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Guidelines

Chronic atrophic gastritis: Natural history, diagnosis and therapeutic management. A position paper by the Italian Society of Hospital Gastroenterologists and Digestive Endoscopists [AIGO], the Italian Society of Digestive Endoscopy [SIED], the Italian Society of Gastroenterology [SIGE], and the Italian Society of Internal Medicine [SIMI]

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ABSTRACT

Chronic atrophic gastritis (CAG) is an underdiagnosed condition characterised by translational features going beyond the strict field of gastroenterology as it may manifest itself by a variable spectrum of gastric and extra-gastric symptoms and signs. It is relatively common among older adults in different parts of the world, but large variations exist. *Helicobacter pylori*-related CAG [multifocal] and autoimmune CAG (corpus-restricted) are apparently two different diseases, but they display overlapping features. Patients with cobalamin and/or iron deficiency anaemia or autoimmune disorders, including autoimmune thyroiditis and type 1 diabetes mellitus, should be offered screening for CAG. Pepsinogens, gastrin-17, and anti-*H. pylori* antibodies serum assays seem to be reliable non-invasive screening tools for the presence of CAG, helpful to identify individuals to refer to gastroscopy with five standard gastric biopsies in order to obtain histological confirmation of diagnosis. Patients with CAG are at increased risk of developing gastric cancer, and they should be estimated with histological staging systems (OLGA or OLGIM). *H. pylori* eradication may be beneficial by modifying the natural history of atrophy, but not that of intestinal metaplasia. Patients with advanced stages of CAG (Stage III/IV OLGA or OLGIM) should undergo endoscopic surveillance every three years, those with autoimmune CAG every three-five years. In patients with CAG, a screening for autoimmune thyroid disease and micronutrient deficiencies, including iron and vitamin B_{12}, should be performed. The optimal treatment for dyspeptic symptoms in patients with CAG remains to be defined. Proton pump inhibitors are not indicated in hypochlorhydric CAG patients.

1. Introduction

Chronic atrophic gastritis (CAG) is a frequently misrecognised condition characterised by translational features involving not only the field of gastroenterology, gastrointestinal endoscopy and pathology, but also that of haematology, neurology, oncology, and endocrinology.

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Atrophy of the gastric mucosa is defined as the decrease or the disappearance of the original gastric glands, which may be replaced by pseudo-pyloric or intestinal metaplasia, or fibrosis [1]. If this pathological process occurs in the corpus, the subsequent reduced mass of specialised parietal cells leads to impaired gastric acid and intrinsic factor secretion, eventually resulting in malabsorption of iron and vitamin B_{12} and consequent anaemia [2,3]. This condition is also linked to an increased risk of gastric cancer as a consequence of the changed intragastric microenvironment [4]. The continuous stimulation of antral gastrin-producing cells with endocrine-like cells hyperplasia may lead to the development of type 1 gastric neuroendocrine tumours [5].

Strickland and Mackay, in their landmark study published in 1973 [6], proposed two distinct forms of chronic gastritis, the essential distinctive criteria of which were supposed to be the presence or lacking of anti-parietal cell antibodies (APCA) together with the presence or absence of antral damage: "Type A showing diffuse corpus atrophic gastritis with sparing of the antral mucosa, positivity to APCA, severe impairment of gastric secretion, and eventually impaired vitamin B_{12} absorption, and Type B showing focal atrophic gastritis involving antral and corpus mucosa, negativity to APCA, and moderate impairment of gastric acid secretion, and rare impairment of vitamin B_{12} absorption" [6]. Type A gastritis was considered to have an autoimmune origin, likely linked to the presence of APCA, and Type B was considered to be caused by environmental factors, later on largely identified as *Helicobacter pylori* infection [4,7]. This approach has led to the common conception of two distinct forms of CAG, which has been transposed into the classification of gastritis in the updated Sydney system [7].

H. pylori is the main aetiologic factor for chronic gastritis worldwide, and long-standing infection may lead to progressive destruction of patches of gastric glands throughout the stomach, described as multifocal atrophic gastritis, which is characterised by a mainly patchy involvement of gastric antral and corpus mucosa [2,3]. The link between *H. pylori* infection and development of CAG, as supposed by the Correa's cascade [4], is supported by several cohort studies [8–10] and by the beneficial effect of eradication of *H. pylori* infection on corpus atrophy (OR 0.9, 95% CI 0.7–1.2), but not on intestinal metaplasia, this latter supposed to have gone beyond the "point of no-return" [11–15].

Autoimmune gastritis is commonly perceived as a distinct form of chronic gastritis with atrophy being restricted to the corpus mucosa, albeit the detailed mechanisms leading to parietal cell destruction have not been fully elucidated. The H^+/K^+-ATPase protein was identified as the "target" antigen of autoimmune antibodies possibly triggering the autoimmune response, ultimately leading to loss of parietal cells and functional impairment of the oxyntic mucosa [16–18]. Most frequently, the positivity against APCA is considered a diagnostic hallmark for autoimmune CAG [19], but strict diagnostic criteria for autoimmune CAG are still missing [2].

From a clinical point of view, CAG often manifests itself with anaemia, in particular pernicious anaemia due to cobalamin [vitamin B_{12}] deficiency or iron-deficiency anaemia [20,21]. Other conditions, such as neuropathy, several autoimmune diseases or the presence of dyspepsia may be clinical clues raising the suspicion of CAG [22,23].

Many questions regarding epidemiology, clinical features, classification and management of patients with CAG are still open and need clarification. An appropriate diagnosis, classification and management of patients with CAG is important to eventually improve quality of life and to reduce the social and economic burden of this condition. Recently, it has been shown that autoimmune CAG is burdened by a relevant diagnostic delay, likely due to lack of awareness, particularly among gastroenterologists [24]. The present position paper addresses CAG in adults and reflects the position on this topic of the Italian Society of Hospital Gastroenterologists and Digestive Endoscopists (AIGO), the Italian Society of Digestive Endoscopy (SIED), the Italian Society of Gastroenterology (SIGE), and the Italian Society of Internal Medicine (SIMI).

