Clinical Approach to Gastric Pre-Cancerous Lesion

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Gastric Pre-Cancerous Lesion

- **Dx**
- **Risk stratification**
- **Predictors of Progression of Gastric IM**

✓ Clinical Features

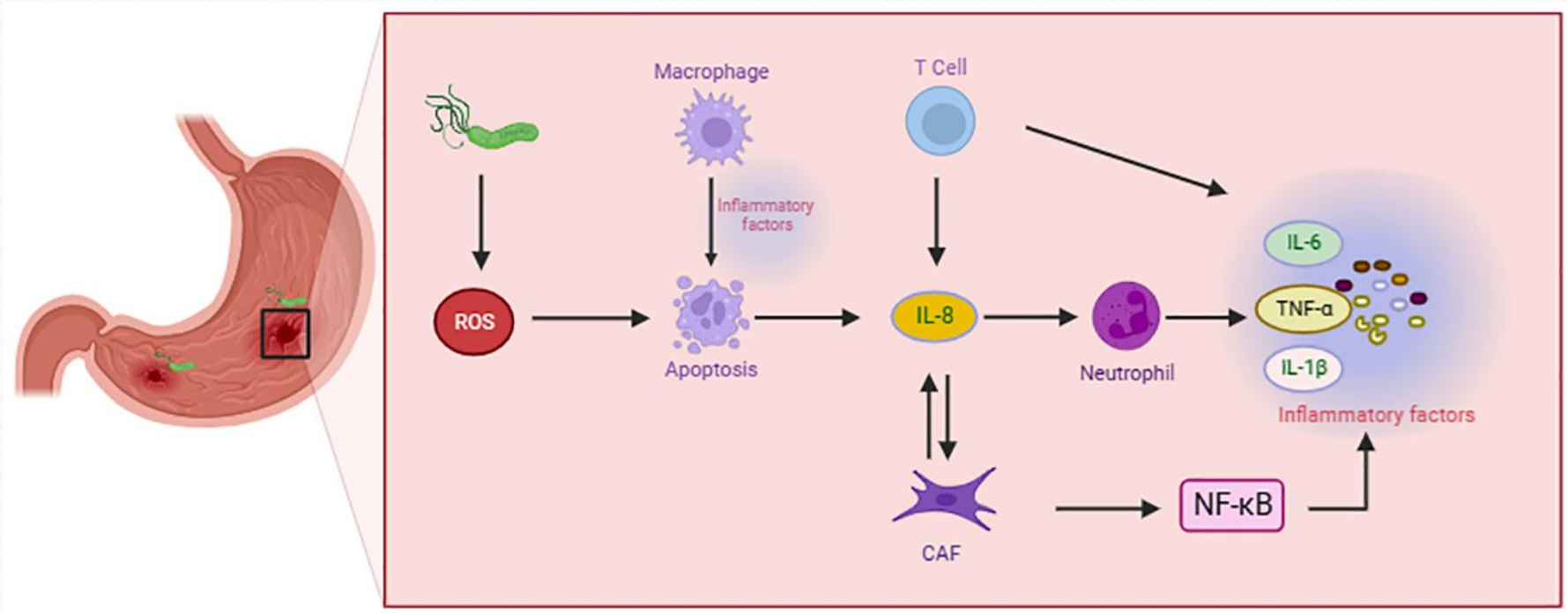
✓ Endoscopic Features

✓ Prevention,surveillance

- **Treatment**

