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Position Paper

Autoimmune gastritis: Diagnosis, clinical management and natural history. A position paper by the Autoimmune gastRitis Italian netwOrk Study grOup (ARIOSO)

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ABSTRACT

Autoimmune atrophic gastritis (AAG) is a non-self-limiting immune-mediated disorder exerting growing interest. The main autoantigen, the beta subunit of the proton pump (*H*+, *K*+-ATPase), is localised on the oxyntic mucosa parietal cells, limiting the autoimmune inflammatory damage to this stomach compartment. Clinical manifestations of AAG may occur late, once corpus-fundus atrophy occurs, and are characterised by loss of gastric acidity, impaired iron and/or cobalamin malabsorption, and increased risk of gastric type 1 neuroendocrine neoplasms and possibly gastric adenocarcinoma. Many topics regarding epidemiology, clinical features, pathogenesis, diagnosis, and management remain to be clarified. AAG patients are frequently misdiagnosed or diagnosed with delay.

AAG still represents a clinical challenge and a great opportunity for advancing our knowledge on gastrointestinal autoimmune diseases and gastric precancerous conditions. The timely and correct diagnosis of AAG patients is clinically relevant to avoid potentially harmful consequences due to micronutrient deficiencies and related anaemia and neoplastic complications.

The current position paper addresses AAG in adults and reflects the views of the Autoimmune gastRitis Italian netwOrk Study grOup (ARIOSO) on its epidemiology, clinical features, pathogenesis, diagnosis, and management.

Improving the understanding of AAG would facilitate timely and accurate diagnosis, enhance clinical management and patients' quality of life, and reduce the economic and social burden of this underrecognized condition.

1. Introduction

Autoimmune atrophic gastritis (AAG) is a non-self-limiting, immune-mediated disorder that has attracted increasing attention in the scientific and medical community in recent years. The main autoantigen has been identified as the proton pump (*H*+, *K*+-ATPase), specifically its beta subunit, localised on the parietal cells

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Table 1
Main characteristics of the participants in the current position paper on autoimmune atrophic gastritis.

Characteristics	Value
Number of participants	11
Age, median (range), years	47 (35–69)
Gender, female (%)	6 (54.5)
Professional experience, median (range), years	22 (6–44)
Academic/hospital position, n (%)	
- department head	2 (18.2)
- full professor	1 (9.1)
- associate professor	5 (45.4)
- biologist PhD	1 (9.1)
- consultant gastroenterologists	2 (18.2)
Research experience >10 years, n (%)	10 (90.9)
University hospital, n (%)	11 (100)

of oxyntic mucosa, limiting the autoimmune inflammatory damage to this stomach compartment, thus sparing the antrum. The clinical manifestations of AAG occur relatively late, once the damage has led to atrophy of the corpus-fundus mucosa combined with pseudopyloric or intestinal metaplasia, and are mainly characterised by impaired gastric acid secretion with loss of gastric acidity, impaired iron and/or cobalamin malabsorption, dyspepsia, and an increased risk of type 1 gastric neuroendocrine neoplasms (t1-gNENs) and gastric cancer (GC), albeit the association with this latter is still debated. As is typical for autoimmune diseases, AAG often presents together with other autoimmune diseases, first of all autoimmune thyroid disease, but also type 1 diabetes, Addison's disease, or others [1,2].

Although the increasing number of studies on AAG over the last few years led to advanced knowledge on this condition, many topics regarding epidemiology, clinical features, pathogenesis, diagnosis, and management remain to be clarified. Patients with AAG are often misdiagnosed or diagnosed with a substantial delay [3]. The timely and correct diagnosis of patients with AAG is clinically relevant to avoid potentially harmful consequences due to micronutrient deficiencies and related anaemia and possible neoplastic complications, to improve quality of life, and to reduce the economic and social burden of this underestimated and often mis- or undiagnosed condition.

The present position paper addresses AAG in adults and reflects the views on this issue of the Autoimmune gastRitis Italian netwOrk Study grOup (ARIOSO).

2. Material and methods

The participants in the current position paper formulated and proposed a list of statements on the most relevant topics related to AAG, focusing on current clinical practice and controversial issues. Table 1 shows the main characteristics of the participants in the current position paper on AAG.

A working party for each topic was created, including two or three participants. A comprehensive literature search on AAG up to March 2025 in the main electronic databases (PubMed, EMBASE, Scopus, Cochrane Library, and Google Scholar) was performed, including: prevalence and incidence, clinical presentation and symptoms, diagnosis, treatment, and follow-up. The search strategy used the MeSH terms "atrophic gastritis", "autoimmune gastritis", "*Helicobacter pylori*", "gastric cancer", "gastric dysplasia", "gastric intestinal metaplasia", "gastric neuroendocrine tumours", and "pernicious anaemia" in various combinations using the Boolean operators AND, OR, and NOT. The literature search was confined to the English language. Letters to the editor, case reports, and meeting abstracts were excluded.

A modified Delphi approach was used to develop and finalise the statements. The statements were shared in two rounds of emails to discuss scientific and clinical relevance, improve clarity and readability, and avoid duplication. They were edited until full agreement among all participants was reached (modified Delphi process) [4]. All participants approved the final draft. Table 2 shows an overview of the included statements. The format of the current position paper is composed of the statements, the evidence level (EL), the recommendation grade (RG), and the summary of evidence. This position paper was drafted according to ACCORD (ACcurate COnsensus Reporting Document) guidelines [4]. However, a formal grading of each statement was omitted, first because this is a position paper, and second because most questions do not follow the PICO framework and do not explore outcomes or interventions but rather address broader clinical questions on AAG.

3. Statements

3.1. Epidemiological and clinical topics

3.1.1. Should AAG be considered a rare disease or restricted to specific geographical areas?

Position statement: AAG should not be considered a rare condition, since it has been described in any population, regardless of sex, age, and ethnicity, with an estimated global prevalence of 3.8 %.

First described by Addison, the epidemiology of AAG has been better defined following the discovery of *Helicobacter pylori* (*H. pylori*), which enabled a distinction between *H. pylori*-associated atrophic gastritis and AAG [1, 5–7]. Before this, most of the studies focused on pernicious anaemia (PA) only, which has been reported to have a prevalence of 2 % in individuals older than 60 years [8]. The global prevalence of biopsy-confirmed AAG has been estimated to be around 0.3–2.7 % [9] to 0.5–4.5 % [1,10]. Further, a recent systematic review on the epidemiology of AAG reported a global prevalence of 3.8 %, though the studies included have a very wide heterogeneity, in some cases reporting a serology-only diagnosis, possibly overestimating this figure [11]. Indeed, this figure may also vary depending on sex (usually more common in females, with an F:M ratio of roughly 2:1), [12,13] age (increasing incidence with increasing age), and geographical area [1]. Most of the studies reporting on its epidemiology were conducted in Europe (especially Italy, Northern Europe, and Turkey) [1,10–17], and therefore it was thought that this condition mainly affected White, Caucasian, and Turkish individuals. However, over the last decades, several series from any part of the world, including, for example, Japan [18], China [19,20], Africa [21,22] and South America [23] have also been reported. It is likely that in some under-represented areas, the true prevalence of AAG is underestimated. According to an Italian study, when applying a serological, extensive screening strategy in an unselected population attending a gastroenterology outpatient clinic, the seroprevalence of AAG was 10.6 %, while the prevalence of biopsy-proven AAG was 4.3 % [24].

3.1.2. Should AAG be considered a synonym of pernicious anaemia (PA)?

Position statement: The term PA should not be used as a synonym of AAG, since PA is only one -usually late- manifestation of AAG.

PA has long been used as an interchangeable term to identify patients with AAG manifesting with a form of megaloblastic, macrocytic anaemia due to vitamin B_{12} (cobalamin) malabsorption and deficiency, sometimes evolving into frank pancytopenia [25]. This has been the most described clinical presentation of AAG [1,8], usually leading to a diagnosis of AAG with no delay [3]. However, with advancing knowledge and diagnostic criteria, several other clinical presentations have been reported (see later). Therefore, this expert consensus discourages using PA as a synonym of

Table 2
Overview of the position paper statements regarding autoimmune gastritis.

