Autoimmune gastritis

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Abstract | Autoimmune gastritis (AIG) is an increasingly prevalent, organ-specific, immune-mediated disorder characterized by the destruction of gastric parietal cells, leading to the loss of intrinsic factor and reduced acid output. These alterations result in malabsorption of iron, vitamin B_{12} (pernicious anaemia) and potentially other micronutrients. For several years, most studies have focused on pernicious anaemia only, generating confusion between the two entities. In AIG, the gastric proton pump, H^+/K^+ ATPase, is the major autoantigen recognized by autoreactive T cells. The T cell-dependent activation of B cells stimulates the production of anti-parietal cell antibodies, the serological hallmark of AIG. The role of *Helicobacter pylori* infection in activating or favouring the autoimmune process is still uncertain. Early histopathological alterations allowing a more precise and prompt recognition have recently been described. AIG is burdened by a substantial diagnostic delay as it can present with varied clinical signs including, among others, gastrointestinal symptoms and neuropsychiatric manifestations. In advanced stages, AIG might progress to neuroendocrine tumours and gastric adenocarcinoma. Management includes early detection through a proactive case-finding strategy, micronutrient supplementation and endoscopic surveillance. This Primer comprehensively describes the most important insights regarding the epidemiology, pathophysiology, diagnosis and management of AIG, focusing on the most controversial, outstanding issues and future directions.

Autoimmune gastritis (AIG), is a non-self-limiting, chronic inflammatory disorder affecting the oxyntic (acid-secreting gastric compartment) mucosa, leading to progressive mucosal atrophy[1–5]. The inflammation is restricted to the corpus and fundus glands of the stomach, sparing the antrum, which distinguishes AIG from other conditions leading to atrophic gastritis (such as *Helicobacter pylori* infection) (FIG. 1). Oxyntic mucosal inflammation and its atrophic progression are the hallmarks of AIG and are considered *sine qua non* (absolutely necessary) for a confirmed diagnosis. The topographical restriction results from the oxyntic location of the parietal cells triggering the autoimmune reaction[6–8]. Parietal cells (also known as oxyntic cells) are epithelial cells that have two main functions: hydrochloric acid secretion and intrinsic factor (vitamin B_{12}-binding glycoprotein) production. Only after the widespread use of gastrointestinal endoscopy[9] and the discovery of anti-intrinsic factor antibodies (IFAs) and anti-parietal cell antibodies (PCAs) in the 1960s[10,11] was AIG recognized as a specific disorder[12].

AIG is caused by the destruction of parietal cells, secondary to the actions of PCA, which recognizes subunits of the proton pump, H^+/K^+ ATPase, which is unique to the parietal cells. The inflammatory process in AIG seems to be mediated by autoreactive T cells, although the exact causative agent is unknown. The destruction of parietal cells leads to an increased pH of the stomach and a loss of intrinsic factor, which, in turn, lead to malabsorption of iron and vitamin B_{12}, causing iron deficiency anaemia and pernicious anaemia, respectively. A common clinical presentation of AIG is indeed iron deficiency anaemia[13–15], which might be present in up to 25–50% of patients with AIG[13,16], whereas pernicious anaemia might be found in up to 15–25% of patients[16–19]. Patients with AIG may complain of subtle or unspecific upper gastrointestinal symptoms, especially dyspepsia, but most patients are usually asymptomatic, before the onset of anaemia or neurological manifestations. Micronutrient malabsorption in AIG is responsible for a wide clinical spectrum and often leads to substantial diagnostic delay, favouring the occurrence of life-threatening and irreversible complications[20–24]. Furthermore, the clinical spectrum of AIG is made complex by its frequent association with other autoimmune diseases, especially Hashimoto thyroiditis and by the increased risk of developing gastric adenocarcinoma and type 1 gastric neuroendocrine tumour (NET)[2,20,22]. Unfortunately, no curative treatment for AIG is currently available and long-term trials investigating

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the use of immunosuppressant therapy in patients with AIG are lacking.

For several years, the term pernicious anaemia has been used as a synonym for AIG, thereby generating a relevant selection bias in studies focusing on AIG, as pernicious anaemia is only a part of the AIG clinical spectrum. This might have led to an underestimation of AIG prevalence. In addition, the classification of AIG has undergone several changes over time (FIG. 2). In fact, before the discovery of *H. pylori*, which causes the most common type of chronic gastritis worldwide, the classification of gastritis was based on a topographical basis rather than on the aetiology, generating some confusion among different types of gastritis. The currently accepted classification of gastritis is the updated version[25] of the Sydney classification system[26], which distinguishes atrophic gastritis and non-atrophic gastritis. In 2015, the Kyoto global consensus proposed an aetiology-based classification[7], which provides more details about the gastritis aetiologies, in addition to incorporating the topographical classification of the Sydney system. This consensus has finally harmonized histopathological and clinical features of gastritis, providing a useful tool for both pathologists and clinicians.

The relatively late discovery of *H. pylori*, the various classifications of gastritis and studies confounding AIG with other forms of gastritis as well as using different diagnostic criteria make it difficult to interpret published data regarding AIG epidemiology and pathophysiology. Moreover, the contribution of *H. pylori* to the autoimmune process in AIG is still disputed. Several new studies have provided novel insights into AIG pathogenesis, its clinical features, early recognition and management. In this Primer, we provide a comprehensive description of this multifaceted disorder, including its epidemiology, pathophysiology in murine models and humans, diagnostic challenges and controversies, and overall management. Finally, we discuss the most pressing questions in the field that will direct future research to better understand and treat this disorder.

Epidemiology

Epidemiological data on AIG are scant and difficult to interpret. According to current evidence, the prevalence of AIG seems likely to have been underestimated, owing to the high rate of asymptomatic or pauci-symptomatic disease course and the lack of proactive screening strategies. The prevalence of AIG also varies depending on the clinical setting of enrolment, ethnicity and the diagnostic criteria applied. For example, patients with AIG-induced iron or vitamin B_{12} deficiency might be asymptomatic and anaemia is often treated without further investigations to determine its aetiology[20,27]. In such cases, AIG remains undiagnosed, hence underestimating its true prevalence. Similarly, in those patients undergoing gastroscopy, biopsy samples are not always acquired or sampling is inconsistent with the recommended biopsy protocols, thereby precluding accurate estimates of AIG incidence[20,28]. Additionally, concurrent *H. pylori* infection in patients with AIG often confounds the correct classification of gastritis owing to antral involvement in infectious gastritis. Finally, in many case series, AIG diagnosis was based on serological markers[29,30], such as PCA or IFA, gastrin-17 or pepsinogen levels only, without confirmatory biopsy. Both false-positive and false-negative results can lead to both AIG over-diagnosis or under-diagnosis; hence, confirmatory biopsy is always necessary for making a diagnosis.

Epidemiological studies providing data on histologically confirmed AIG in the general population are lacking. Given that AIG is often indolent in early stages, its prevalence has been estimated to be ~0.5–4.5% globally[31], widely varying depending on the setting of enrolment, age, sex and ethnicity (TABLE 1). Hence, this information should be cautiously interpreted in the light of these variables. To the best of our knowledge, no ad hoc Western (including both Europe and America) population-based studies focusing on prevalence of histologically proven AIG are available. Nevertheless, AIG epidemiological data from Asian jurisdictions are emerging. A retrospective Chinese study estimated an annual detection rate of 0.9% of histologically and serologically diagnosed AIG[32]. A Japanese study including 6,739 individuals undergoing routine medical checks found endoscopically and serologically confirmed AIG in 0.49% of patients[33]. One study found a higher prevalence of AIG in Italy than in Asian jurisdictions. Amongst 2,286 patients attending a gastroenterology outpatient clinic over 4 years, 4.3% were diagnosed with AIG by both histology and serology[34]. In the cross-sectional central European histoGERD trial, among 1,123 individuals undergoing gastric biopsy, 2.3% were diagnosed with AIG, with a female to male ratio of 2.25:1 (REF.[35]).

Studies in which the prevalence of AIG was estimated on the basis of the presence of PCAs or IFAs have reported a higher prevalence (8–20%) than studies that estimated prevalence based on histology[30]. Different case series from various regions have shown that PCAs can be found in up to 85–90% of adults with pernicious anaemia and AIG, whereas IFAs are present in 35–60% of patients with pernicious anaemia and AIG[17,36]. The prevalence of AIG based on cases of pernicious anaemia is estimated to be ~0.1% in the general population and ~2% in individuals >60 years of age[17,27,37]. Low serum vitamin B_{12} and the presence of IFAs confirm a diagnosis of pernicious anaemia and should not be misdiagnosed as megaloblastic anaemia resulting from insufficient

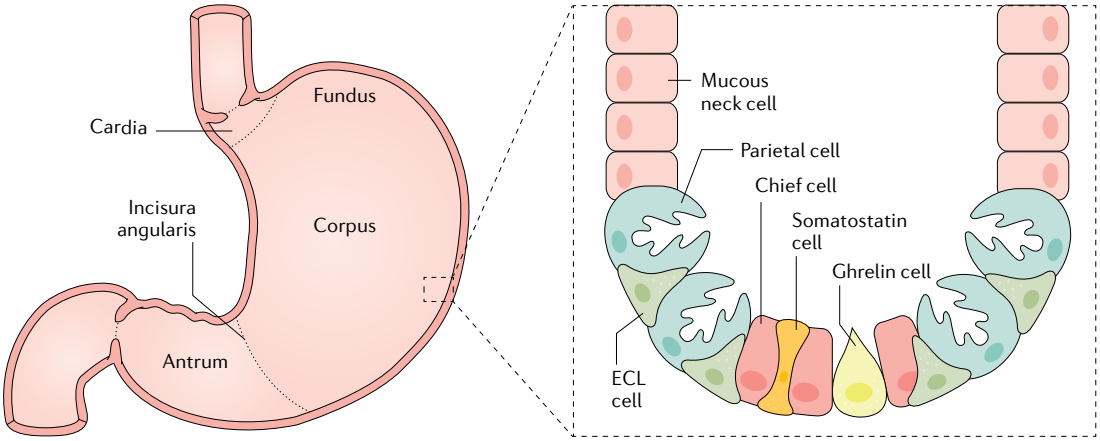

Fig. 1 | **Anatomical localization of AIG.** The gastric mucosa includes two phenotypic and functional compartments, namely, the cranial oxyntic and the distal mucosecreting. The different biological profiles of the oxyntic and mucosecreting gastric mucosa result in different susceptibilities to environmental or host-related noxious agents. In the native stomach, the oxyntic mucosa covers the cranial two-thirds of the mucosal surface (that is, the fundus and the corpus mucosa) and is gradually replaced distally by the antral mucosecreting glands. The boundary between these two functional areas follows a rounded line, cranially centred at the incisura angularis. Autoimmune gastritis (AIG) affects the corpus and fundus, causing mucosal atrophy that spares the antrum. Parietal cells, which are the main target cells in AIG, are located only in the oxyntic mucosa and produce hydrochloric acid and intrinsic factor. Parietal cells reside along with other cells including chief cells (also known as zymogenic cells, which mainly produce pepsinogen), mucous neck cells (which produce mucins), enterochromaffin-like (ECL) cells, ghrelin cells and somatostatin cells.

vitamin B_{12} intake, long-term proton pump inhibitor use and small-bowel bacterial overgrowth[27]. Pernicious anaemia was once considered a disorder mainly affecting elderly women of Northern European ethnicity (with a female to male ratio of ~2:1), but subsequent studies have found a similar prevalence of pernicious anaemia in different ethnic groups (white, Caucasian, African American, and non-white Hispanic), affecting any age group[20,34,38–41]. In fact, in studies from Turkey and Italy, the mean ages of men with pernicious anaemia were in the range 49–55 years and of women with pernicious anaemia were in the range 40–61 years[20,34,40,41].

