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Autoimmune gastritis
emerging insights and clinical management

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Introduction

- Autoimmune gastritis

-Chronic, non-self limiting, immune-mediated disorder that affects the oxyntic mucosa of the stomach, leading to progressive atrophy and the disappearance of gastric glands that are replaced by metaplasia

-Destruction of parietal cell → hypochlorhydria → malabsorption of iron, folic acid, calcium, Vit B12

-RE.GA.IN consensus : serologic marker + endoscopic features + histological features

Epidemiology

- Systematic review published in 2025 including 47 studies found a global prevalence of AIG of 3.85%

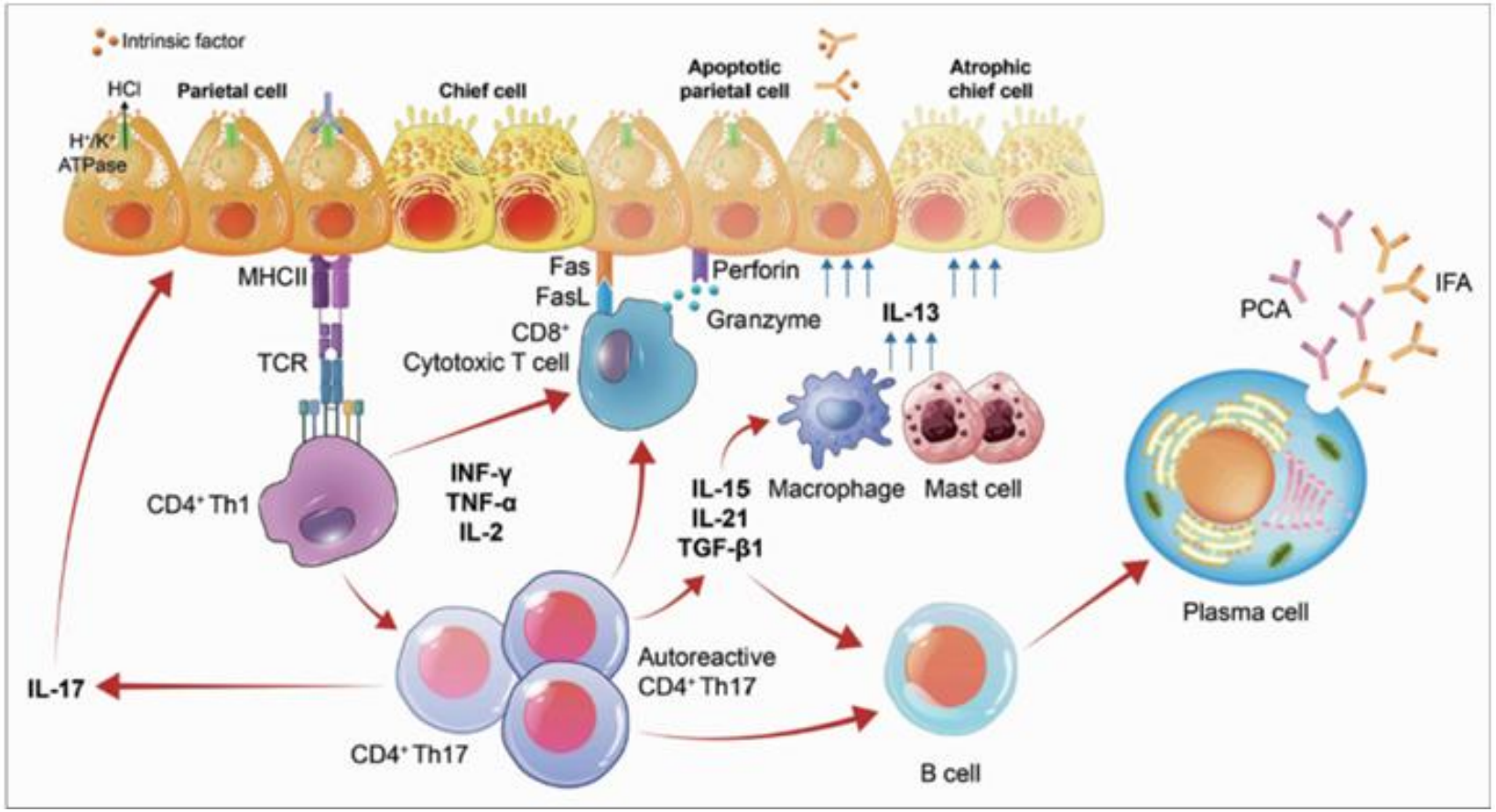
- Several studies based solely on serological antibodies or serological biopsy (pooled prevalence ranging from 3.99 to 7.07% in Europe and 3.17 to 8.0% in Asia, respectively), and others on histology or histology plus serology (pooled prevalence ranging from 2.51 to 3.84% in Europe and 0.88 to 1.26% in Asia, respectively)

