Consensus on chronic gastritis in china (9-10 November 2012 Shanghai)

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Abstract: Since the Consensus on chronic gastritis in China [1] was formed during the Chinese National Chronic Gastritis Meeting held in September 2006 in Shanghai, much progress has been made in the diagnosis and treatment of chronic gastritis, including the Operative Link for Gastritis Assessment (OLGA) [2, 3] and the European Consensus On management of precancerous conditions of gastric cancer [4]. The Maastricht-IV consensus [5] proposed the relationship between Helicobacter pylori (H. pylori) with chronic gastritis and gastric cancer, as well as the effects of H. pylori eradication [1]. Progress in endoscopic and pathological diagnosis techniques for chronic gastritis requires the previous consensus to be updated. Therefore, the “2012 Chinese National Consensus Meeting on the Diagnosis and Treatment of Chronic Gastritis” was held in Shanghai on 9-10 November 2012, sponsored by the Chinese Society of Gastroenterology, undertaken by Renji Hospital of Shanghai Jiaotong University School of Medicine and Shanghai Institute of Digestive Disease. Eighty-two gastroenterology experts from all over China discussed and revised the previous draft and passed the consensus by an anonymous vote. The voting options were: 1. Totally agree; 2. Agree, but have some reservations; 3. Agree, but have greater reservations; 4. Disagree, but have reservations; 5. Totally disagree. If the item received “1” > 66.7% or “1+2” > 85% of the votes, the term was then considered as passed and included in the consensus. The terms with otherwise votes were considered failed to pass and not reported here. This consensus is aimed to serve as the position statement of Chinese Society Gastroenterology on the prevention, diagnosis, treatment and follow-up of chronic gastritis.

Keywords: Chronic gastritis, epidemiology, H. pylori, diagnosis, treatment, follow-up

Since the Consensus on chronic gastritis in China [1] was formed during the Chinese National Chronic Gastritis Meeting held in September 2006 in Shanghai, much progress has been made in the diagnosis and treatment of chronic gastritis. This includes the Operative Link for Gastritis Assessment (OLGA) [2, 3] and the European Consensus On management of precancerous conditions of gastric cancer [4]. The Maastricht-IV consensus [5] proposed the relationship between Helicobacter pylori (H. pylori) with chronic gastritis and gastric cancer, as well as the effects of H. pylori eradication [1]. Progress in endoscopic and pathological diagnosis techniques for chronic gastritis requires the previous consensus to be updated. Therefore, the “2012 Chinese National Consensus Meeting on the Diagnosis and Treatment of Chronic Gastritis” was held in Shanghai on 9-10 November 2012, sponsored by the Chinese Society of Gastroenterology, undertaken by Renji Hospital of Shanghai Jiaotong University School of Medicine and Shanghai Institute of Digestive Disease. Eighty-two gastroenterology experts from all over China discussed and revised the previous draft and passed the consensus by an anonymous vote. The voting options were: 1. Totally agree; 2. Agree, but have some reservations; 3. Agree, but have greater reservations; 4. Disagree, but have reservations; 5. Totally disagree. If the item received “1” > 66.7% or “1+2” > 85%, the term was considered as passed. The full text of the consensus is as follows:

Epidemiology

1. Exact morbidity is difficult to obtain because most chronic gastritis patients lack symptoms. The estimated morbidity of chronic gastritis...
patients is roughly comparable with the *H. pylori* infection in local population, and may be slightly higher than that of *H. pylori* infection [6].

Almost all patients recently infected with *H. pylori* have chronic gastritis (see the next section). When tested with serological methods, most positive cases (recent or previous infection) have chronic gastritis. In addition to *H. pylori* infection, factors such as bile reflux, drugs and autoimmunity can also cause chronic gastritis. Therefore, the morbidity of chronic gastritis is probably higher, or slightly higher, than that of *H. pylori* infection.

2. The morbidity of chronic gastritis generally increases with age, especially for chronic atrophic gastritis.

The morbidity of chronic gastritis generally increases with age, including chronic atrophic gastritis, which is mainly related to increasing infection with *H. pylori* with age, atrophy and intestinal metaplasia (IM), which are also related to aging. This also reflects the evolution of gastric mucosal damage caused by the immune response to *H. pylori* infection [7]. The morbidity has little to do with gender.

3. The proportion of chronic atrophic gastritis in chronic gastritis patients varies greatly in different countries and regions. Generally, it is positively correlated with the incidence of gastric cancer [8].

Chronic atrophic gastritis is a result of *H. pylori* infection, together with environmental factors and genetic factors. The morbidity of chronic atrophic gastritis varies greatly in different countries and regions; which is associated with regional infection rates of *H. pylori*, differences in virulence genes of *H. pylori*, environmental factors and genetic background. The morbidity of chronic atrophic gastritis in high-risk areas for gastric cancer is higher than that in low-risk areas.

4. The morbidity of chronic atrophic gastritis is comparatively high in China: the correspondence rate between macroscopic observation and pathological diagnosis under endoscopy remains to be further improved.