Anaemia was found in ~50% of patients at AIG diagnosis; iron deficiency anaemia was more common in younger women (<50 years of age) than in older women (>65 years of age) and men, and pernicious anaemia was frequently observed in elderly men. A high prevalence (57.3%) of iron deficiency was observed even in patients without anaemia[42]. Patients with unexplained iron deficiency anaemia or those with refractory iron deficiency anaemia (that is, those who do not respond to iron supplementation) should be investigated for AIG. Refractory iron deficiency anaemia is present in 15–27% of patients, which is 4–6-fold higher than in patients with coeliac disease, one of the most common causes of iron deficiency anaemia[13,43–46]. Of 160 patients with AIG (only a proportion of whom had histologically confirmed AIG as not all underwent endoscopy), 83 presented with iron deficiency anaemia, 48 with normocytic indices (no change in the size of red blood cells (RBCs)) and 29 with macrocytic anaemia (increased RBC size)[14]. The mean age of patients with iron deficiency anaemia was 41 ± 15 years, which was 21 years younger than the mean age of patients with macrocytosis. This finding is in line with the fact that iron deficiency usually occurs earlier in the natural history of AIG. A larger, multicentre study involving 654 patients with AIG confirmed by histology and serology showed a similar trend in the proportion of patients with microcytic or macrocytic anaemia in different age groups[42].

With active and regular endoscopic or histological surveillance in patients with AIG and/or pernicious anaemia, type 1 gastric NETs are observed in 4–12% of patients[47–50]. These patients also carry a 3–7-fold increased risk of gastric adenocarcinoma, with an incidence of 0.9–9%[47,51,52]. Indeed, a prospective cohort study involving 200 patients with histologically proven AIG with a mean follow-up of 7.5 years found an annual incidence of 0.25% per person-year for gastric cancer (95% CI 0.07–0.6%), 0.43% per person-year for gastric dysplasia (95% CI 0.2–0.9%) and 0.68% per person-year for type 1 gastric NET (95% CI 0.3–1.2%)[50]. A meta-analysis of 27 studies including 22,417 patients with pernicious anaemia found a pooled gastric cancer (all types) incidence of 0.27% per person-year and a pooled gastric cancer recurrence rate of 6.8% (95% CI 2.6–18.1%)[52]. Finally, in a long-term, prospective study focusing on the natural history of AIG in 282 individuals, gastric adenocarcinoma was not detected in these patients[23]. Hence, the risk of developing gastric adenocarcinoma in particular in patients with AIG, although not negligible, seems to be lower than that related to *H. pylori* infection[53]. A study from the USA involving 59 patients with AIG found an incidence of 14.2 per 1,000 person-year for gastric cancer (~6.4 years after the index gastroscopy)[54].

Comorbidities

All diseases in the spectrum of autoimmune diseases may be potentially associated with gastric autoimmunity. The prevalence of AIG is 3–5 times greater in patients with autoimmune thyroid disease or type 1 diabetes mellitus

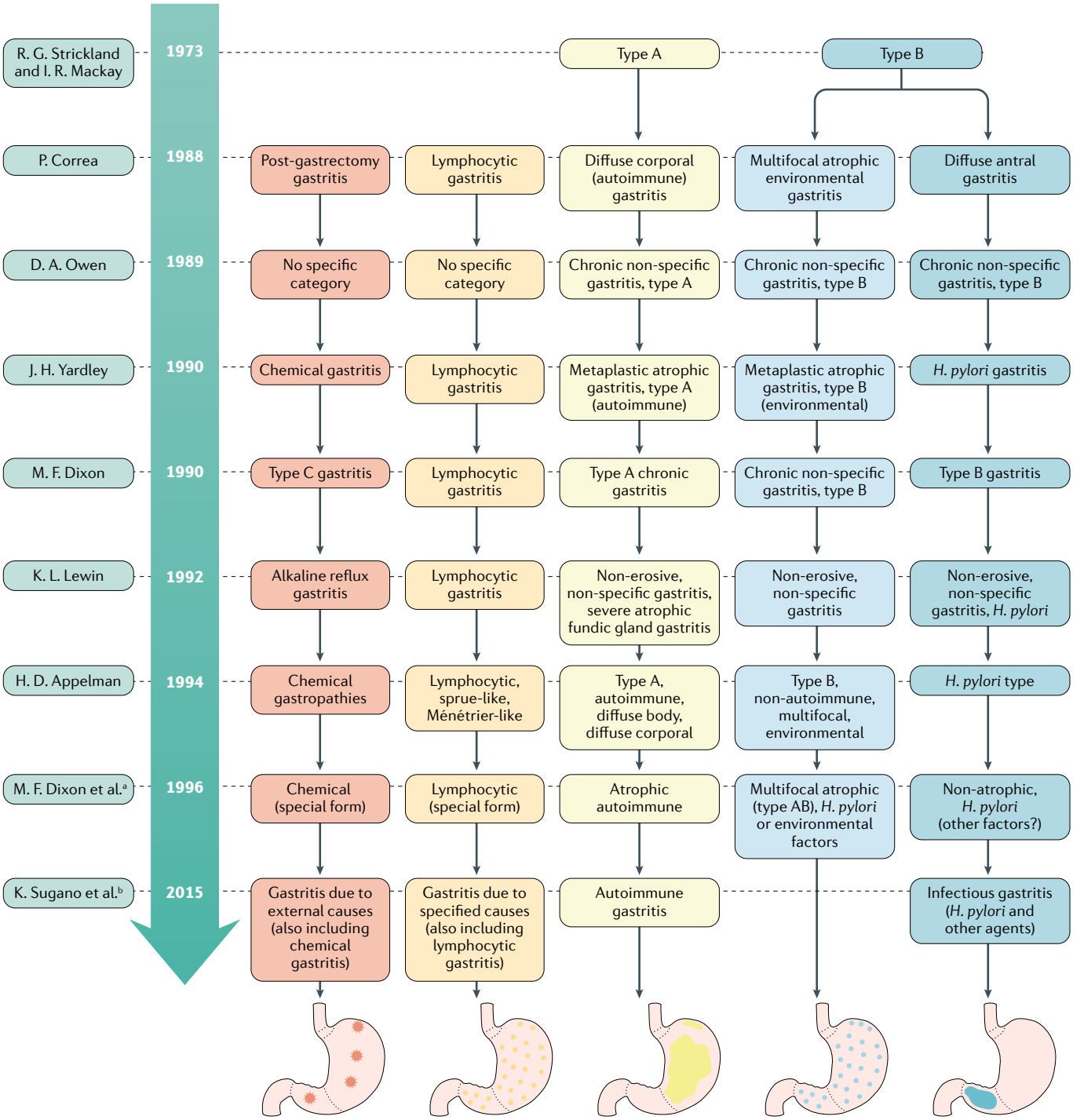

Fig. 2 | **Summary of classifications of gastritis.** Classifications of gastritis and their relative nomenclature have changed over time and these changes reflect the progressive knowledge accumulated about this disease. Initially, Strickland and Mackay introduced the concept of two distinct forms of gastritis, namely type A (corpus-restricted and fundus-restricted gastritis) and type B (antrum-predominant gastritis with minor and focal changes in the corpus mucosa). The aetiology of type A and type B gastritis was identified following a few years and definitions of gastritis have slightly changed over time. The discovery of *Helicobacter pylori* marked a turning point and led to the modern classifications. Both topography and aetiology are essential for classifying gastritis. The schematics of the stomach at the bottom of the timeline show the topographical distribution of mucosal damage in each type of gastritis. [a]The so-called updated Sydney system, which is a revision of the Sydney classification proposed in 1991 (not shown). [b]Kyoto global consensus focused on gastritis aetiology, recommending that gastritis be categorized according to gastric anatomical localization.

(T1DM)[29,31] than in the general population. In a case series including 99 patients with AIG, >50% had another autoimmune disease and 13% had two or more autoimmune diseases[34]; these findings were also confirmed in other series. The association between AIG and autoimmune thyroiditis is considered a specific syndrome, known as thyrogastric syndrome[55]. Hashimoto thyroiditis is the most commonly associated autoimmune

Table 1 | **Relevant characteristics of studies reporting the prevalence of AIG**

Region	Study design and setting	Prevalence (%)	Diagnostic criteria	Mean age of patients (years)	Ref.
Austria, Germany	Multicentre study in patients undergoing gastroscopy	2.3	H	52	35
Canary Islands	Population-based, cross-sectional serology study in the general population	7.8	SAb	53	168
China	Retrospective evaluation of patients undergoing gastroscopy	3.1	H, SAb	60	32
Germany	Population-based cross-sectional serology study in the general population	19.5	SAb	62	141
Italy	Patients referred to a gastroenterological outpatient clinic	4.3	H, SAb	59	34
Italy	Cross-sectional study in healthy blood donors	10	SAb	45	169
Japan	Healthy individuals undergoing gastroscopy as a part of routine check-up	0.5	E, SAb, Sb	51	33

AIG, autoimmune gastritis; E, endoscopy; H, histological evaluation of gastric biopsies; SAb, serological testing of anti-parietal cell antibody and/or anti-intrinsic factor antibody; Sb, serological biopsy measuring gastrin-17 and/or pepsinogen levels or pepsinogen ratio.

disorder with AIG, while the association between Graves' disease and AIG has seldom been reported[20,31,34]. In fact, the prevalence of Hashimoto thyroiditis is 3–8-fold higher in patients with AIG than in the general population[56]. An observational study from Italy found that 53% of patients with AIG had autoimmune thyroid disease of any type and the risk factors associated with the development of thyroiditis were female sex (OR 5.6), PCA positivity (OR 2.5) and intestinal metaplasia (OR 2.2)[57]. Moreover, the incidence of other autoimmune diseases was higher in patients with AIG and concurrent thyroiditis than in patients with AIG only.