- AIG can be found in up to 50% of patients with iron deficiency anemia of unknown origin. Autoimmune thyroid disease, T1DM, vitiligo, Addison disease, autoimmune liver disease and celiac disease are associated with AIG

- In one multicenter pediatric series from the USA, the most common causes of diagnosis were iron deficiency anemia (75%), growth retardation (34%) and autoimmune comorbidities (48.8%), the most common of which were autoimmune thyroid disease and T1DM

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Pathogenesis



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- Conducted in mouse models, especially BALB/c mice undergoing thymectomy
- Parietal cells expressing MHC class II molecules activate $CD4^+$ Th1 cells, which secrete pro-inflammatory cytokines, such as TNF, IFN-γ, and IL-2. The autoreactivity of $CD4^+$ Th1 cells induces proliferation of $CD8^+$ cytotoxic T cells and triggers Fas–Fas ligand pathway-mediated apoptosis and perforin-mediated cytotoxicity in parietal cells
- Macrophages and mast cells secrete IL-13, leading to atrophy of the oxyntic mucosa and intraepithelial metaplasia
- Thymic stromal lymphopoietin (TSLP) has been found to be upregulated in the gastric mucosa of individuals with AIG, possibly as a compensatory response to limit inflammation, owing to its anti-inflammatory properties

Pathogenesis : H. pylori dependent/independent pathway

Table 1 | Proposed pathways of AIG development: *Helicobacter pylori*-dependent versus *H. pylori*-independent

Pathway	Description	Molecular evidence	Clinical evidence
H. pylori-dependent	Hypothesis suggests that *H. pylori* infection might initiate autoimmunity via molecular mimicry; AIG in this context often presents with fewer systemic autoimmune features	Molecular mimicry between *H. pylori* antigens and H^+–K^+ ATPase has been demonstrated; some pro-inflammatory cytokines are found in both *H. pylori*-induced gastritis and in AIG gastric mucosa; pathological lesions in the oxyntic mucosa in patients with AIG and previous *H. pylori* are indistinguishable from those in patients who never had the infection	A varied proportion of patients with AIG had a history of *H. pylori* infection; anti-parietal cell antibodies are present in patients with *H. pylori* infection up to 1 year after eradication; there are fewer autoimmune features in those patients with AIG with *H. pylori* infection
H. pylori-independent	This model represents a pathway independent of *H. pylori*, with direct autoimmune targeting of gastric parietal cells; AIG in the absence of previous *H. pylori* infection is frequently reported and is often characterized by classic autoimmune features	Anti-parietal cell antibodies target the ATPase subunits, which are the major autoantigen in AIG; autoreactive $CD4^+$ T cells are found in the mucosa of patients with AIG, determining the typical atrophic lesions; some HLA, which predisposes to AIG, are shared with other autoimmune diseases, such as autoimmune thyroid disease	Several 'pure' AIG series (i.e., with no previous *H. pylori* infection) have been repeatedly reported; anti-parietal cell antibodies have been found to be less prevalent in patients with previous *H. pylori* infection; AIG has typical autoimmune features (e.g., more common in women, association with several autoimmune comorbidities)