Immune cells contribute to the advancement of gastric precancerous lesions8

Frontiers in Immunology10.3389/fimmu.2023.1297101

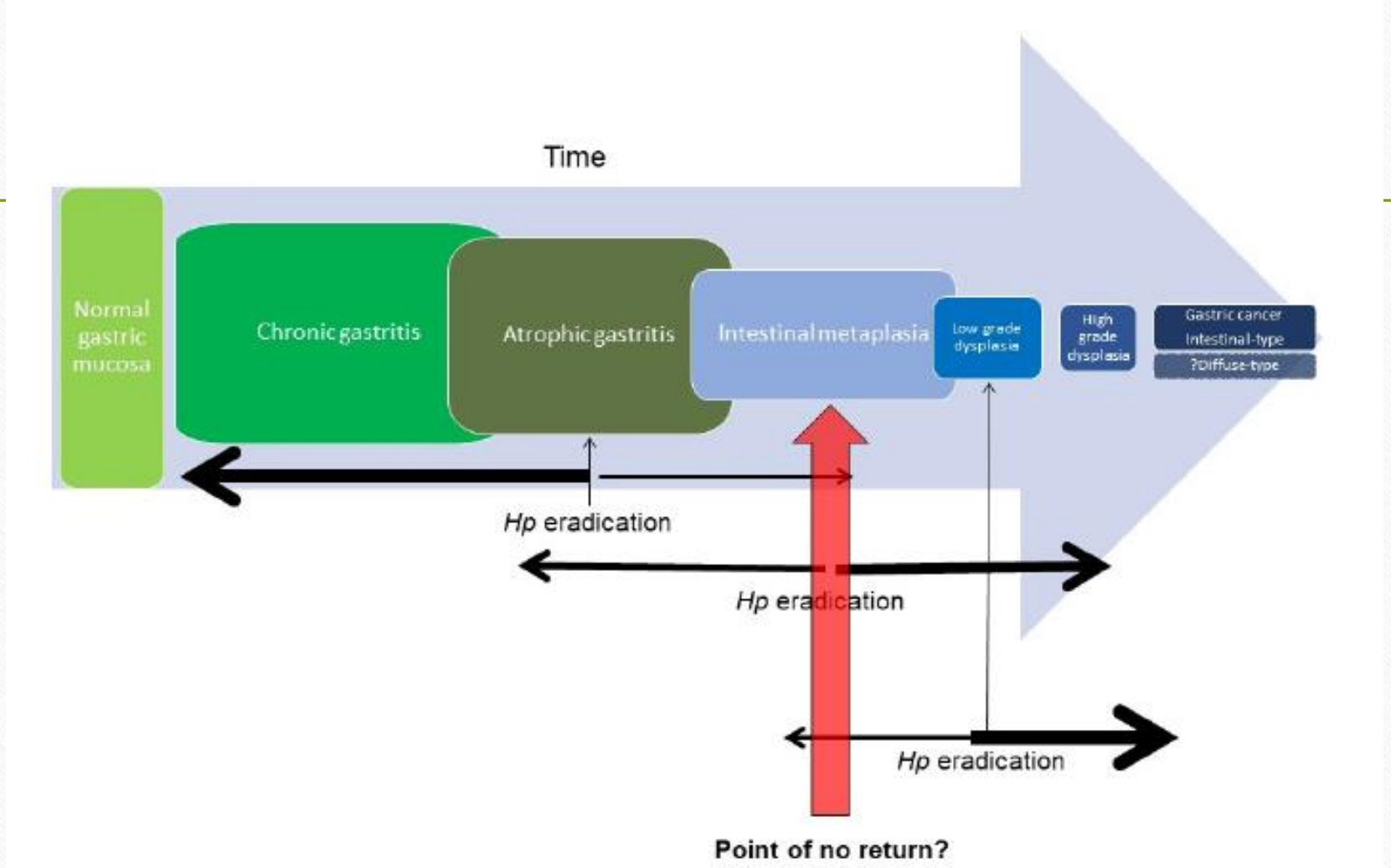


Summary of inflammatory molecules and microorganisms implicated in gastric precancerous lesions8

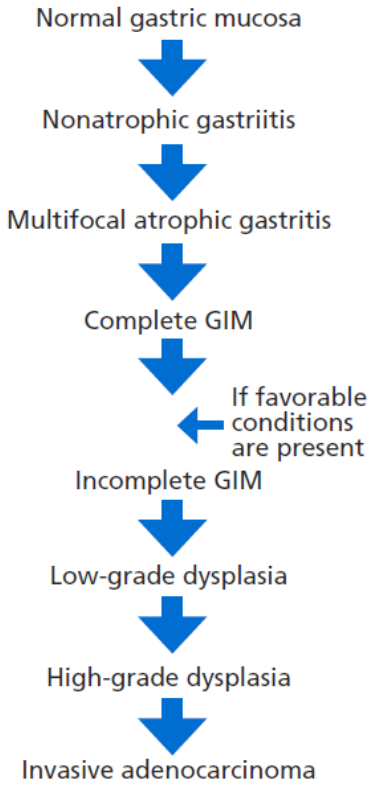
Frontiers in Immunology10.3389/fimmu.2023.1297101