In 2011, a cross-sectional survey was conducted under the organization of Chinese Society of Digestive Endoscopy, covering 10 cities, 30 centers and 8907 chronic gastritis patients with upper gastrointestinal symptoms confirmed by gastroscopy. The results showed that chronic non-atrophic gastritis was the most common (59.3%) among various chronic gastritis types, followed by chronic non-atrophic or atrophic gastritis with erosions (49.4%), chronic atrophic gastritis was up to 23.2% (but mostly were mild). The *H. pylori* positive rate was 33.5% in the gastric antrum and 23.0% in the corpus gastricum. The proportion of atrophy suggested by pathological changes of the gastric antrum was 35.1%, which was higher than that of endoscopy (23.2%). The atrophy rate associated with IM was 32.0% and was 10.6% for intraepithelial neoplasia (synonymous with dysplasia, for details see the Appendix). The research showed that currently, the morbidity of chronic atrophic gastritis is comparatively high in China. The correspondence rate between macroscopic observation and pathological diagnosis under endoscopy remains to be further improved.

Endoscopy

1. Endoscopic diagnosis of chronic gastritis indicates mucosal inflammatory changes observed by the naked eye or by special imaging methods; however, the results of pathological examination are required to make a final judgment.

The diagnosis of chronic atrophic gastritis is performed by endoscopic and pathological methods; however, the rate of atrophy confirmed by both endoscopy and pathological diagnosis is comparatively low [9, 10]: the definitive judgment depends mainly on pathological examination.

2. Under endoscopy, chronic gastritis can be categorized into non-atrophic gastritis (previously known as superficial gastritis) and atrophic gastritis. If there are also flattened or uplifted erosions, hemorrhage, coarse rugae or bile reflux, then the diagnosis is non-atrophic gastritis or atrophic gastritis accompanied with erosion, bile reflux, etc.

The fundamental lesions of most chronic gastritis are inflammations (hyperemia and exudations) or atrophy; therefore, it is reasonable to categorize chronic gastritis into non-atrophic...
gastritis and atrophic gastritis, which also favors the unification of pathological diagnosis.

3. Under endoscopy, the fundamental manifestations of chronic non-atrophic gastritis show as mucosal erythema, mucosal hemorrhagic spots or plaques, coarse mucosa with or without edema, and hyperemia and exudations. There are two types of erosive gastritis: flattened or uplifted. The former is characterized by single or multiple erosive lesions, whose sizes vary from pinpoint to a few centimeters. The latter is characterized by single or multiple verrucous uplifts, bulking folds or papular uplifts. Their largest diameter is 5~10 mm, and mucosal defects or umbilical sag are visible on the apex, with erosion in the center.

4. Under endoscopy, the fundamental manifestations of chronic atrophic gastritis are alternating red and white mucosa, with white predominant. The rugae become flattened or even disappear; some mucosal blood vessels are exposed, sometimes with granular or nodular appearance on the mucosa.

5. Diagnosis of special types of gastritis must consider both the etiology and pathology. The classification of special types of gastritis is related to their etiology and pathology, including chemical, radioactive, lymphocytic, granulomatous, eosinophilic and other infectious diseases.

6. At endoscopy, chronic gastritis can be subclassified into antral gastritis, corpus gastritis, pangastritis with antrum predominant or pangastritis with corpus predominant, according to the distribution of lesions.

Under endoscopy, it is difficult to grade the lesions of chronic gastritis into mild, moderate and severe, mainly because of subjective factors and the cumbersome nature of endoscopic classification [10]. Reasonable and practical grading needs to be further studied and improved.

7. Magnifying endoscopy plus staining has helped the pathological classification of gastritis under endoscopy. Magnifying endoscopy plus staining may facilitate more subtle and detailed observation of the gastric mucosa, which is valuable for the diagnosis and differential diagnosis of gastritis, as well as the early discovery of intraepithelial neoplasia and IM. Nowadays, magnifying endoscopy plus methylene blue staining is highly accurate for IM and intraepithelial neoplasia detection [11]. Hematoxylin and indigo carmine staining also have a role in the diagnosis of intraepithelial neoplasia [12, 13].

8. Endoscopic electronic dyeing technology plus magnifying endoscopy has a certain value for the diagnosis and differential diagnosis of chronic gastritis. With confocal laser endomicroscopy, it is feasible to observe the microstructure of the gastric mucosa in real time. The diagnosis of chronic gastritis, IM and intraepithelial neoplasia is highly consistent with that of biopsy [14]. Electron staining plus magnifying endoscopy is comparatively highly sensitive and specific for chronic gastritis and precancerous lesions of gastric cancer [15, 17-19]; however, there is no unified standard for its specific performance and classification.

With optical biopsy technology (hereinafter referred to as a biopsy) such as confocal laser endomicroscopy, it is feasible to observe the gastric mucosa at the cellular level. It also permits identification of microstructural changes of the gastric pit, epithelial cells and goblet cells in real time, having a certain reference value for the diagnosis of chronic gastritis and the grading of histological changes (chronic inflammation, activity, atrophy and IM) [20-23]. At the same time, optical biopsy can be used to selectively target suspected sites, which helps to improve the sampling accuracy [24].