Histopathology : Non atrophic phase

- Potential AIG

-Serological presence of PCA, the gastric mucosa appears non-atrophic and typically lacks evidence of substantial lamina propria inflammation

-Risk of evolving into overt AIG over time, in most patients within 5 years
-Cut-off of more than 7 intraepithelial lymphocytes per 100 epithelial cells was found to be associated with progression into overt AIG

- Early AIG

-Pre-atrophic phase, marked by inflammation of the oxyntic mucosa, characterized by dense, full-thickness or deep lamina propria chronic inflammatory infiltrates, prominent eosinophils in the lamina propria, and parietal cell pseudohypertrophy

Histopathology : Atrophic phase

- Gradual loss of oxyntic glands and the initial development of metaplastic changes and hyperplasia of ECL cells due to hypergastrinemia
- Pseudopyloric metaplasia (also known as spasmolytic polypeptide-expressing metaplasia)99, as well as intestinal and pancreatic metaplasia
- Mucosal atrophy can be graded according to the extent of involvement of the oxyntic mucosa (mild, 1–30%; moderate, 31–60%; severe, >60%)
- Atrophic changes are typically restricted to the oxyntic mucosa. However, the antral mucosa might show G cell hyperplasia, reflecting elevated gastrin serum levels

Histopathology : Complicated phase

- Type1 gastric NET and, more rarely, gastric dysplasia, adenomas and gastric adenocarcinoma

- Type1 NET

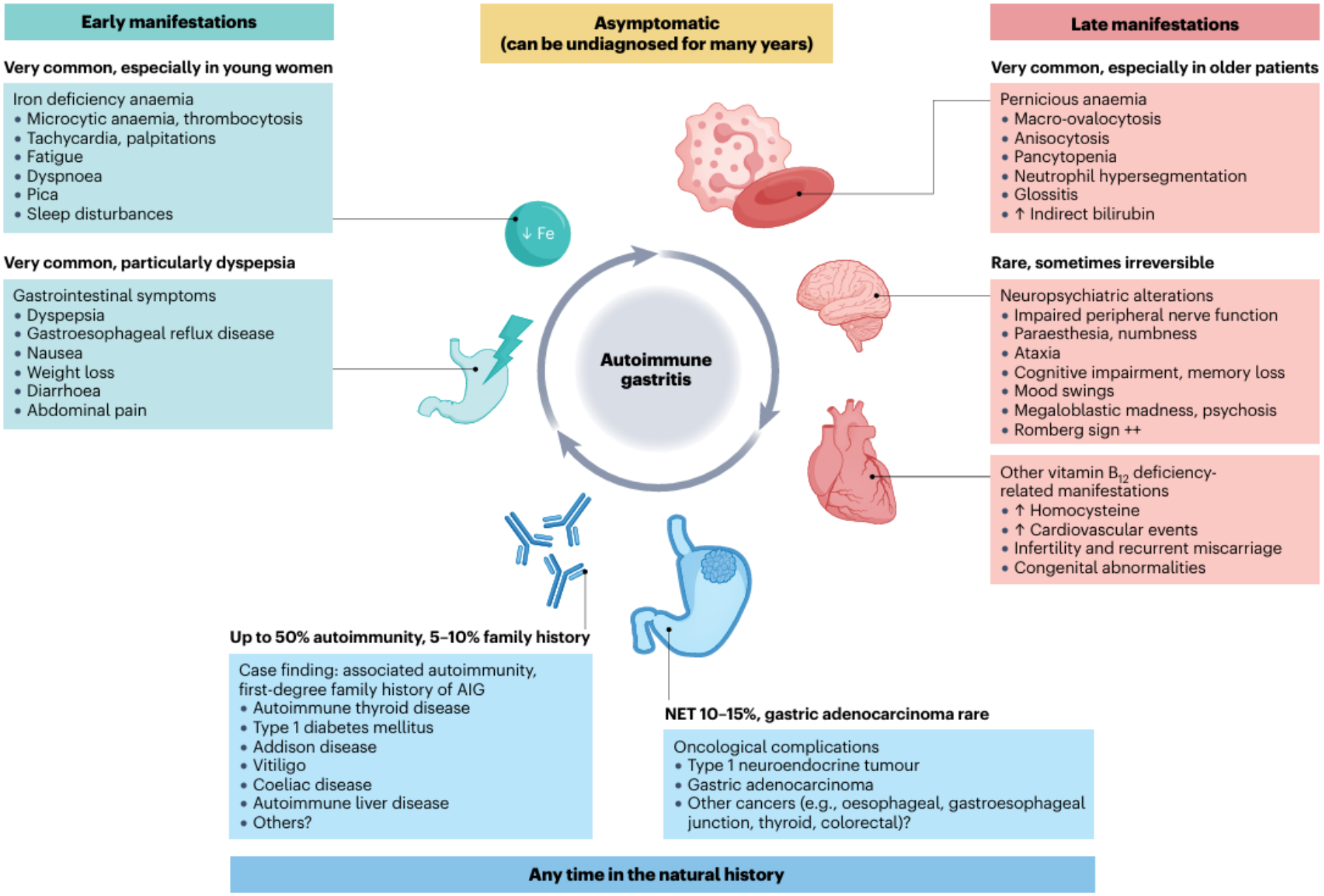
-Indolent clinical course. Most are ≤1.0 cm in size, of low grade and multifocal