3.1. Epidemiological and clinical topics	**Position paper statements**
3.1.1. Should AAG be considered a rare disease or restricted to specific geographical areas?	AAG should not be considered a rare condition, since it has been described in any population, regardless of sex, age, and ethnicity, with an estimated global prevalence of 3.8 %.
3.1.2. Should AAG be considered a synonym of pernicious anaemia?	The term PA should not be used as a synonym of AAG, since PA is only one -usually late- manifestation of AAG.
3.1.3. Should AAG be considered a clinically silent disease?	AAG is characterised by a wide range of clinical presentations beyond gastroenterological and haematological signs and symptoms. Up to 30 % of patients may have no symptoms at the time of diagnosis.
3.1.4 The natural history of AAG: which changes occur over time?	AAG is a progressively worsening condition, where gastric atrophy progresses from a mild to a severe stage in virtually all cases. gNENs have extensively been described as a complication of AAG, occurring in up to 10–15 % of patients. GC may also occur, though less frequently.
3.2. Pathogenetic topics	
3.2.1. What are the main pathogenetic features of AAG?	AAG is characterized by increased lympho-mononuclear infiltration of the oxyntic mucosa and increased production of pro-inflammatory cytokines. Early, pre-atrophic phase is characterized by increase oxyntic mucosa intraepithelial lymphocytosis.
3.2.2. Does *Helicobacter pylori* infection have a role in the pathogenesis of AAG?	In a subset of patients, *H. pylori* infection has a role in the pathogenesis of AAG, likely initiating the autoimmune process leading to the typical pathological lesions. The pathogenetic bases and the disease trigger of another subset of patients, who have never been infected, are unknown.
3.2.3. What role does genetics play in the pathogenesis of AAG?	Some HLA haplotypes have been found to be common in AAG and other autoimmune conditions, but data are scarce.
3.2.4. What role do gastric autoantibodies play in the pathogenesis of AAG?	The role of gastric autoantibodies in causing the atrophic damage of oxyntic mucosa remains to be clarified.
3.3. Diagnostic topics	
3.3.1. Should screening for AAG be applied broadly to the general population, or should it be limited to high-risk individuals?	While AAG screening has clear benefits in high-risk individuals, the available evidence does not support a general population screening strategy. A more targeted approach is cost-effective and clinically justified, probably improving early detection.
3.3.2. Are noninvasive screening tools for AAG in high-risk individuals available and valid?	There is no single absolutely accurate non-invasive test for the diagnosis of AAG. A combination of serum antibodies (PCA, IFA) and other markers (pepsinogens, gastrin-17) have a good overall accuracy of roughly 80 % in addressing AAG diagnosis, that must be confirmed with histology in all cases.
3.3.3. Should a diagnosis of AAG be based on histological evaluation of gastric antrum and corpus biopsies?	The diagnosis of AAG must always be made on histological grounds. A complete evaluation of both antrum and corpus is needed in all cases for classifying the type of gastritis.
3.3.4. Are the endoscopic criteria to establish AAG diagnosis available and valid?	Because the endoscopic appearance of AAG varies with lesion severity and may be nonspecific, no standardized classification allows for diagnosis based solely on endoscopy.
3.3.5. Should active or past *Helicobacter pylori* infection be ruled out in AAG?	The exclusion or confirmation of active or past *H. pylori* infection by histopathology, serology assay of IgG anti-*H. pylori* antibodies, as well as anamnestic data are an essential step in the diagnostic work-up of AAG.
3.3.6. Are the current histological scoring systems (updated Sydney system, OLGA, OLGIM) useful in AAG?	OLGA and OLGIM systems, though considered useful for assessing GC risk, often underestimate AAG severity because they consider antral involvement, which is typically absent in AAG.
3.3.7. Are the current diagnostic criteria for AAG satisfactory?	The current diagnostic criteria for AAG are not entirely satisfactory due to reliance on partially consistent biomarkers, seronegative cases, challenges in histological diagnosis, and inhomogeneity between Eastern and Western countries. A combination of serology, endoscopy, and histopathology should be considered the best approach.
3.4. Management	
3.4.1. Should patients with AAG be treated for concomitant *Helicobacter pylori* infection?	H. pylori infection should be treated in all patients with AAG.
3.4.2. May the treatment of *Helicobacter pylori* infection in patients with AAG modify the natural history or the outcome of the disease?	It is unlikely that *H. pylori* eradication improves gastric lesions that have already developed. However, eradication does reduce mucosal inflammation and may help prevent long-term complications.
3.4.3. Are the proposed eradication regimens valid in AAG?	There are not enough studies to recommend specific treatment regimens for *H. pylori* eradication in AAG, albeit eradication may be yielded without PPIs.
3.4.4. May patients with AAG benefit from endoscopic surveillance for early diagnosis of gastric neoplastic lesions?	There is enough evidence supporting that patients with AAG benefit from endoscopic surveillance for early diagnosis of gastric t1-gNENs or, less commonly, gastric dysplasia or GC. A proper timing and a more granular risk stratification need to be elucidated.
3.4.5. Should surveillance endoscopy in patients with AAG be performed by electronic chromoendoscopy and/or gastric biopsies (random/targeted)?	The optimal surveillance strategy for AAG involves high-definition endoscopy and electronic chromoendoscopy combined with targeted biopsies of abnormal areas and random biopsies from the antrum and corpus.
3.4.6. Is the screening for comorbidities (autoimmune thyroiditis, diabetes, other autoimmune diseases) or associated conditions (iron and/or cobalamin deficiency with or without anaemia) useful in AAG patients	All newly diagnosed AAG patients should be screened for micronutrient deficiencies, anaemia, and other associated autoimmunity, including autoimmune thyroid disease and coeliac disease.
3.4.7. What is the treatment of micronutrient deficiencies in AAG?	Patients with AAG require lifelong supplementation of vitamin B12, preferably via a parenteral route. Folic acid should be supplemented as well, for a synergistic effect with vitamin B12. Other micronutrients, such as iron and vitamin D, should be regularly checked and supplemented if depleted.
3.4.8. Which is the treatment of dyspeptic symptoms in patients with AAG (antisecretory or prokinetic drugs, other agents)?	PPIs should not be routinely offered to patients with AAG, since they may increase the risk of developing neuroendocrine neoplasms. In specific cases, such as gastric bleeding or Barrett's oesophagus, PPI may still be used. There is no solid evidence on the effectiveness and safety of prokinetics or other medications to treat dyspepsia in AAG.

AAG, autoimmune atrophic gastritis, NA, not applicable.
t1-gNENs, type 1 gastric neuroendocrine neoplasms.

AAG, since the clinical spectrum is much broader. Moreover, megaloblastic, macrocytic anaemia also occurs in case of vitamin B_{12} deficiency due to causes other than AAG (e.g., dietary restrictions, previous gastrointestinal surgery, *H. pylori* infection) [26].

3.1.3. Should AAG be considered a clinically silent disease?

Position statement: AAG is characterised by a wide range of clinical presentations beyond gastroenterological and haematological signs and symptoms. Up to 30 % of patients may have no symptoms at the time of diagnosis.

The clinical spectrum of AAG ranges from being completely asymptomatic, to gastrointestinal symptoms (e.g., dyspepsia, abdominal pain, weight loss), neurological abnormalities (e.g., mood alterations, other psychiatric manifestations, paraesthesia, dementia, sometimes irreversible), haematological alterations (e.g., anaemia, both vitamin B_{12}- and iron-deficiency related), fertility issues, cardiovascular manifestations secondary to hyperhomocysteinaemia, and association to other autoimmune diseases (e.g., autoimmune polyglandular syndromes, autoimmune thyroid disease) [1,3,10–15,17,24]. According to the available studies, up to 30 % of AAG patients may be diagnosed in the absence of any symptom [12,15] or in case of nuanced clinical manifestations not reaching the threshold for seeking medical help. It is not known why some patients develop certain manifestations, for example, PA, and not others, such as neurological abnormalities; genetic factors have been suggested to possibly influence clinical manifestations of AAG (see *3.2.3*). Since vitamin B_{12} deficiency takes many years to become clinically evident [26], patients may be asymptomatic for a long time before diagnosing AAG. Serological screening in individuals having a first-degree family history of AAG or having other autoimmune disorders may allow early diagnosis of AAG when still asymptomatic [24,27].