9. It is suggested that two or more biopsy specimens should be taken, according to the nature of the lesions and need.

Endoscopists should provide necessary information to the pathologist, concerning the sampling sites, endoscopic findings and a brief history. Conditionally, a biopsy can be performed under the guide of pigment staining or electron staining plus magnifying endoscopy. Key biopsy sites should be located in the gastric antrum, stomach angle, in the lesser curvature of the corpus gastricum and in suspicious lesions.
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Histopathology

1. Gastric mucosal inflammation caused by various etiologies is termed gastritis [25]. Acute gastritis is characterized by acute inflammatory cells infiltration (neutrophils), while chronic gastritis is characterized by chronic inflammatory cells infiltration (mononuclear cells, mainly lymphocytes and plasma cells). Active chronic gastritis or chronic gastritis with activity is associated with chronic inflammatory cell infiltration in the gastric mucosa.

The gastrointestinal mucosa is the main part of the human immune system, having physiological immune cells (mainly lymphocytes, tissue cells, dendritic cells and plasma cells). Under routine microscopy, it is difficult to distinguish immune cells from chronic inflammatory cells histopathologically. Pathologists advise that for specimens with only one mononuclear cell infiltration per gland on average, they should not be considered as “pathological” gastric mucosa.

2. For accurate judgment and a high degree of reproducibility, the basic requirement of gastric mucosa biopsy specimens is: the number and positions of sampling sites of biopsy specimens should be determined by the endoscopist, according to the need. They should be fixed as soon as possible after sampling and attention should be paid to the embedding direction.

3. The observation of chronic gastritis includes five histological changes and four grades [26]. The five histological changes include H. pylori infection, chronic inflammation (mononuclear cells infiltration), activity (neutrophils infiltration), atrophy (reduction of the proper gastric glands) and IM (intestinal metaplasia). The four grades are: 0, none; +, mild; ++, moderate; +++, severe. See Appendix of “visual analog scale”.

Relationship between helicobacter infection and chronic gastritis

At present, nearly 40 species in the genus helicobacter have been confirmed [27] with new species being discovered all the time. H. pylori or Helicobacter hellmannii infection can cause chronic gastritis.

1. H. pylori infection is the major etiology of active chronic gastritis.

The relationship between H. pylori infection and active chronic gastritis coincides with the four fundamental requirements of Koch’s postulation concerning the definition of a pathogen as the etiology of a disease: H. pylori infection is present in the gastric mucosa in 80-95% of patients with active chronic gastritis, and the 5-20% H. pylori negative chronic gastritis cases merely reflects the diverse causes of chronic gastritis; in patients with H. pylori-related gastritis, the distribution of H. pylori coincides with inflammation; eradication of H. pylori can lead to regression of gastric mucosal inflammation. Generally, the regression of neutrophils comes sooner, whereas the regression of lymphocytes and plasma cells needs more time [28]. H. pylori infection-induced gastritis has been confirmed in volunteers [29] and in animal models.

In nodular gastritis, the H. pylori infection rate is the highest, close to 100% [30, 31]. This type of gastritis mostly occurs among young women [32] and the characteristic histopathological feature of the gastric mucosa is a large number of lymphoid follicles [30, 32].

2. Almost all H. pylori infection can cause an active inflammation of the gastric mucosa. Gastric mucosal atrophy and IM occurs in some patients after long-term infection. The synergistic effect of H. pylori, the host and environmental factors determines the type and progress of H. pylori-related gastritis.

Almost all H. pylori infection can cause an active inflammation of the gastric mucosa, the presence of which is highly suggestive of H. pylori infection [28]. An inflammatory and immune response induced by long-term H. pylori infection can cause the development of gastric mucosal atrophy and IM in some patients [33, 34]. There are two prominent types of H. pylori-related chronic gastritis: pangastritis with antrum predominant and pangastritis with corpus predominant. An increase in gastric acid secretion occurs in the former, which increases the risk of developing a duodenal ulcer, whereas gastric acid decreases in the latter and the risk of developing gastric cancer increases. The synergistic effect of the host (gene polymorphism of cytokines [35, 36], such as interleukin-1B), environmental factors (such as smoking or a high-salt diet) and H. pylori factors (virulence genes) determines the type of H.
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*pylori*-related gastritis and the development and progress of atrophy and IM [37].

3. Eradication of *H. pylori* can improve the dyspeptic symptoms in some chronic gastritis patients.

Most patients with *H. pylori*-related gastritis have no symptoms. Patients with dyspeptic symptoms might belong to the category of functional dyspepsia [38]. Therefore, determining whether eradication of *H. pylori* can eliminate the dyspeptic symptoms of chronic gastritis should be based on the results of studies on functional dyspepsia. Meta-analysis has shown that eradication of *H. pylori* can result in the long-term improvement of dyspeptic symptoms in some patients with functional dyspepsia, which also is a cost-effective strategy for eliminating or ameliorating dyspeptic symptoms [39]. Several studies have shown that for patients with a high gastric mucosal inflammation and activity [40], or mainly with epigastric pain [41], significant improvement in their symptoms can be achieved by eradicating *H. pylori*.

4. Eradication of *H. pylori* can eliminate the activity of *H. pylori*-related chronic gastritis, alleviate the chronic inflammatory reaction, prevent further development of gastric mucosa atrophy and IM and even reverse the atrophy in some patients.