2. Material and methods

From each of the four scientific societies two members were appointed to participate in the present position paper. The participants formulated and proposed a list of answerable clinical questions on the most relevant topics related to CAG, focusing on current practice and areas of controversy (Table 1). These questions were exchanged and discussed through email to share relevance, improve clarity, and avoid duplication, and edited until absolute agreement was reached [modified Delphi process]. For each topic, a working party was created, which included two or three participants of at least two scientific societies. A comprehensive literature search of the PubMed, MEDLINE, EMBASE, Scopus, Cochrane Library and Google Scholar electronic databases up to February 2019 on CAG was performed including: prevalence, incidence, diagnosis, symptoms, treatment, and follow-up. The search strategy used the MeSH terms "atrophic gastritis", "autoimmune gastritis", "Helicobacter pylori", "gastric cancer", "gastric dysplasia", "intestinal metaplasia" in various combinations using the Boolean operators AND, OR, and NOT. The literature search was limited to the English language. Meeting abstracts, letters to the editor, case reports, or case series reporting less than five patients were excluded.

In order to assess the strength of the recommendations and the evidence, the GRADE system was used [25]. Recommendations were either strong (1: desirable effects outweigh undesirable effects) or conditional (2: trade-offs are less certain), and the quality of evidence was either strong (A: further research is unlikely to change confidence in the estimate), moderate (B: further research is likely to change confidence in the estimate), low (C: further research is very likely to change confidence in the estimate), or very low (D: the estimate of the effect is very uncertain).

An initial draft was edited by various text email exchanges and a meeting of the working parties was held [Rome, March 2019] to share methods, timelines, and the entire process. The draft was edited until agreement was reached (modified Delphi process). The Delphi process lead to a change of view from a previous position avoiding any uneasiness among participants. A revised final draft was externally reviewed and approved by the Executive Boards of the four scientific societies.

The format of the present position paper includes the clinical question, the statements, the evidence level (EL) and the recommendation grade (RG), and the summary of evidence.

3. Statements

3.1. Epidemiological and clinical issues

3.1.1. Should CAG be considered a prevalent disease, mainly affecting the elderly?

CAG should be considered a prevalent disease which is relatively common among older adults in different parts of the world, but large variations exist [EL: C; RG: 2].

Epidemiological data about CAG prevalence in different parts of the world are sparse, and results are difficult to compare due to methodological differences between studies in terms of definition and diagnosis of CAG and study populations. In studies reporting from Asian countries, CAG diagnosis included all atrophic lesions irrespective of atrophy localisation in the gastric mucosa; in the majority of the studies conducted in Western countries, CAG diagnosis included only patients with a corpus atrophic involvement,

Table 1
Summary of the clinical questions regarding chronic atrophic gastritis.

Clinical questions	EL[a]	RG[a]
1. Epidemiological and clinical issues:		
1.1 Should CAG be considered a prevalent disease, mainly affecting the elderly?	C	2
1.2 Should CAG be considered a clinically silent disease?	C	2
2. Pathogenic issues:		
2.1 *Helicobacter pylori*-related CAG and autoimmune CAG are clearly different diseases?	B	2
3. Diagnostic issues:		
3.1 Are there specific subgroups of high-risk subjects who should be screened for CAG?	C	1
3.2 Are there available valid non-invasive screening tools for CAG?	B	2
3.3 The appropriate histological diagnosis of CAG is formulated on gastric mucosa biopsies yielded according to a standard biopsy?	A	1
3.4 Are the current histological scoring systems (OLGA, OLGIM) useful for assessing gastric cancer risk?	A	1
4 Management		
4.1 The treatment of *Helicobacter pylori* infection in patients with CAG may be considered beneficial for the outcome of the disease)?	B	1
4.2 Should patients with CAG undergo surveillance endoscopy with gastric biopsies for early diagnosis of gastric neoplasia?	C	1
4.3 Is a proactive screening for associated autoimmune diseases and/or micronutrient deficiencies (iron and/or cobalamin) useful in patients with CAG?	B	1
4.4 Should patients with CAG and dyspeptic symptoms be treated?	C	2

[a] EL, Evidence level, and RG, grade of recommendation, graded according to reference (Balshem [25]).

such as corpus-restricted atrophic gastritis or multifocal atrophic gastritis. Further, different diagnostic methods for the diagnosis of CAG, i.e. surrogate serological markers of gastric function [pepsinogen I or pepsinogen I/pepsinogen II ratio] or histopathology of endoscopic biopsy specimens, make reported prevalence data not comparable [26–28]. Serological studies conducted in different parts of the world reported a prevalence of CAG up to 27% [26,29–34]. According to a systematic review [35], the worldwide prevalence estimates of CAG were 23.9% and 27.0% in the general population and in selected groups, respectively, when serology was used, and 33.4% in the general population and 31.6% in selected groups on the basis of biopsies. An increase of the prevalence of CAG with age was shown in serological studies [26,30,31,34], further confirmed by a large histological study [36]. When comparing individuals under and over 40 years of age, a two times higher prevalence in CAG [biopsy- or serology-based] for the older group was shown [36]. In contrast, a Swedish cross-sectional study [37] based on serological diagnosis of CAG reported an unexpected age-trend with an increase in the prevalence of CAG among adults aged 35–44 years from 22 to 64/1000 between 1990 and 2009, but a decreased prevalence of CAG in participants aged 55–64 years from 124 to 49/1000 in the same observation period.

With regard to the incidence of CAG, a systematic review [31] based on studies published between 1988 and 2008 showed a wide range (0%–10.9%) of incidence rates per year, probably explained by the different clinical settings in which the diagnoses were made. A long-term nationwide Dutch study [36] showed that the incidence of CAG declined over the study period (1991–2005) by 8.2% per year without differences between gender.

Thus, epidemiological data on prevalence, incidence, and age trends of CAG are inhomogeneous due to methodological differences between studies, and do not allow to draw definite conclusions. Large multicentre high-quality studies are needed to provide a clearer insight into the real frequency and age trends of CAG.

3.1.2. Should CAG be considered a disease with a wide spectrum of clinical manifestations?

CAG should be considered a multifaceted disease as it may manifest itself by a variable spectrum of gastric and extra-gastric symptoms and signs [EL: C; RG: 2].

The clinical spectrum of CAG is not clearly defined and often unspecific. Studies were mainly conducted on autoimmune CAG, while data on clinical presentation of *H. pylori*-related CAG are scarce. When CAG involves the corpus mucosa, haematological alterations represent the main clinical presentation, as a result of micronutrient deficiencies. Sometimes, CAG may remain clinically silent for many years as micronutrient deficiencies take time to develop [20].