- Intestinal-type adenoma, rarely pyloric gland adenoma

- Adenocarcinoma

-Mixed neuroendocrine–non-neuroendocrine neoplasms(MiNEN) or adenocarcinomas with amphicrine features
-Patients with longstanding, previously unrecognized, severe AIG
-Preferential location of AIG-related gastric cancer was found to be the proximal stomach, and distant metastases were rare

Clinical manifestations



Clinical manifestations

Box 1 | 'Red flag' items to raise suspicion of autoimmune gastritis in clinical practice

Neuropsychiatric manifestations

1. Tiredness, fatigue, muscle weakness
2. Difficulty concentrating
3. Foggy mind
4. Problems with balance or vertigo
5. Problems with coordination
6. Difficulty getting up with eyes closed and/or in the dark
7. Memory loss
8. Mood alterations
9. Tingling in the hands and feet (paraesthesia)

Gastrointestinal manifestations

10. Loss of appetite and/or weight loss
11. Diarrhoea
12. Motor digestive disorders (slow digestion, swollen stomach or heaviness, nausea)
13. Ulcer-like digestive disorders (stomach pain)
14. Burning or swollen tongue (glossitis)
15. Gastro-oesophageal reflux (acid regurgitation, pyrosis)

Haematological manifestations

16. Anaemia
17. Shortness of breath (dyspnoea)

Cardiological manifestations

18. Previous ischaemic events (stroke, heart attack, transient ischaemic attack)

Associated autoimmunity

19. Autoimmune thyroid disorders (Hashimoto thyroiditis, Graves disease)
20. Type 1 diabetes mellitus
21. Addison disease
22. Vitiligo
23. Other autoimmune diseases

Fertility issues

24. Infertility, recurrent miscarriage

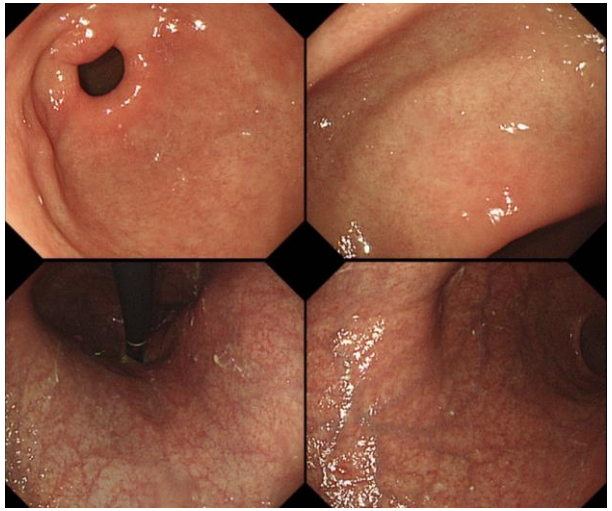
Family history

25. Family history of autoimmune gastritis or pernicious anaemia

As this tool has not yet been validated, there is no specific cut-off value, but all these signs and symptoms, and other characteristics have been reported in this population. Adapted with permission from ref. 134, Elsevier.