Many studies have confirmed that eradication of *H. pylori* could cause histological changes in the gastric mucosa in chronic gastritis patients, including elimination of the activity and reducing the degree of chronic inflammation [40, 42]. Meta-analysis has shown that eradication of *H. pylori* can result in the reversion of gastric mucosal atrophy in some patients, but causes only slight reversion of IM [43, 44]. Many factors can influence the judgment the reversion of atrophy and IM, such as the variation of biopsy sites; the follow-up period, the mimicked "atrophy" caused by mass inflammatory cell infiltration in the gastric mucosa with *H. pylori* infection, and so on. There may be a point of no return during the progress of atrophy, beyond which reversion is difficult. Many studies have shown that eradication of *H. pylori* could prevent the further progress of gastric mucosal atrophy and IM to some extent [40, 42, 45-47].

5. Helicobacter helimannii infection can also cause chronic gastritis [48-50].

In chronic gastritis patients, the *Helicobacter helimannii* infection rate is about 0.15%–0.20%. Compared with *H. pylori* infection, *Helicobacter helimannii* infection causes much less gastric mucosal inflammation, and eradication of *Helicobacter helimannii* can also result in the recession of gastric mucosal inflammation [51]. *Helicobacter helimannii* infection can also cause mucosa-associated lymphoid tissue (MALT) lymphoma [50].

**Clinical manifestations, diagnosis and treatment**

1. Most chronic gastritis patients [52] have no symptoms. In patients who do have symptoms, they are mainly non-specific dyspepsia: the presence or absence of dyspeptic symptoms and severity of dyspeptic symptoms have no significant relation to histopathological grades and endoscopic findings of chronic gastritis [55].

Some chronic gastritis patients have dyspepsia symptoms, such as epigastric pain, abdominal fullness, etc. There is no significant difference in clinical manifestations and psychological status between chronic gastritis with dyspepsia symptoms and patients with functional dyspepsia [54]. Some scholars have found that 85% of patients with functional dyspepsia have gastritis, and 51% are accompanied by *H. pylori* infection [55], which varies by regions. Gastroesophageal reflux and alimentary canal motility disorders are present in some chronic gastritis patients at the same time, especially in elderly patients with severe esophageal sphincter relaxation and gastrointestinal motility disorder [56]. Epidemiological studies have shown that about 50%–70% of the elderly present with chronic atrophic gastritis [57]. The symptoms in patients are non-specific, even with different endoscopic performances and histopathological results, and the severity of symptoms has no significant relation to histopathological grades and endoscopic findings [53].

2. The diagnosis of chronic gastritis depends mainly on endoscopic examination and biopsy of gastric mucosa, especially the latter.
Given that most chronic gastritis patients have no symptoms, and the symptoms and signs are not specific even if they are present. Therefore, diagnosis of chronic gastritis cannot be made through symptoms and signs. The diagnosis of chronic gastritis depends mainly on endoscopic examination and histopathological examination of biopsy specimens, especially the latter (for details, see the sections entitled “Endoscopy” and “Histopathology”).

3. Diagnosis of chronic gastritis should include the etiology, and *H. pylori* should be routinely tested for.

*H. pylori* infection is the major cause of chronic gastritis, and *H. pylori* detection should be routine in the etiological diagnosis of chronic gastritis. In patients with atrophic corpus gastritis, serum gastrin G17 is markedly elevated, and the serum level of pepsinogen I or the pepsinogen I/II ratio is significantly reduced. In patients with atrophic antral gastritis, serum G-17 is reduced, and the serum level of pepsinogen I or pepsinogen I/II ratio is normal. Both serum G-17 and serum level of pepsinogen I or pepsinogen I/II ratio are reduced in patients with atrophic pangastritis. The determination of serum gastrin G17, and pepsinogen I and II may be helpful for judging the presence of gastric mucosal atrophy and the site of atrophy [58-60]. Atrophic corpus gastritis can be caused by *H. pylori* infection or by autoimmunity [61, 62]. For gastritis suspected of being caused by autoimmunity, serum gastrin, vitamin B12, parietal cell antibodies and intrinsic factor antibodies should be measured.

4. The therapeutic aim for chronic gastritis is to ameliorate the symptoms and reduce the inflammation of gastric mucosa. Therapy should target the etiology as much as possible, and follow the principle of individualization.

The therapeutic aim for chronic gastritis is to ameliorate the symptoms and improve the histopathology of gastric mucosa. The management of the dyspeptic symptoms of chronic gastritis is similar to that of functional dyspepsia. For those chronic non-atrophic gastritis patients with negative *H. pylori* and absence of symptoms, specific treatment is not required. However, for those with atrophic gastritis, especially severe atrophic gastritis or gastritis accompanied by intraepithelial neoplasia, special attention should be paid to the prevention of canceration.

5. Eradication of *H. pylori* is recommended in patients with *H. pylori*-positive chronic gastritis associated with gastric mucosa atrophy, erosions or dyspeptic symptoms.