Besides thyroiditis, the other frequently associated autoimmune disorders are T1DM, Addison disease and vitiligo. Furthermore, PCA positivity is found in 10–15% of children (<18 years of age) and 15–25% of adults (40.8 ± 12.1 years of age) with T1DM[15,58]. In a study including 88 patients with T1DM (of whom 47 were PCA-positive) undergoing gastroscopy with gastric biopsy, histologically confirmed AIG was detected in 57% of PCA-positive patients and 10% of PCA-negative patients[48]. This study stresses the need for histological assessment for making the diagnosis of AIG, given that PCA may be negative in a substantial proportion of patients. Moreover, in the same study, PCA-positive patients demonstrated severe corpus atrophy compared with PCA-negative patients. By contrast, a study involving 1,072 patients with T1DM found an AIG prevalence of 7.5% among PCA-positive patients, with no histological confirmation[59]. In addition, up to 20% of patients with Addison disease were diagnosed with AIG (based on PCA positivity alone)[60] and 10–15% of patients with vitiligo had histologically confirmed AIG[61,62]. Finally, data regarding the association between AIG and other autoimmune diseases including primary hyperparathyroidism[63], rheumatoid arthritis[34], myasthenia gravis[64], coeliac disease[34,65], chronic spontaneous urticaria[66], perioral cutaneous autoimmune conditions (for example, erosive oral lichen planus)[67], inflammatory bowel disease[68], autoimmune haemolytic anaemia[68], systemic lupus erythematosus[68] and autoimmune liver disease[69] are sparse and fragmentary.

Metaplasia
The transformation of a specific cell type into another mature cell type.

Canaliculi
Secretory channels through which hydrochloric acid is actively transported.

Risk factors

Ageing and sex. The substantial latency between the asymptomatic onset of AIG and the manifestation of clinical symptoms (if any) might potentially skew the strength of ageing as a risk factor. The prevalence of AIG increases with age as well as the prevalence of PCA positivity, increasing from 2.5% in the third decade to 12% in the eighth decade in the general population[37,70]. Interestingly, although data suggest that AIG is more common in the elderly population, this might be owing to the relative paucity of studies investigating AIG in the paediatric population. In a few case series, histologically confirmed or serologically confirmed AIG has been found in paediatric patients, with autoimmunity (especially autoimmune thyroid disease) or iron deficiency anaemia being the most common causes of diagnosis[71–73].

Among adults, women are more frequently affected by AIG, with an average female to male ratio of 2–3:1. Several studies have confirmed the predominance of AIG in women of different ethnicities[74–83], as also observed in autoimmune thyroid disease[84], with the exception of a Turkish study, which found predominance in men[40], and a Japanese study, which found no significant sex difference[33].

H. pylori *infection.* The role of *H. pylori* infection in AIG is still uncertain. One study demonstrated cross-reactivity between *H. pylori*-induced antibodies and human oxyntic mucosa, in particular with the luminal surface of glandular cells and secretory canaliculi of parietal cells[85]. Additionally, some studies have shown concurrent *H. pylori* infection in patients with AIG[86–88]. Similarly, PCA can also be present in *H. pylori*-related atrophic and non-atrophic gastritis[89]. PCA positivity was found in all patients with *H. pylori*-positive multifocal atrophic gastritis[90].

Genetic risk factors. Studies have shown a strong familial clustering for AIG[91]. Concordance of pernicious anaemia was observed in 12 sets of monozygotic twins, suggesting a possible genetic predisposition to

AIG[92]. Although firm evidence is still lacking, a first-degree family history of AIG has been reported in up to 16.5% of patients with AIG[20]. First-degree relatives of T1DM probands with PCA had a higher frequency of thyrogastric antibodies than relatives of PCA-negative T1DM probands and the general population[15]. This implies that individuals with PCA positivity seem to harbour a genetic predisposition to the development of autoimmunity, which can also be present in first-degree relatives.

Genetic risk factors predisposing individuals to AIG are poorly understood. Patients with AIG and pernicious anaemia associated with autoimmune endocrine diseases were reported to have an increased frequency of the serotypes HLA-B8 (relative risk 2.2), HLA-B18 (relative risk 9.0), and HLA-Bw*15 (relative risk 2.0), whereas those without autoimmune endocrine diseases showed increased frequencies of HLA-B7 (relative risk 1.6) and HLA-B12 (relative risk 3.1)[93]. However, given that this is just a single observation, comparing the findings of previously published studies investigating other autoimmune diseases is difficult. Whether these serotypes have a predisposing or a protective effect on the development of AIG is unclear and more studies are needed to confirm a possible causative relationship. Another study found an increased frequency of HLA-DR2 or HLA-DR4 (relative risk 6.9) and HLA-DR4 or HLA-DR5 (relative risk 5.4) in patients with pernicious anaemia without endocrine comorbidities[94]. Heterogeneity in HLA haplotypes in different clinical subgroups might reflect the genetic heterogeneity of pernicious anaemia and, possibly, AIG. One study found a weak association between AIG and HLA-DR5, in linkage disequilibrium with *DQA1*0501:DQB1*0301* (REF.[95]).

So far, two studies have specifically focused on HLA haplotypes in patients with AIG[96,97]. In an Italian study, the prevalence of HLA-DRB1*03 and HLA-DRB1*04 alleles was higher ($P < 0.01$) in patients with AIG than in the control group (general population from the same geographical area)[96]. In the same study, HLA-DRB1*03 and HLA-DRB1*04 were also mostly associated with autoimmune thyroid diseases ($P < 0.01$) and the presence of intestinal metaplasia ($P < 0.01$). By contrast, HLA-DRB1*01 was more common in healthy individuals ($P < 0.01$). A Finnish study found an association between AIG and HLA-DRB1*04 and HLA-DQB1*03, but not with HLA-DRB1*03 (REF.[97]). These three HLA haplotypes are also frequently associated with other autoimmune conditions, such as T1DM, rheumatoid arthritis and systemic lupus erythematosus[98], thereby supporting a common HLA-dependent autoimmune pathway.

Mechanisms/pathophysiology

The aetiology and exact order of events leading to the development of AIG are unclear. The mechanisms underlying AIG are complex and, in particular, the trigger of autoimmunity and the underlying early events causing the immunological cascade and the progression to mucosal damage are yet to be clearly defined. Accordingly, we describe here the current knowledge regarding AIG pathophysiology (FIG. 3).

Histological changes

Two phenotypic phases, both typically restricted to the oxyntic mucosa, can be distinguished in the natural history of AIG. The early phase (also referred to as the non-atrophic phase) is characterized by oxyntic inflammation involving a polymorphic cell population such as lymphocytes, plasma cells, mast cells and a variable number of polymorphs (acute inflammatory cells), including a prominent eosinophilic component. Lymphocytes may be structurally organized in lymphoid follicles in the gastric mucosa, consistent with the activation of an inflammatory process. The late phase or the atrophic stage is characterized by longstanding inflammation that causes major structural alterations of the glandular compartment, resulting in progressive loss of the native oxyntic glands. This resultant mucosal atrophy is promoted by pro-inflammatory cytokines, including IL-11 (REF.[99]) and IL-17A[100]. The most simple atrophic change ('glandular vanishing') involves the replacement of single glandular units by micro-scars of inflamed fibrous tissue, owing to the infiltration of immune cells. Glandular vanishing mostly coexists with metaplastic transformations, that is, the development of metaplasia, of the oxyntic glands. Two types of mucosal metaplasia usually coexist, namely pseudo-pyloric metaplasia and intestinal metaplasia.

Pseudo-pyloric metaplasia refers to the presence of antral type of glands in the corpus or fundus of the stomach, which is referred to as oxyntic antralization, that can occur in AIG. Most recently, based on its molecular and immunohistochemical profiles, this metaplastic transformation has been relabelled as spasmolytic polypeptide-expressing metaplasia (SPEM). This term better reflects its molecular profile, rather than its histopathological appearance. SPEM cell lineage expresses *TFF2* (encoding a protein involved in mucosal protection) and *MUC6* (encoding a protein involved in the mucosal epithelial barrier). The origin of SPEM lineage is still debated and current experimental evidence suggests that it originates from a 'compensatory' proliferation of neck cells, as a consequence of the destruction of the oxyntic glands[101]. In individuals with *H. pylori* infection, oxyntic antralization allows *H. pylori* to expand its intragastric niche[102], potentially perpetuating the bacterial damage. As AIG progresses, both native oxyntic and/or SPEM-transformed glands might undergo further metaplastic changes, which is marked by the emergence of metaplastic glands co-expressing TFF2 and MUC2, early markers of intestinal commitment[103]. A further definitive intestinal metaplasia is associated with the expression of CDX2, a transcription factor of the ParaHox family, crucial for intestinal organogenesis[104,105]. The mechanisms underlying the development of intestinalized goblet cell-rich glands in AIG are only partially elucidated. The goblet cells, which appear as pale cells with haematoxylin and eosin staining due to the presence of mucin, are hypothesized to originate via an earlier SPEM stage or from the native oxyntic glands[106]. Different variants of intestinal metaplasia have been classified according to their differential expression of sialo-mucins and sulfo-mucins in goblet cells (complete intestinal metaplasia) and