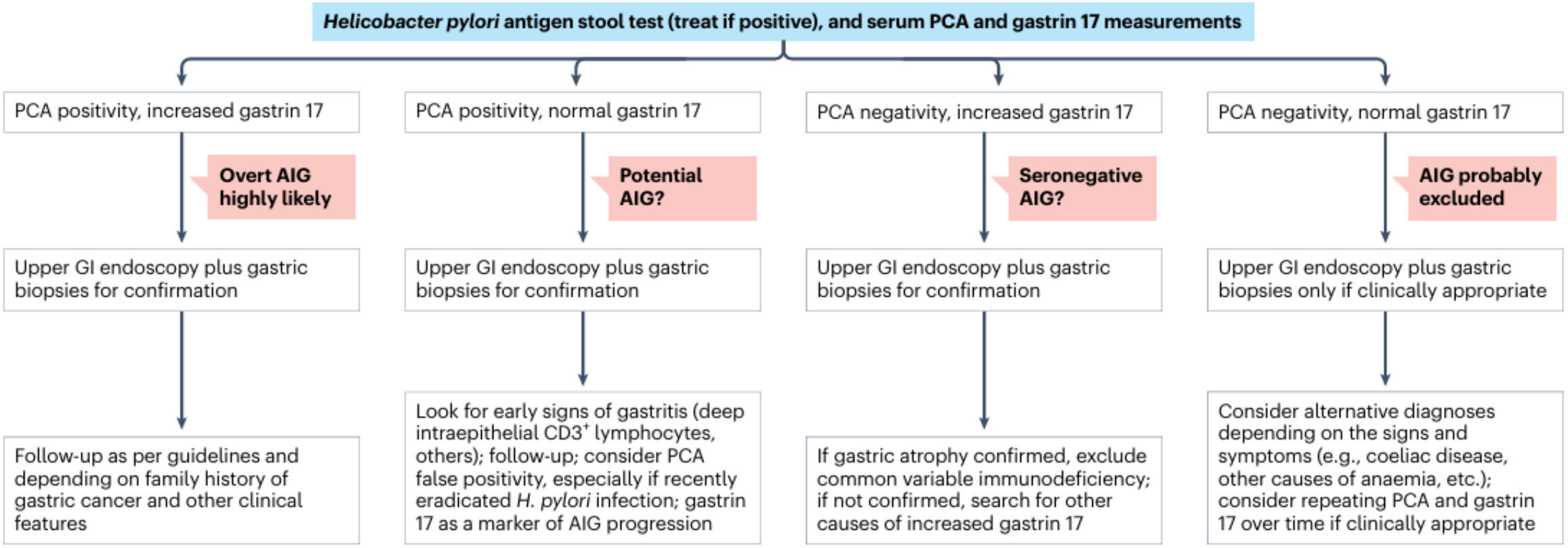
Diagnosis

- RE.GA.IN world consensus : Diagnosed based on serological, endoscopic and histopathological data
- Japanese guidelines require that patients meet either the endoscopic or the histological criteria, in the presence of a positive serology
- PCA is the hallmarker, 80% accuracy with ELISA
- Intrinsic factor autoantibodies are roughly 100% specific but only 20% sensitivity
- GastroPanel : anti-H. pylori antibodies, serum fasting gastrin 17, and pepsinogen I and II.
- Fasting gastrin 17 alone proved accurate in detecting overt AIG and progression from potential to overt AIG, with essentially 100% accuracy, and its serological levels parallel the severity of atrophy
- Patient must be off proton pump inhibitor therapy at the time of blood withdrawal
- Flattening of the gastric corpus/fundus folds, prominent vessels and pale mucosa
- Sydney–Houston criteria : at least two biopsies from the antrum, one from the incisura angularis, and two from the corpus, with additional biopsies for visible mucosal alterations