Name	Type	Function description	Implicated in GPL	PMID
Gut microbiome	Microorganism	Digestion, development, fecundity, and lifespan	Impact immune responses and inflammatory cytokines release	30510004
Bile acid	Endogenous metabolites	Dissolve lipid, modulate hepatic and intestinal functions and improve insulin sensitivity	Stimulate macrophages, release exosomes	32033746
IL-8	Chemokine	Mediate the inflammatory response	lead to DNA and tissue damage	14760971
IL-1β	pro-inflammatory cytokine	Stimulate the synthesis of prostaglandins, activate neutrophils, T-cell and B-cell	Recruit and activate immune cells	17676045
IL-33	Cytokine	Initiate the release of T-helper type 2-associated cytokines	Upregulate cells apoptosis, increase caspase-3, decrease Bcl-xL	32151084
iNOS	messenger molecule	Produce nitric oxide and involve in inflammation	Modulate the inflammation	10348815
COX-2	enzyme	An enzyme that is phosphorylated by oxidation	Modulate the inflammation	10348815

Schematic of progression along Correa cascade



The Correa cascade illustrates the progression from precancerous histologic changes in the gastric mucosa to the developmeny of gastric intestinal metaplasia



Progression of GIM to gastric cancer

- Well documented
- A total of **10 cohort studies**, including 2 that were US-based, involving **25,912 patients with GIM**
- Pooled incidence rate of gastric cancer of more than **12 cases per 10,000 person-years**
- Cancer progression is more likely in patients with GIM who develop dysplasia.
- In a study from the Netherlands, the **annual incidence of gastric cancer was**

✓ **0.25% with GIM**

✓ **0.6% with mild-to-moderate dysplasia**

✓ **6% with severe dysplasia at baseline.**

- *CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 91 • NUMBER 1 JANUARY 2024*

Risk factors for progression to malignancy in gastric intestinal metaplasia

	Relative risk	95% confidence interval
Incomplete gastric intestinal metaplasia[1]	3.33	1.96–5.64
Extensive gastric intestinal metaplasia[1]	2.07	0.97–4.42
Family history of a first-degree relative with gastric cancer[1]	4.5	1.3–15.5
Smoking[26]	1.57	1.24–1.98
Alcohol[26]	1.29	1.12–1.50

Screening tests, must fulfill certain criteria WHO

- The diagnosed condition should be **an important health problem.**

✓ As GPCs are formed ahead of GC, their diagnosis and surveillance are important to closely monitor people who are at risk of developing GC and eventually treat the disease at the early stage

*Cancers **2024**, 16, 2254. https://doi.org/10.3390/cancers16122254*

Screening tests, must fulfill certain criteria, WHO

- The test must **be safe** to administer and acceptable to the population.
- ✓ While endoscopy is an invasive test and not well accepted by patients, we should consider embracing the development of noninvasive markers to improve the adherence of patients.
- The test should be reasonable in terms of **cost**.
- Tests should be **affordable to be accepted** by health systems, especially in low- and middle-income countries, where most of the GC cases occur.
- Tests should lead to the **improvement of health outcomes**.
- ✓ By implementing screening tests for GPC, we can, in consequence, decrease the mortality of GC
- Test should be sensitive.
- ✓ **High sensitivity with high specificity** is the main goal of screening tests.
- To date, different molecular targets have been analyzed as potential biomarkers in patients at risk of GC
- *Cancers **2024**, 16, 2254. https://doi.org/10.3390/cancers16122254*

Non-invasive marker / endoscopic examination with gastric biopsies

- Single biomarker with sufficiently high sensitivity and specificity

✓ **Has yet to be identified or validated**.

- **Pepsinogens** are the most studied biomarkers, and potentially combining pepsinogens with one or more of the emerging tests could potentially improve the performance of non-invasive testing for GPC.
- **Careful endoscopic examination with gastric biopsies for histological assessment**