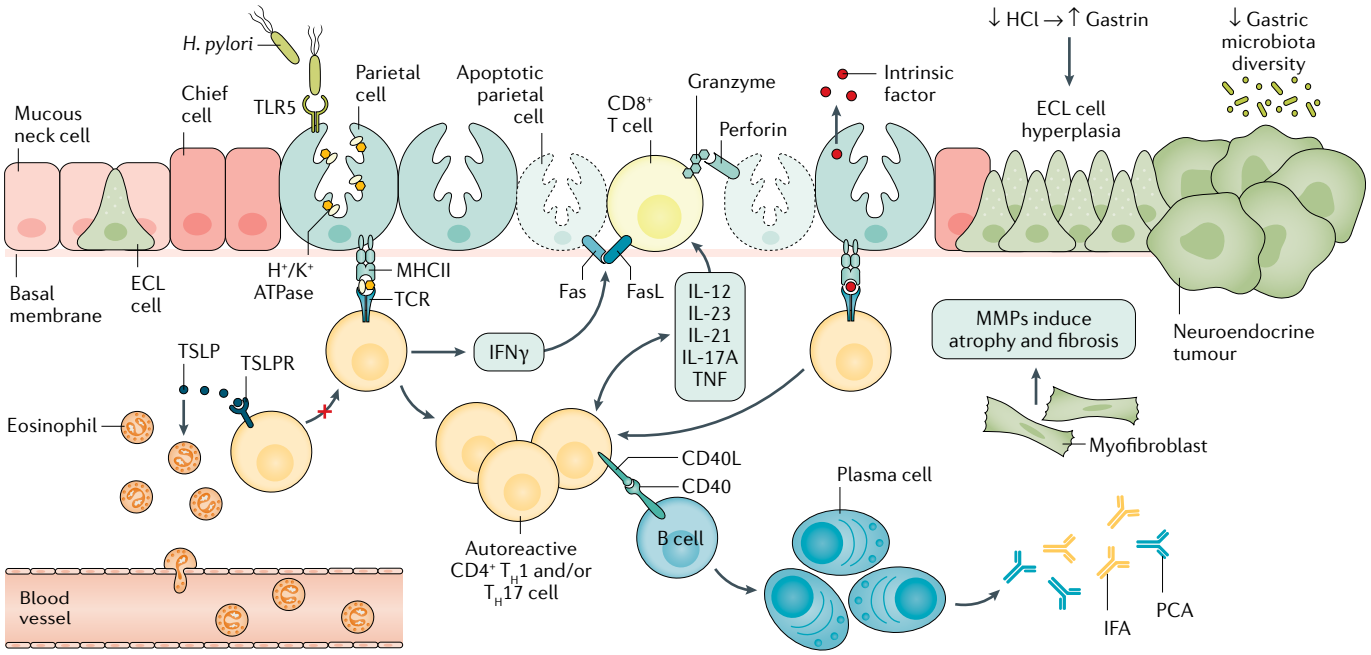

Fig. 3 | **Pathogenetic mechanisms of AIG.** The oxyntic mucosa consists of many cells, including chief cells, mucous neck cells, enterochromaffin-like (ECL) cells and parietal cells. The gastric proton pump, H^+/K^+ ATPase, on parietal cells is the major target autoantigen recognized by anti-parietal cell antibodies (PCAs). PCA targets both the α-subunits and β-subunits of the proton pump. Anti-intrinsic factor antibodies (IFAs) are also found in patients with AIG. A number of pro-inflammatory cytokines are produced by activated autoreactive T cells, amplifying the immune response and favouring parietal cell apoptosis, through a Fas–Fas ligand (FasL) and perforin–granzyme mechanism. The consequent extensive tissue remodelling, possibly sustained by gastric myofibroblasts and conspicuous eosinophil infiltration, can lead to the atrophy of the oxyntic mucosa. *Helicobacter pylori* might promote the autoimmune process (through molecular mimicry) in a subset of patients, especially in those carrying specific toll-like receptors (TLRs), such as TLR5 rs5744174 C-allele. Thymic stromal lymphopoietin (TSLP) seems to negatively regulate the onset of AIG, at least in experimental models. Finally, the achlorhydric state might increase gastrin-17 levels and favour gastric microbiota alterations, that both promote the development of gastric neoplastic lesions, particularly type 1 gastric neuroendocrine tumours (NETs). IFN, interferon; MHC, major histocompatibility complex; MMPs, matrix metalloproteinases; T_H cell, T helper cell; TSLPR, thymic stromal lymphopoietin receptor.

columnar cells (incomplete intestinal metaplasia), respectively[107–111]. Of note, very little is known about the exact prevalence of intestinal metaplasia in patients with AIG at various stages. In patients with AIG with previous or concomitant *H. pylori* infection, atrophic metaplastic lesions might involve both muco-secreting antral glands (*H. pylori*-mediated) and corpus or fundus oxyntic mucosa (immune-mediated). The risk of gastric adenocarcinoma development is higher in such an extensive atrophic setting than in single or pure oxyntic gland-restricted autoimmune damage[112–114].

Immune pathways

The pathogenetic mechanisms that trigger the destruction of parietal cells in AIG are still poorly understood and most of our knowledge originates from preliminary studies involving few patients and findings from experimental AIG animal models[115–125] (BOX 1). The gastric proton pump H^+/K^+ ATPase located on parietal cells is the major target autoantigen recognized by the PCA[126]. The major epitope is located between residues 360 and 525 on the cytosolic side of the secretory membrane[127] and both the α-subunit (100 kDa, catalytic) and β-subunit (60–90 kDa, glycoprotein) are targeted by the PCA[128]. In in vitro studies, PCA demonstrated a complement-dependent cytotoxic activity against gastric parietal cells[129]. However, circulating PCAs alone are unlikely to have a direct pathogenetic role, as has been shown in other studies on experimental AIG (BOX 1). Further, patients with AIG can be PCA-negative[20,130] and, in fact, AIG has also been found in a relatively high proportion of patients with common variable immunodeficiency (an immune disorder characterized by recurrent infections and low immunoglobulin levels), most of whom are PCA-negative[131]. In these patients, cell-mediated immunity is thought to play a major part in the development of AIG and can only be diagnosed by histology. IgG4-producing plasma cells have also been found in the mucosa of patients with AIG, but only in those who had developed pernicious anaemia, without proving a possible pathogenetic effect[132]. Thus, despite being considered the hallmark of autoimmunity in AIG, PCA and IFA seem to have no direct role in the apoptosis of parietal cells in humans and are not constantly present in AIG.

The major pathogenetic role in AIG is instead attributed to autoreactive T helper 1 (T_H1) cells and cytotoxic T cells, which are found in the mucosa of patients with

Box 1 | **Animal models of AIG**

Four different experimental autoimmune gastritis (AIG) mouse models — lymphopenic, non-lymphopenic, transgenic and spontaneous — have been developed[115,116]. In albino BALB/c mice, neonatal thymectomy induces AIG in up to 70% of the mice, but autoimmunity can also be elicited by immunization with gastric mucosal extracts in non-thymectomized mice[115,117,118]. AIG can be induced in 0–77% of mice of different strains, suggesting that different genetic backgrounds might play a role in AIG development[119].

One study investigated the role of anti-parietal cell antibodies (PCAs) in AIG pathogenesis in an experimental model[120]. A group of mice were treated with PCAs from the serum of patients with AIG. The mice demonstrated a marked reduction in parietal cells, with no inflammation in the gastric mucosa. This finding supports the hypothesis that humoral immunity alone is not sufficient to cause AIG in vivo.

Another important milestone in experimental AIG was achieved in a study investigating the role of thymic stromal lymphopoietin (TSLP), a key, epithelium-derived, anti-inflammatory cytokine involved in T cell maturation[121,122]. TSLP receptor-deficient mice had an earlier and more aggressive form of atrophic gastritis, with a predominance of $CD4^+$ T cells and high PCA levels. Hence, TSLP seems to negatively regulate the development of AIG.

Other pro-inflammatory cytokines found to be overexpressed in experimental AIG include TNF, IL-21 and IL-17A[123–125].

AIG[133]. However, the triggers for the expansion of these clones are unknown. According to one landmark study, H^+/K^+ ATPase was able to induce ex vivo proliferation of gastric mucosa $CD4^+$ T cell clones, most of which were T_H1 cells[133] (FIG. 3). Moreover, these cells produced TNF and IFNγ, thereby confirming a typical T_H1 cytokine profile. Autoreactive H^+/K^+ ATPase-specific T cells also trigger immunoglobulin production by B cells. Most of the autoreactive T cells demonstrated perforin-mediated cytotoxicity, directed against H^+/K^+ ATPase-pulsed autologous Epstein–Barr virus-transformed B cells (which act as antigen-presenting cells), and Fas–Fas ligand pathway-mediated apoptosis. Epstein–Barr virus-transformed B cells are commonly used as a model of autologous antigen-presenting cells; hence, they are perfectly suited to studying AIG. A new study focused on the immune response elicited by intrinsic factor in seven patients with pernicious anaemia[134]. Activated autoreactive $CD4^+$ T cells that recognized intrinsic factor were found in the gastric mucosa of patients and most of these cells showed a T_H17 or a T_H1 phenotype and secreted TNF and IL-21. Intrinsic factor was also able to activate cytotoxic T cells against parietal cells. Notably, these autoreactive T cell clones were not found in patients with *H. pylori* infection.

Defective spleen function (hyposplenism), defined by a pitted RBC count of >4%, has been found in 55% of patients with AIG[135]. This might promote or maintain the inflammatory processes underlying AIG. However, this possibility still needs to be confirmed. Similarly, hyposplenism is also implicated to some extent in the pathogenesis of other immune-mediated gastrointestinal conditions, such as coeliac disease and inflammatory bowel disease[136,137].

Role of H. pylori

Studies have shown that up to 30% of individuals with *H. pylori* infection display autoantibodies to the canaliculi of parietal cells. These autoantibodies disappear after eradication of infection. Hence, an association between *H. pylori* infection and development of AIG has been hypothesized. However, whether *H. pylori* can initiate the immunological process leading to the development of AIG remains to be elucidated[138]. According to a study involving four women with AIG and concurrent *H. pylori* infection, in vivo-activated gastric $CD4^+$ T cells from the patients showed cross-reactivity with both H^+/K^+ ATPase and *H. pylori* antigens[139]. More in-depth, biopsy specimens of their gastric mucosa were cultured in IL-2-conditioned medium to expand T cells, which were isolated and cloned. These T cells were then cultured with H^+/K^+ ATPase, *H. pylori* antigens or both. Each clone was retested for proliferation to the individual peptide components of the pool that had induced a high mitogenic index. The study identified nine cross-reactive epitopes belonging to *H. pylori* proteins, which induced T cell in vitro proliferation and expression of a T_H1 profile, possibly via molecular mimicry. This finding might underline two different mechanisms of AIG pathogenesis, one dependent on a pure autoimmune process directed against parietal cells and the other favoured by *H. pylori* infection. Although intriguing, these findings should not be over-interpreted, as only a few patients were included, and do not explain why *H. pylori* infection (active or past) is less common in patients with AIG[20,34].

Moreover, the prevalence of AIG seems to be decreased in geographical areas with a high prevalence of *H. pylori* infection, such as South America and Africa[140]. A Japanese study found an inverse trend between the overall decreased prevalence of *H. pylori* and the increased prevalence of AIG[75]. Furthermore, in a large epidemiological study in Germany, PCA was inversely correlated with anti-*H. pylori* antibodies[141]. Taking these data together, factors other than the infection per se could potentially explain these apparent discrepancies. For example, the demonstration that patients with AIG were more likely to express specific Toll-like receptors (TLRs), such as TLR5 rs5744174 C (cytosine) allele or T (thymine) allele, could explain the different immune responses against *H. pylori* and different susceptibility to the development of gastric cancer[142]. TLRs are proteins that have a key role in immune responses directed against infections, but they have also been implicated in other inflammatory processes and in carcinogenesis. TLRs are primarily expressed on the surface of immune cells, especially macrophages and dendritic cells, but they can also be expressed on other cells, such as lymphocytes and endothelial cells. A number of different TLR C or T variants have been associated with different disorders. In this study, patients with *H. pylori* infection who developed gastric cancer showed the TLR5 T/T genotype more frequently than patients with AIG and no gastric cancer, and both groups showed a trend towards an increased anti-*H. pylori* antibody titre compared with individuals with either C/C or C/T genotypes. The assessment of TLR5 genotypes could be helpful for stratifying patients for the risk of developing gastric cancer.