Whether eradication of *H. pylori* is needed for *H. pylori*-related gastritis is still a matter of controversy. The Chinese consensus on the treatment of *H. pylori* infection [63] recommends *H. pylori* eradication therapy for those with gastric mucosa atrophy, erosions or dyspeptic symptoms. As mentioned above, the main symptoms of chronic gastritis are dyspepsia, mainly functional dyspepsia. Eradication therapy can result in the long-term improvement of functional dyspeptic symptoms in *H. pylori*-positive patient [64, 65]. Such eradication can improve the histopathology of the gastric mucosa [66], help prevent peptic ulcers and gastric cancer, and is cost-effective.

6. For patients with gastric mucosal erosion and/or with sour regurgitation and epigastric pain, antacids, *H*₂ receptor antagonists or proton pump inhibitors (PPIs) can be administered according to the conditions or severity of symptoms.

Gastric acid and pepsin play an important role in the occurrence of gastric mucosal erosion (especially flattened erosion), sour regurgitation, epigastric pain, and other symptoms. Antacids or acid suppression therapy could heal the erosion and eliminate the above symptoms. The effect of antacids is transient, while PPIs have strong and persistent acid suppression effects, and include omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole, which can be selected according to the conditions or severity of symptoms [67]. For some patients, it may be a more economical option to choose moderate acid suppression therapy, with fewer adverse reactions.

7. According to the symptoms of patients, prokinetics or digestive enzyme preparations can be considered. Prokinetics may be used in the patients who mainly have upper abdominal fullness, nausea and vomiting. Those associated with bile reflux may consider prokinetics and/or gastric protective agents that have the effect of binding bile acids. Those with dyspepsia symp-
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Symptoms, such as abdominal fullness obviously related with feeding and lack of appetite, may consider digestive enzyme preparations. More data are needed.

Bile reflux is also a potential etiology of chronic gastritis. Insufficiency of the pyloric sphincter leads to the reflux of bile into the stomach, lessening or destroying the barrier function of the gastric mucosa, which would expose the gastric mucosa to digestive fluid, resulting in inflammation, erosions, hemorrhage and epithelial metaplasia. Upper abdominal fullness, or nausea and vomiting may be related to the delay in gastric emptying. Gastric dynamic anomaly is a factor that should not be ignored for chronic gastritis [68]. Prokinetics such as Mosapride, Itopride and domperidone, may improve the above-mentioned symptoms [69, 70] and may also prevent or reduce bile reflux. Gastric mucosa-protective agents, such as sucralfate, teprenone, gefarnate, rebamipide, and ecabet [71-77], may strengthen the gastric mucosal barrier, and promoting healing of gastric mucosal erosions. However, the ameliorating effect on these symptoms is still controversial. A hydrotalcite preparation [78, 79] may strengthen the gastric mucosal barrier and bind bile acid, thereby eliminating or reducing the gastric mucosal damage caused by bile reflux.

Under the circumstance that gastric mucosal lesions (such as those accompanied by peptic ulcers and severe erosion) are not caused by abdominal fullness because of the delay in gastric emptying, by gastric outlet obstruction, by reduced gastric mucosa barrier or by hyperacidity, digestive enzyme preparations (such as Compound Azimtamide, Oryz-Aspergillus Enzyme, Pancreatin tablets, and all kinds of pancreatin) can be selected to alleviate dyspepsia symptoms, like abdominal fullness, obviously related to feeding and lack of appetite [80, 81].

8. Anti-depression and anti-anxiety drugs may be used in, but not limited to, the chronic gastritis patients with obvious psychiatric factors.

Psychological factors are associated with dyspepsia symptoms. For those with somniphathy, obvious mental factors, or no or poor response to conventional treatment, psychological therapy may be considered.

9. Chinese traditional medicine can be used for the treatment of chronic gastritis.

Outcome of chronic gastritis, follow-up of chronic atrophic gastritis and prevention of canceration

1. Outcomes of chronic gastritis include reversion, persistent stabilization and aggravation. Most chronic atrophic gastritis is stable, but further progress may occur in moderate or severe patients without any intervention. The risk of developing into gastric cancer increases for those patients accompanied with intraepithelial neoplasia [82-84].

Most chronic atrophic gastritis is relatively stable, especially for those without *H. pylori* infection. The presence of histopathological changes, such as atrophy, may increase with age [85]. Current opinion states that persistent *H. pylori* infection can lead to chronic atrophic gastritis, regardless of age.

Repeated or persistent *H. pylori* infection and poor dietary habits can potentially aggravate atrophy and IM of the gastric mucosa [86]. The following factors can all increase or aggravate the risk of chronic atrophic gastritis, even the possibility of canceration [87, 88]: excessive nitrate and nitrite in the water and soil; disproportionate trace elements; smoking; chronic alcohol intake; lack of fresh vegetables, fruits, and essential nutrients; regular consumption of fast-food, such as mildew, pickled, smoked and fried foods; excessive intake of salt; and a family history of gastric cancer.

Chronic atrophic gastritis is often accompanied with IM, and a minority have intraepithelial neoplasia. After long-term evolution, some cases develop into gastric cancer [82-84]. Most patients with low-grade intraepithelial neoplasia can revert, having little possibility of canceration [86, 89, 90].