3.1.4. The natural history of AAG: which changes occur over time?

Position statement: AAG is a progressively worsening condition, where gastric atrophy progresses from a mild to a severe stage in virtually all cases. gNENs have extensively been described as a complication of AAG, occurring in up to 10–15 % of patients. GC may also occur, though less frequently.

A few studies on the natural history of AAG have been published over the last years, with a median time of follow-up of roughly ten years, and in some cases, including patients observed for 20 years, including the whole history of AAG, from the potential to the late complicated phase [28–32]. Essentially, all the studies showed that AAG is a progressively worsening condition. Patients with potential autoimmune gastritis, defined as the presence of parietal cell autoantibodies (PCA) in the absence of gastric atrophy, have a risk of developing overt AAG over time, since roughly half of them will develop corpus atrophy within five years of observation, and almost 75 % will develop corpus atrophy over a longer time span [29,32]. In all cases, over time, AAG patients evolve from mild to severe atrophy [29,30] while only a minority develop neoplastic complications, namely t1-gNENs [28–32] and GC [30]. The risk of developing t1-gNENs is well established and consistently reported in all series investigating the natural history of AAG, affecting 10–15 % of AAG patients lifelong [28–32]. Conversely, whether AAG patients are at increased risk of developing GC is still debated [31,33,34]. Most series agree that this risk, if present, is anyway very low or nearly absent in pure AAG; [28,29,31] however, when considering patients who had a previous *H. pylori* infection, [29,34] this risk may significantly increase. Note that the studies about the natural history of AAG were all conducted in tertiary referral centres where endoscopic surveillance is certainly more intensive and may not be extended to the general population.

From a pathogenic point of view, it has been recently shown that AAG patients exhibit cancer-related metaplastic cells, similarly to *H. pylori* gastritis, uniquely expressing ANPEP/CD13 in both cases. [35] This corroborates the hypothesis that AAG may actually evolve into GC, at least in a subset of patients. More prospective studies are needed to clarify this.

3.2. Pathogenetic topics

3.2.1. What are the main pathogenetic features of AAG?

Position statement: AAG is characterized by increased lymphomononuclear infiltration of the oxyntic mucosa and increased production of pro-inflammatory cytokines. Early, pre-atrophic phase is characterized by increase oxyntic mucosa intraepithelial lymphocytosis.

AAG is an inflammatory disorder limited to the gastric corpus-fundus, characterised by the destruction of gastric parietal cells and atrophy of the oxyntic mucosa, which induces intrinsic factor deficiency and hypo-achlorhydria, frequently associated with Basedow-Graves' disease, Hashimoto's thyroiditis and other autoimmune diseases. AAG is characterised by lymphocytic infiltrates (predominantly T cells and plasma cells) in the gastric submucosa and lamina propria, and by the ongoing destruction of parietal and zymogenic cells [1,2]. Key point in AAG is the autoimmune attack mediated by T cells specific for gastric $H+K$+-ATPase and for intrinsic factor and by autoantibodies directed against the gastric H+,K+-ATPase (PCA) and intrinsic factor (IFA). The main drivers of gastric inflammation and pathology in AAG are CD4+ *T* cells specific for H+,K+-ATPase and intrinsic factor. The T cells specific for gastric H+,K+-ATPase and for intrinsic factor induce gastric damage by production of several cytokines, such as IFN-γ, TNF-α and IL-17, by induction of cell death through Fas–Fas ligand-mediated apoptosis, as well as through perforin-mediated cytotoxicity against parietal cells and by helper activity for autoantibody production [1,36]. At immunofluorescence, both IL-7R and TSLP are more expressed in AAG patients [37]. In addition to T cells, CD38+ plasma B cells are more frequent in the lamina propria of AAG patients compared with healthy controls [38].

Clinical studies characterising the very first inflammatory events in patients are lacking. A recent study showed pathological features of potential autoimmune gastritis, defined by PCA positivity in the absence of gastric atrophy; intraepithelial lymphocyte (IEL) infiltration in the gastric corpus of these patients was characterised by deep, CD3+ IEL count. A deep CD3+ IEL cut-off of >7/100 epithelial cells permitted discrimination of any autoimmune gastritis stage and severity (AUC=0.842), thus suggesting an increased deep CD3+ IEL infiltration of the oxyntic mucosa as marker of potential autoimmune gastritis [39].

3.2.2. Does helicobacter pylori infection have a role in the pathogenesis of AAG?

Position statement: In a subset of patients, *H. pylori* infection has a role in the pathogenesis of AAG, likely initiating the autoimmune process leading to the typical pathological lesions. The pathogenetic bases and the disease trigger of another subset of patients, who have never been infected, are unknown.

It has been highlighted that *H. pylori* expresses antigens with epitopes that are structurally similar to epitopes of the gastric autoantigen H+,K+-ATPase resulting in a mechanism of molecular mimicry. It has been clearly demonstrated that in *H. pylori*-infected patients with AAG, the CD4+ *T* helper cells that infiltrate the gastric mucosa cross-recognise the epitopes of self-gastric parietal cell H+,K+-ATPase and of various proteins and, following activation, produce IFN-γ and TNF-α, induce cell death of gastric parietal cells via Fas ligand-mediated-apoptosis and perforin-mediated cytotoxicity, and promote the production of anti-H+,K+-ATPase autoantibodies. Thus, *H. pylori* infection can start or worsen gastric autoimmunity, leading to atrophy [40,41]. Furthermore, *H. pylori*-infected

patients with AAG have circulating autoantibodies against *H+,K+*-ATPase, significantly decreasing after *H. pylori* eradication [42–44].

There are very few studies documenting *H. pylori* in well-characterised patients with AAG. An observational study on consecutive patients with histologically diagnosed corpus-restricted atrophy showed *H. pylori* positivity at histology or serology in 9.8 % and 35.8 % and previous eradication treatment in 3.3 % of patients [30]. A recent multicenter study on AAG patients reported previous *H. pylori* exposure in 27.7 % [14]. In conclusion, a subset of patients with corpus-restricted atrophy consistent with AAG display active *H. pylori* infection or *H. pylori* exposure, supporting the possible role of infection in the pathogenesis of AAG or the possible overlapping or co-presence of gastric autoimmunity and the highly prevalent *H. pylori* infection.

3.2.3. What role does genetics play in the pathogenesis of AAG?

Position statement: Some HLA haplotypes have been found to be common in AAG and other autoimmune conditions, but data are scarce.

Several factors are involved in the genetic predisposition to the development of gastric autoimmunity, such as peculiar MHC class II haplotypes that enable presentation of *H+,K+*-ATPase, intrinsic factor or *H+,K+*-ATPase-*H. pylori* cross-reactive epitopes, as well as genetic factors that favour the survival of autoreactive T cells, breakdown of gastric tolerance, *H. pylori*-induced inflammation with the production of high levels of different cytokines such as IFN-γ, TNF-α, IL-17, as well as factors that promote the ongoing long-lasting activation of Fas ligand and perforin-mediated cytotoxicity against parietal cells [1,37,41].

Conversely, only two studies assessed HLA haplotypes in AAG patients: an Italian study evaluated the prevalence of HLA-DRB1 in 89 patients and showed that more than half carried HLA-DRB1×03 or *04 alleles, typically associated with autoimmune diseases, thus suggesting a genetic predisposition to autoimmunity [45]. Another study on twelve Finnish patients with AAG confirmed that HLA-DRB1×04 and DQB1×03 alleles may predispose to AAG, while HLA-B8-DRB1×03 did not [46]. Another study showed that a polymorphic variant of the transcobalamin 2 (TCN2) gene related to lower vitamin B_{12} levels was more common in patients with PA than controls, suggesting that genetic factors may determine AAG presenting with PA [47].