Bacteria in the gut other than *H. pylori* are also postulated to have a role in AIG pathogenesis, especially in gastric carcinogenesis. A more diverse microbial pattern

was found in patients with AIG than in patients with *H. pylori*-induced atrophic gastritis or in those treated with proton pump inhibitors, but the implication of this finding still needs to be clarified[143].

Achlorhydria and its consequences

The parietal cells have a unique structure and one of the highest densities of mitochondria in the human body owing to the high demand for ATP, used by the proton pump to generate the typical acidic environment found in the stomach during food digestion. The presence of numerous secretory canaliculi provides the parietal cells with a high surface area[144]. Parietal cell function is strictly regulated by both endocrinal and neuronal stimulation via the vagus nerve. The secretion of hydrochloric acid and intrinsic factor is stimulated by histamine, produced by enterochromaffin-like (ECL) cells in the corpus or fundus glands, and by gastrin, secreted by gastrin-producing cells in the antrum. With progressive destruction of parietal cells, hydrochloric acid and intrinsic factor production decreases, alongside a simultaneous progressive hyperplasia of gastrin-producing cells and ECL cells, all of which characterize early stages of AIG. As the disease progresses, the corpus and fundus atrophy becomes extensive, intragastric pH increases (achlorhydria) and ECL cell hyperplasia that was initially linear, becomes micronodular and, in more advanced stages, can advance to type 1 gastric NET.

Lack of gastric acidity in AIG is the key causative factor for abnormal iron absorption[145]. In fact, the reduction of ferric iron to ferrous iron is favoured by an acid environment, which is typically found in a normal stomach. Similarly, other studies have also shown that iron absorption is dependent on normal gastric hydrochloric acid secretion, which is essential for dissolving and reducing dietary iron[146,147]. Iron is mostly stored in the liver and iron stores are usually depleted over a few months in the presence of increased requirement, decreased intake or malabsorption. By contrast, vitamin B_{12} stores in the liver are depleted over several years. Consequently, iron deficiency anaemia manifests earlier than pernicious anaemia.

Other micronutrient deficiencies

Deficiency of several other vitamins and micronutrients in patients with AIG has been reported[148]. However, collectively, present knowledge on the relationship between AIG and vitamin C (ascorbic acid), vitamin D and calcium homeostasis is limited and controversial. Hence, further studies are required to establish the relationship, if any, between AIG and a deficiency of these micronutrients.

The prevalence of vitamin C deficiency in individuals with AIG is unknown. A study of metabolic interrelationships in patients with pernicious anaemia found subnormal plasma ascorbate concentrations before vitamin B_{12} therapy[149]. Low plasma ascorbate concentrations improved following vitamin B_{12} administration and normalization of methylmalonate excretion (a biochemical index indicative of vitamin B_{12} deficiency), which might underlie a potential interconnection between vitamin B_{12} and vitamin C metabolism.

The absorption of calcium begins in the acidic environment of the stomach with the dissolution of calcium salts to form calcium chloride, which further dissociates to Ca^{2+} (REF.[150]). One study reported that the absorption of calcium carbonate and calcium citrate, measured by a modified double-isotope procedure, was lower in patients with achlorhydria than in healthy individuals[151]. However, other studies have found normal calcium absorption in patients with AIG and, therefore, the issue of calcium malabsorption in patients with AIG remains controversial[152].

Additionally, one study found significantly lower 25-hydroxyvitamin D levels in patients with AIG than in patients with non-atrophic gastritis or in the general population[153]. The authors speculated that vitamin D deficiency in AIG might lead to a loss of immune-regulatory and anti-inflammatory functions of 1,25-dihydroxyvitamin D and might be a risk factor in the development of autoimmunity. Finally, studies have found an increased prevalence of hyperparathyroidism secondary to vitamin D deficiency in patients with AIG[76].

Diagnosis, screening and prevention

Clinical features

AIG is usually under-diagnosed; the clinical presentation is usually non-specific and nuanced, which leads to substantial diagnostic delay[20]. Until micronutrient deficiencies manifest, patients might be asymptomatic as most symptoms are mild or might complain of gastrointestinal symptoms, especially dyspepsia, as found in many series[20,34,41,74,154].

Gastrointestinal symptoms. Gastrointestinal symptoms are very common in patients with AIG. Achlorhydria can impair gastric motility and might favour bacterial overgrowth in the small intestine, which, in turn, are responsible for gastrointestinal symptoms[155]. Surprisingly, the presence of dyspepsia is associated with longer AIG diagnostic delay (>24 months), especially if the patient had a previous misdiagnosis of functional dyspepsia[20]. In fact, in patients with dyspeptic symptoms with no alarm features, apart from ruling out *H. pylori* infection with non-invasive tests, no further investigations for the presence of other organic conditions, such as AIG, are performed and the patients remain undiagnosed. Postprandial fullness, early satiety, nausea and weight loss are among the most common symptoms experienced by patients with AIG[20,34,41,154]. To note, the findings in two series indicate that the presence of gastroesophageal reflux disease should not rule out a concomitant diagnosis of AIG[78,156]. Non-acid reflux was found to be the cause of gastroesophageal reflux disease in most patients with AIG.

Haematological manifestations. Anaemia (any type) is the most characteristic feature of AIG that often leads to its diagnosis[157]. Pernicious anaemia is a form of megaloblastic anaemia characterized by vitamin B_{12} deficiency, macro-ovalocytes, anisocytosis, hyper-segmented neutrophils and, in some cases, pancytopenia. Before the onset of overt anaemia, a few haematological alterations can

Macro-ovalocytes
Abnormally large red blood cells.

Anisocytosis
The co-presence of erythrocytes of different sizes in the peripheral blood.

Hyper-segmented neutrophils
Neutrophils presenting more than three nuclear segments.

Pancytopenia
Low levels of haemoglobin, platelets and white blood cells in the peripheral blood.

Mean corpuscular volume
The mean volume of erythrocytes in the peripheral blood.

Paraesthesia
An abnormal sensation that may include a burning, tingling or prickling.

Proprioception
The sense of position and movement of the body.

Ataxia
A condition causing abnormal body movements and loss of coordination.

Hyperhomocysteinaemia
Increased serum levels of homocysteine.

be present, including isolated mean corpuscular volume alterations and/or anisocytosis only[20,34]. Especially in young women in whom menstruation and pregnancy add a strain on nutritional requirements, iron deficiency usually develops years before the depletion of cobalamin stores[14,44]. Patients with combined vitamin B_{12} and iron deficiency, as commonly observed in late stages of AIG, might have dimorphic anaemia, which is usually characterized by normal mean corpuscular volume and anisocytosis. Dimorphic anaemia was found in ~30% of patients with AIG[42]. In pernicious anaemia and iron deficiency anaemia, fatigue and dyspnoea (laboured breathing) may be present. In more severely affected patients, anaemia might precipitate ischaemic heart disease.

Neurological manifestations. Vitamin B_{12} deficiency can cause neurological damage owing to impaired production of succinyl coenzyme A, which is essential for myelin sheath formation[158]. Both the central nervous system and the peripheral nervous system might be affected[159]. Subacute combined degeneration of the dorsal columns of the spinal cord can occur owing to demyelination. From a clinical point of view, patients may complain of a wide variety of symptoms including impaired sensory and peripheral nerve function, paraesthesia, numbness, abnormal proprioception, ataxia, cognitive impairment, mood disorders and frank psychosis (that is, overt psychosis)[20,34,159]. Neurological alterations must be promptly recognized, as they may not be even reversible after supplementation therapy.

Other manifestations. Other infrequent manifestations of AIG include hyperhomocysteinaemia, infertility and recurrent miscarriage. Hyperhomocysteinaemia (a risk factor for atherosclerosis) is another consequence of vitamin B_{12} deficiency in patients with AIG[20,160]. In a small fraction of these patients, ischaemic cardiovascular disease has been reported as the main presenting symptom of AIG[20,160]. Vitamin B_{12} deficiency is a well-established risk factor for infertility, very early recurrent miscarriage (that is, before a gestational sac is observed on ultrasonography), failure of conception with the use of assisted reproductive technologies, pregnancy complications (such as pre-term birth or miscarriage) and neural tube defects[161,162]. Pregnancy outcomes in women with AIG are poorly documented, although data on this topic are emerging[20,21].

Diagnosis

Laboratory diagnosis. A number of laboratory tests are useful for indicating AIG diagnosis and for determining which patients need upper gastrointestinal endoscopy with gastric biopsy for confirmation. Immunofluorescence to identify PCA continues to be used in diagnostic immunology laboratories. Identification of H^+/K^+ ATPase as the target autoantigen has led to the development of an enzyme-linked immunosorbent assay (ELISA) for the detection of PCA[163]. Although an assay sensitivity of 82% and specificity of 90% was initially reported, current studies have shown excellent agreement between ELISA and immunofluorescence (75% for AIG and 100% for pernicious anaemia)[164]. Nonetheless, observational studies have produced discrepant results: ELISA was shown to be ~30% more sensitive than immunofluorescence, and ELISA-positive tests and immunofluorescence-negative tests were both demonstrated to be true positives by immunoblotting with gastric membranes[165].

In a further study involving 165 patients with biopsy-proven AIG and 113 dyspeptic controls, ELISA was used to detect PCA and IFA. PCAs were found in 81% of patients with AIG and in 10% of controls (according to the manufacturer's threshold recommendation), while IFAs were detected in only 27% of patients with AIG. Identifying PCA and IFA in the same individuals significantly increased the diagnostic performance of ELISA, yielding a 73% sensitivity[36]. However, these findings are inconsistent with those of a study assessing the frequency of antibody positivity (PCA and/or IFA) over a 3-year period and the usefulness of IFA in 91 PCA-negative patients with low vitamin B_{12} levels[166]. In this study, IFA had an overall sensitivity of 60% and a specificity of 98% in diagnosing pernicious anaemia and AIG. In a prospective 5-year study involving 208 adults with autoimmune thyroid disease, PCA identified by ELISA predicted the subsequent development of AIG[167]. The analysis revealed a trend in which the autoantibody levels increased progressively over time, peaked and then reduced, following the progressive disappearance of the target autoantigen. However, this trend was not confirmed in a later study; the levels of PCA in patients with AIG did not correlate with the severity of atrophy[23]. In a German study involving the general population (50–74 years of age), PCA positivity was found in ~20% of the individuals[141]. In another study involving the general population in the Canary Islands, the rate of PCA positivity was 7.8%[168]. Further, an Italian study found PCA in 10.3% of healthy blood donors[169]. Hence, some concerns remain over the use of serological screening with PCA without histological confirmation, and this approach alone cannot be used as a diagnostic tool in AIG. In fact, the true diagnostic accuracy of PCA in AIG is not known[170].