2. *H. pylori*-related antral gastritis frequently develops into a duodenal ulcer; gastric ulcers commonly occur in multifocal atrophic gastritis.

Some patients with *H. pylori*-related gastritis (< 20%) might develop a peptic ulcer; patients with antral gastritis frequently develop a duodenal ulcer, and patients with multifocal atro-
Gastric gastritis commonly develop a gastric ulcer [91]. Some cases of chronic non-atrophic gastritis may progress to chronic atrophic gastritis.

3. Patients with chronic atrophic gastritis, especially those with moderate or severe IM or intraepithelial neoplasia, should be followed up regularly with endoscopic and histopathological examinations.

It is generally believed that a certain canceration rate is present for moderate and severe chronic atrophic gastritis. To decrease the incidence of gastric cancer, and to benefit the patients and keep costs down patients with moderate to severe chronic atrophic gastritis accompanied with IM should be followed up once a year with a biopsy. Those without IM or intraepithelial neoplasia should be followed up with endoscopy and histopathology [93]. Patients with low-grade intraepithelial neoplasia confirmed not to be from the adjacent cancerous tissues, should be followed up once every 6 months in accordance with the endoscopic and clinical findings. Those with high-grade intraepithelial neoplasia should be confirmed immediately, with surgical treatment or local treatment under endoscopy when necessary [1].

To facilitate the monitoring and follow-up of lesions, conditionally mucosa target biopsy (MTB) should be considered [94, 95]. This technology adopts mucosa target biopsy forceps and calibration solution for positioning the biopsy sites and sampling at the same time, enabling the accurate positioning of suspicious lesions and long-term follow-up review. For erosive gastritis, the lesion is the recommended positioning site, while for chronic atrophic gastritis, the gastric antrum at the lesser and greater curvature, stomach angle, corpus gastricum at the lesser and greater curvature, and lesions are the recommended sites.

In addition, atrophied lesion manifest as “focal distribution”; the change of target sites is not equal to that of non-targeted sites. Endoscopists cannot simply resample the last biopsy site and neglect the biopsy of new lesions. Currently opinion states that the scope of atrophy or IM (see the OLGA staging system in “issues need further study” of this consensus) is an important indicator for judging the severity, which cannot be reflected by target biopsy.

4. Eradication of H. pylori may slow canceration process and reduce the incidence of gastric cancer, but the best intervention time is before the onset of precancerous lesions (including atrophy, IM and intraepithelial neoplasia).

More studies have found that H. pylori infection promotes the development of chronic atrophic gastritis into gastric cancer [96]. Eradication of H. pylori can significantly slow the progress of precancerous lesions, and may reduce the risk of gastric cancer [97-99].

According to newly published research on eradication of H. pylori with a follow-up period of 14.7 years, the incidences of gastric cancer were 3.0% and 4.6% for H. pylori eradication group (1130 cases) and placebo group (1128 cases), respectively [100]. Eradication of H. pylori shows better prevention of canceration for mild chronic atrophic gastritis [46]. Eradication of H. pylori is beneficial to the histopathological improvement of precancerous lesions [45].

Some bioactive vitamins [100-104], such as vitamin C [105-108] and the trace element selenium [109-111] may reduce the risk of gastric cancer. For some patients with low folate levels, a moderate supplementation of folic acid can improve the histopathological conditions of chronic atrophic gastritis, preventing the occurrence of gastric cancer [112-120].

Issues requiring further study

1. The influence of H. pylori virulence genes on different clinical outcomes after H. pylori infection requires further research and comprehensive analysis.

H. pylori infection has different clinical outcomes, such as chronic non-atrophic gastritis, atrophic gastritis, peptic ulcers and gastric cancer. It is generally believed that the variability of outcomes of H. pylori infection is a combined result of H. pylori, the host and environmental factors. H. pylori’s influence mainly resides in its virulence or the virulence-related genes, such as cagA, vacA and cagA, and pathogenicity island genes, iceA and babA2. However, the relationship between the infection of H. pylori...
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2. *H. pylori* infection may play a role in the pathogenesis of lymphocytic gastritis, Ménétrier disease and autoimmune gastritis or Russell body gastritis.

(1) Lymphocytic gastritis is a rare, specific type of chronic gastritis whose etiology is not yet fully clear. Its histopathological characteristic is marked lymphocytic infiltration in the gastric mucosal epithelium. A large sample (51 cases) multi-center study showed that for the majority of patients with *H. pylori*-positive lymphocytic gastritis (95.8%), their gastritis was significantly ameliorated after eradication of *H. pylori*. In contrast, there was only a 53.8% improvement in patients treated with omeprazole or placebo, and for those who had not improved, all showed improvement after eradication of *H. pylori* [123]. These results suggest that eradication of *H. pylori* is effective in some cases of *H. pylori*-positive lymphocytic gastritis.

(2) Ménétrier disease: giant mucosal rugae and hypoproteinemia are the main characteristics. Its etiology is not yet known. There are several reports showing that *H. pylori*-positive Ménétrier disease remitted or healed after eradication of *H. pylori* [127, 128]. Therefore, *H. pylori* eradication therapy should be considered as a treatment for *H. pylori*-positive Ménétrier disease [126].