3.2.4. Which role do gastric autoantibodies play in the pathogenesis of AAG?

Position statement: The role of gastric autoantibodies in causing the atrophic damage of oxyntic mucosa remains to be clarified.

PCA (autoantibodies against *H+,K+*-ATPase) and IFA may theoretically exert gastric damage in patients with AAG via several mechanisms, although this has never been demonstrated in human AAG. Moreover, some AAG patients may have a seronegative disease, pointing at other tissue damage mechanisms. PCA may favour the killing of parietal cells via activation of antibody-dependent cellular cytotoxicity. IFA mainly exert damage via intrinsic factor deficiency, with subsequent deficient absorption of vitamin B_{12} and consequent onset of PA, neurological involvement, and all other clinical sequela related to vitamin B_{12} deficiency [1,44,48].

3.3. Diagnostic topics

3.3.1. Should screening for AAG be applied broadly to the general population, or should it be limited to high-risk individuals?

Position statement: While AAG screening has clear benefits in high-risk individuals, the available evidence does not support a general population screening strategy. A more targeted approach is cost-effective and clinically justified, probably improving early detection.

Screening the general population for AAG would involve substantial healthcare expenditures requiring laboratory tests, endoscopy, and histological evaluations to confirm the diagnosis. While AAG prevalence may be rising—with one case-finding study identifying a prevalence of 15.5 % [24]—the overall clinical prevalence in the general population remains relatively low, ranging from approximately 2 % to 5 % [7,49]. Screening on a broad scale would likely yield a high number of false positive results, leading to unnecessary diagnostic procedures and patient anxiety. The burden on the healthcare infrastructure in managing an extensive screening program could outweigh the potential benefits and the cost-effectiveness of detecting subclinical or early-stage disease in the general population is questionable. While early identification of AAG could prevent long-term complications, the overall yield of such a program may not justify the significant financial and logistical demands on healthcare systems.

Therefore, a more efficient and cost-effective approach is to focus screening on high-risk populations, where the prevalence of AAG is significantly higher [24,27]. These groups include individuals with a family history of autoimmune diseases, those diagnosed with PA, type 1 diabetes, [50] autoimmune thyroiditis, [51] autoimmune polyendocrine syndromes, [52] dyspeptic patients, [53] and individuals with fertility issues, as emerging evidence suggests a possible association [54]. In these populations, AAG prevalence is reported to range from 5 % to 10 %, with early detection being critical to managing complications like PA and gastric malignancies [33].

3.3.2. Are noninvasive screening tools for AAG in high-risk individuals available and valid?

Position statement: There is no single absolutely accurate noninvasive test for the diagnosis of AAG. A combination of serum antibodies (PCA, IFA) and other markers (pepsinogens, gastrin-17) have a good overall accuracy of roughly 80 % in addressing AAG diagnosis, that must be confirmed with histology in all cases.

The diagnosis of AAG is histopathology-based on gastric biopsies taken during gastroscopy. The pre-endoscopic screening with serum markers is fully indicated in patients with clinical suspicion for AAG, such as patients with autoimmune thyroid disease, type 1 diabetes. When one of them turns out positive, gastroscopy with biopsies should be performed to confirm or rule out AAG diagnosis. Instead, patients with a high clinical suspicion for AAG, such as patients with iron-deficiency anaemia not otherwise explained, vitamin B_{12} deficiency, uninvestigated dyspepsia or family history of GC, should promptly undergo gastroscopy with antral and corpus biopsies to confirm or rule out AAG or other disorders by histopathological assessment, while serum markers may be viewed as complementary for AAG diagnosis [27]. This approach is in keeping with the recent RE.GA.IN consensus [7].

Two different groups of noninvasive markers are available, the first one includes serum markers related to gastric autoimmunity, such as PCA and IFA; the second one includes serum markers of the damaged gastric oxyntic mucosa and the consequent impaired gastric acid secretion, such as pepsinogens (PG) and gastrin. The first group is typically associated with AAG, while the second one has been mainly associated with gastric atrophy caused by *H. pylori* infection [1,7,27].

For the assessment of PCA, considered the hallmark of AAG, [1], different ELISA kits showed an 80–100 % sensitivity and a 90–99 % specificity, while IIF showed a 95–99 % sensitivity and a 99 % specificity; however, ELISA kits are preferred because they can quantify the PCA titer [56,57]. A not-yet-commercially-available solution-phase luminescent immunoprecipitation assay LIPS able to separately detect the subunits A and B of PCA (ATP4A and ATP4B), displayed a 100 % sensitivity and a 90 % specificity [58]. Unfortunately, PCA test positive in up to 9 % of healthy people [59,60] and

up to 20 % of patients with *H. pylori*-related non-atrophic or multifocal atrophic gastritis [59]. PCA-positive patients without gastric atrophy were monitored by yearly gastroscopy, and overt AAG occurred in nearly half of them at a median follow-up of two years [32]. PCA positivity may therefore indicate potential autoimmune gastritis, representing a very early stage of gastric autoimmunity. However, the absence of PCA does not rule out AAG, as seronegative AAG has been reported [1,2].

IFAs are generally considered a serum marker of PA [61], showing a 32–37 % sensitivity and 95–100 % specificity [57,58]. Remarkably, IFA positivity was shown in patients with corpus atrophy without PA, and even without vitamin B_{12} deficiency, [57,62] thus probably representing an early marker of PA, years before its clinical onset [26]. The combined assessment of both PCA and IFA may increase the diagnostic reliability [27,57,62].

Increased gastrin levels result from the positive feedback induced by impaired gastric acid secretion [1,2]. The most relevant pitfalls of gastrin assessment are antisecretory drugs such as proton pump inhibitors (PPIs) and active *H. pylori* infection, which may lead to hypergastrinaemia in the absence of corpus atrophy [27]. The outdated original RIA assays have been substituted by commercial ELISA kits [63].

Low PG levels are another serum marker of gastric atrophy: the chief cells of the gastric corpus mucosa produce PGI and PGII, while the pyloric glands of the antral mucosa produce PGII only [64]. Corpus mucosa atrophy with the loss of chief cells gives rise to a linear decrease in serum PGI but not PGII levels, together with a concomitant gradual decrease of the PGI/PGII ratio; a higher GC risk has been observed in cases with a low PGI/PGII ratio [65]. In contrast to gastrin, PG assessment is not influenced by PPIs, while a lower PGI/PGII ratio may reflect mucosal inflammation present in *H. pylori*-related multifocal atrophic gastritis [27]. A meta-analysis on the diagnostic accuracy of PG as a serum marker showed a summary sensitivity and specificity for atrophic gastritis diagnosis of 69 % and 88 % [66]. A systematic review showed the performance of the whole panel test, including gastrin-17, with summary sensitivities and specificities of 70.4 % and 98.4 % for diagnosing corpus-limited atrophic gastritis (AAG) [67]. Another study investigated the diagnostic reliability of gastrin and PG in diagnosing AAG: serum gastrin showed a 83.9 % sensitivity and 93.4 % specificity, PGI a 90.3 % sensitivity and 91 % specificity, and the PGI/PGII ratio a 83.9 % sensitivity and 93.7 % specificity [68].

The expression “serum gastric biopsy” for noninvasive preendoscopic assessment was coined several years ago [69]. By combining PCA and PGI, an 87 % sensitivity and 78 % specificity for AAG were shown [70]. More recently, assessing PCA, IFA, PGI/II, and gastrin-17 ELISAs to assess AAG showed that the PGI/II ratio was the best-performing single marker with a 79 % sensitivity and 90 % specificity with an AUC of 0.90; the combination of PCA and PGI/II obtained a 97 % sensitivity and 78 % specificity with an AUC of 0.93 [71]. In sera of 344 patients investigated by gastroscopy plus biopsies, 44 of whom with AAG, at multivariate analysis, PGI was significantly associated with AAG ($p < 0.001$) [72].