PCA prevalence in healthy individuals is dependent on the detection method[169,170]. In different series, 2–9% of healthy adults demonstrated PCA positivity[29,30], and PCA might be found in the serum of individuals with other autoimmune diseases or with multifocal atrophic gastritis[30,36]. Additionally, the sole presence of PCA in the absence of atrophy might potentially represent a very early stage of AIG and, therefore, these individuals should be followed up[23]. In a 5-year prospective study involving 186 patients with T1DM, the association between PCA and low pepsinogen I identified patients with a higher risk of developing vitamin B_{12} deficiency[171]. Currently, a novel luminescent immunoprecipitation system for the detection of PCA has been proposed in patients with AIG[90,172], but its validation in clinical practice is still awaited.

A study suggested that testing for pepsinogen I, pepsinogen II, pepsinogen I to pepsinogen II ratio and gastrin-17 can diagnose any type of atrophic gastritis[173]. These serum biomarker tests are commonly referred to

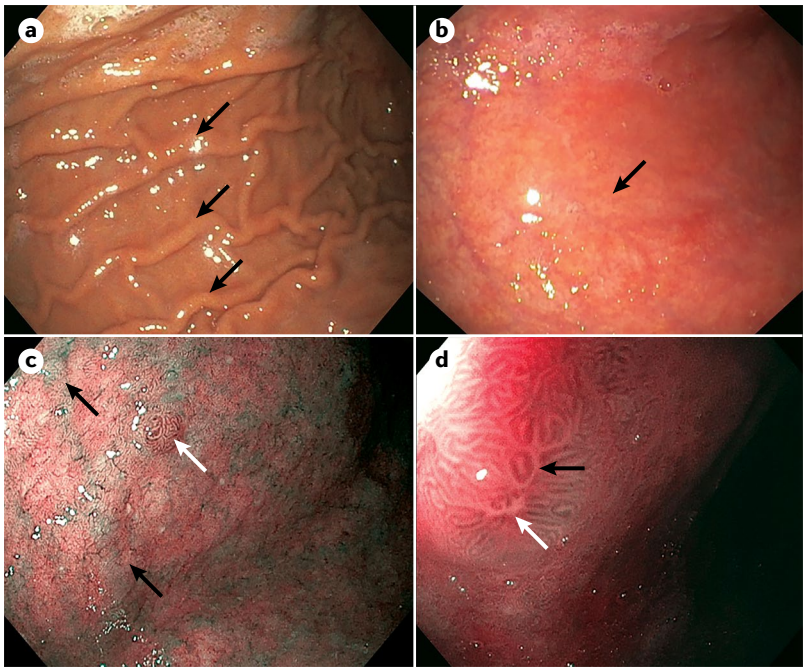

Fig. 4 | **Endoscopic images of the stomach.** High-resolution, white-light, endoscopic images show the gastric corpus (front view; panel **a**) of a normal stomach compared with the gastric corpus (front view; panel **b**) of a patient with overt autoimmune gastritis (AIG); high-resolution, narrow-band imaging (NBI; also known as electronic chromoendoscopy), endoscopic images show the gastric corpus (front view; panel **c**) in a patient with overt AIG and a sessile polyp (a flat polyp that does not have a stalk; Paris classification 0–Is) showing intestinal metaplasia with no dysplasia, compared with a sessile polyp with a central erosion (front view; panel **d**), which turned out to be type 1 gastric neuroendocrine tumour (NET). Of note, gastric folds are easily recognizable in a healthy stomach (black arrows; panel **a**). Typical endoscopic features, that may not be present in all patients with AIG (especially when atrophy is only mild and patchy) include loss of gastric corpus folds showing a flattened mucosa (black arrow; panel **b**) and prominence of vessels (black arrows; panel **c**). Similar features can be seen in the fundus mucosa. Other findings may include diffuse or patchy redness, mucosal swelling and areas of intestinal metaplasia (which are better visualized with chromoendoscopy, white arrow; panel **c**). In this case, the whole polyp surface is covered by a regular, tubulovillous (ridged) pattern, with no vascular alterations. The same pattern can be seen in the polyp shown in panel **d** (black arrow), with the exception of a slightly depressed central area affected by an erosion (white arrow). The presence of polyps in patients with AIG should raise suspicion of a type 1 gastric NET.

as serological gastric biopsy. Pepsinogen I is secreted by chief cells of the oxyntic mucosa, whereas pepsinogen II is produced by the pyloric glands. Hence, pepsinogen I decreases in patients with AIG, whereas pepsinogen II decreases in patients with antral atrophy. Combinations of these tests with antibody to *H. pylori* can also identify exposure to this microorganism. The pepsinogen I to pepsinogen II ratio gave the best sensitivity (96.1%) and negative predictive value (97.7%), pepsinogen I demonstrated the highest specificity (94.6%) and pepsinogen II a high negative predictive value (90.7%) for diagnosing gastric atrophy. However, IgG antibodies against *H. pylori* showed poor sensitivity and specificity (58.8% and 26.5%, respectively) for detecting patients who had been exposed to *H. pylori*. The authors concluded that the pepsinogen I to pepsinogen II ratio is the most suitable single measurement for screening for atrophic gastritis. Concordance between these serum biomarkers and gastric biopsy is very high, although discrimination between antrum versus corpus atrophy might be less accurate[174]. Nevertheless, histopathological analysis is still necessary for confirming the diagnosis of AIG. Serum ghrelin, a hormone mainly produced by endocrine cells of the gastric oxyntic mucosa, is an emergent and promising new biomarker for gastric atrophy. In one study serum ghrelin was associated with the highest sensitivity and specificity (97.3 and 100%, respectively) in detecting gastric atrophy in general and was superior to the pepsinogen I to pepsinogen II ratio and gastrin-17, irrespective of *H. pylori* infection[175].

Finally, a simple, inexpensive laboratory score that takes into consideration haemoglobin levels (1.5 points if <12 g/dl), mean cell volume (1 point if >98 fl) and gastrin-17 levels (4 points if >120 pg/ml) displayed high accuracy (86% sensitivity, 84% specificity) in detecting AIG using a score of ≥2 (REF.[176]). In nearly all patients not taking a proton pump inhibitor and in whom Zollinger–Ellison syndrome (a gastrinoma leading to excessive gastric acid production) is excluded, gastrin-17 level alone can detect patients with AIG, especially in the atrophic stage. Lastly, a marked increase in gastrin-17 level compared with a previously measured level can predict the development of type 1 gastric NET[23].

Endoscopy. Upper gastrointestinal endoscopy is performed to obtain gastric biopsies, which are necessary to establish an accurate diagnosis of gastritis. In the early, non-atrophic or mild-atrophic stage, the gastric mucosa does not display any specific morphological alterations, except for the oxyntic-restricted pattern of the inflammatory lesions, which might not be evident on endoscopic examination. The development of frank atrophy markedly alters the gross mucosal appearance (FIG. 4). The native oxyntic mucosa flattens owing to the progressive loss of its folded pattern and might appear pale with prominent blood vessels. In these patients, gastric samples should be obtained for assessing the presence, grade and aetiology of the gastritis.

Histology. The histopathological spectrum of atrophic lesions includes different characteristic features and grades[5,177,178] (BOX 2). The biopsy protocol suggested by the updated Sydney system recommends two antral biopsy samples, one sample from the incisura angularis and two samples obtained cranially to the pyloric oxyntic border, which allows comparison of histological features across compartments[25].

Biopsy samples obtained from the distal antral mucosa usually do not show inflammatory or atrophic changes. Samples from the incisura angularis usually

Box 2 | **Atrophy in gastric mucosa**

Different subtypes of atrophy may coexist. The final atrophy severity score (grade 0, 1, 2 or 3) assigned to the antrum and corpus is the mean score of the atrophic lesions. Each compartment is scored globally as follows: 1, atrophy covering 1–30% of the area of each biopsy sample; 2, atrophy covering 31–60% of the area of each biopsy sample; and 3, atrophy covering >60% of the area of each biopsy sample.

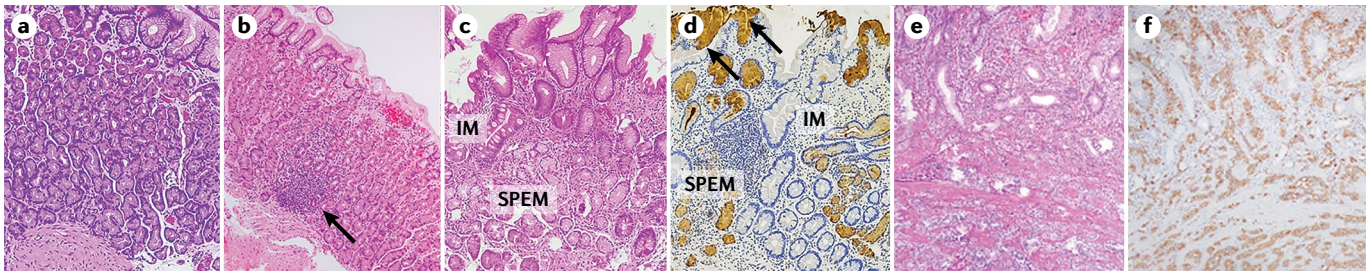

Fig. 5 | **Histopathological spectrum of AIG. a** | Native oxyntic mucosa of a normal stomach. Parietal and chief cells are interspersed in tubular glands. The specimen includes the muscularis mucosa layer (haematoxylin and eosin staining; original magnification ×10). **b** | Non-atrophic autoimmune gastritis (AIG). The inflammatory infiltrate consists of mononuclear cells (lymphocytes that are also organized in nodular structures, coexisting with scattered plasma cells; arrow) expanding the lamina propria. The infiltrate is clearly evident even within the interfoveolar layer. The gland structure is retained, without loss of native glands (haematoxylin and eosin staining; original magnification ×10). **c** | Atrophic-metaplastic AIG. Metaplastic glands have completely replaced the native glandular population, which results in the loss of appropriate glandular units. The metaplastic glands include both subtypes of metaplasia (IM, intestinal metaplasia; SPEM, pseudopyloric metaplasia; haematoxylin and eosin staining; original magnification ×10). **d** | A serial section obtained from the same paraffin-embedded biopsy specimen as panel **c** clearly showing TFF2-immunoreactivity (light brown) in both the superficial foveolar epithelium and the metaplastic epithelium. Of note, intestinal metaplasia-transformed glands do not show TFF2 immunopositivity. As an internal control, the foveolar epithelium shows native TFF2 expression (black arrows; sample shows TFF2 immunostaining; original magnification ×10). **e** | Type 1 gastric neuroendocrine tumour (NET) developing in the gastric corpus mucosa in a patient with AIG with severe atrophy (haematoxylin and eosin staining; original magnification ×100). **f** | A serial section obtained from the same paraffin-embedded biopsy specimen as panel **e** showing type 1 gastric NET, with strong and diffuse chromogranin-A immunopositivity (chromogranin-A immunostaining; original magnification ×100). Parts **e** and **f** images courtesy of F. Capuano and A. Vanoli, IRCCS San Matteo Hospital Foundation, University of Pavia, Italy.

show no prominent lesions if samples are obtained from the mucosecreting antral compartment. Biopsy samples from transitional areas where mucosecreting and oxyntic glands coexist might display inflammatory lesions, including a dense monocytic infiltrate (FIG. 5). Eosinophils and mast cells might be present in variable quantities in the lamina propria in AIG. Scattered neutrophils, usually considered a marker of *H. pylori* infection, are also detectable within the lamina propria and in the dilated glandular lumens in non *H. pylori* gastritis associated witch patchy oxyntic gland destruction[108,110,179]. Although none of these features is disease-specific in a single biopsy specimen, a normal antrum versus an inflamed oxyntic mucosa should point to early-stage AIG. On the contrary, the presence of active gastritis and intestinal metaplasia predominantly involving the antrum is indicative of an *H. pylori* infection[110].