In contrast with the classical perception that CAG is silent from a gastroenterological perspective, some evidence emerged that patients with CAG often complain of gastrointestinal symptoms. An observational study on autoimmune CAG [22] showed that clinical clues leading to the diagnosis were haematological findings (anaemia, macrocytosis, increased red cell distribution) in 37.4%. Less frequently, CAG was suspected for neurological symptoms, associated autoimmune diseases, positive family history, or the diagnosis of CAG was made by chance. Dyspeptic symptoms, such as epigastric pain, early satiety, and/or postprandial fullness, were present in 35.5%, 10%, and/or 7%, respectively, whereas reflux-like symptoms, such as heartburn and acid regurgitation, in 24.2% and 12.1%, respectively. Finally, dysphagia, glossitis, and lower gastrointestinal symptoms were less frequent, but none of the aforementioned gastrointestinal symptoms raised the clinical suspicion of autoimmune CAG. This unspecific clinical picture was confirmed in a cross-sectional study [38] in which symptoms that led to diagnosis of autoimmune CAG were abdominal bloating alone or combined with pain, nausea or constipation, iron or cobalamin deficiency, and miscellaneous symptoms. Concerning gastrointestinal symptoms in patients with autoimmune CAG, their presence was reported in 56.7%, most frequently early satiety and postprandial fullness [39]. In about one fourth of patients with autoimmune CAG, the presence of gastroesophageal reflux symptoms (heartburn and regurgitation) was observed [40,41].

A multicentre study on 668 patients with upper gastrointestinal symptoms showed the presence of CAG [autoimmune and not] in 30.1%, and observed that reflux or dyspeptic symptoms had a similar frequency in patients with or without CAG [23]. In this study, amongst all dyspeptic symptoms, postprandial fullness emerged as clinical predictor for autoimmune CAG [23]. Thus, attention should be paid to dyspeptic and/or gastroesophageal reflux symptoms as possible clinical clues to raise the suspicion of both autoimmune and non-autoimmune CAG.

Within the haematological cluster, a common CAG presentation is pernicious anaemia, a megaloblastic anaemia arising from vitamin B_{12} malabsorption due to intrinsic factor deficiency [21,42,43], or iron deficiency anaemia as a consequence of iron malabsorption due to reduced acid secretion associated with normal or low cobalamin levels [20]. It has been reported that iron deficiency anaemia may occur prior to the appearance of vitamin B_{12} deficiency and pernicious anaemia in a subgroup of CAG patients ranging from 35% to 58%, in particular in younger women [20]. The presence of CAG

as the only cause of refractory iron deficiency anaemia has been observed in several reports [21,44,45], and iron deficiency anaemia was found to be the presenting feature in 83 (52%) out of 160 CAG patients, suggesting that iron deficiency anaemia might be the most common haematological presentation of this condition [45].

Vitamin B_{12} deficiency has been associated with neurological, cognitive, psychotic, and mood impairment, and it should be early treated to prevent irreversible brain damage and to reduce morbidity [46–49]. A recent cross-sectional Chinese study [50] showed that the prevalence of CAG was significantly higher amongst patients with peripheral neuropathy (76.5% versus 59.2%, $p < 0.0001$), and serum vitamin B_{12} levels showed a positive correlation with sensory nerve conduction velocity improving after vitamin supplementation. Iron deficiency has also been described as having a negative impact on cognition, behaviour, and motor skills [51]. Considering that in CAG both - iron and vitamin B_{12} deficiencies - may coexist, a timely and correct diagnosis of this condition is particularly important in the elderly. A recent study [52] described, besides vitamin B_{12} and iron deficiency, also vitamin D deficiency in CAG patients, albeit not adjusted for age and post-menopausal status.

CAG is linked to hyperhomocysteinaemia via vitamin B_{12} malabsorption [53]. Increased homocysteine levels due to vitamin B_{12} deficiency may lead in turn to venous thromboembolism at different sites as revealing symptom of CAG [54–57]. Increased levels of homocysteine are considered a risk factor for cardiovascular diseases [58]. However, a large German serological cohort study did not observe significant associations for patients with CAG and cardiovascular disease (myocardial infarction or stroke) or mortality [59].

Another clinical cluster of autoimmune CAG is the association with autoimmune diseases, most frequently autoimmune thyroid disease and type I diabetes, less frequently vitiligo, psoriasis, coeliac disease, connective tissue disorders, and others [22,60,61]. Thus, the presence of these diseases may sometimes be the only clue for the clinical suspicion of CAG. CAG has a wide clinical spectrum encompassing gastroenterological, haematological and neurological manifestations together with clinical manifestations of associated autoimmune diseases. Thus, CAG harbours in one disorder the emerging concept of clinical complexity [62], explainable with the multifaceted clinical consequences of long-standing atrophic damage of the gastric oxyntic mucosa. Table 2 summarises the most relevant clinical features of CAG.

Table 2
Clinical scenarios of chronic atrophic gastritis.

Clinical clusters	Clinical signs or symptoms	Level of suspicion
Haematological	Iron deficiency anaemia	++
	Pernicious anaemia	+++
	Increased red cell distribution width	++
Gastroenterological	Dyspeptic symptoms	
	- Post-prandial fullness	++
	- Early satiety	++
	- Epigastric pain	+
	Reflux-like symptoms	
	- Heartburn	+
	- Regurgitation	+
Neurological	Peripheral neuropathy	+
	Paraesthesia (arms and legs)	++
	Cognitive and mood impairment	+
Autoimmunity	Autoimmune thyroid disease	+++
	Type 1 diabetes	++
	Vitiligo	+
	Coeliac disease	+
First-degree familiality	Gastric cancer	+++
	Type 1 neuroendocrine tumour	++
	Chronic atrophic gastritis	++
		+

+ low; ++ moderate, +++ high.

3.2. Pathogenic issues

3.2.1. H. pylori-related CAG and autoimmune CAG are clearly different diseases?

H. pylori-related CAG [multifocal] and autoimmune CAG [corpus-restricted] seem to be different diseases, but display common, overlapping features [EL: B; RG: 2].

The currently used updated Sydney System considers two types of atrophic gastritis, namely autoimmune atrophic gastritis [formerly known as type A] and multifocal atrophic gastritis (formerly known as type B) [7]. APCA positivity is commonly considered a diagnostic hallmark for autoimmune CAG [19] together with the histological feature of a spared antral mucosa [3,6,7]. In contrast with the concept that autoimmune and *H. pylori*-related multifocal CAG are two clearly distinct entities, overlapping features have been reported.