Endotoday

Diagnosis : PCA, gastrin 17, endoscopy



Clinical management

- Goal of treatment : Supplementation of nutrients, check for accompanied autoimmune diseases, detect for gastric cancer
- Assess : CBC, vitamin B12, folic acid, iron status, vitamin D, calcium, fasting gastrin 17
- Autoimmune diseases : TSH, anti thyroid autoantibodies, celiac disease(anti-tissue transglutaminase IgA, total IgA)
- Recommend PCA test to first-degree relatives

Clinical management : Vitamin B12 deficiency

- Levels below 200 pg/ml are generally indicative of true deficiency; between 200 and 350 pg/ml fall within a diagnostic ‘grey zone’, in which deficiency might still be present

- Main goal is to ensure adequate supplementation of depleted vitamins and minerals, which is also key for preventing complications and improving quality of life. As intrinsic factor is lacking in AIG, vitamin B12 should be supplemented lifelong

- Vitamin B12 should be supplemented parenterally (intramuscular injections) with cyanocobalamin at a dose in the range 1,000–5,000 IU twice or once a week for up to 1 month, followed by one injection of 1,000 IU or 5,000 IU injection every 1 to 3 months, depending on serum vitamin B12 levels.

- Oral supplementation is avoided, in pernicious anemia and neurologic complications

Clinical management : Iron, folic acid, vitamin D, calcium

- Follow the general recommendations for iron deficiency anaemia
- If oral iron is not tolerated or ineffective, intravenous formulations(ferric carboxymaltose) should be considered
- Folic acid, vitamin D and calcium should all be supplemented
- Folic acid should ideally be supplemented alongside vitamin B12 , as these two vitamins work synergistically in DNA synthesis, red blood cell formation and homocysteine metabolism

Clinical management

Box 2 | Practical guidance to follow and mistakes to avoid in the clinical management of autoimmune gastritis

Practical guidance

- Assess cell blood count, vitamins (B_{12}, vitamin D, folic acid) and micronutrients (iron, calcium), and fasting gastrin 17 at diagnosis and regularly.
- An increase in serum fasting gastrin 17 in patients with potential autoimmune gastritis (AIG) can indicate evolution into overt AIG.
- Parietal cell antibodies can be tested once at diagnosis; repeated testing might be appropriate in potential AIG, but has no role in an established diagnosis of overt AIG.
- Screen for associated autoimmunity: autoimmune thyroid diseases (anti-thyroid peroxidase, anti-thyroglobulin, anti-thyroid-stimulating hormone (TSH) receptor), coeliac disease (anti-tissue transglutaminase IgA with reflex total IgA), and other autoimmune conditions based on symptoms and clinical history.
- Recommend that first-degree relatives be tested with anti-parietal cell antibodies.
- Pre-conceptional assessment should ideally be performed to ensure that all vitamins and other micronutrients are properly supplemented.

Mistakes to avoid

- Oral vitamin B_{12} may be less effective in AIG and should not be offered in highly symptomatic patients who require a rapid increase in vitamin levels; the preferred route of vitamin B_{12} administration in AIG is intramuscular.
- When assessing serum vitamin B_{12}, wait at least 1 month after the last injection, as testing sooner can yield falsely elevated results.
- Be careful to supplement folic acid without assessing vitamin B_{12} status, as this can cause neurological complications.
- Proton pump inhibitors should be avoided in AIG, as they might increase the risk of neuroendocrine tumours; in rare cases, such as reflux oesophagitis, Barrett oesophagus or concomitant peptic ulcer, prescription might be necessary, but the risk–benefit profile must be carefully evaluated.
- Although rare, AIG can also occur in children; therefore, AIG should be considered as a cause of anaemia in this population.
- Subtle or single cell blood count alterations, such as isolated macrocytosis or isolated anisocytosis, and mild neurological alterations can occur in early phases of AIG and should not be overlooked.