All the inflammatory lesions described in the early stage persist in the florid atrophic stage. The histology pattern, however, is dominated by the advent of the whole spectrum of the atrophic transformation. SPEM is often extensive, intestinal metaplasia becomes increasingly prominent and pancreatic metaplasia may be present (FIG. 5). The restriction of these metaplastic lesions to the oxyntic mucosa further supports the diagnosis of AIG. The atrophic changes may coexist with hyperplastic polyps. Immunohistochemistry may facilitate diagnosis by identifying hyperplastic ECL cells via chromogranin or synaptophysin immunoreactivity. These late-stage lesions mostly coexist with prominent ECL cell hyperplasia, including linear and nodular hyperplasia, or ECL cell dysplasia (that is, true NET).

Distinguishing non-atrophic gastritis from atrophic gastritis results in an earlier identification of the aetiopathogenesis and an appropriate endoscopic follow-up, if needed. Proper follow-up is crucial, as atrophy usually worsens over time and PCA-positive patients with no gastric atrophy (potential AIG) can develop atrophy over time[23]. In addition, other causes of atrophy exist, such as the spread of *H. pylori* from the antral zone to the oxyntic mucosa, resulting in both non-atrophic and atrophic corpus gastritis[180] (TABLE 2). In most of these patients, oxyntic involvement is associated with a similar or more severe inflammation of the antrum (pangastritis). However, in some patients, the inflammation in the antrum might be scarce, generating confusion, and might lead to the suspicion of an autoimmune aetiology. In such patients, a clear diagnosis cannot always be established. Indeed, if multiple aetiologies are present, some features might overlap within the same patient (TABLE 2).

Histopathological classification

AIG diagnosis and classification are based on distinctive histopathological features. Before the discovery of *H. pylori*, early studies classified gastritis into two distinct forms, namely type A and type B. Type A gastritis is characterized by corpus atrophy sparing the antrum, PCA positivity and marked impairment of acid secretion, whereas type B gastritis demonstrates antrum involvement with minor and focal changes in the corpus mucosa, PCA negativity and mild impairment of acid secretion[12]. Following the distinction of type A and type B gastritis, different histopathological classifications were proposed, some of which are still in use[25,181–186] (FIG. 2). For example, the terms type A gastritis, metaplastic atrophic gastritis, autoimmune atrophic gastritis and AIG are often used interchangeably, although the recommendation is to use the currently accepted classifications, namely the updated Sydney system and the Kyoto global consensus[7,25].

The updated Sydney system takes into account different characteristics of gastritis, including topography

Hyperplastic polyps
A type of polyp characterized by little malignant potential.

Table 2 | **Differential diagnosis of AIG**

Features	AIG	HpAG	HpNAG	DG
Clinical characteristics				
Iron deficiency with or without anaemia	++	++	+	+
Vitamin B_{12} deficiency with or without anaemia	++	++	–	–
Postprandial distress syndrome	++	++	+	+
Epigastric pain syndrome	+	+	++	++
Autoimmune comorbidities	++	+	–	–
Serological biomarkers				
Low pepsinogen I	++	++	–	–
High fasting gastrin-17	++	++	–	–
Positivity to anti-parietal cell antibodies	++	+	+	–
Positivity to anti-intrinsic factor antibodies	+	–	–	–
Positivity to anti-*H. pylori* antibodies[a]	–	++	++	–
Endoscopic characteristics				
No endoscopic findings	+	+	+	–
Mucosal erosions or peptic ulcer	–	–	+	++
Reduced gastric juice and/or increased pH	++	+	–	–
Loss of folded pattern of corpus mucosa (flattened corpus mucosa)	++	+	–	–
Pallor of the corpus or fundus mucosa	++	+	–	–
Prominent blood vessels	++	+	–	–
Corpus intestinal metaplasia (chromoendoscopy)	++	++	–	–
Polyps	+	+	+	–
Gastric cancer	+	+	+	–
Type 1 gastric neuroendocrine tumour	++	+	–	–
Histopathological characteristics — corpus mucosa				
Mononuclear cell infiltration	++	++	+	–
Neutrophil infiltration	+	+	+	+
Mucosal atrophy	++	++	–	–
Intestinal metaplasia	++	++	+	–
Pseudopyloric metaplasia	++	+	–	–
Enterochromaffin-like cell hyperplasia	++	+	–	–
H. pylori	–	+	+	–
Histopathological characteristics — antral mucosa				
Mononuclear cell infiltration	–	++	++	–
Neutrophil infiltration	–	+	++	+
Mucosal atrophy	–	++	–	–
Intestinal metaplasia	–	++	+	–
G cell hyperplasia	++	+	–	–
H. pylori	–	++	++	–

Some features may overlap if multiple aetiologies are present in the same patient. ++, commonly associated; +, sometimes associated; –, not associated; AIG, autoimmune gastritis; DG, drug-induced gastropathy; HpAG, *Helicobacter pylori*-related pangastritis (also known as multifocal atrophic gastritis); HpNAG, non-atrophic *H. pylori*-related gastritis (antrum-predominant).
[a]Might be positive even after *H. pylori* eradication, in any type of gastritis.

(antrum or incisura angularis or corpus), morphology (atrophic versus non-atrophic, presence or absence of inflammation, metaplastic or non-metaplastic) and aetiology (autoimmune, *H. pylori* or other causes). A visual analogue scale (normal, mild, moderate and marked alteration) has been proposed for the assessment of the presence of *H. pylori*, degree of neutrophil and mononuclear cell infiltration, degree of atrophy and presence of metaplasia. The location of inflammation and atrophy, along with the presence or absence of *H. pylori*, are used for classifying gastritis and as an indicator of its aetiology. The Operative Link on Gastritis Assessment (OLGA) is

Box 3 | **OLGA classification for gastritis**

The Operative Link on Gastritis Assessment (OLGA) is a tool that stratifies patients according to the risk of developing gastric malignancy. At the level of each single biopsy, atrophy (any subtype) is scored as the percentage of the area affected by atrophy. The 'compartmental score' (0, 1, 2 or 3) is calculated as the average of the scores of the whole set of specimens obtained from the same compartment (specimens obtained from the antrum or angularis incisura versus specimens obtained from the oxyntic mucosa). The stage of gastritis is obtained by summing the atrophy values of the antrum and corpus. In AIG, the antrum is not atrophic by definition.

another scoring system proposed specifically for classifying atrophy[5]. The OLGA score takes into account both antrum and corpus atrophy (BOX 3). The advantage of this scoring system is its ability to stratify patients according to the risk of developing gastric adenocarcinoma; the risk of cancer development is higher for patients with OLGA stage IV. Finally, the Kyoto global consensus had the aim of achieving a global consensus on *H. pylori* gastritis and attempting conceptual changes in overall gastritis classification, also in light of the International Classification of Diseases. According to the Kyoto consensus, the updated Sydney system should still be used for histological diagnosis of gastritis, while proposing at the same time an aetiological classification.

Screening for AIG

The cost-effectiveness of extensive screening programmes for AIG has not been investigated so far. We recommend a proactive case-finding strategy in individuals at high risk of AIG by means of the available laboratory tests. Measurement of PCA and gastrin-17, and the pepsinogen I to pepsinogen II ratio seem to be the most accurate tests for first-line screening of AIG. Screening for PCA alone would miss those patients who are negative for this antibody, whereas gastrin-17 levels are raised in nearly all patients with AIG who have developed overt atrophy[176]. Hence, a combined measure is most likely to be more effective. Individuals at high risk include those with autoimmune diseases, unexplained iron deficiency anaemia, pernicious anaemia, a first-degree family history of AIG, haematological alterations, gastrointestinal complaints, unexplained neuropsychiatric alterations and infertility or recurrent miscarriage. These individuals are likely to benefit from a screening strategy.

Screening for neoplastic changes

AIG predisposes patients to develop both type 1 gastric NET and gastric adenocarcinoma[19]. Persistently increased levels of gastrin-17 is a well-known risk factor for ECL cell hyperplasia, dysplasia and type 1 gastric NET[187]. Additionally, impaired acid secretion probably alters the composition of the gastric microbiota, although their role in gastric carcinogenesis is still debated[188]. *H. pylori* should be eradicated whenever detected[189] as its eradication might decrease the risk of adenocarcinoma[190].

The intragastric distribution of pre-malignant alterations (metaplasia, atrophy and dysplasia) is one determinant of gastric cancer risk. The multifocal pattern described as extensive atrophic gastritis has been associated with the highest risk of gastric cancer, as well as with the presence of intestinal metaplasia[191–193]. Most of the available evidence about gastric cancer risk associated with AIG was obtained in patients with pernicious anaemia and derived from cohort[43,50,51,194–199] and case–control studies[200,201].

The optimal endoscopic follow-up interval of patients with AIG still remains to be defined. One study compared the most effective follow-up interval in patients with AIG by randomly assigning 22 and 20 patients to a 24-month or a 48-month follow-up endoscopy, respectively[202]. Gastric cancer was not found in either group and a 4-year follow-up after diagnosis seemed to be safe and sufficient for early detection of potential neoplastic lesions[202]. According to the revised European MAPS (management of epithelial precancerous conditions and lesions) guidelines, AIG is considered a precancerous condition despite the heterogeneity of current evidence, and the guidelines recommend endoscopic surveillance with histological confirmation at an interval of 3–5 years[203]. In patients with extensive atrophy or intestinal metaplasia and a first-degree family history of gastric cancer, a more frequent follow-up is recommended.