(i) A mutual link between autoimmune CAG and *H. pylori* infection has been reported albeit data are still conflicting. *H. pylori*-induced antibodies have been shown to cross-react with human gastric mucosa [63], probably due to antigenic mimicry between aminoacidic sequences of *H. pylori* and the H^+/K^+-ATPase localised on parietal cells [64–66]. A high homology [72% in 25 amino acids overlap] between the alpha-subunit of *H. pylori* urease and that of the autoantigen H^+/K^+-ATPase has been shown [67]. Some studies reported positivity to *H. pylori* [by histology, ELISA and immunblotting serology] in patients with autoimmune CAG [68–71]. These data are in contrast with an inverse epidemiological correlation between autoimmune CAG and *H. pylori*-related CAG reported in an older study, being the former more prevalent in world regions with a low prevalence of *H. pylori* [72].

(ii) Although there are no studies assessing the performance in a case-finding strategy, APCA are commonly considered the hallmark for the diagnosis of autoimmune CAG [19,73]. However, APCA may be present in *H. pylori*-related CAG and non-atrophic gastritis [63], and may disappear in late stages of autoimmune CAG [74]. In a case-control study, positivity to serological autoantibodies against ATP4A and ATP4B subunits of parietal cells was shown in all patients with *H. pylori*-positive multifocal CAG [75]. Another case-control study assessed APCA by ELISA and showed a similar proportion of positivity to APCA in patients with multifocal CAG and in those with corpus-restricted CAG [76], thus strongly suggesting that positivity against APCA seems not to be an exclusive feature of corpus-restricted CAG but an expression of the damaged oxyntic mucosa, also in *H. pylori*-infected CAG patients.

(iii) The pattern of anaemia (overt pernicious anaemia, latent pernicious anaemia, iron deficiency anaemia], the co-presence of other autoimmune diseases, and the presence of autoimmunity-related HLA haplotypes were also reported to have similar frequency in corpus-restricted and multifocal CAG patients [76,77], thus suggesting overlapping clinical features amongst the two clinical entities.

(iv) The increased risk of gastric cancer, originally accepted for *H. pylori*-related multifocal CAG as part of the proposed Correa's cascade, has been also proved in a meta-analysis regarding

autoimmune CAG associated with pernicious anaemia [78]. The recent second version of MAPS guidelines now includes autoimmune gastritis as a condition in which endoscopic follow-up for early diagnosis of gastric cancer is recommended every 3–5 years [79]. These data raise the question as to whether a complete distinction of the two different nosological entities is really justified and useful and as to whether the current diagnostic criteria are still valid.

3.3. Diagnostic issues

3.3.1. Are there specific subgroups of high-risk subjects who should be screened for CAG?

Patients suffering from cobalamin deficiency anaemia, iron deficiency anaemia or autoimmune disorders, including autoimmune thyroiditis and type 1 diabetes mellitus, should be screened for CAG [EL: C; RG: 1].

Patients with persistent uninvestigated dyspepsia, with long-term use of proton pump inhibitors and first-degree relatives of patients with gastric cancer or CAG might benefit from CAG screening [EL: C; RG 2]

CAG has been associated with a number of autoimmune conditions, with a variable strength of association [80]. Autoimmune thyropathies, especially Hashimoto's thyroiditis and, to a lesser extent, Grave's disease, are the most commonly associated autoimmune comorbidities [22,60,61,81]. This link is so strict that the term "thyrogastric syndrome" has been used for years to indicate the presence of both conditions in the same individual [82]. It has been estimated that patients with autoimmune thyropathy and/or type 1 diabetes carry a 3- to 5-fold increased risk of suffering from autoimmune CAG, thus justifying a proactive strategy for early recognition [83]. This figure does not seem to be dependent on ethnicity, given that it has been described in series from different world regions. In a large Italian study involving 208 patients with autoimmune thyroid disease, 24.5% of them were APCA positive [74], but histological confirmation of CAG diagnosis was not performed. In another Italian report, 22 [35%] of 62 patients with autoimmune thyroid disease had histologically proven CAG [autoimmune and not], in whom anaemia was more frequently associated as in patients without CAG (82% vs 22%, $p < 0.0001$) [81]. In a recent study conducted on 243 Brazilian patients with autoimmune thyropathies, APCA were present in 20% of the cases [84]. Only a small proportion of patients underwent gastroscopy, but among those who did, autoimmune CAG was confirmed by histopathology in roughly 50% of the cases.

In a further Italian series of 99 patients with autoimmune CAG, Hashimoto's thyroiditis was the most frequently associated autoimmune condition (30.2%), followed by Graves' disease [6.1%] [22]. A similar figure was later confirmed by a subsequent study involving 291 autoimmune CAG patients [24]. An Italian cross-sectional study reported that of the 319 consecutive outpatients with CAG (autoimmune and not autoimmune), 53% had an associated thyroid disorder, and half of them were unaware of it. The thyroid disease was autoimmune in 75.7%. Risk factors for having autoimmune thyroid disease in CAG patients were female gender (OR 5.6) positivity to APCA [OR 2.5, and presence of metaplastic atrophy (OR 2.2) [61]. Autoimmune thyroid disease and CAG seem to occur in a closely linked fashion, supporting an active screening approach to exclude an occult autoimmune thyroid disease in both autoimmune and not autoimmune CAG patients.

Type 1 diabetes mellitus is another autoimmune condition associated with CAG in up to 10% of the cases [85]. In a study involving 88 consecutive diabetic patients [47 APCA-positive, 41 APCA-negative] who underwent gastroscopy, autoimmune CAG was proven by gastric biopsies in 57% of APCA-positive patients and in 10% of APCA-negative patients [86]. In a more recent study conducted on 1072 patients suffering from type 1 diabetes, APCA were present in 79/1055 cases (7.5%) [87]. CAG diagnosis was not confirmed by histology in this study. The association of CAG with other autoimmune conditions is less clear and supported by weaker evidence. Vitiligo and Addison's disease may cluster with pernicious anaemia/autoimmune CAG in rare forms of autoimmune polyendocrine syndromes [88]. Otherwise, the association of either vitiligo or Addison's disease has only been reported in a few case series [22,60,89,90]. Evidence regarding the possible association with coeliac disease has grown in recent years [22,60], but more studies are needed to confirm this hypothesis. Besides autoimmune disorders, other high-risk groups should be screened for CAG. In particular, this condition is characterized by malabsorption of vitamin B_{12} and iron, causing variable haematological alterations, including not only macrocytic and iron deficiency anaemia, but also scanty and more subtle alterations, such as isolated mean cell volume alterations [macro- or microcytosis], anisocytosis, dimorphic anaemia, and pancytopenia [20,22,24]. A prospective screening study [21] detected CAG in 37.5% of patients with macrocytic and in 19.5% of those with microcytic iron-deficiency anaemia. Microcytic CAG patients were on average 20 years younger than those with macrocytic anaemia.

