell (e.g. common variable immunodeficiency (CVID) type 1, ICOS gene; Wiskott– Aldrich syndrome, WAS gene) and Treg cell defects (e.g. immune dysregulation, polyendocrinopathy, enteropathy X-linked (IPEX), FOXP3 gene; and VEOIBD due to CTLA4 mutations), IL-10 sig- nalling defects (IL10RA, IL10RB, IL10 genes), and defects in in- testinal innervation (e.g. Hirschsprung's disease, RET gene). As detailed in Table 15.5.1, gastrointestinal manifestations may in- clude continuous and discontinuous colitis, ileitis, and fistula and Table 15.5.1 Genetic defects associated with inflammatory bowel disease-like immunopathology Group of defects (monogenic disorder) Gene Mode of inheritance Epithelial barrier and epithelial response defects X-linked ectodermal dysplasia and immunodeficiency Hyper-IgM syndrome, atypical inflammatory bowel disease-like enterocolitis with villous atrophy and epithelial cell shedding Dystrophic epidermolysis bullosa Moderately severe colitis Kindler syndrome Haemorrhagic continuous colitis Adam-17 deficiency Skin, hair, and gut pathology Familial diarrhoea Neonatal diarrhoea with discontinuous colitis IKBKG COL7A1 FERMT1 ADAM17 GUY2YC X-linked Autosomal recessive Autosomal recessive Autosomal recessive Autosomal dominant Neutropenia and defects in phagocyte bacterial killing Chronic granulomatous disease Colitis with pigmented macrophages and granulomas Glycogen storage disease type 1b Neutropenia, defective chemotaxis, ileitis, and colitis Congenital neutropenia Neutropenia, discontinuous colitis Leucocyte adhesion deficiency 1 Defects in chemotaxis, phagocytosis, discontinuous ulcerative stomatitis, ileocolitis, fistulas, strictures, perianal abscess CYBB CYBA, NCF1, NCF2, NCF4 SLC37A4 G6PC3 ITGB2 X-linked Autosomal recessive Autosomal recessive Autosomal recessive Autosomal recessive Hyper- and autoinflammatory disorders Mevalonate kinase deficiency Febrile attacks, lymphadenopathy, polyarthritis, hypogammaglobulinaemia, colitis Familial Mediterranean fever Periodic fevers, continuous colitis X-linked lymphoproliferative syndrome 1 Gastrointestinal symptoms of colitis and gastritis X-linked lymphoproliferative syndrome 2 Very early onset and fistulating disease Phospholipase Cγ2 defects Autoinflammatory disease with mild immunodeficiency, skin lesions, continuous colitis Familial haemophagocytic lymphohistiocytosis type 5 Fever, splenomegaly, hypogammaglobulinaemia, diffuse discontinuous colitis Hermansky–Pudlak syndrome Oculocutaneous albinism and bleeding diathesis, neutropenia, lung fibrosis, granulomatous colitis MVK MEFV SH2D1A XIAP PLCG2 STXBP2 HPS1, HPS4, HPS6 Autosomal recessive Autosomal recessive X-linked X-linked Autosomal dominant Autosomal recessive Autosomal recessive

 abscess formation. While some defects affect mechanisms critic- ally involved in preventing autoimmunity, such as mutations in FOXP3 (encoding the transcription factor critically required for Treg cell development and function) which cause multiorgan auto- immunity prominently involving the gastrointestinal tract (some- times also referred to as autoimmune enteropathy), many of these genetic defects affect mechanisms involved in innate host defence and inflammatory functions. Typical examples are chronic granu- lomatous disease, caused by mutations in the reactive oxygen species-producing NADPH oxidase system, or leucocyte adhesion deficiency, caused by mutations in an integrin gene which leads to defects in chemotaxis, phagocytosis, and bacterial killing. Of note, defects in innate immune function, and hyperactive adaptive immune function, both can result in intestinal inflammation as ex- emplified by these monogenic disorders. Interestingly, the group of genes mutations of which

cause VEOIBD (defined as onset <6 years of age) are, with very few ex- ceptions (IL10, IL10RB, IL2RA), distinct from the susceptibility loci that have been associated with risk for inflammatory bowel disease, consistent with the difference in time of onset and clinical manifest- ation, and response to treatment, altogether showcasing difference in pathogenesis. Identifying the genetic cause of these monogenic disorders can sometimes guide or determine therapeutic options when the biological mechanisms involved are already known, for ex- ample, allogenic haematopoietic stem cell transplantation has been successfully performed in VEOIBD patients carrying mutations in genes encoding IL-10 receptor subunits. Gastrointestinal manifestations of classical primary immunodeficiency disorders As monogenic disorders causing intestinal inflammation often also involve manifestations outside of the intestinal tract, there is some overlap with classical primary immunodeficiency disorders. Primary immunodeficiency disorders (Table 15.5.2) refer to a het- erogeneous group of diseases characterized by a genetic defect in the maturation or development of specific components of the immune system resulting in an increased susceptibility to infection. Primary immunodeficiency disorders commonly present in early childhood with recurrent infections. Common gastrointestinal manifestations include infections, but may also include intestinal inflammation of Group of defects (monogenic disorder) Gene Mode of inheritance B-cell and antibody defects Common variable immunodeficiency (CVID) type 1 Autoimmunity (rheumatoid arthritis, psoriasis) and inflammatory bowel disease CVID type 8 Defective B-cell activation, neutropenia, autoimmunity, duodenal villous atrophy, lymphocytic or discontinuous colitis Wiskott–Aldrich syndrome Eczema, thrombocytopenia, vasculitis and ulcerative colitis-like continuous inflammation Agammaglobulinaemia Reduced levels of antibodies, peripheral B cells, autoimmunity (arthritis, haemolytic arthritis, thrombocytopenia or neutropenia), discontinuous colitis Erythema nodosum, arthritis, colitis, complete absence of B cells in the bone marrow Hyper-IgM syndrome Oral ulcers, chronic neutropenia, colitis Omenn syndrome Erythroderma, increased serum IgE, desquamation, lymphadenopathy, chronic ulcerating intestinal inflammation Hyper-IgE syndrome Eczema, raised serum IgE, multiple allergies, buccal granulomatous disease Trichohepatoenteric syndrome Intractable diarrhoea, hepatopathy, trichorrhexis nodosa, low immunoglobulin levels, and defect in vaccine response PTEN hamartoma tumour syndrome Gastrointestinal lymphoid hyperplasia, inflammatory polyps, colitis ICOS LRBA WAS BTK PIK3R1 CD40LG DCLRE1C DOCK8 SKIV2L, TTC37 PTEN Autosomal recessive Autosomal recessive X-linked X-linked Autosomal recessive X-linked Autosomal recessive Autosomal recessive Autosomal recessive Autosomal dominant Treg cell defects and immune dysregulation Immune dysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) Polyendocrinopathy, high IgE, colitis and subtotal villous atrophy IL-10 signalling defects Bloody diarrhoea, perianal fistula, discontinuous colitis with deep ulcerations reminiscent of Crohn’s disease CTLA4 mutations Impaired Treg cells, hypogammaglobulinaemia, recurrent infections, multiple autoimmune clinical features FOXP3 IL2RA IL10, IL10RA, IL10RB CTLA4 X-linked Autosomal recessive Autosomal recessive Autosomal dominant Defects in intestinal innervation Hirschsprung’s disease Enterocolitis with cryptitis and crypt abscesses RET Autosomal dominant Adapted by permission from BMJ Publishing Group Limited: Uhlig HH (2013). Monogenic diseases associated with intestinal inflammation: implications for the understanding of inflammatory bowel disease. Gut, 62, 1795–805, © 2013. Table 15.5.1 Continued