✓ Most reliable method for GPC detection and grading

Cancers ***2024****, 16, 2254. https://doi.org/10.3390/cancers16122254.*

An algorithmic approach to diagnosis and management/ Sydney protocol

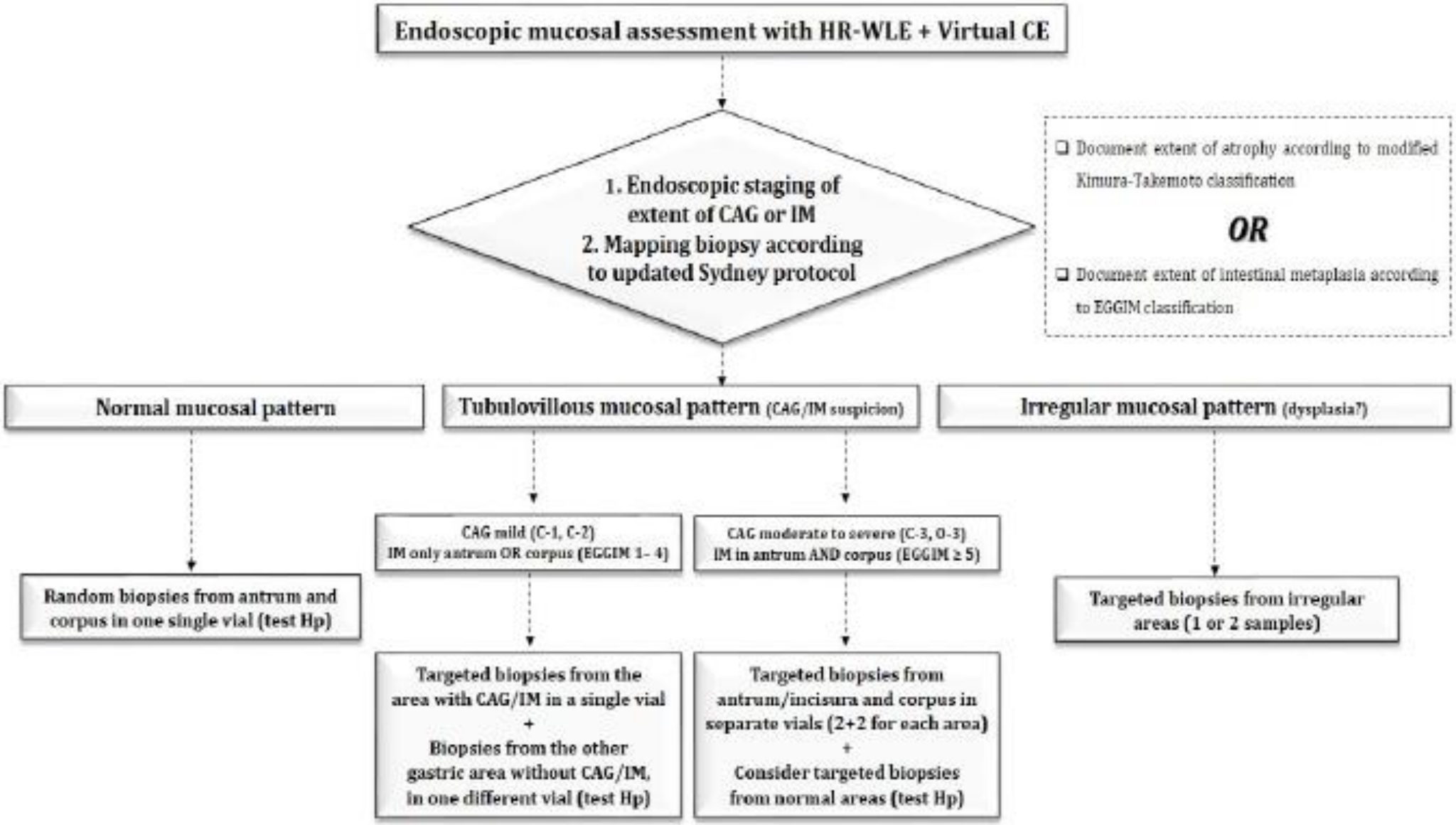
- Collection of 5 nontargeted biopsy specimens:
- 2 from the antrum (at the lesser and greater curvature), 2 from the corpus (at the lesser and greater curvature), and 1 from the incisura.
- It is recommended that these biopsy specimens be placed in separate jars
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Sydney protocol

- Careful inspection with
- ✓ High-definition white-light endoscopy rather than standard-definition endoscopy.
- ✓ Adequate air insufflation, use of mucolytic and defoaming agents (for improved visibility), appropriate withdrawal times, and photodocumentation are key for a quality endoscopic examination.
- NBI, iScan, FICE, and magnification should be encouraged
- ✓ Improve the detection of GIM
- ✓ Allows for more targeted biopsies for GIM
- *CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 91 • NUMBER 1 JANUARY 2024*