In patients with persistent uninvestigated dyspepsia the presence of CAG should be excluded.

In patients with non-investigated upper GI symptoms, reflux and dyspeptic symptoms were associated similarly in patients with and without CAG, thus not representing a pre-endoscopic clue to rule out CAG, while postprandial fullness was reported as a clinical predictor for autoimmune CAG [23].

An increased risk of CAG in first-degree relatives of patients with gastric cancer and *H. pylori* infection was shown [91,92], not confirmed by other reports [93–97]. A meta-analysis found that first degree relatives of gastric cancer patients had a significantly higher risk for developing CAG, in parallel with a significantly higher risk of being infected by *H. pylori* [98]. A large Swedish population-based observational study observed a significant trend of increased incidence rates of gastric cancer in patients with positive family history of precancerous lesions [SIR 1.5–1.6] and gastric cancer (SIR 2.3); Cox models showed that a family history of any precancerous changes and gastric cancer was associated with a 2.5-fold and a 3.8-fold increment in non-cardia gastric cancer hazard, compared with siblings of index persons with normal or minor mucosal changes [99]. A recent Japanese study on *H. pylori*-infected patients [100] showed that a first degree family history of gastric cancer, absence of duodenal ulcer, and older age were independent risk factors for the development of CAG among *H. pylori*-infected patients, as assessed by endoscopy.

Long-term use of proton pump inhibitors (PPI) has been widely accepted to aggravate corpus CAG in *H. pylori*-infected patients [101–104], and long-term PPI treatment in *H. pylori*-infected subjects has been suggested to be linked to a higher risk for gastric cancer. A meta-analysis on 13 studies including 1465 patients under long-term PPI therapy and 1603 controls reported a slightly higher prevalence of CAG in the PPI group compared to controls (15.8% vs 13.29%, OR 1.55, 95% CI 1.00–2.41) [105]; in the three studies with significant OR patients were followed-up for 1, 5, and 6.5 years.

There is a body of evidence to support a case-finding strategy in high-risk individuals, including patients with autoimmune thyropaties and type 1 diabetes mellitus, and in patients with red blood cells alterations, such as unexplained iron deficiency anaemia, macrocytosis, or macrocytic anaemia. Patients with persistent uninvestigated dyspepsia, those with positive family history of gastric cancer or precancerous lesions, and those on long-term

treatment with PPI may benefit from gastroscopy with standard biopsy sampling to rule out the presence of CAG.

3.3.2. Are there available valid non-invasive screening tools for CAG?

Pepsinogens and a combination of pepsinogens, gastrin-17 and anti-H. pylori antibodies serum assays seem to be reliable non-invasive tools for screening in subjects or populations at high risk of CAG to identify those to refer to gastroscopy with gastric biopsies for histological confirmation [EL: B; RG: 2].

There is general consensus that serological tests may be useful to identify individuals with CAG [106,107]. Serological tests are ideal for screening subgroups of subjects or populations at high risk of CAG in order to identify those to refer to gastroscopy with standard gastric biopsy sampling. In addition, an accurate non-invasive test may be useful for epidemiological studies on CAG in the community. Currently, available serological tools include pepsinogens I and II, gastrin-17 and anti-*H. pylori* antibody. Pepsinogen-I (PG-I) is secreted only by oxyntic glands, while pepsinogen II [PG-II] is also produced in the gastric antrum and duodenum, and gastrin-17 (G-17) is produced by G cells in the antrum. Serum PG-I levels and/or the PG-I/PG-II ratio have been reported to be lower in patients with corpus CAG, whereas a low G-17 serum level should indicate the presence of antrum CAG [108].

A meta-analysis of 31 studies, including 2265 patients with CAG, showed that serum pepsinogens could be useful for the non-invasive diagnosis of CAG, regardless of site and extension. However, the summary sensitivity of serum pepsinogens was 69% [95% CI 55–80%] and the summary specificity was 88% [95% CI 77–94%] [109]. This meta-analysis showed some limits because of a substantial heterogeneity between the included studies. Different cut-offs were used, but most studies used PGI < 70 ng/mL and PGI/PGII ratio < 3. However, to date, different methods can be used to dose pepsinogens, and absolute levels may vary depending on the analytical technology [110]. Thus, the cut-off points cannot be generalised to all pepsinogen assays, and only those validated for the particular assay should be used.

A meta-analysis of 13 studies including 894 patients with CAG was performed to assess the diagnostic value of serum G-17 [111]. The overall sensitivity of G-17 was only 48% [95% CI 45–51%] and the overall specificity was 79% (95% CI 77–81%), suggesting that G-17, when used alone, is a poor serological biomarker of CAG. Subgroup analysis showed that studies performed on patients from non-Asian countries (Turkey, Latvia, Chile, Italy, Finland, and Lithuania) showed higher diagnostic performance levels than studies on patients from Asian countries (Iran and China) [111]. A higher diagnostic performance of G-17 (AUC = 0.83) in patients with autoimmune CAG has been reported, when compared with *H. pylori*-related CAG (AUC = 0.62) [112].

A combination of pepsinogens (PGI and PGII), G-17 and anti-*H. pylori* antibodies serum assays [panel test] seems to have a slightly higher diagnostic performance than serum pepsinogens and G-17 tests alone. A meta-analysis published in 2017, pooled 20 studies with a total of 4241 patients to assess the diagnostic performance of the panel test for the diagnosis of CAG at any site and severity [113]. The summary sensitivity of the panel test was 74.7% [95% CI: 62–84.3%] and the summary specificity was 95.6% (95% CI: 92.6–97.4%). Adding *H. pylori* serology to serum PGs may help to identify individuals at increased risk for gastric cancer [114]. This meta-analysis carries several limitations, such as the high heterogeneity and the low methodological quality of the included studies. A selection bias may have affected the results of a number of studies. Unfortunately, these meta-analyses [109,113] did not assess the performance of pepsinogens [109] and panel test [113] for the diagnosis of advanced stages of CAG [Operative Link for Gastritis Assessment, OLGA, and Operative Link for Gastric Intestinal Metaplasia, OLGIM, stages III e IV] that are those really needing endoscopic surveillance. Nevertheless, a previous study proposed a step-by-step diagnostic algorithm based on gastrin G-17 and PGI together with the age of patients for the initial assessment and management of patients with autoimmune CAG with a high-risk OLGIM stage [115].