 Table 15.5.2 Specific primary immunodeficiency syndromes and their gastrointestinal manifestations Primary immunodeficiency disease and pathogenesis Infectious gastrointestinal complications Noninfectious gastrointestinal complications

Antibody defect Selective IgA deficiency This is the most common primary immunodeficiency syndrome, with highest prevalence rates of 1:160–1:300 reported for Caucasian populations. The genetic basis is not well defined and the IgA deficiency may result from immune dysregulation of terminal B cells' maturation into IgA-secreting plasma cells. Most patients are asymptomatic, possibly as a result of compensatory increase in IgM secretion Upper respiratory tract infections are more common, but there is an increased incidence of gastrointestinal infections, most notably with Giardia lamblia. Colonization by trophozoites in the small intestine results in bloating, cramping, excessive flatus, and watery diarrhoea. Chronic infection can lead to malabsorption of lipids resulting in steatorrhea and villus flattening. Diagnosis is made by stool examination or duodenal aspirates for Giardia lamblia cysts or trophozoites. Despite treatment with metronidazole, the parasitic load can be unremitting suggesting that luminal IgA may be required for parasite clearance There is an association with coeliac disease. Nodular lymphoid hyperplasia is a common feature Common variable immunodeficiency (CVID) syndrome CVID is the most common symptomatic primary immunodeficiency and characterized by low levels of IgG together with reduced levels of IgA and/or IgM, poor response to immunizations and absence of other immunodeficiency states. In addition to recurrent bacterial respiratory tract infections, patients have a wide range of clinical manifestations: autoimmune diseases (e.g. immune thrombocytopenic purpura, autoimmune haemolytic anaemia), granulomatous/lymphoid infiltrative disorders and increase risk of malignancy. Treatment is with monthly IgG infusions. CIVD is a pathophysiologically heterogeneous entity Diarrhoea is a common presenting symptom. Infective causes of acute diarrhoea include norovirus, campylobacter jejuni, or salmonella. Giardiasis can cause refractory diarrhoea with features of malabsorption and weight loss. Other causes of chronic diarrhoea include cytomegalovirus, cryptosporidium, or norovirus An inflammatory bowel disease-like pathology and coeliac-like sprue may develop. This can lead to a protein losing enteropathy and malabsorption. Other gastrointestinal manifestations include bacterial overgrowth, pernicious anaemia, nodular lymphoid hyperplasia, and lymphoma X-linked agammaglobulinaemia This is a humoral immunodeficiency characterized by the absence of immunoglobulins. It results from genetic mutations in the signal transduction molecule Bruton tyrosine kinase (BTK) leading to a maturation block in B- cell development. Clinical presentation occurs after the age of 3 months (once maternal IgG is catabolized) and is characterized by recurrent bacterial infections and particularly affect the respiratory and nervous system. Treatment is with replacement immunoglobulin. Infections are treated with multiple and prolonged courses of antibiotics In the gastrointestinal tract Salmonella and Campylobacter spp. can cause gastroenteritis. Enteroviral pathogens such as ECHO virus and Coxsackievirus cause hepatitis, meningoencephalitis, and dermatomyositis. This is rare in the setting of immunoglobulin substitution therapy Small-bowel strictures and fissures resembling Crohn's disease can occur. There is an increased risk of colonic and gastric adenocarcinomas Hyper-IgM syndrome This is a heterogeneous group of diseases characterized by defective class-switch recombination resulting in increased IgM production and inability to generate other immunoglobulin subtypes. The two most common genetic defects include CD40 ligand or CD40 deficiency or a deficiency in activation-induced cytidine deamidase (AID). Clinical features depend on the underlying genetic defect. Treatment options include immunoglobulin replacement; in CD40 ligand deficiency, haematopoietic stem cell transplantation offers a curative option Protracted and recurrent diarrhoea is a common clinical feature. In half of all cases the infectious agent cannot be identified. The most common pathogen is Cryptosporidium parvum. Infection with Giardia lamblia, salmonella, Entamoeba histolytica, and cytomegalovirus have also been described Chronic intestinal inflammation resembling inflammatory bowel disease