3.3.3. Should a diagnosis of AAG be based on histological evaluation of gastric antrum and corpus biopsies?

Position statement: The diagnosis of AAG must always be made on histological grounds. A complete evaluation of both antrum and corpus is needed in all cases for classifying the type of gastritis.

The diagnosis of AAG should be based on a histological evaluation of both antral and corpus biopsies. An accurate endoscopic examination is essential for patients with suspected AAG [1,2,7,73–77]. This approach helps to distinguish AAG from other forms of chronic gastritis, such as *H. pylori*-associated gastritis, which primarily involves the antrum. Notably, these two conditions can coexist, potentially increasing the risk of GC [1,2,7]. Therefore, obtaining biopsies from all stomach parts allows for a comprehensive evaluation of the gastric mucosa and ensures adequate classification and surveillance. Endoscopic biopsies should be taken according to the updated Sydney system, which includes two samples from the antrum, two biopsies from the body and one from the *incisura angularis* [6] with separate sampling and biopsies of any suspicious regions.

3.3.4. Are endoscopic criteria to establish the diagnosis of AAG available and valid?

Position statement: Because the endoscopic appearance of AAG varies with lesion severity and may be nonspecific, no standardized classification allows for diagnosis based solely on endoscopy.

Endoscopic examination and histopathology play a crucial role in diagnosing AAG, but its independent validity remains a matter of ongoing research. Endoscopic findings in AAG typically include a pale, atrophic gastric mucosa with visible submucosal vessels and loss of gastric folds in the affected area [6,73–75]. However, these findings are not specific to AAG alone, as similar patterns can be seen in other types of atrophic gastritis, such as those caused by *H. pylori* infection. Some studies also described endoscopic features of early-stage AAG and highlighted distinct pictures like a "bamboo joint-like appearance" and "salmon roe-like swelling" of the gastric mucosa, which seem highly specific to early autoimmune gastritis [18]. Another significant endoscopic feature of AAG is the presence of multiple gastric polyps. The recently published AGAPE study highlights the substantial occurrence of gastric polyps in AAG patients, including non-neoplastic polyps such as inflammatory and hyperplastic polyps [78].

More recently, narrow-band imaging (NBI) has been used to improve the detection of gastric intestinal metaplasia in AAG patients, with studies indicating high sensitivity but lower specificity due to overlaps with pseudopyloric metaplasia [79,80]. Again, a novel AI-based endoscopic diagnostic system, SEER-SCOPE AI, has demonstrated expert-level accuracy in distinguishing AAG from other forms of gastritis, suggesting a promising future for improving endoscopic diagnosis [81]. However, despite characteristic endoscopic findings, histopathology remains the gold standard for diagnosing AAG, as non-specific features and overlap with other gastritis types can lead to misdiagnosis [7,27].

3.3.5. Should active or past helicobacter pylori infection be ruled out in AAG?

Position statement: The exclusion or confirmation of active or past *H. pylori* infection by histopathology, serology assay of IgG anti-*H. pylori* antibodies, as well as anamnestic data are an essential step in the diagnostic work-up of AAG.

AAG is considered the prototype of a host-related gastric inflammatory condition, unlike gastric atrophy induced by *H. pylori* infection, which displays an environmental-related condition. The role of past or active *H. pylori* infection in AAG has not been definitively clarified so far. In a subset of AAG patients, *H. pylori* itself may trigger the autoimmune inflammatory process [7]. According to elegant experiments, one reason may be antigen mimicry between proton pump antigens in the parietal cells of the oxyntic mucosa and *H. pylori*-induced antibodies (see *3.2.2.*) [40–44].

A recent multicentre study on nearly 1600 patients with AAG showed some interesting distinguishing features between pure and *H. pylori*-related AAG: compared to *H. pylori*-exposed patients, naïve *H. pylori* AAG patients displayed more frequently 1st-degree family history for AAG ($p = 0.012$), type 1 diabetes ($p = 0.024$), and PA ($p = 0.003$) [14]. Anyhow, the main histopathological feature which distinguishes AAG from *H. pylori*-induced gastric atrophy is a spared antral mucosa [1,7]. A recent study showed that in a subset of corpus atrophic gastritis with concomitant antral gastritis, antral mucosa may heal at long-term follow-up irrespective of

previous *H. pylori* eradication treatment, thus mimicking AAG [82] and making the distinction between primary and secondary AAG challenging. This finding conflicts with the concept that the hallmark of *H. pylori* "naïve" gastritis is represented by a spared antral mucosa [7].

Albeit the mechanisms leading to gastric carcinogenesis are highly complex and multifactorial, one of the leading causes of GC is represented by *H. pylori* infection. The most frequent clinical-histological background in which GC of the intestinal type develops is gastric atrophy extended to the corpus mucosa with intestinal metaplasia, according to the multistep cascade proposed by Correa, which was afterwards confirmed by longitudinal studies [7,83]. GC cancer risk is well established in *H. pylori*-related multifocal atrophic gastritis, while in AAG, this risk is still under debate [1,7]. One crucial point to better define GC risk in AAG patients is to thoroughly rule out the confounding role of *H. pylori* infection, whose presence is difficult to determine in AAG due to the altered intragastric environment, making it difficult to dissect between *H. pylori* or gastric autoimmunity itself as a possible initiator of gastric carcinogenesis [82,84]. In advanced corpus atrophic gastritis, the histopathological detection of *H. pylori* is challenging. Routinely available noninvasive tests for the diagnosis of *H. pylori* infection (serology, urea breath test, stool antigen tests) may not be reliable [85].

3.3.6. Are the current histological scoring systems (updated sydney system, OLGA, OLGIM) useful in AAG?

Position statement: OLGA and OLGIM systems, though considered useful for assessing GC risk, often underestimate AAG severity because they consider antral involvement, which is typically absent in AAG.

The current histological scoring systems are useful in evaluating AAG, but have some limitations.

These systems comprise the updated Sydney System, for gastritis classification, assessing inflammation, atrophy, and intestinal metaplasia, and the OLGA (Operative Link on Gastritis Assessment) and OLGIM (Operative Link on Gastric Intestinal Metaplasia Assessment) grading systems for risk stratification of GC by assessing atrophic gastritis and intestinal metaplasia severity.

The updated Sydney System remains the foundation for histological diagnosis, but its reproducibility is sometimes challenged by interobserver variability, particularly in atrophy and inflammation grading [1,6,7]. The grading of atrophy and chronic inflammation shows low to moderate agreement among pathologists, with only substantial interobserver agreement for atrophy (κ = 0.31–0.6) [86]. In contrast, intestinal metaplasia has a higher agreement (kappa = 0.62–0.9), likely due to its well-defined histological features [87].

OLGA and OLGIM staging systems are widely accepted for risk stratification of GC by assessing atrophic gastritis and intestinal metaplasia severity [88]. They allow the identification of high-risk patients with extensive gastric atrophy and/or intestinal metaplasia who need endoscopic surveillance.

However, OLGA and OLGIM staging systems do not typically reach high stages in AAG because this condition predominantly affects the gastric corpus while sparing the antrum. Since these staging systems combine atrophic changes observed in both the corpus and antrum, AAG cases tend to be classified as low-risk (stages I–II) rather than high-risk (stages III–IV). This is because the absence of significant atrophy in the antrum reduces the overall staging score, potentially underestimating the severity of corpus-restricted atrophy. Consequently, while OLGA and OLGIM remain useful for assessing GC risk in multifocal atrophic gastritis, their application in AAG is limited [7].

3.3.7. Are the current diagnostic criteria for AAG satisfactory?

Position statement: The current diagnostic criteria for AAG are not entirely satisfactory due to reliance on partially consistent biomarkers, seronegative cases, challenges in histological diagnosis, and inhomogeneity between Eastern and Western countries. A combination of serology, endoscopy, and histopathology should be considered the best approach.