Algorithm for the assessment of the gastric mucosa for potential precancerous conditions

- *Curr. Oncol.* ***2024****, 31, 3923–3938. https://doi.org/10.3390/curroncol31070290*


Endoscopic mucosal assessment with HR-WLE + Virtual CE
1. Endoscopic staging of extent of CAG or IM
2. Mapping biopsy according to updated Sydney protocol
Document extent of atrophy according to modified Kimura-Takemoto classification
OR
Document extent of intestinal metaplasia according to EGGIM classification
Normal mucosal pattern
Tubulovillous mucosal pattern (CAG/IM suspicion)
Irregular mucosal pattern (dysplasia?)
Random biopsies from antrum and corpus in one single vial (test Hp)
CAG mild (C-1, C-2) IM only antrum OR corpus (EGGIM 1- 4)
CAG moderate to severe (C-3, O-3) IM in antrum AND corpus (EGGIM ≥ 5)
Targeted biopsies from irregular areas (1 or 2 samples)
Targeted biopsies from the area with CAG/IM in a single vial + Biopsies from the other gastric area without CAG/IM, in one different vial (test Hp)
Targeted biopsies from antrum/incisura and corpus in separate vials (2+2 for each area) + Consider targeted biopsies from normal areas (test Hp)

Global differences in guideline recommendations

- The optimal follow-up of patients with isolated glands of GIM remains **controversial**, with significant differences in guidelines in the Eastern and Western regions of the world
- *CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 91 • NUMBER 1 JANUARY 2024*

Comparison of gastric IM guidelines from ESGE, BSG and ACG

	ESGE (2019)	BSG (2019)	AGA (2020)
Extensive IM	Thrice yearly	Thrice yearly	Routine surveillance not recommended. Patients with GIM at higher risk for gastric cancer who place high value on potential but uncertain reductions in gastric cancer mortality, and who place a low value on the potential risks of surveillance endoscopies, may reasonably elect for surveillance. Consider surveillance 3–5 times a year.
Limited IM, no risk factors	No surveillance	No surveillance	
Limited IM, family history OR incomplete or persistent H pylori	Thrice yearly	Thrice yearly	
Limited IM, severe atrophy	Thrice yearly	Thrice yearly	
Limited IM, severe atrophy, family history	Considered 1–2 times a year	Thrice yearly	
Autoimmune gastritis	Considered 3–5 times a year		

Variations in society recommendation for the management of gastric intestinal metaplasia

Geographic location	Society recommendations
East Asia	Endoscopic or radiographic screening of all men and women at age 50 or older[29] In patients with gastric intestinal metaplasia and high-risk features, endoscopy recommended in 1 to 3 years
Europe	Patients with extensive gastric intestinal metaplasia should undergo endoscopic surveillance every 3 years Consider endoscopic surveillance in patients with gastric intestinal metaplasia limited to the corpus or antrum of the stomach but with a family history of gastric cancer, persistent *Helicobacter pylori* infection, incomplete gastric intestinal metaplasia, or autoimmune gastritis[30]
United States	AGA recommends against routine endoscopic surveillance after gastric intestinal metaplasia is detected in the general population, but if *H pylori* is detected, treatment is encouraged Patients with gastric intestinal metaplasia and risk factors associated with progression could be considered for endoscopic surveillance every 3 to 5 years if the patient favors surveillance (which has an unclear impact on mortality risk) vs endoscopic evaluation, which has a risk of complications[31] ASGE recommends endoscopic surveillance exclusively in patients with risk factors, but not in the general cohort of patients in whom gastric intestinal metaplasia is detected[32]

Recommendations for Eastern regions

- In countries such **as Japan**, where the incidence of gastric cancer is high, national screening programs recommend
- ✓ **Mass endoscopic** or radiographic screening of all men and women at age 50 or older
- For patients found to have **GIM** without malignancy on initial screening,
- ✓ **Surveillance endoscopy in 1 to 3 years** is recommended
- ➢ **If they have GIM with high-risk features**
- ❑ **Incomplete GIM**
- ❑ **Extensive GIM**
- ❑ **Family history of gastric cancer**
- ❑ **Smoking**
- ❑ **Excessive alcohol use**
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Recommendations for Western regions
British Society of Gastroenterology