may occur. In CD40 deficiency, aphthous stomatitis and an increased incidence of lymphoma, hepatocarcinoma, cholangiocarcinoma, and neuroectodermal tumours of the gastrointestinal system can develop Combined T- and B-cell immunodeficiency Severe combined immunodeficiency (SCID) Genetic defects in the development of T cells, B cells, and in some cases natural killer cells lead to cellular and humoral immunodeficiency collectively termed SCID. Life-threatening infections lead to overwhelming sepsis and high infant mortality. Haematopoietic stem cell transplantation is curative Persistent mucocutaneous candidiasis of oral cavities and the oesophagus can compromise oral intake leading to malnutrition and failure to thrive. Rotavirus is the most common cause of protracted and refractory diarrhoea. Other gastrointestinal pathogens include picornavirus, parvovirus, adenovirus, cytomegalovirus, salmonella, Giardia lamblia, Escherichia coli, and Cryptosporidium GVHD affecting the gastrointestinal tract can occur in response to blood transfusion Ataxia–telangiectasia (AT) This is an autosomal recessive neurodegenerative disorder characterized by defective DNA repair resulting from mutations in the ataxia telangiectasia mutated (ATM) gene. Clinical features include neurological abnormalities, particularly progressive cerebellar ataxia and oculomotor problems, facial and conjunctival telangiectasia, and increased incidence of malignancy. Immunodeficiency is both cellular and humoral. Treatment is supportive, no cure is yet available Infections tend to be sinopulmonary and are not particularly a problem in the gastrointestinal tract. Dysphagia is often a feature together with dysarthria Increased susceptibility to develop adenocarcinomas and lymphoreticular malignancies of the gastrointestinal tract

15.5 Immune disorders of the gastrointestinal tract 2789 various types, nodular hyperplasia, and malabsorption. There is also an increased incidence of malignancies. Infections Primary immune defects can affect the humoral (B-cell) response and cellular (T-cell) immune system; both T- and B-cell immunity or innate defects. The second most common site for infection is the gastrointestinal tract second only to the respiratory system. Clinical features include persistent diarrhoea, malabsorption, weight loss, and failure to thrive. Often the type of infective pathogen reflects the underlying immune defect. Viral and fungal infections are more common in T-cell defects and bacterial infec- tions in B-cell immune defects. The disease course can be frequent, more severe and prolonged compared to immunocompetent indi- viduals, often with unexpected recurrence after standard therapy (e.g. patients with selective IgA deficiency infection with Giardia lamblia often require multiple and longer courses of antibiotics). Infections with atypical or opportunistic pathogens are also more common (e.g. microsporidia, Cryptosporidium spp.). Autoimmune and inflammatory disorders Some primary immunodeficiency disorders may be associated with intestinal inflammation (Table 15.5.1). In some cases, gastrointes- tinal symptoms such as bloody diarrhoea, vomiting, and abdominal pain can be the primary presenting feature. Features that suggest an underlying primary immunodeficiency disease or monogenic dis- order include early age of onset with aggressive disease, failure to re- spond to conventional therapy, and histopathology that differs from classical findings. CVID (see Chapter 4.4) may present with sprue-like disease. CVID sprue-like disease presents with diarrhoea, malabsorption, and weight loss. Small-bowel biopsies share findings common to classical coeliac disease (e.g. villous atrophy, increased intraepithelial lymphocytes, and crypt hyperplasia) but distinguishing features Primary immunodeficiency disease and pathogenesis Infectious gastrointestinal complications Noninfectious gastrointestinal complications Wiskott–Aldrich syndrome This is an X-linked disease characterized by recurrent infections, thrombocytopenia bleeding, and eczema. It results from genetic mutations in the Wiskott–Aldrich syndrome protein gene (WASP), a key regulator of the

actin cytoskeleton in haematopoietic cells. Loss of WASP signalling leads to impaired antibody production and T-cell lymphopenia. Haematopoietic stem cell transplantation offers a cure Individuals are susceptible to infection by all classes of micro-organisms. Infectious diarrhoea can occur but respiratory and ear infections are more common Bloody diarrhoea is common, especially in infancy and is related to thrombocytopenia Disorders of phagocytic function Chronic granulomatous disease (CGD) This genetic disorder arises from mutations in key genes that regulate the phagocytic oxidative metabolism. These mutations result in inactivation or loss of function in one of the subunits of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex thereby impairing the generation of superoxide and the bactericidal capabilities of phagocytes. Clinical features include bacterial and fungal infections and hepatic and gastrointestinal disorders. The X-linked mode of inheritance is more common than the autosomal recessive and therefore there is a male preponderance There is an increased susceptibility to pyogenic and fungal infections including salmonella, enterococci, and Candida Gastrointestinal manifestations are common in CGD, including granulomatous colitis. It can present with diarrhoea, abdominal pain, perianal abscesses, and fissures. Granulomata formation in the intestinal tract can resemble Crohn's disease or cause obstructive symptoms Immune dysregulation syndromes Immune dysfunction, polyendocrinopathy, enteropathy, X-linked (IPEX) This X-linked immunodysregulatory syndrome is caused by loss-of-function mutations in transcription factor FOXP3. This leads to decreased and dysfunctional Treg cells. IPEX is characterized by a triad of clinical features: enteropathy, autoimmune endocrinopathy, and dermatitis. IPEX-like syndromes, common causes include CD25, STAT2b deficiencies and lipopolysaccharide (LPS)- responsive beige-like anchor (LRBA) mutations, share the similar clinical features Although infectious diarrhoea can occur, significant infections are more likely to be meningitis, pneumonia, and osteomyelitis Autoimmune and allergic enteropathy is a hallmark of IPEX syndrome. Diarrhoea is severe, watery, and mucoid or bloody. Malabsorption with electrolyte imbalance and protein loss often occurs. Histopathology findings are not specific, but resemble other immune-related enteropathies (coeliac disease, GVHD) Food allergies have also been described and can be IgE or non-IgE mediated Complement deficiency Hereditary angio-oedema This results from deficiency or dysfunction of C1 esterase inhibitor resulting in excessive generation of bradykinin, a potent vasodilatory mediator. This leads to recurrent episodes of angio-oedema predominantly affecting skin and the gastrointestinal and respiratory system. The most serious being laryngeal oedema leading to airway obstruction Gastrointestinal infections are not a feature of this condition Individuals commonly present with abdominal pain, vomiting and watery diarrhoea related to bowel wall oedema, which may present segmental Table 15.5.2 Continued