The current diagnostic criteria for AAG present several challenges and limitations. Indeed, the existing histologic, serologic, and biochemical methods are helpful, but not entirely satisfactory (see *3.3.2.* and *3.3.6.*). AAG diagnosis is complex due to its possible overlap with *H. pylori*-related atrophic gastritis, and no universally accepted diagnostic criteria exist. The hallmark of histopathology-based diagnosis of AAG is a spared antral mucosa, and it has been stated that a spared antral mucosa is the most reliable marker to exclude *H. pylori* [7]. A recent study questioned this concept, showing that, in multifocal atrophic gastritis, antral mucosa, even when atrophic, may heal over time, mimicking AAG, making it hard to distinguish between primary and secondary AAG [82].

PCA and IFA are typical markers of AAG but are not always present and, according to current standards in Western countries, they are not necessary for AAG diagnosis. [1,7], even if American and British guidelines suggest their assessment to support the diagnosis of AAG [75,76]. In contrast, in Eastern countries, according to commonly applied Japanese diagnostic criteria, patients are considered compatible with AAG if they meet (i) either the endoscopic and/or histopathological findings, and (ii) PCA or IFA positivity [80].

Approximately 20 % of patients with AAG are seronegative at the time of histological diagnosis, especially in later stages of the disease and at older age [27,89]. As the disease progresses, the destruction of parietal cells may become so extensive that the immune system no longer reacts, leading to a natural decline or disappearance of PCA over time, and, in elderly individuals, immune system changes and the prolonged course of the disease may also contribute to seronegativity, making reliance on antibody testing alone insufficient for diagnosis.

The gold standard for AAG diagnosis remains histopathological confirmation from gastric biopsies, as per the RE.GA.IN consensus [7]. Still, early-stage changes may not always be evident, the biopsy site may not be clearly specified, the sampling may be inadequate, or it may not have been performed according to the updated Sydney protocol [75,90]. Eosinophil infiltration has been proposed as a potential diagnostic marker, especially when the biopsy site and/or clinical history is uncertain, [91] and in children [92].

Regarding noninvasive tests, serological biomarker panels like GastroPanel® show promise for early screening but need further validation, as previous studies mainly focused on multifocal atrophic gastritis rather than AAG (see *3.3.2*) [27,55]. A proposed biochemical score combining markers like vitamin B_{12}, haemoglobin, gastrin, and chromogranin A has shown good accuracy, but further validation is required [93].

3.4. Management

3.4.1. Should patients with AAG be treated for concomitant H. pylori infection?

Position statement: *H. pylori* infection should be treated in all patients with AAG.

H. pylori has been classified as a type I carcinogen by the WHO - International Agency for Research on Cancer [7,94]. The risk of developing GC is three- to six-fold higher in infected patients, and it is significantly reduced following bacterial eradication [95]. A metaanalysis of RCTs demonstrated that patients receiving eradication therapy had a lower risk of developing GC (RR 0.54, 95 % CI

0.40–0.72) and a reduction in GC-related mortality (RR 0.61, 95 % CI 0.40–0.92) [96].

Whether *H. pylori* can initiate the immunological process leading to the development of AAG remains to be definitively proven, as discussed [1,41,97]. *H. pylori* infection may be responsible for an increased neoplastic risk in patients with AAG. Early studies reported an increased GC risk associated with AAG in cohorts of subjects with unknown concurrent (in the pre-*H. pylori* era) or previous (in patients that cleared the bacteria) *H. pylori* infection. Due to this mixed aetiology, these cohorts were inadequate to provide accurate information on the risk of GC in patients with AAG. A recently published, long-term prospective study evaluated GC risk in 211 pure AAG patients demonstrated only five cases of low-grade epithelial dysplasia, and no cases of high-grade dysplasia or invasive GC after a cumulative follow-up time of 10,541 person-years [31]. The virtually absent risk of GC has been confirmed by other authors [29], while in prospective single-centre and retrospective multicenter studies, the estimated risk of GC in patients with AAG, although different from zero, has been reported as low [14,30]. According to the available evidence, we cannot exclude the occurrence of GC in patients with AAG without previous or concurrent *H. pylori* infection, even though this risk is low. The multifocal pattern (described as extensive atrophic gastritis) and the presence of intestinal metaplasia, have been associated with the highest risk of GC [74–76,98,99]. In AAG patients and 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 GC development is higher in such an extensive atrophic setting than in single or pure oxyntic gland-restricted autoimmune damage. (100). Therefore, in patients with AAG and concurrent *H. pylori* infection, the eradication of the infection is mandatory in order to prevent the progression of damage and the possible development of GC [7].

Dimorphic anaemia, characterised by normal mean corpuscular volume and anisocytosis and caused by a combined iron and vitamin B_{12} anaemia, is common (30 % of patients) in late stages of AAG. (101). Iron-deficiency anaemia and vitamin B_{12} deficiency can also be related to *H. pylori* infection [94]. Therefore, in AAG, eradication of *H. pylori* is also suggested to eliminate its contribution to iron and vitamin B_{12} deficiency.

3.4.2. May the treatment of H. pylori infection in patients with AAG modify the natural history or the outcome of the disease?

Position statement: It is unlikely that *H. pylori* eradication improves gastric lesions that have already developed. However, eradication does reduce mucosal inflammation and may help prevent long-term complications.

Patients with AAG carry an increased risk of developing GC and t1-gNENs [1,2,8]. While the risk of GC in AAG is low according to the most recent available evidence [13,29–31], t1-gNENs are observed in 4–12 % of patients undergoing endoscopic and histologic surveillance [1].

Gastric carcinogenesis is a multistep process, in which gastric atrophy and intestinal metaplasia represent precancerous conditions [83]. Even in AAG patients, infection with *H. pylori* represents an additional stimulus to chronic inflammation on the gastric mucosa that contributes to the development of chronic atrophic gastritis, intestinal metaplasia, and GC. Therefore, it is reasonable to assume that bacterial eradication may be a preventive strategy that induces the regression of these conditions [7,83,94]. Keeping in mind that the search of *H. pylori* infection with noninvasive tests (urea breath test or stool antigen test) may not be reliable in corpus-involving chronic atrophic gastritis with reduced gastric acid secretion, [85] the infection should be eradicated whenever detected [83,102]. However, once chronic atrophic gastritis and intestinal metaplasia are established, their reversibility by *H. pylori* eradication remains controversial. A metaanalysis evaluating the role of *H. pylori* eradication in preventing GC showed that curing the infection has long-term beneficial effects on gastric atrophy, but less or not at all on intestinal metaplasia. (103–105) Therefore, intestinal metaplasia is not reversible or reversible to a much lesser extent following *H. pylori* eradication, as it probably represents the "point of no return" in the gastric carcinogenetic cascade. Despite the theoretical irreversibility of chronic atrophic gastritis with intestinal metaplasia, curing *H. pylori* is suggested even in these patients, aiming to reduce its progression.

Persistently increased levels of gastrin-17 are a well-known risk factor for enterochromaffin-like (ECL) cell hyperplasia, dysplasia and gastric t1-gNENs. (106) In the natural history of AAG, a progression from linear and nodular ECL-cells hyperplasia to adenomatoid hyperplasia/dysplasia, as well as gastric t1-gNENs, mostly occurs in patients with extensive oxyntic mucosa atrophy [30,31]. The association between oxyntic atrophy and adenomatoid hyperplasia and t1-gNENs is well established, as is the predictive value of adenomatoid hyperplasia/dysplasia in the development of t1-gNENs [1,107]. By contrast, *H. pylori* infection does not have a direct role in the development of t1-gNENs. A recently published multicenter retrospective study demonstrated that gastric t1-gNENs developed in 10.1 % of patients with *H. pylori*-naïve and in 8.1 % of *H. pylori*-exposed AAG patients (adjusted HR 0.74, 95 % CI 0.41–1.35) [14]. A previous study showed that the cure of *H. pylori* infection in patients with atrophic gastritis may reverse some negative consequences on acid secretion and body ECL cell hyperplasia, with more than half of patients showing reduced ECL cell hyperplasia after histologically documented cure of infection. (108) Whether this may impact gastric t1-gNENs development remains to be proven. Considering the lack of a direct association between *H. pylori* infection and t1-gNENs in AAG, it is reasonable to conclude that the infection and its eradication do not substantially influence the outcome of the disease in terms of t1-gNENs development.