Other suggested serum biomarkers of gastric atrophy, such as serum ghrelin [116] and volatile organic compounds in exhaled air [117], need further studies before they can be recommended for clinical application. APCA has been reported to be a promising, reliable marker of damage of gastric oxyntic mucosa, not only in patients with autoimmune CAG [19,118], but also in multifocal *H. pylori*-related CAG [75,76], but validation is still needed.

Thus, pepsinogens and a combination of pepsinogens, G-17, and anti-*H. pylori* antibodies serum assays seem to be reliable non-invasive screening tools to detect among patients at increased risk of CAG those to refer to gastroscopy with biopsies in order to obtain histological confirmation.

3.3.3. The appropriate histological diagnosis of CAG is based on gastric mucosa biopsies according to a standard biopsy protocol?

The standard protocol with 5 biopsies is appropriate for detecting precancerous conditions in the stomach [EL: A; RG: 1].

The updated Sydney System advises taking five biopsies on standard sites of stomach for a correct gastritis assessment [7]. As compared to the previous System suggesting two biopsies of the antrum and two of the corpus mucosa [119], a further biopsy of the *incisura angularis* was deemed to be relevant for increasing detection of precancerous conditions [atrophy and metaplasia] in the stomach. Indeed, it has been established that intestinal metaplasia starts from the angulus and spreads towards both, the antral and corpus gastric mucosa [120]. Of note, the adjunctive biopsy is achieved without increasing procedure costs, as it should be placed in the same vial of antral biopsies [121]. By following this standard protocol, intestinal metaplasia is detected in 90% of cases [122]. When adding two further biopsies (one in the antrum and one on the lesser curve) the sensitivity increases to 95%, and it reaches 97% with 9 biopsies [122]. Most likely, the small increase in the intestinal metaplasia detection rate following the more extensive sampling does not justify procedure prolongation, and the augmented patient's discomfort [123]. Indeed, even the more recent OLGA/OLGIM gastritis scoring systems advise to perform five biopsies in the standard sites [121,123].

When gastric biopsies are correctly taken at endoscopy, an appropriate histological assessment for precancerous conditions is crucial, according to a specific tutorial for pathologists [121]. Besides the initial detection, this standard biopsy protocol has been also applied for the follow-up of gastric precancerous conditions, allowing early detection of either low- or high-grade intraepithelial neoplasia [NIN] [125]. In those patients with NIN at histology and without identifiable endoscopic lesions, a more extensive [three in the antrum, four along the lesser curvature, and three in the gastric body] biopsy sampling is needed [126]. Moreover, the use of narrow band imaging [NBI] is strongly advised in these cases to detect early foci of cancer fitting for complete endoscopic removal [127,128].

In the last years, evidence suggests that narrow-band imaging [NBI] endoscopy can be used to grade gastric intestinal metaplasia [129], shifting from random biopsies to "target biopsies" of those areas highly suspicious for intestinal metaplasia and increasing diagnostic accuracy of metaplastic CAG [130]. A real-time study showed that NBI had a high concordance with gastric histology, globally increased diagnostic accuracy as compared to traditional white-light endoscopy (WLE) (NBI 94% vs WLE 83%; $P < 0.001$), and significantly increased sensitivity for the recognition of intestinal metaplasia (87% vs 53%; $p < 0.001$). Interestingly, the gain of bene-

fit of NBI in terms of diagnostic accuracy was greater for advanced stages of intestinal metaplasia [131]. A recent study validated an endoscopic classification of intestinal metaplasia by NBI as compared to histology with promising results [132]. However, the NBI technique and skilled operators are still not sufficiently spread to permit a general recommendation of NBI endoscopy with target biopsies of suspicious areas instead of traditional WLE with random biopsies and histopathological evaluation.

3.3.4. *Are the current histological scoring systems [OLGA, OLGIM] useful for assessing gastric cancer risk?*

Patients with CAG are at increased risk of developing gastric cancer, and CAG grading with OLGA-OLGIM systems allows tailoring the cancer risk [EL: A; RG: 1].

Histological staging systems, OLGA and OLGIM, rank gastritis from stages 0 to IV by an assessment of both, severity and topography of atrophic-metaplastic changes [124,133]. A total of five gastric biopsies, (see Statement 3.3.3), are needed to adequately apply these systems. The staging of gastritis has received wide acceptance for stratifying patients according to their predicted cancer risk [106,107]. Of note, the risk of developing gastric neoplasia parallels with the OLGA-OLGIM stage, as documented by retrospective studies [134,135] and, more recently, in prospective studies [125,136]. In detail, it was found that gastric neoplasia (NIN or gastric cancer) developed at long-term follow-up only in those patients with III-IV gastritis stages. Therefore, a scheduled surveillance is recommended only in these patients, which represent less than 5% of cases with chronic gastritis [128]. Data of a recent meta-analysis corroborate the value of monitoring patients accordingly to OLGA-OLGIM staging [137]. Unfortunately, the application of OLGA-OLGIM systems in clinical practice seems to be still limited. Data of an Italian survey showed that these histological staging systems were used in less than 20% of cases who underwent upper endoscopy with gastric biopsies, so that a clinically relevant information is lacking for the majority of cases in clinical practice [138].

This evidence highlighted the usefulness of applying the OLGA-OLGIM staging in CAG patients for scheduling an appropriate surveillance program. Such an approach is expected to improve detection of neoplastic complications in CAG patients in earlier stages. Therefore, the application of histological staging systems in patients with CAG needs to be implemented and encouraged in clinical practice.

3.4. *Management*

3.4.1. *The treatment of* H. pylori *infection in patients with CAG may be considered beneficial for the outcome of the disease?*

H. pylori eradication in patients with CAG may be beneficial by affecting the natural history of atrophy, but not intestinal metaplasia [EL: B; RG: 1].