 include a reduced number of plasma cells in the lamina propria and preservation of IECs at the villous tip. In addition, there is a lack of antibodies to gliadin, tissue transglutaminase, endomysium, or reticulin, no association with HLA DQ2/DQ8, and no clinical im- provement on dietary gluten withdrawal. Classical coeliac disease (see Chapter 15.10.3) can occur in se- lective IgA deficiency, a primary immunodeficiency syndrome (see Chapter 4.4), and although the clinical course is similar to immuno- competent individuals, diagnosis may be missed if screening with tissue transglutaminase IgA. To avoid this, screening should be done either by concomitantly measuring serum IgA concentrations or tissue transglutaminase IgA and IgG. Nodular lymphoid hyperplasia is characterized by the presence of nodules often found in multiples throughout the intestine, 5 mm or greater in diameter, which are associated with mucosal flattening and malabsorption. Occasionally these lesions can develop a

size that may cause intestinal obstruction. Diagnosis is via small-bowel radiological imaging or video capsule imaging. Nodular lymphoid hyperplasia is found in patients with CVID syndrome and selective IgA immunodeficiency, but may also be found in healthy individ- uals. These nodules contain numerous lymphoid follicles with ger- minal centres in lamina propria or submucosa with large numbers of B cells. Whether nodular lymphoid hyperplasia is a risk factor for the development of lymphoma is a matter of controversy. Malignancy Malignancy is the second most common cause of death in patients with primary immunodeficiency disorders, second to infections. Patients with primary immunodeficiency disorders can be at an in- creased risk of gastrointestinal malignancies (e.g. lymphoma and adenocarcinoma). The increased susceptibility to cancer is thought to arise from a variety of mechanisms that include Helicobacter pylori infection, atrophic gastritis, genetic instability, and decreased immunosurveillance and immune-mediated clearance of oncogenic viruses such as human papilloma virus and Epstein–Barr virus. The most common types of cancer include non-Hodgkin's lymphoma and Hodgkin's lymphoma. Two primary immunodeficiency dis- orders account for the majority of primary immunodeficiency disorder-associated cancers, CVID and ataxia–telangiectasia. Malabsorption Malabsorption as a result of persistent diarrhoea is a common clin- ical feature of primary immunodeficiency disorders. The chronic impaired absorption of nutrients leads to electrolyte imbalances, malnutrition, and, in children, a failure to thrive. Treatment is by addressing the underlying immune defect and by nutritional sup- plementation which in some severe cases can include parenteral nutrition. Secondary immunodeficiency and the gastrointestinal tract Secondary immunodeficiency disorders are more common and can be the result of metabolic disease (e.g. diabetes mellitus, liver cirrhosis, and malnutrition), HIV infection, and malignancies (e.g. multiple myeloma and leukaemia). Other causes include immunosuppressive drugs (e.g. chemotherapy) and protein loss (e.g. nephrotic syndrome, protein-losing enteropathy). In the gastrointestinal tract, secondary immunodeficiency can arise from a protein-losing enteropathy (which can be primary or secondary). Gastrointestinal manifestations related to secondary immuno- deficiency include increased susceptibility to infections, especially opportunistic pathogens (e.g. cryptococcosis, candida, and cyto- megalovirus in HIV-infected individuals). Protein-losing enteropathy Immunodeficiency can arise from protein-losing enteropathies of the gastrointestinal tract, characterized by a severe loss of serum proteins into the intestinal lumen outstripping protein synthesis leading to hypoalbuminaemia. Secondary immunodeficiency de- velops with loss of immunoglobulins and lymphocytes. This can be caused by intestinal mucosal disease (e.g. Menetrier's disease, Crohn's disease, or coeliac disease) or by impaired lymphatic drainage. The latter mechanism can be the result of granuloma- tous or malignant involvement of the lymphatic system or related to intestinal lymphangiectasia. Secondary causes of intestinal lym- phangiectasia include cardiac failure or retroperitoneal lymph node enlargement. Primary intestinal lymphangiectasia presents typically in childhood with persistent diarrhoea and oedema. Endoscopically white villi (dilated lacteals), white nodules, and submucosal elevations can be seen (Fig. 15.5.2). The diagnosis is histologically confirmed by demonstration of dilated lymphatics. Treatment is attempted with dietary modification to a low-fat diet and substituting long-chain fatty acids with medium-chain fatty acids. Fig. 15.5.2 Wireless capsule endoscopy demonstrating plump, white intestinal villous tips containing chyle in a patient with protein-losing enteropathy. From Mulliken JB, Burrows PE, Fishman SJ (eds) (2013). Mulliken and Young's vascular anomalies: hemangionas and malformations. By permission of Oxford University Press.