3.4.3. Are the proposed eradication regimens valid in AAG?

Position statement: There are not enough studies to recommend specific treatment regimens for *H. pylori* eradication in AAG, albeit eradication may be yielded without PPIs.

Treatment regimens to eradicate *H. pylori* infection are commonly bismuth-based and less frequently sequential or hybrid. (109–111) RCTs found that classical bismuth quadruple therapies combining bismuth with metronidazole, tetracycline, and proton pump inhibitors (PPIs) are more effective in eradicating *H. pylori* infection than triple therapies. (112,113) The intrinsic drawbacks related to the multi-pill administration have been overcome since a single-pill bismuth-based therapy (SPBT) is available, showing high efficacy not only in clinical trials, but also in clinical practice. (109)

Previous studies on the efficacy of eradication regimens were not specifically conducted on patients with AAG. This disorder is characterised by impaired gastric acid secretion and increased intragastric pH, making the use of PPIs questionable. (114) A recent study assessed in 76 patients with corpus atrophic gastritis and histologically proven *H. pylori* positivity the tolerability and efficacy of modified eradication regimens without using PPIs as first-line treatment of *H. pylori* infection. Concomitant or sequential amoxicillin-based therapy (ABT, $n = 30$) and single-pill bismuth treatment (SPBT; $n = 46$) were prescribed without PPIs. An overall eradication rate of 90.1 %, 95 %CI 69.4 %–115.1 % was obtained, and was higher for SPBT than ABT (97.7 %, 95 %CI 70.4 %–132.0 % vs 78.6 %, 95 %CI 49.2 %–118.9 %, $p = 0.013$), thus showing that in patients with corpus atrophic gastritis, cure of *H. pylori* infection can be yielded in >90 % without using PPIs. (115)

3.4.4. May patients with AAG benefit from endoscopic surveillance for early diagnosis of gastric neoplastic lesions?

Position statement: There is enough evidence supporting that patients with AAG benefit from endoscopic surveillance for early diagnosis of gastric t1-gNENs or, less commonly, gastric dysplasia or GC. A proper timing and a more granular risk stratification need to be elucidated.

As stated above, patients with AAG carry an increased risk of developing gastric t1-gNENs and GC [1,2]. Recent prospective studies on histologically proven patients with AAG or corpus-restricted gastritis consistently confirm the increased risk of gastric t1-gNENs, while evidence of increased GC risk is still conflicting. At follow-up ranging from 4.3 to 7 years, two studies [29,31] reported five and 14 cases with incident low-grade dysplasia, two studies [29,30] four and one cases with incident high-grade dysplasia, and one study [30] observed six patients with incident GC. In a retrospective multicenter study, the estimated risk of GC in patients with AAG has been reported as very low, although higher than zero [14]. These diverging results may be due to the different proportions of included patients with *H. pylori*-related AAG, as *H. pylori* infection was excluded in two studies. In contrast, one study did not exclude patients with active or previous *H. pylori* infection but showed that none of the incident GC of high-grade dysplasia occurred in patients with evidence of *H. pylori* and only two low-grade dysplasia were found in *H. pylori* positives. However, as observed in other inflammatory cancers where chronic inflammation may progress to cancer over time once a certain threshold of damage has been established, the longstanding inflammatory damage of corpus atrophy and even more of intestinal metaplasia may progress to neoplastic complications irrespective of the initial trigger.

Nevertheless, the most recent European guidelines recommend that patients with AAG should receive high-quality endoscopic follow-up every three years for early detection of gastric t1-gNENs and GC [74]. Current American guidelines, instead, state that the optimal surveillance for patients with AAG is still unclear and the interval of endoscopic surveillance should be patient-based, considering individualised assessment and shared decision making [75]. The British guidelines do not give specific surveillance indications for AAG, limiting the indication of surveillance every three years to patients with extensive atrophy and/or intestinal metaplasia, but, notably, they consider PA amongst the stronger risk factors for GC [76]. However, it should be borne in mind that in patients with a first-degree family history for GC or persistent *H. pylori* infection, endoscopic surveillance should be considered every one to two years.

3.4.5. Should surveillance endoscopy in patients with AAG be performed by electronic chromoendoscopy and/or gastric biopsies (random/targeted)?

Position statement: The optimal surveillance strategy for AAG involves high-definition endoscopy and electronic chromoendoscopy combined with targeted biopsies of abnormal areas and random biopsies from the antrum and corpus.

Endoscopically, AAG is particularly challenging to distinguish from healthy mucosa, especially in its early stages. In more advanced phases, acute inflammation may occur, characterised by flattened gastric corpus folds, mucosal swelling, and redness. As the disease progresses, the corpus and fundus atrophy may become apparent, presenting as pale mucosa with visible submucosal vessels due to mucosal thinning, while the antrum generally remains unaffected [74,75,80]. To maximise diagnostic accuracy, endoscopists should ensure optimal mucosal visualisation. Defoaming and mucolytic agents, such as simethicone and 1 % N-acetylcysteine, may be beneficial, as water irrigation alone may not be sufficient for effective mucosal washing [73–77].

High-definition endoscopy combined with chromoendoscopy (CE) is superior to high-definition white-light endoscopy for diagnosing gastric precancerous conditions and early neoplastic lesions [73,74]. Whenever available and with proper training, electronic CE, with or without magnification, should be used to diagnose precancerous gastric conditions, guide biopsy sampling for staging atrophic and metaplastic changes, and aid in detecting neoplastic lesions [73–77].

Despite the high resolution of advanced endoscopic techniques, current recommendations still advocate for a standardised biopsy protocol at diagnosis. Biopsies should be taken from at least two specific sites—the antrum and corpus, at the lesser and greater curvatures—and labelled separately in two distinct vials. Additional biopsies should be obtained from any visible neoplastic-suspicious lesions [73–77]. The most recent European guidelines (MAPS III) suggest that routine gastric biopsies during surveillance endoscopy of patients with advanced atrophy or metaplasia at baseline endoscopy are not required when no endoscopically visible lesions are observed [74].

3.4.6. Is the screening for comorbidities or associated conditions useful in AAG patients?

Position statement: All newly diagnosed AAG patients should be screened for micronutrient deficiencies, anaemia, and other associated autoimmunity, including autoimmune thyroid disease and coeliac disease.

Patients with AAG have an increased risk of developing malabsorption of several nutrients, in particular vitamin B_{12}, iron, calcium, and vitamin D (116,117), and are also more likely to have concomitant autoimmune comorbidities. For this reason, at the first evaluation, all patients should be screened for micronutrient deficiencies and anaemia [1,2,101]. Moreover, those autoimmune comorbid conditions that may be asymptomatic or mildly symptomatic should be looked for, such as autoimmune thyroid disease, by the dosage of TSH, anti-thyroid peroxidase antibodies, anti-tireoglobulin antibodies, and anti-TSH receptor, and coeliac disease, by the dosage of anti-tissue transglutaminase IgA antibodies. Other conditions should be looked for according to clinical manifestations. Since a significant proportion of patients with common variable immune deficiency have atrophic pangastritis, in patients with this condition, total immunoglobulins and IgA, IgG, and IgM should be assessed [1].

3.4.7. What is the treatment of micronutrient deficiencies in AAG?

Position statement: Patients with AAG require lifelong supplementation of vitamin B12, preferably via a parenteral route. Folic acid should be supplemented as well, for a synergistic effect with vitamin B12. Other micronutrients, such as iron and vitamin D, should be regularly checked and supplemented if depleted.