H. pylori is still a widespread infection causing chronic active gastritis in all colonised subjects [137–139]. It has been classified as type I gastric carcinogen by the International Agency for Research on Cancer more than 25 years ago [140]. The risk of developing gastric neoplasia is 3- to 6-fold increased in infected patients [141–143], and it is significantly reduced (RR: 0.56; 95% CI = 0.48–0.66) following bacterial eradication according to data of a recent meta-analysis [144]. Gastric carcinogenesis is a multistep process including gastric atrophy and intestinal metaplasia — configuring CAG — that represent precancerous conditions [145]. Since chronic inflammation induced by *H. pylori* infection on gastric mucosa may evolve to CAG with intestinal metaplasia, it is logical to assume that bacterial eradication may be a prevention strategy inducing regression of these conditions [146–150]. It is therefore important to accurately search for the presence of *H. pylori* in CAG patients by using invasive (presence of *H. pylori* or acute inflammatory infiltrate at biopsies) or non-invasive methods (IgG antibodies against *H. pylori*) and to keep in mind that other non-invasive tests as urea breath test or stool antigen test may not be reliable in corpus-involving CAG with reduced gastric acid secretion, possibly giving false-negative results [151].

However, reversibility of CAG and intestinal metaplasia by *H. pylori* eradication remains controversial. A systematic review and meta-analysis on the role of *H. pylori* eradication in preventing gastric cancer showed that curing the infection has beneficial long-term effects on gastric atrophy, but not on intestinal metaplasia [15]. Therefore, development of intestinal metaplasia in the stomach is not reversible following *H. pylori* eradication, and it probably represents the 'point of no return' in the gastric carcinogenetic cascade. Consequently, more efforts should be directed at preventing the development of such a condition by treating the infection early in life. Despite the apparent irreversibility of CAG with intestinal metaplasia, curing *H. pylori* is advised even in these patients aiming to reduce its progression. Patients with persistent CAG following bacterial eradication as well as those without infection at diagnosis, need of appropriate follow-up aimed to detect dysplasia and early stage carcinoma (see Statement 3.4.2).

3.4.2. *Should patients with CAG undergo surveillance endoscopy with gastric biopsies for early diagnosis of gastric neoplasia?*

Patients with advanced stages of CAG, i.e. patients with atrophy or intestinal metaplasia of at least moderate severity affecting both the antrum and corpus (Stage III/IV OLGA or OLGIM) should undergo endoscopic surveillance every 3 years, ideally with high quality endoscopy [EL: C; RG: 1].

Patients with autoimmune CAG, in particular when associated with pernicious anaemia, should receive endoscopic surveillance every 3–5 years [EL: B; RG 2].

Patients with CAG and/or intestinal metaplasia are at increased risk of developing gastric cancer [152,153]. Therefore, surveillance in these patients could increase detection of neoplastic lesions at an early stage and improve patients' survival. The recently updated European guidelines [79] on gastric precancerous conditions recommend endoscopic surveillance every three years in patients with CAG with or without intestinal metaplasia in both, the antrum and the corpus [79]. By using a Markov model, it was shown that this time interval is cost-effective in countries with at least an intermediate risk of gastric cancer [154]. Another study provided similar results with a cost-effective study carried out in Italy [155]. However, the choice of such an interval was not substantiated by any cohort study and, probably, it deserves a re-evaluation [120]. Indeed, at least two studies in which a 2-year interval control was performed in patients with high-risk showed that some neoplastic lesions developed earlier than the proposed 3 years follow-up [120,125]. A 2-year interval could be more cautiously considered in patients with advanced stages of CAG [Stage III/IV OLGA or OLGIM] and positive family history of gastric cancer.

Data of a large, retrospective study found that some neoplastic lesions developed also in patients with stage II OLGA [135] and stage I/II OLGIM [156,157]. A prospective study on 200 CAG patients with a median follow-up of 7.5 years, found that 6 out of the 11 epithelial gastric neoplastic lesions detected during follow-up were associated with Stages I/II OLGA and OLGIM [158].

Therefore, further data are required to evaluate whether a scheduled follow-up is needed also in these patients. However, according with European guideline, patients with mild-moderate atrophic gastritis only in antrum should not receive endoscopic surveillance. An endoscopic surveillance every three years may be a reasonable approach in these patients if there are other risk factors for gastric cancer, such as a first-degree family history. There are no large cohort studies assessing the risk of gastric cancer in patients with autoimmune CAG; however, these patients have

also an increased risk of developing neuroendocrine [carcinoid] tumours of the stomach [158]. A systematic review of 27 studies showed a pooled gastric cancer incidence-rate in CAG with pernicious anaemia of 0.27% per person-years and a nearly 7-fold RR of gastric cancer in pernicious anaemia patients [159]. According to MAPSII guidelines, an endoscopic surveillance every three years may be suggested also in patients with autoimmune CAG.

Whenever possible, endoscopic surveillance should be performed with high quality endoscopy [high definition endoscopy with conventional chromoendoscopy or virtual chromoendoscopy - NBI]. Two meta-analyses reported a very high accuracy of both conventional [sensitivity = 90%, specificity = 82%] and virtual chromoendoscopy [sensitivity = 90%, specificity = 83%] for the diagnosis of dysplasia and early gastric cancer in patients with precancerous conditions [129,160].

3.4.3. Is a proactive diagnostic work-up for associated autoimmune diseases and/or micronutrient deficiencies [iron and/or cobalamin] useful in patients with CAG?

Patients with CAG should be screened for autoimmune thyroid disease and micronutrient deficiencies, including iron and vitamin B_{12} [EL: B; RG: 1].

Up to 50% of patients with CAG present at least one autoimmune comorbidity [22,24,60,61,161], being Hashimoto's thyroiditis the most frequent, as reported in different case series. The onset of Hashimoto's thyroiditis may be subtle and accompanied by unspecific symptoms, and an early diagnosis could prevent more severe complications related to the impaired thyroid function. There is enough evidence for supporting a proactive serological screening through the assessment of thyroid function and thyroid autoantibodies in CAG patients.