15.5 Immune disorders of the gastrointestinal tract 2791 Acquired immunodeficiency syndrome: HIV Gastrointestinal manifestations of HIV infection are common, also consistent with the gastrointestinal tract being a major site for HIV replication. This is attributed to HIV preferentially targeting acti- vated memory CD4+ T cells expressing chemokine receptor 5 (the main coreceptor HIV uses to gain entry into target cells) which are plentiful in the gastrointestinal tract. Severe depletion of CD4+ lymphocytes in the lamina propria and of intraepithelial lympho- cytes occurs during primary infection and persists throughout the course of the infection, and highly active antiretroviral therapy may not lead to full restoration of the GALT. Over half of all affected individuals report gastrointestinal symptoms with a much higher prevalence in developing countries. The most common symptom is diarrhoea which can occur during seroconversion or with more ad- vanced disease. When CD4+ T-cell numbers in peripheral blood fall to less than 100 to 200 cells/mm3, opportunistic infections from a myriad of bacteria, viruses, fungi, or parasitic pathogens can ensue. Table 15.5.3 summarizes major gastrointestinal inflammatory, in- fectious, and neoplastic diseases associated with HIV infection. Highly active antiretroviral therapy has profoundly decreased the incidence of HIV- associated opportunistic intestinal infections. However, immune reconstitution in GALT is typically incomplete, often leading to reactivation and disease progression. This has been attributed to persistent viral replication, preferential depletion of Th17 cells, and increased microbial translocation secondary to de- fects in the intestinal mucosal barrier resulting in systemic immune activation. Once identifiable infections and other causes of diarrhoea have been excluded, an entity referred to as HIV/AIDS enteropathy may be present in a small percentage of patients. This may present with profound diarrhoea, malnutrition, and wasting. HIV enteropathy is related to increased inflammation and immune activation associ- ated with decreased mucosal repair and regeneration. However, the precise aetiology of HIV enteropathy remains insufficiently under- stood, and might involve the HIV virus itself, but also atypical viral pathogens. Therapy-associated immune-mediated affection of the gastrointestinal tract Graft-versus-host disease Graft-versus-host disease (GvHD) is a multisystem autoimmune disease most commonly occurring in recipients of allogeneic haem- atopoietic stem cell transplants where the conditioning protocol leads to mucosal damage and in the gastrointestinal tract increased translocation of microbial signals that activate antigen-presenting cells. These host antigen-presenting cells engage with donor T cells that differentiate, proliferate, and trigger an effector cascade medi- ated by cytotoxic T cells and natural killer cells and a cytokine storm (e.g. TNFα) leading to tissue damage and destruction. Historically, GvHD was divided into acute and chronic GvHD if onset of symptoms was before or after 100 days following transplant- ation. However, a National Institutes of Health consensus has reclas- sified acute and chronic GvHD based on clinical findings. Acute GvHD is characterized by epithelial cell death, the most commonly affected organs being skin, liver, and gut. Gastrointestinal involvement of the lower gastrointestinal tract typically presents with secretory, voluminous diarrhoea and abdominal pain. Severity of the diarrhoea determines the degree of gastrointestinal involve- ment and can lead to a protein-losing enteropathy. Upper gastro- intestinal manifestations include anorexia, nausea and vomiting, mucositis, and dyspepsia. CT findings are nonspecific and diagnosis is made on endoscopic appearance (denuded mucosal patches, ery- thema, and ulceration) and histopathological findings characterized by apoptotic epithelial cells and crypt loss. Treatment is supportive (e.g. enteral and parenteral nutrition), steroids and immunosuppres- sive medication and vigilance for secondary infective pathogens. The pathogenesis of chronic GvHD is less well understood. It is marked by sclerosis and fibrosis with a wider spectrum of organ involvement to also include lungs, eyes, and the musculoskeletal system. In the gastrointestinal system, the proximal part is more commonly

affected and oesophageal reflux and dysphagia, small- bowel overgrowth, and mucositis are the predominant manifest- ations. Secondary opportunistic infections often occur as there is an immune deficiency associated with chronic GvHD related to various factors (conditioning-induced and/or age-associated thymic involu- tion, thymic GvHD, or GvHD prophylaxis or treatment). Treatment strategies are similar to those for acute GvHD. Neutropenic enterocolitis Neutropenic enterocolitis (typhlitis) can occur in any patient with severe neutropenia. It most commonly occurs 7 to 10 days following chemotherapy and can affect any part of the gastrointestinal tract but has a predilection for the caecum. It is thought to be the re- sult of mucosal injury secondary to cytotoxic chemotherapy in the context of neutropenia and therefore impaired host defence often leading to polymicrobial infection of the bowel and occasional sys- temic dissemination. Candida spp. are the most common cause of fungaemia secondary to neutropenic enterocolitis. Patients pre- sent with fever, abdominal pain, and diarrhoea that can be watery or bloody. Diagnosis is made based on characteristic CT findings that include bowel wall oedema, thickening, mesenteric stranding,
Table 15.5.3 Gastrointestinal site-specific common HIV-associated pathogens and processes
Gastrointestinal site Common HIV-associated pathogens and processes Oesophagus Candidiasis, cytomegalovirus (CMV) and herpes simplex virus (HSV) infection, Kaposi's sarcoma (KS), and idiopathic ulceration Stomach CMV, Mycobacterium avium-intracellulare (MAI), and neoplasia (KS, lymphoma) Small bowel MAI, protozoa (giardia, isospora, cryptosporidia, amoebae, microsporidia), and helminths (Strongyloides stercoralis) Large intestine Viral pathogens: CMV, HSV Bacterial pathogens: clostridia, salmonella, shigella, campylobacter. Fungal pathogens: cryptococcosis, histoplasmosis Neoplastic processes: KS, lymphoma

 and pneumatosis (Fig. 15.5.3). The rising incidence of neutropenic enterocolitis is attributed to the increased use of cytotoxic chemo- therapy agents that cause gastrointestinal mucositis. Treatment includes an antimicrobial regimen (including antibacterial and antifungal agents), supportive measures (transfusions, enteral and parenteral nutrition), and in severe cases, the use of granulo- cyte colony-stimulating factor to enhance recovery of leucocyte numbers. Intestinal inflammation caused by
checkpoint inhibitors Blockade of the coinhibitory molecules cytotoxic T lymphocyte- associated antigen 4 (CTLA4) or programmed cell death protein 1 (PD-1) dampens negative regulation of T cells and provides ef- fective treatment against tumours (e.g. melanoma). However, a large proportion of patients on such treatment develop immune- related adverse events, most prominently diarrhoea and entero- colitis. Up to one-third of patients on anti-CTLA4 monoclonal antibodies and slightly fewer on anti-PD1 monoclonal antibodies develop diarrhoea within weeks and a few months of treatment. Clinical manifestations are abdominal pain, diarrhoea, and per rectal bleeding or mucus discharge. Cross-sectional imaging shows mesenteric engorgement and bowel wall thickening. Endoscopy usually demonstrates diffuse inflammation, with the histological presentation characteristically lacking features of chronicity that are typically seen in ulcerative colitis. Therapy usually consists of corticosteroids, with escalation to anti-TNF in case of clinical and endoscopic nonresponse. Discontinuation of checkpoint inhibitor therapy might need to be considered, and colectomy required in select cases. Food allergy It is important to distinguish between food allergy/hypersensitivity and food intolerance. In contrast to food intolerance, food allergy is an immunologically mediated hypersensitive response to dietary proteins. Class 1 food allergens (e.g. cow's milk, peanut, soybean, and fish) are primary sensitizers, a process that can occur in the gastrointestinal tract. They are heat stable and resistant to acid and proteolytic degradation. Class 2 allergens (e.g. Latex, banana, and avocado) cross react with plant-derived