(3) Autoimmune gastritis: a type of gastritis developed on the basis of autoimmunity, characterized by inflammation and atrophy of the corpus mucosa. In genetically susceptible individuals, *H. pylori* infection can activate gastric CD4+ Th1 lymphocytes, which may cross-identify the epitopes shared by protein and parietal H+K+-ATPase; i.e., it participates in the process of gastric autoimmunity through a molecular mimicry mechanism. *H. pylori* plays a role in the early stage of autoimmune gastritis, before the development of atrophy, and eradication of *H. pylori* may form a partial cure for autoimmune gastritis.

(4) Russell body gastritis: a rare kind of gastritis characterized with marked plasma cell infiltration in the gastric mucosa, with many Russell bodies (PAS staining positive) in the cytoplasm. This type of gastritis can be complicated by gastric ulcers, and should be histologically differentiated from signet-ring cell carcinoma and MALT lymphoma. Eradication of *H. pylori* can improve most Russell body gastritis [128-131].

Table 1. The OLGA staging frame

<table>
<thead>
<tr>
<th>Atrophy Score</th>
<th>Corpus</th>
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<tbody>
<tr>
<td><strong>Antrum</strong></td>
<td></td>
</tr>
<tr>
<td>No Atrophy (score 0) (including incisura angularis)</td>
<td>STAGE 0</td>
</tr>
<tr>
<td>Mild Atrophy (score 1) (including incisura angularis)</td>
<td>STAGE I</td>
</tr>
<tr>
<td>Moderate Atrophy (score 2) (including incisura angularis)</td>
<td>STAGE II</td>
</tr>
<tr>
<td>Severe Atrophy (score 3) (including incisura angularis)</td>
<td>STAGE III</td>
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</table>

3. The prevention of gastric cancer by cyclooxygenase (COX) 2 inhibitors requires further study.

Some reports have suggested that COX2 inhibitors could reduce the incidence of gastric cancer [47, 132]; however, given the possibility of induced cardiovascular events, it is not recommended for application in the general population.
4. Whether the OLGA staging system proposed by some international experts is suitable for application in China has yet to be determined.

In 2005, the international group of pathologists (Atrophy club) put forward forward staging criteria for gastric mucosa inflammation and atrophy, summarized as the OLGA staging system [2, 3] which were different from the updated Sydney classification system of gastritis [91] (Table 1). The OLGA system aims to comprehensively analyze the histopathology, clinical manifestations and canceration risk of chronic gastritis. However, whether it is suitable for the clinical work in China is yet to be determined.

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Appendix: pathological diagnosis criteria of chronic gastritis and related matters needing attention

Visual analogue scale

Notes [133]:

1. Common lesions of chronic gastritis are mainly grouped into atrophic and non-atrophic. “Superficial” is no longer used because “superficial” is the opposite of “deep”, which is used to distinguish depth, and cannot reflect the amount of gastric mucosal glands.

2. Chronic gastritis can be subclassified into antral gastritis, corpus gastritis and pangastri
tis according to the distribution of lesions.

3. A small proportion of chronic gastritis cases are special types of gastritis, such as chemical, lymphocytic, granulomatous, eosinophilic, collagenous, radioactive, infectious (bacterial, viral, fungal and parasitic) gastritis and Méné-
trier disease.

4. Definition of atrophy [3, 134]: atrophy of the gastric mucosa indicates the reduction of gas-
tric glands proper. Histopathologically there are two types: (1) metaplastic atrophy, when the gastric mucosa lamina propria are partly or all replaced by intestinal epithelial glands; and (2) non-metaplastic atrophy, when the amount of gastric glands proper in the gastric mucosa is diminished, and replaced by fibrous or fibro-
muscular tissue, or inflammatory cells (mainly chronic inflammatory cells).

5. A diagnosis of chronic atrophic gastritis can be made if the histopathology has shown atro-
phic changes of the gastric glands proper, no matter what number of biopsy specimens show atrophy and degrees of atrophy. Clinicians can finally judge the extent and degree of atrophy according to the results of histopathological examination and endoscopic findings.

6. Mucosal atrophy at an early stage, or multifo
cal chronic atrophic gastritis, has a patchy dis-
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As the destruction of gastric glands frequently occurs in specimens taken from the edges of erosive or ulcerated mucosa, the resulting decrease in the amount of gastric glands cannot be regarded as chronic atrophic gastritis. Furthermore, the biopsy tissue may be too thin, and inappropriate dissection of embedded tissue might also influence the judgment of atrophy. If full lamina propria are not visible, one cannot judge the presence of atrophy.

7. The histopathological changes of each biopsy specimen from different sites should be reported [135, 136]. The biopsy specimens from different sites should be separately fixed and clearly labeled. Serial numbers and embedding should be given to each specimen during the pathological examination. After observation, reports should be separately issued on specimens from different sites. This kind of report could provide more direct information to the clinician, helping endoscopists to inspect their observation ability under the gastroscope and improve their judgment accuracy.