Vitamin B_{12} should be replaced parenterally, especially in cases of severe clinical manifestations. Usually, a dose of 1000 UI of cyanocobalamin per month up to 5000 UI every three months as an intramuscular injection is enough for supplementation. No studies have assessed novel oral, sublingual formulations in AAG patients [1,118].

Regarding iron, no trials assess the use of oral or parenteral formulations. Therefore, we suggest following the general guidelines on iron deficiency anaemia, thus starting with an oral formulation, preferably not pH-dependent formulations (e.g., liposomal formulations), if tolerated, and in case of mild anaemia, and preferring intravenous formulations in case of more severe anaemia or intolerance to oral supplementation. A recent study assessed the efficacy of intravenous ferric carboxymaltose treatment of iron deficiency anaemia in patients with corpus atrophic gastritis, showing that recovery from iron deficiency anaemia was obtained in 78.4 % of patients at 12 weeks and was maintained until 24 months in

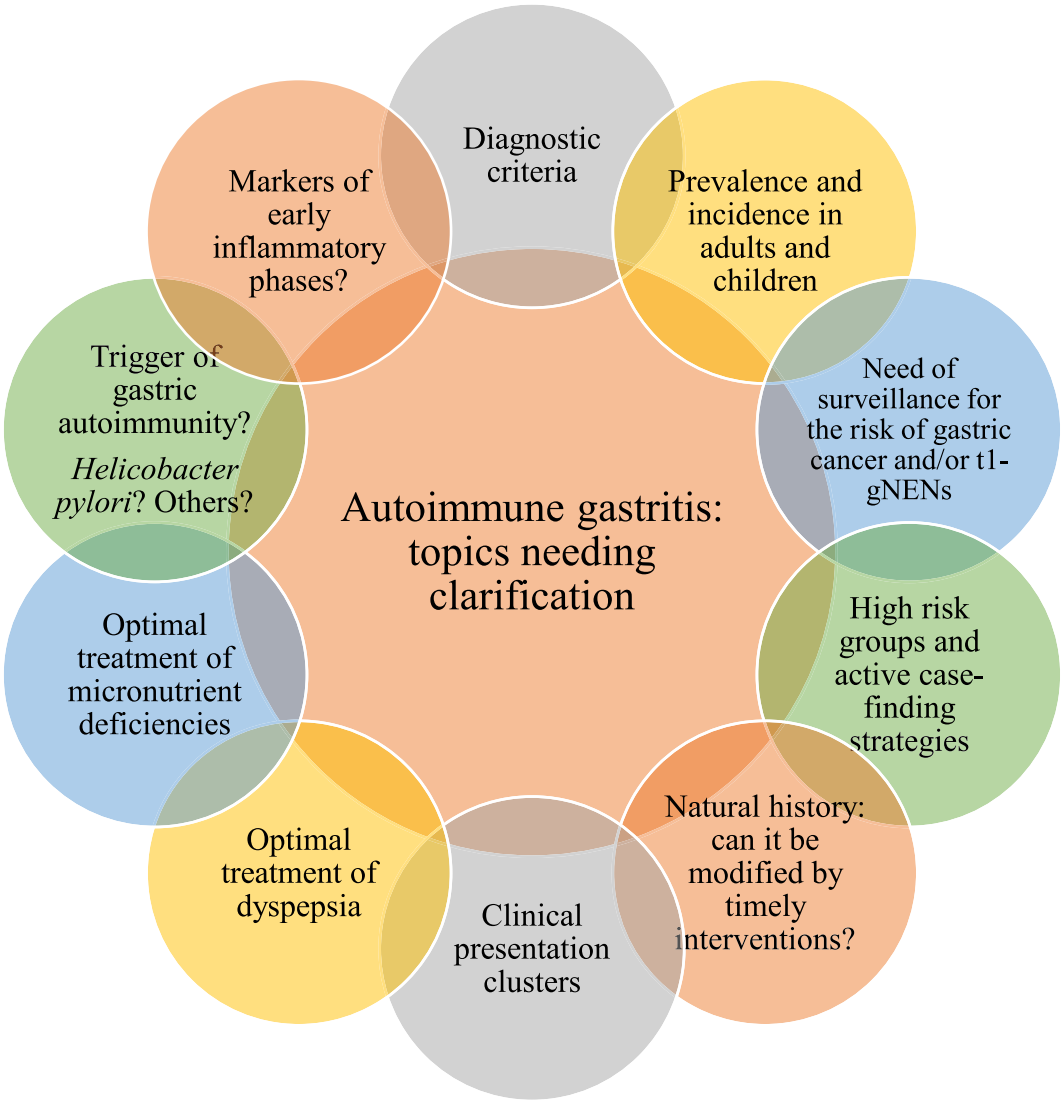

Fig. 1. Agenda for future research in autoimmune gastritis.

44.6 % of them, confirming intravenous iron treatment as a valid treatment approach. (119)

Folic acid should always be supplemented along with vitamin B_{12} to avoid the folic trap or folic acid depletion over time. Assessment of homocysteine levels helps rule out the confounding factor of MTHFR mutation and monitor response to folic acid and vitamin B_{12} supplementation.

It is currently unknown whether supplementation of other B vitamins is strictly needed in AAG, but this should be considered on a single-patient basis, especially those having thromboembolic manifestations.

Vitamin D should be supplemented as well when depleted, since a few studies showed that this vitamin may be malabsorbed in AAG. (120)

3.4.8. What is the treatment of dyspeptic symptoms in patients with AAG?

Position statement: PPIs should not be routinely offered to patients with AAG, since they may increase the risk of developing neuroendocrine neoplasms. In specific cases, such as gastric bleeding or Barrett's oesophagus, PPI may still be used. There is no solid evidence on the effectiveness and safety of prokinetics or other medications to treat dyspepsia in AAG.

Currently, no trials have assessed the safety and effectiveness of antisecretory or prokinetic drugs, or other agents, to treat dyspepsia or gastroesophageal reflux disease in AAG patients. Indeed, the extensive use of PPIs should be discouraged, since it has been shown that their use may increase the risk of developing t1-gNENs, and, albeit uncommon in AAG, the risk of GC [1,114]. However, it should be noted that, especially in the initial phases of AAG, patients may still have a residual acid production, with gastroesophageal reflux disease assessed with pH-impedance. These patients may benefit from courses of PPIs to treat symptoms and to prevent complications (e.g., reflux oesophagitis, Barrett's oesophagus). In later phases, patients with AAG may experience symptoms related to non-acid reflux as assessed with pH-impedance (121), who may sometimes respond to a course of antiacids, but treatment is challenging. Prokinetics (e.g., domperidone, levosulpiride, ginger extracts, others) may be used, as indicated in functional dyspepsia, but again, dedicated studies on AAG are lacking. According to some evidence, zinc-l-carnosine may exert an anti-inflammatory property in the stomach cells [38].

4. Conclusions

The present position paper reflects the effort to converge specific expertise of a group of long-experienced experts in the field of AAG to find answers to clinically and scientifically relevant questions on AAG based on the current knowledge and scientific evidence.

Key points emerging from this position paper are that, notwithstanding increasing interest in this disease and a growing number of studies over the last years, scientific evidence is still scarce and many points still need definitive clarification. In particular, clinically relevant issues such as the role of *H. pylori* infection, diagnostic criteria, the need for surveillance, and treatment issues suffer from a lack of well-conducted, extensive studies providing high-level evidence and still rely mainly on the experience of the single centres where patients are diagnosed, treated and monitored. Thus, much work on AAG remains to be done, as shown in the proposed research agenda (Fig. 1), and internationally shared criteria for diagnosis and management of AAG are urgently needed. An increasing understanding of AAG would ultimately lead to a correct and timely diagnosis, improve clinical management and quality of life of patients, and reduce the economic and social burden of this underestimated condition.

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Declaration of competing interest

The authors declare that they have no competing interests to disclose.

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