proteins. They are heat labile and therefore the allergen may be tolerated in the heated form, but not in the raw state (e.g. egg allergy). The immunological process of food allergies can be classified as either IgE mediated or non-IgE mediated. IgE mediated This is an immediate hypersensitivity reaction characterized by mast cell activation most commonly seen in children who often outgrow the allergy. The most common allergens include milk, soy, peanut, wheat, egg, and seeds. Diagnosis is confirmed with skin prick testing and serum IgE levels. Gastrointestinal symptoms include nausea, vomiting, abdominal pain, and cramping. Diarrhoea is found less frequently. Extraintestinal manifestations can be life-threatening and include urticaria, angio-oedema, and atopic dermatitis. Fig. 15.5.3 Neutropenic enterocolitis in a bone marrow transplant patient with myeloma. Axial CT images following intravenous contrast show that the small bowel (arrows in lower images) as well as the walls of the cecum and ascending colon are thickened (arrows in upper images). Note pericaecal phlegmon and also abnormal bone trabeculae in vertebrae and pelvis from myeloma. From Levy AD, Mortele KJ, Yeh BM (eds) (2015). Gastrointestinal imaging. By permission of Oxford University Press.

15.5 Immune disorders of the gastrointestinal tract 2793 Oral allergy syndrome Oral allergy syndrome describes a condition where cross-reactivity between pollen and certain food allergens results in individuals al- lergic to pollen experiencing hypersensitivity reactions following the ingestion of certain foods (Table 15.5.4). Non-IgE mediated Non-IgE-mediated food allergy is a delayed immunological reaction which can be immune complex mediated or cell mediated. Food protein-induced enterocolitis syndrome is a non-IgE-mediated gastrointestinal food hypersensitivity that presents in infancy. Clinical features include profuse, repetitive vomiting and diarrhoea, leading to dehydration and lethargy in the acute setting, or weight loss and failure to thrive in a chronic form. The most common food triggers are cow’s milk or soy protein. Other triggers include rice and oats. There are no definitive diagnostic tests and treatment is dietary elimination of the food trigger. Investigation and treatment strategies for food allergies Diagnosis of a food allergy involves reproducible symptoms after exposure to the allergen with evidence of an underlying immuno- logical mechanism. The depth of investigation depends on the age of the patient, the severity of symptoms, and the nutritional import- ance of the allergen. It may be more practicable to advocate food avoidance in some cases without investigations. The primary investigative modality is a skin prick test with food extract and control solution. A positive result is the formation of wheal and flare skin reaction. Serum-specific IgE testing is another common test. Both these tests do not predict or correlate with se- verity of allergic reactions and only determine sensitization to a food allergen. Clinical food allergy can only be assessed in an oral food challenge study which is the next step after positive skin prick test or serum-specific IgE testing. Patients are fed incrementally larger extracts of the food allergen and monitored for clinical signs. This test is contraindicated in patients with a history of food-induced anaphylaxis. Ideally this should be performed in a double-blind, placebo-controlled manner to ensure reliable and unbiased results. Studies assessing primary preventative measures suggest that increasing maternal ingestion of common dietary food allergens and not delaying weaning beyond 4 to 6 months of age may possibly de- crease the development of food allergy. Treatment of food allergies involves avoidance of the food al- lergen. This entails education not only of the patient but often of their caregivers as food allergies are more common in children and allergens (e.g. milk and egg) may be hidden in foods. For those with food-induced anaphylaxis, carriage of an adrenaline autoinjector is recommended. Immunotherapy can be used to desensitize individuals to certain allergens by building tolerance through continuous oral exposure. Immunotherapy for peanut allergy has

received substantial media attention. Peanut allergy is common, lifelong, and exposure to small amounts can cause life-threatening reaction. Recent randomized controlled trials have demonstrated that the majority of patients can achieve desensitization and although adverse events did occur, al- though they were mostly mild. Food intolerance Food intolerance is not immunologically mediated and is relatively common, affecting 20% of the general population with gastrointes- tinal symptoms being the most commonly reported. The most common functional gastrointestinal disorder at least partly attrib- uted to food intolerance is irritable bowel syndrome. Extraintestinal manifestations may include asthma, migraine, malaise, and eczema. Treatment for irritable bowel syndrome is often dietary manipula- tion, for example, an exclusion diet with gradual reintroduction to identify any food triggers or a low FODMAP (fermentable oligo-, di-, monosaccharide, and polyol) diet. FODMAPs are poorly absorbed, osmotically active, and fermented by intestinal bacteria to produce hydrogen instead of methane, which is thought to contribute to in- testinal distension, bloating, and dysmotility. The aetiology of food intolerance can be pharmacological, en- zyme/transport related, or as a result of noncoeliac gluten sensitivity. There are a number of chemicals present in food that can potentiate pharmacological effects on the gastrointestinal neuroendocrine system leading to a myriad of symptoms. The most commonly de- scribed chemicals include salicylates, vasoactive amines (e.g. his- tamine), glutamates (e.g. monosodium glutamate), and caffeine. Lactose intolerance is the most common enzyme/transport-related food intolerance (see Chapter 15.10.5). Lactase-phlorizin hydrolase, commonly referred to as lactase is a β-galactosidase enzyme that catalyses the breakdown of lactose, a disaccharide in mammalian milk, to its constituent monosaccharides glucose and galactose. This enzyme is encoded by LCT and is secreted by the brush border cells of the small intestine. In most adults, this enzyme is downregulated post weaning and ingestion of milk or milk-containing products leads to symptoms typical of lactose nonpersistence (lactose intoler- ance): diarrhoea, abdominal pain, and flatulence. Approximately 30% of the world population display lactase persistence where lac- tase activity persists into adulthood. This genetic trait is geograph- ically distinct and strongly correlated with the dairying history of that population. Noncoeliac gluten sensitivity describes gastrointes- tinal symptoms attributed to the ingestion of gluten in the absence of any diagnostic features to suggest coeliac disease or a wheat al- lergy. Hereditary Fructose Intolerance is another genetic enzyme deficiency with a birth frequency of about 1 in 20 000 and leads to marked dietary idiosyncrasy (see Chapter 12.3.2). This recessive disease is caused by mutations in ‘liver’ aldolase B—an isozyme ex- pressed in small intestinal mucosa, liver and renal tubule. The disease is principally provoked by ingestion of fructose and sucrose, which induce a severe metabolic disturbance including hypoglycaemia with injury to the organs in which the aldolase is expressed. Since the con- dition can be reversed by dietary exclusion of the offending sugars, and is readily diagnosed by molecular analysis of the ALDOB gene, careful dietary history-taking is of paramount importance. Table 15.5.4 Typical cross-reactivity associations between inhalant allergen and food allergens Allergen Food allergens Birch pollen Apple, raw potato, carrot, celery, hazelnut, pear, peach, plum, cherry Mugwort pollen Celery, apple, peanut, kiwi fruit, carrot, parsley, spices (fennel, coriander, aniseed, cumin) Ragweed pollen Melons (e.g., watermelon, cantaloupe, and honeydew), bananas Latex Avocado, kiwi fruit, chestnut, papaya, banana