Magnification chromoendoscopy and narrow-band imaging, with or without magnification, have been shown to improve the detection of gastric pre-neoplastic conditions[204,205]. Narrow-band imaging endoscopy can be used to grade gastric intestinal metaplasia, shifting from random biopsies to targeted biopsies of mucosa with a high suspicion of intestinal metaplasia, increasing diagnostic accuracy, with high concordance with gastric histology[204,205].

The cost–benefit profile of a hypothetical endoscopic surveillance programme for AIG has not been evaluated. The costs of surveillance endoscopy were estimated in a cohort of patients with corpus-predominant atrophic gastritis followed up over 7.5 years, showing that 19 surveillance endoscopy examinations every 4 years must be performed to detect one gastric tumour. By restricting surveillance to patients with pernicious anaemia only, a reduction in the cost per lesion would be obtained, while still detecting 74% of neoplasms[206].

Prevention

Strategies to prevent the progression of early-stage AIG to advanced-stage AIG (more severe lesions) are currently unavailable. According to a large study focusing on the natural history of AIG, in all patients mild atrophy progresses to severe atrophy within a median of 3 years from the time of diagnosis[23]. Atrophy regression was never noted. The only available strategy to prevent haematological or neurological symptoms is the early recognition of AIG and proper vitamin B_{12} and iron supplementation.

Management

Micronutrient supplementation is the mainstay of therapy for patients with AIG. Haematological alterations are usually reversible upon treatment but neurological alterations might not be reversible. Management

Chromoendoscopy
An endoscopic technique that uses specific stains (both electronic and dyes) for highlighting mucosal lesions.

Narrow-band imaging
An imaging technique used during endoscopic examinations in which only two wavelengths can be visualized, namely blue light and green light.

of gastrointestinal symptoms is challenging owing to lack of specific therapeutic options for treating these symptoms. According to a position paper dealing with AIG[22], the use of proton pump inhibitors should be discouraged, as evidence for their efficacy in AIG is lacking and they can theoretically worsen ECL cell hyperplasia.

Despite AIG being an immune-mediated condition, no anti-inflammatory, immunosuppressive or biological therapy is available for its treatment, mostly owing to lack of studies testing different drugs. In a study including seven patients with pernicious anaemia, treatment with oral prednisolone for at least 2 months did not result in improvement of gastric lesions[207]. However, one study found a modest effect on mucosal recovery with azathioprine in patients with different types of gastritis[208]. No studies or randomized clinical trials regarding the use of monoclonal antibodies directed against pro-inflammatory cytokines in AIG are available.

Iron supplementation

Iron deficiency anaemia and its treatment have been the subject of several extensive reviews over the past 10 years[209–211]. Oral iron is comparable in efficacy to intravenous iron in the treatment of iron deficiency anaemia associated with a number of clinical conditions[212,213]. A variety of effective oral iron compounds such as ferrous sulfate, ferrous fumarate, ferrous gluconate and ferrous glycine-sulfate, and ferric protein–succinylate, ferric mannitol–ovalbumin and ferric polymaltose complex are available for treating iron deficiency. Slow-release ferrous sulfate preparations offer good bioavailability, effectiveness and acceptable tolerability. Oral iron is better absorbed if taken on an empty stomach, but this may increase gastrointestinal side effects, such as dyspeptic symptoms, abdominal pain, constipation and diarrhoea.

Clinical evidence supporting the use of oral iron therapy before intravenous iron therapy is currently not available, and information on when to switch from one route to the other is lacking. Patients with iron deficiency anaemia showing haemoglobin increases of <1 g/dl at 2 weeks following oral iron supplementation have been suggested to be switched to intravenous treatment[214]. However, in many patients, a test period of 8 weeks may be preferable before switching from oral to intravenous delivery[46]. Iron supplementation also improves quality of life, although the superiority of intravenous iron over oral iron has not been demonstrated in this regard[215]. Patients who fail to respond to oral supplementation require parenteral iron therapy. In patients with AIG, blood transfusion might be required only in exceptional situations, as severe anaemia in these patients is uncommon. Serious hypersensitivity reactions are rare, but potentially life threatening, and may be observed with all iron preparations[216].

Vitamin B_{12} supplementation

In patients with newly diagnosed vitamin B_{12} deficiency, parenteral supplementation is recommended to attain rapid and optimal correction. Rapid replenishment of vitamin B_{12} deficiency is particularly important when neurological symptoms are present. Parenteral vitamin B_{12} can be administered as hydroxocobalamin, cyanocobalamin or methylcobalamin, but commercial availability of the three forms varies among different parts of the world. For maintenance, oral supplementation with cyanocobalamin and parenteral administration can theoretically be equally effective, because oral vitamin B_{12} absorption takes place by simple diffusion through the intestinal wall, but only when high doses of the vitamin are administered. A Cochrane review comparing the effects of oral and intramuscular vitamin B_{12} treatment found low-quality evidence showing that oral and intramuscular vitamin B_{12} have similar effects in normalizing serum vitamin B_{12} levels, although oral treatment costs less[217]. Of note, of all the studies considered in this review, only a few with a small sample size specifically focused on pernicious anaemia and showed clinical benefit only in a fraction of these patients. Oral replacement has been developed as a way of avoiding the discomfort, inconvenience and cost of monthly injections that need to be administered by a nurse[218]. However, oral supplementation requires a strict treatment observance of the patient and high-dose daily intake, which might affect adherence to treatment compared with one injection per month or even fewer administrations. Patients with symptomatic vitamin B_{12} deficiency, especially those with neurological deficits, or with critically low serum levels of vitamin B_{12}, should always be treated with intramuscular vitamin B_{12}. Folic acid supplementation during concomitant vitamin B_{12} deficiency might temporarily revert haematological alterations, but could paradoxically worsen neurological damage via the 'folate trap' mechanism[158]. Vitamin B_{12} and folic acid share a common metabolic pathway and vitamin B_{12} deficiency can reduce methionine synthetase levels, causing a functional folate deficiency by trapping folate as a 5-methyl derivative. Folic acid supplementation would compensate for this functional deficiency, while worsening other vitamin B_{12} deficiency-related manifestations.

Quality of life

Ad hoc studies exploring quality of life in patients with AIG are lacking. The only study reported found that 58% of patients with AIG had an impaired psychological profile, including anxiety and depression[78].

The impact of dyspepsia on quality of life in patients with AIG has never been addressed, although these symptoms may constitute an important burden for these patients, as observed in those with functional dyspepsia who are more likely to experience disruption in their daily activities and have been shown to have poorer mental health, social functioning and health perception[219]. In addition, micronutrient deficiencies and anaemia cause a variety of symptoms such as fatigue, decreased attention, brittle nails, hair loss and impaired wound healing. Pale skin, dyspnoea, tachycardia and headache are common in more severe AIG stages. In the elderly population, chest pain and palpitations can also occur[27,220]. Severe anaemia can also precipitate or cause ischaemic heart disease. If not promptly recognized and treated, these symptoms can substantially

impair patients' quality of life before a confirmed AIG diagnosis.

Neurological symptoms might manifest as a result of demyelination with subsequent vacuolar degeneration and reactive gliosis. The spinal cord is the main region affected by demyelination and atrophy, possibly followed by axonal loss, which may cause spastic paraparesis, ataxic unsteady gait, altered nerve reflexes and visual disturbances[221,222]. Sensory polyneuropathy manifests with symmetric glove-and-stocking numbness, paraesthesia and pins-and-needles sensation[222]. Symptoms due to extrapyramidal or autonomic nervous system impairment (for example, erectile dysfunction and bladder and faecal incontinence) are rare but severely affect quality of life[27,221,222]. Evidence from the literature suggests that vitamin B_{12} deficiency may be associated with the onset of cognitive deficits and memory loss, especially in elderly patients, posing a particular challenge in differential diagnosis with dementia[221]. Finally, psychiatric disorders such as manic and depressive episodes, chronic fatigue syndrome and psychosis, that is, the so-called megaloblastic madness, can frequently be observed[17].

Several studies have shown an association between vitamin B_{12} deficiency and infertility, pregnancy complications and fetal malformations[21,161,162]. Adequate vitamin B_{12} supplementation before pregnancy has been demonstrated to reduce obstetric complications and to improve success of assisted reproduction[162]. Only one case report of infertility and recurrent miscarriage in a woman with AIG has been reported so far[21]. After vitamin B_{12} supplementation, the woman delivered a healthy baby. However, important aspects related to pregnancy and fertility issues in patients with AIG, such as proper micronutrient supplementation, patients' concerns of having a complicated pregnancy or fetal malformations, voluntary childlessness and disease stigmatization have not been studied so far.

Outlook

Despite recent advances in the understanding of this complex and multifaceted condition, many unmet needs and uncertainties still exist, including disease pathogenesis, prevention, treatment and early detection. Although important discoveries and a better characterization of AIG clinical features have been made over the past few decades, our knowledge regarding the fine pathogenetic mechanisms and the aetiology of AIG is still very limited. In particular, the exact trigger of the autoimmune process directed against parietal cells is not known and the potential role of *H. pylori* infection and genetic predisposition are uncertain. Additionally, the exact role of humoral and cell-mediated immune responses in the onset of AIG are not completely clear. Furthermore, the transferability of findings from mouse models of experimental AIG that provide important insights into human AIG seems to be limited and novel animal models of AIG are warranted. For example, contrary to mouse models, a proportion of patients with AIG display no disease-specific autoantibody at any disease stage, which seems paradoxical. Similarly, key cellular players as well as tissue remodelling processes are still unknown. Apart from lifelong micronutrient supplementation, no therapy is currently available for preventing, reverting or at least improving histopathological gastric lesions that usually worsen over time[23,50]. Immunomodulators or biological therapies could be used for targeting key cellular players such as autoreactive T cells and cytokines such as TNF in AIG. However, at this stage, the mechanistic understanding of AIG seems to be more compelling than designing new therapies. The life-threatening complications of AIG support the need for a proper case-finding strategy for early diagnosis. Studies assessing the cost-effectiveness of such a strategy as well as studies investigating the best routes (oral versus parenteral) of micronutrient supplementation, predictors of unfavourable disease course and patients' quality of life are eagerly awaited. Furthermore, early diagnosis is crucial to prevent vitamin B_{12} and iron deficiency-related manifestations and for scheduling a proper endoscopic surveillance. Diagnostic delay has been attributed to both patients' and physicians' unawareness of AIG[20]. Thus, the application of a proactive case-finding strategy, the use of advanced endoscopic techniques, proper gastric biopsy sampling and histopathological evaluation by an expert pathologist are certainly warranted to reduce diagnostic delay, especially in early AIG.

Hence AIG, a common disorder with distinct features, is better managed within a multidisciplinary team involving pathologists, gastroenterologists, internists, oncologists, neurologists and other specialists depending on the clinical manifestations. We envisage that in the near future, AIG will attract more scientific attention to address all the aforementioned unsolved issues.

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Author contributions
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