Surveillance for gastric cancers : Type 1 gastric NET

- Endoscopic surveillance has the aim of early detection of type 1 gastric NETs and gastric adenocarcinoma
- NET incidence rate of 0.83% cases per person-year according to a systematic review
- Endoscopic resection or submucosal dissection, depending on the size
- For staging purposes, EUS is recommended to assess the extent of infiltration and local lymph node involvement for lesions greater than 1 cm
- More advanced imaging (such as CT or MRI) is instead warranted for larger lesions.
- 68Ga-DOTATATE PET is useful to detect very small metastatic lesions, and should be performed in selected patients

Surveillance for gastric cancers : Adenocarcinoma

- Gastric adenocarcinoma can occur especially in older patients (≥65 years old) and in those unaware of having AIG and therefore not under surveillance

- Risk of developing gastric adenocarcinoma seems to be lower than found in older studies that mostly focused only on pernicious anemia, possibly owing to a better awareness of this condition, earlier treatment with vitamin supplementation, and better endoscopic techniques that can identify small mucosal lesions.

- ESGE / EHMSG / ESP (2025) : Every 3 years

- ACG(2025) : insufficient evidence to support routine surveillance

- Authors' conclusion : endoscopic surveillance every 3–5 years, in specialized AIG referral center

Unmet needs and future perspectives

Table 2 | AIG: unmet needs and research priorities

Unmet need	Comments	Research priorities
Standardized diagnostic criteria	Lack of uniform diagnostic definitions and proper nomenclature of the various stages and clinical forms	Establish clear, universally accepted diagnostic guidelines and proper nomenclature
Non-invasive diagnostic tools	Absence of highly accurate biomarker-based tests for early-stage AIG, especially for the seronegative forms	Improve early detection before irreversible damage (atrophy, metaplasia, dysplasia) occurs
Recognition of potential or early disease	Difficult to identify patients before the onset of overt atrophy, anaemia or other symptoms	Better understanding of autoimmune mechanisms and their triggers
Cancer risk stratification	No clear algorithms to determine which patients are at higher risk of gastric cancer or type I neuroendocrine tumours	Define clinical course and risk of progression to gastric neoplasia (e.g., neuroendocrine tumours, adenocarcinoma), also including potential and seronegative AIG
Surveillance guidelines	Although guidelines exist, there is uncertainty around optimal timing and frequency of endoscopic follow-up	Understand associations with other autoimmune disorders (e.g., type 1 diabetes mellitus, thyroiditis, Addison disease)
Management of nutrient deficiencies	Non-standardized approaches to iron, vitamin B_{12} and folate monitoring and replacement	Develop targeted disease-modifying therapies beyond vitamin B_{12} or other micronutrient supplementation
Patient and clinician awareness	AIG remains under-recognized, contributing to diagnostic delay	Clarify prevalence, incidence and global burden
Poor knowledge of paediatric and young-onset disease	There are few and fragmentary data on the characteristics of AIG in this setting	Assess the clinical aspects and outcomes of specific populations, namely paediatric patients, women of childbearing age and ethnic minority groups

Take home message

- AIG is a non-self-limiting, immune-mediated disorder that affects the oxyntic mucosa of the stomach
- Two different pathogenic pathways one related to Helicobacter pylori and one unrelated; these two patient groups might display distinct features.
- Novel forms of the disease have been described, 'potential' AIG and 'seronegative' AIG
- Diagnostic criteria : Serologic test(PCA, gastrin 17) + Endoscopic findings + Histologic findings
- AIG can be asymptomatic or present with a range of manifestations, including hematological, gastrointestinal, neurological, gynecological, oncological and other symptoms
- Endoscopic surveillance in AIG has the aim of early detection of type 1 gastric NETs
- Risk of developing gastric adenocarcinoma remains debated; evidence suggests that there is a risk, but it seems to be low in referral centers
- Treatment of choice are supplementation of nutrients and endoscopic follow up