 Eosinophilic gastrointestinal tract disorders Eosinophilic gastrointestinal tract disorders encompasses a wide range of diseases including eosinophilic esophagitis (EoO), eosino- philic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis in the absence of known causes for eosino- philia. EoO is discussed

in more detail in the following subsection. Common presenting symptoms of the other eosinophilic disorders include abdominal pain, vomiting, and diarrhoea. Association with a food allergen is common and treatment is with steroids and dietary elimination. Eosinophilic oesophagitis Initially described in 1993 and thought to be a rare disease, EoO is a relatively new clinical entity in which the prevalence and interest has grown over the last 15 years. It is an immune-mediated dis- ease characterized by a mainly Th2-type immune response leading to eosinophilic recruitment. The subsequent eosinophil degranulation results in tissue remodelling that predisposes to fibrosis. Diagnosis is based on a combination of histological and clinical features. The histological hallmark is the presence of eosinophil-predominant inflammation with a peak value of more than 15 eosinophils per high-power field. The finding of eo- sinophils in the oesophageal squamous epithelium is abnormal and not specific to EoO as it is associated with other conditions (e.g. gastro-oesophageal reflux disease, infections, drug hyper- sensitivity, autoimmune and connective tissue disorders, and hypereosinophilic syndrome). Multiple biopsies from the distal and proximal oesophagus as well as the antrum and duodenum can help distinguish EoO from other conditions. This together with classical clinical features is necessary for an accurate diag- nosis. Clinical characteristics include a male preponderance and history of atopic diathesis (asthma, food allergy, eczema, allergic rhinitis). In childhood, the main presenting symptoms are feeding difficulties, vomiting, and pain. Adults tend to present with solid food dysphagia, often with food bolus impaction necessitating endoscopic removal. At endoscopy, common findings are char- acteristic linear furrows, circular rings, whitish plaques, and pap- ules, although none of these are pathognomonic for EoO. In some cases, benign oesophageal strictures have been described and have been successfully endoscopically dilated. Initially treatment consists of an 8-week trial of a proton pump inhibitor. If there is histological and symptomatic reso- lution following this, it is likely the diagnosis was either gastro- oesophageal reflux or proton pump inhibitor-responsive oesophageal eosinophilia (PPI-ROE). It is currently not clear if PPI-ROE is a separate entity or a subtype of EoO. If repeat oesophageal biopsies reveal persistent eosinophilia, treatment with topical steroids (e.g. fluticasone or budesonide, swal- lowed instead of inhaled) is recommended and largely effective. Maintenance therapy is recommended as cessation often leads to symptomatic recurrence. In more aggressive cases, longer or higher doses of topical steroids, systemic steroids, or elimin- ation diets have been tried. There is little evidence for the role of mast cell stabilizers, leukotriene antagonists, or biological ther- apies yet. Identification of specific food allergic triggers either through elimination diets or patch testing is recommended, es- pecially in the paediatric population. Autoimmune conditions and the gastrointestinal tract Autoimmune gastrointestinal dysmotility Autoimmune gastrointestinal dysmotility is a gastrointestinal-specific manifestation of autoimmune dysautonomia that can either be idio- pathic or paraneoplastic in origin. Autoimmune dysautonomia de- scribes the neural-specific IgG or effector T cell-mediated impaired function of peripheral autonomic synapses, ganglionic neurons, autonomic nerve fibres, and central autonomic pathways. Common symptoms relate to the underlying gastrointestinal dysmotility (gas- troparesis, constipation, diarrhoea, pseudo-obstruction) and the onset can be acute or insidious. Investigations include nonspecific ob- jective assessment of gastrointestinal motility (gastrointestinal transit studies, gastroduodenal manometry, or colonic barostat testing to assess colonic contractions). Laboratory tests include serological testing for specific antibodies. The most specific autoantibody marker of autoimmune dysautonomia is the neuronal ganglionic alpha-3- acetylcholine receptor (AChR) autoantibody. Additional markers of paraneoplastic or idiopathic dysautonomia include antineuronal nu- clear antibody-type 1 (ANNA-1), CRMP-5-IgG, N-type voltage-gated calcium channel, muscle AChR, striational, glutamic acid decarb- oxylase 65, and

peripherin. Treatment may consist of pyridostigmine (a cholinesterase inhibitor) for pseudo-obstruction, while immuno- therapy with intravenous immunoglobulin has also been trialled for this rare condition. Autoimmune pancreatitis Autoimmune pancreatitis (AIP) is a relatively rare fibroinflammatory disorder initially described in Japan in the 1960s. Over time it has become clear that there are two distinct clinical subtypes. Type 1 AIP is part of a multiorgan, systemic IgG4-related disease and histologically characterized by lymphoplasmacytic sclerosing pan- creatitis rich in IgG4-positive cells. Type 2 AIP is less common and defined by ductal neutrophilic infiltration, ductal destruction, and the classic ductal epithelial lesion with a paucity of IgG4-positive cells. Despite the histological differences, both subtypes share similar clinical features and treatment strategies. AIP can present with features of obstructive jaundice secondary to pancreatic duct strictures, or more commonly a focal enlargement of the pancreatic head. Other presenting symptoms include acute pancreatitis and ab- dominal pain. In type 1 AIP, clinical features can suggest other organ involvement (e.g. Sjögren's disease secondary to saliva gland infiltra- tion, interstitial nephritis, retroperitoneal fibrosis, and biliary dis- ease). In the presence of a pancreatic head mass, a common clinical scenario is distinguishing autoimmune pancreatitis from pancre- atic cancer. This is achieved through a combination of radiological imaging with assessment of serological markers. Typical radiological features of AIP include diffuse pancreatic enlargement with delayed enhancement, pancreatic ductal strictures without dilatation, and minimal peripancreatic fat stranding. Serological markers, such as raised IgG4 antibody levels and antiplasminogen-binding protein,