8. “Dysplasia” has long been used to represent a precancerous lesion. Recently, it has been replaced by “intraepithelial neoplasia” [137, 138]. Dysplasia can be categorized as mild, moderate and severe, while intraepithelial neoplasia can be categorized into low grade and high grade. Dysplasia and intraepithelial neoplasia are synonyms, but intraepithelial neoplasia is the term recommended by the International Agency for Research on Cancer, World Health Organization. The use of this term, together with its translation into Chinese, has not yet been agreed both internationally and in this country.

9. Detailed information of five histological changes and four grades.

(1) H. pylori infection: Observe H. pylori on the surface of mucus layer of gastric mucosa, superficial epithelium, pit epithelium and glandular epithelium. 0: no H. pylori seen in specific stain section; +: a few H. pylori are present occasionally or on less than 1/3 of the full length of the specimen; + +: the distribution of H. pylori exceeds 1/3 but is less than 2/3 of the full length of the specimen, or it is continuously but sparsely distributed through the superficial epithelium; + + +: H. pylori appears in clumps, distributed on the full length of the specimen. Usually, there is no H. pylori colonization on the surface of the intestinal metaplasia, and the non-intestinal metaplasia sites should be explored. For patients with an obvious inflammation, yet in whom no H. pylori is found in the HE stained section, a specific stain and careful observation should be done. The Giemsa stain is recommended, but other stains to which the endoscopist is accustomed can also be used.

(2) Chronic inflammation (mononuclear cell infiltration): Chronic gastritis can be graded according to the density of chronic inflammatory cells and the depth of infiltration in the mucosal layer, depending mainly on the former. 0: no more than five mononuclear cells in each high power field (including the indistinguishable lymphocytes and plasma cells under optical microscope), if the number slightly exceeds this figure but no obvious endoscopic abnormality is present, pathologically it can be diagnosed as fundamentally normal; +: a few chronic inflammatory cells localized in the superficial layer of the mucosa, but not over more than 1/3 of the mucosal layer; + +: a more intensive accumulation of chronic inflammatory cells, but not exceeding 2/3 of the mucosal layer; + + +: an intensive accumulation of chronic inflammatory cells occupying the whole mucous layer. When calculating the density, one should avoid the areas of lymphoid follicles and surrounding small lymphocytes.

(3) Activity (neutrophils infiltration). 0: no neutrophils infiltration in a chronic inflammatory background; +: some neutrophil infiltration in the mucosal lamina propria; + +: more neutrophils visible in the mucosa layer, also between superficial epithelial cells, pit epithelial cells or ductal epithelial cells; + + +: a more intensive neutrophils infiltration, or an abscess on pits can be seen in addition to what is seen in moderate activity.

(4) Atrophy: the degree of atrophy is calculated in ranks of a 1/3 reduction of the gastric gland proper. 0: the number of gastric gland proper is not reduced; +: the number of gastric gland proper is reduced by no more than 1/3 of the original glands; + +: the number of gastric gland proper is reduces by 1/3 to 2/3 of the original glands. + + +: the number of gastric gland proper is reduced by more than 2/3 of the original glands.
glands, with only a few glands remaining or all have completely disappeared. IM limited to areas of gastric pits should not be considered as atrophy. Lymphoid follicles appearing in the mucosal layer also cannot be considered as atrophy, and should depend on the condition of the glands in their peripheral areas. The histopathological process of mucosal damage induced by all causes may lead to the reduction of gastric glands, it does not necessarily indicate chronic atrophic gastritis. If the specimen is too shallow to reach the muscularis mucosa, a diagnosis of atrophy cannot be made.

(5) Intestinal metaplasia (IM). 0: without IM; +: the IM area accounts for less than 1/3 of the total area of the glands and superficial epithelium; ++: IM accounts for 1/3 to 2/3; +++: IM accounts for more than 2/3.

(6) Other histological characteristics: Histological changes do not need to be graded, but should be mentioned when they appear. They may be divided into two types: non-specific and specific. The former includes lymphofollicular, pit epithelial hyperplasia, pancreatic metaplasia and pseudo-pyloric metaplasia. The latter includes granulomatous, clustering eosinophils infiltration, obvious intraepithelial lymphocyte infiltration and specific pathogens. Pseudo-pyloric metaplasia is a marker of acid secretory gland atrophy. The sampling site should be checked when judgment is made. Mucus secretory glands seen in the gastric angularis should not be diagnosed as pseudo-pyloric metaplasia.

(7) Grades should be noted when accompanied with intraepithelial neoplasia.

10. Sampling of gastroscope biopsy specimens: due to the uneven distribution of histopathological changes of chronic gastritis, such as inflammatory reaction degree, gland IM, gland atrophy and interstitial proliferation, certain basic conditions must be met for the gastroscope biopsy.

(1) The diameter of the gastroscope biopsy forceps must more than 2 mm (both the width and depth of a gastric area are 1.5 mm); biopsy forceps can be opened fully (or half).

(2) The biopsy samples must be placed immediately into fixative (within 10 seconds would be better, lest drying affects production; fixative is 4% formaldehyde solution in neutral buffer).

(3) The surface and deeper layers of the mucosa should be confirmed by a pathologist when embedding, ensuring that the full mucous layer can be observed after sectioning; otherwise, the fundamental conditions for determining the presence or absence of atrophy will not be met.