Different micronutrients should be assessed in patients with CAG. Vitamin B_{12} absorption is strictly dependent on the production of intrinsic factor by parietal cells, that are reduced or completely destroyed in patients with gastric corpus/fundus atrophy [3]. Lifelong supplementation with parenteral cobalamin is therefore warranted [162]. In routine practice, evaluation of serum vitamin B_{12} is the most commonly available test and is considered as a first-line examination. However, it should be noted that in case of a value just above the lower limit of normal, the test should not be considered reliable, as this may indicate a subclinical deficiency. Holotranscobalamin (i.e., active transcobalamin-bound B_{12}) is considered a more sensitive marker for vitamin B_{12} deficiency and should be used if available [162]. Serum homocysteine may also be assessed as indirect marker of potential vitamin B_{12} deficiency, even if it is influenced by other parameters, such as folic acid and methylenetetrahydrofolate reductase mutations [163]. Given the strict link with both, vitamin B_{12} and homocysteine metabolism, folic acid should also be assessed in these patients to correctly interpret low vitamin B_{12} levels or high homocysteine levels.

Similarly, iron absorption, which occurs in the duodenum, is favoured by gastric acid, the production of which is impaired in these patients. Patients with CAG extended to the corpus mucosa may develop iron deficiency anaemia years before megaloblastic anaemia. Also, other more subtle blood cell alterations may occur, including isolated micro- or macrocytosis, anisocytosis, and dimorphic anaemia [22,164,165]. Hence, serum iron, transferrin, and ferritin should also be checked and supplemented on an as per need basis.

Other micronutrients might be deficient in patients with autoimmune CAG, including calcium and vitamin D, eventually leading to osteopenia and/or osteoporosis [52,164]. In a recent single-centre study conducted on 122 patients with autoimmune CAG, 25-OH vitamin D was the most commonly deficient micronutrient (62% of patients), even more than vitamin B_{12} [52], but unfortunately not adjusted for gender and postmenopausal state. Instead, folic acid, phosphate, and magnesium deficiencies were only reported in a few patients. These results need to be confirmed in larger, prospective studies.

3.4.4. Should patients with CAG and dyspeptic symptoms be treated?

There is poor evidence regarding best treatment for dyspeptic symptoms in patients with CAG, and proton pump inhibitors are not indicated in hypochlorhydric CAG patients [EL: C; RG: 2]

In general, for dyspepsia only limited treatment options are available including eradication treatment for *H. pylori*, acid suppressive therapy (PPI, H_2-antagonists), prokinetic agents, neuromodulators, herbal agents, and even non pharmacological treatments (acupuncture, cognitive behavioural therapy and hypnotherapy), with conflicting results in terms of efficacy [166], except for recommendation of *H. pylori* eradication and PPIs, made on the basis of high-quality evidence, for all other treatment approaches the evidence is moderate-low, often limited by low or very low-quality evidence [167].

As far as regards the treatment options of dyspepsia in CAG patients, *H. pylori* eradication may be considered a beneficial approach for regression of inflammation and cancer prevention [see Statement 3.4.1]. With regard to the effect of eradication treatment of dyspeptic symptoms in CAG patients, two Japanese studies have been performed. A randomised double-blinded placebo-controlled trial [168] compared triple eradication therapy for *H. pylori* [n = 45] with placebo [n = 45] in histologically diagnosed patients with CAG involving corpus mucosa, and showed at 3-years follow-up that dyspeptic symptoms scores improved significantly in the patients cured from infection, while no effect was observed in the placebo group. The other, more recent study [169] showed a positive effect of *H. pylori* eradication treatment on dyspeptic symptoms in endoscopically diagnosed patients with CAG, this effect lasted until one year after treatment and was associated with a higher pre-treatment symptom score and age under 70 years.

With regard to antisecretory drugs, in particular PPI, as treatment option for dyspepsia in CAG patients two concerns may rise. Firstly, in CAG patients with involvement of the corpus mucosa, notably linked to reduced gastric acid secretion and consequent hypochlorhydria, the treatment with antisecretory drugs may not be indicated [170]. Albeit no specific studies have been performed, this treatment option for relieving dyspepsia in CAG patients should be discouraged.

In five patients with gastroesophageal reflux symptoms and concomitant autoimmune CAG, PPI turned out to be ineffective, due to the non-acid nature of reflux in four of them, and thus were discontinued [40]. Secondly, the long-term use of PPI has been linked to development or progression of gastric pre-malignant lesions. A systematic review [171] addressed this question comparing the development/progression of atrophic gastritis, intestinal metaplasia, enterochromaffin-like [ECL] cell hyperplasia, and dysplasia, in subjects on PPI therapy for six months or more. With the limits of low-quality evidence, the long-term PPI treatment led to higher risk of progression of ECL cell hyperplasia, but no clear evidence emerged that it could increase the progression of CAG or intestinal metaplasia [171].

There are no ad hoc studies exploring the efficacy of prokinetics, neuromodulators, herbal agents, or non-pharmacological treatments in CAG patients with dyspeptic symptoms.

4. Conclusion remarks

The present position paper represents the result of the effort to converge for the first time the specific expertise on CAG of academic and hospital gastroenterologists, internists, and gastrointestinal

Table 3
Agenda for future research.

- To better define the clinical syndrome and related clinical clusters associated with chronic atrophic gastritis
- To better define specific diagnostic criteria for autoimmune atrophic gastritis and *H. pylori*-related multifocal atrophic gastritis
- To assess prevalence of chronic atrophic gastritis, in particular corpus-involving chronic atrophic gastritis at higher risk for neoplastic complications
- To better define the optimal management to prevent and treat micronutrient deficiencies associated with chronic atrophic gastritis
- To better define the optimal management to treat dyspeptic symptoms associated with chronic atrophic gastritis
- To stratify patients harbouring risk factors (family history for gastric cancer, autoimmune pattern, intestinal metaplasia, OLGA/OLGIM III–IV) associated with long-term neoplastic complications in order to optimise and limit the burden of endoscopic surveillance

OLGA = Operative Link for Gastritis Assessment.
OLGIM = Operative Link for Gastric Intestinal Metaplasia.

endoscopists, in order to merge the current knowledge and perspectives on this condition in a unique point of view. Evidence on many critical issues is still scanty and a lot of research remains to be done (Table 3). However, two important key points emerging from this position paper are that CAG is characterized by a multifaceted clinical picture and that its origin and natural history are probably much more complex as nowadays known. This disease should be viewed holistically as a complex clinical syndrome whose common denominator is represented by the presence of gastric atrophy, rather than being approached piecemeal for its autoimmune features, its haematological consequences or its link to long-term neoplastic complications. The definition of shared diagnostic criteria and awareness raising amongst physicians from diverse specialties should be goals in order to make a prompt and correct diagnosis of this basically benign condition with potential long-term morbidity when it remains unrecognised.

Conflicts of interest
None declared.

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