 are helpful, but not specific to AIP and often histological confirm- ation is required. As AIP is extremely steroid responsive, response to therapy is part of the diagnostic criteria. There are several dif- ferent diagnostic criteria proposed, such as the Japanese guidelines, the Korean criteria, the Asian consensus criteria, the Italian criteria, and the Mayo Clinic HISORt (Histology, Imaging, Serology, Other organ involvement, and Response to steroids). Patients are treated with prolonged courses of steroids (up to 3 years). Relapse rates vary between 30 and 50% and can be treated with a further course of cor-ticosteroids and an immunomodulatory agent (e.g. azathioprine). Gastrointestinal manifestations of systemic autoimmune diseases Systemic autoimmune diseases can have a number of gastrointestinal manifestations that either reflect the underlying autoimmune process or are related to treatment (Table 15.5.5). Common gastrointestinal manifestations of systemic vasculitides include intestinal ulceration, dysmotility, mesenteric ischaemia, and mesenteric infarction. As therapy often includes the use of nonsteroidal anti-inflammatory and immunosuppressive agents, gastrointestinal complications of therapy include peptic ulceration and infectious causes of diarrhoea. FURTHER READING Agarwal S, Cunningham-Rundles C (2019). Gastrointestinal mani- festations and complications of primary immunodeficiency dis- orders. Immunol Allergy Clin North Am, 39, 81–94. Agarwal S, Mayer L (2013). Diagnosis and treatment of gastrointes- tinal disorders in patients with primary immunodeficiency. Clin Gastroenterol Hepatol, 11, 1050–63. Artis D, Spits H (2015). The biology of innate lymphoid cells. Nature, 517, 293–301. Cheroutre H, Lambolez F, Mucida D (2011). The light and dark sides of intestinal intraepithelial lymphocytes. Nat Rev Immunol, 11, 445–56. Dellon ES, et al. (2013). ACG clinical guideline: evidenced based ap- proach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol, 108, 679–92. Flanagan EP, et al. (2014). Immunotherapy trial as diagnostic test in evaluating patients with presumed autoimmune gastrointestinal dysmotility. Neurogastroenterol Motil, 26, 1285–97. Ho MH, Wong WH,

Chang C (2014). Clinical spectrum of food
allergies: a comprehensive review. Clin Rev Allergy Immunol, 46, 225–40. Table 15.5.5 Gastrointestinal manifestations of systemic autoimmune diseases Systemic autoimmune disease Autoimmune process Gastrointestinal manifestations Systemic lupus erythematosus (SLE) Systemic vasculitis. Gastrointestinal manifestations tend to reflect active disease Oral ulcers can be discoid, ulcerative, or erythematosus. Gastrointestinal vasculitis includes features varying from segmental oedema to discrete ulceration, gangrene, and perforation. Intestinal dysmotility is common. Venous thrombosis can cause intestinal infarction. Other gastrointestinal features include protein-losing enteropathy, pancreatitis, ascites, liver steatosis, chronic hepatitis and Budd–Chiari syndrome Rheumatoid arthritis (RA) RA is characterized by inflammation of the synovium and surrounding structures. Rheumatoid vasculitis affects 5% of patients with intestinal involvement in approximately 20% Ischaemic ulcers, intestinal infarction, and pancolitis that closely resembles ulcerative colitis can occur. Upper gastrointestinal manifestations include oesophageal dysmotility and chronic atrophic gastritis associated with hypergastrinaemia and hypo- or achlorhydria. The latter can promote small-bowel bacterial overgrowth. Chronic diarrhoea can result from secondary amyloidosis Sjögren’s syndrome Autoimmune disease with histological hallmark of lymphocytic infiltration of the exocrine glands resulting in acinar gland degeneration, necrosis, atrophy, and decreasing lacrimosalivary function Extraglandular involvement occurs in 5–10% of patients and can present with dysphagia, dyspepsia, nausea, and dysmotility Behçet’s disease Multisystemic immune-mediated disorder characterized by recurrent oral and/or genital ulcers, arthritis, skin manifestations, and ocular, vascular, neurological, or intestinal involvement Intestinal ulcers can be found throughout the gastrointestinal tract, but are most common in the ileocecal region. As vasculitis is rarely observed in endoscopic or surgical specimens and there are no specific laboratory markers for intestinal Behçet’s disease, it is therefore challenging to distinguish from Crohn’s disease Systemic sclerosis (scleroderma) Immune activation, vascular damage, and excessive synthesis of extracellular matrix with deposition of increased amounts of structurally normal collagen leading to fibrosis Although any part of the gastrointestinal tract can be affected, 90% of patients will have oesophageal involvement. Oesophageal dysmotility commonly results in dysphagia and dyspepsia Henoch–Schönlein purpura Small vessel vasculitis mediated by IgA immune complex deposition. Gastrointestinal symptoms in 75% of patients. Most common symptoms and signs are abdominal pain and haemorrhage secondary to intestinal mucosal ulceration. Polymyositis and dermatomyositis Connective tissue disorder characterized by inflammation of striated muscle (to a lesser extend smooth muscle) Patient often present with delayed oesophageal and gastric emptying Eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg–Strauss syndrome) Allergic granulomatous angiitis 50% of patients report gastrointestinal symptoms which include bloody diarrhoea, ulcers and abdominal pain. Eosinophilic gastroenteritis can present in the prodromal phase

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