- Endoscopic surveillance every 3 years if

✓ **Extensive GIM** (ie, affecting the antrum and corpus),

✓ **Antral GIM** with risk factors such as ***H pylori***

✓ **Family history** of gastric cancer

- *CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 91 • NUMBER 1 JANUARY 2024*

A 2019 consensus guideline by **4 European organizations** agreed with the British Society of Gastroenterology

- The guideline recommends that patients with GIM who are considered at high risk, including those with histologically proven GIM of the corpus and antrum, undergo endoscopic surveillance **every 3 years**.
- The guideline advises consideration of surveillance if GIM is present only in the corpus or antrum but the patient has a family history of gastric cancer, **persistent *H pylori***, **incomplete GIM**, or **autoimmune gastritis**
- *CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 91 • NUMBER 1 JANUARY 2024*

US recommendations
AGA

- The American Gastroenterological Association guidelines recommend

✓ **Against routine endoscopic surveillance** after GIM is detected in the general population

➢ ***If H pylori*** is detected, treatment is encouraged.

- Patients with GIM and risk factors associated with progression can be considered for

✓ **Endoscopic surveillance every 3 to 5 years**

➢ If the patient **favors surveillance**, which has an unclear impact on mortality risk, vs endoscopic evaluation, which has potential complications.

- *CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 91 • NUMBER 1 JANUARY 2024*

American Society for Gastrointestinal Endoscopy

- ASGE recommendations are **similar to those of European** groups for **HIGH RISK paatient**
- ✓ Highest risk: incomplete GIM, extensive GIM, or family history of gastric cancer
- ✓ Overall increased risk: certain racial or ethnic minorities **immigrating** from high-incidence regions.
- They advise endoscopic surveillance exclusively for patients with risk factors, but not for the general cohort of patients in whom GIM is detected
- *CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 91 • NUMBER 1 JANUARY 2024*

Severity of gastric intestinal metaplasia predicts the risk of gastric cancer: a prospective multicentre cohort study in **Singapore**

- Our GCEP cohort findings suggest that risk stratification using OLGIM offers a feasible method of prioritising

✓ High-risk patients (OLGIM III–IV) for early endoscopy surveillance in 2 years

✓ Intermediate-risk patients (OLGIM II) for endoscopy in 5 years

✓ No metaplasia or focal IM (OLGIM 0–I) may not require surveillance endoscopy.

- *Lee JWJ, et al. Gut 2022;**71**:854–863.*

Guideline

Thieme

Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European *Helicobacter* and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019

Authors

Pedro Pimentel-Nunes[1,2,3], Diogo Libânio[1,2], Ricardo Marcos-Pinto[2,4], Miguel Areia[2,5], Marcis Leja[6], Gianluca Esposito[7], Monica Garrido[4], Ilze Kikuste[6], Francis Megraud[8], Tamara Matysiak-Budnik[9], Bruno Annibale[7],

Dysplasia in the absence of an endoscopically defined lesion

- Immediate high quality endoscopic reassessment with **CE (virtual or dye-based)** .

✓ No lesion is detected

➢ Biopsies for staging of gastritis (if not previously done)

➢ Endoscopic surveillance **within 6 months** (if **high grade dysplasia**) to **12 months** (if low grade dysplasia) are recommended

(low quality evidence, strong recommendation)

Pimentel-Nunes Pedro et al. MAPS II … Endoscopy 2019; 51

The Role of Artificial Intelligence (AI)

- In a prospective study, **Zhao et al**. developed a diagnostic model for **atrophic gastritis** and found that its utilization led to a higher diagnostic rate compared to endoscopists

✓ **35.8% vs. 24.6%,** including the diagnosis of moderate and severe atrophy in the gastric fundus and body.

Curr. Oncol. ***2024****, 31*

The Role of Artificial Intelligence (AI)

- A recent **meta-analysis** including **12 mainly retrospective** studies assessed the performance of AI in recognizing **intestinal metaplasia** and identified pooled
- Sensitivity and specificity
- 94% (95% CI: 0.92–0.96, I2 = 43.71%) and 93% (95% CI: 0.89–0.95, I2 = 84.78%), respectively

Curr. Oncol. ***2024****, 31*

Management / Endoscopic management

- Limited to detection and surveillance
- No other methods are currently available for this
- *CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 91 • NUMBER 1 JANUARY 2024*

Endoscopic resection

- Early gastrointestinal tumors are now treated with endoscopic organ preservation instead of surgery.
- Endoscopic resection (ER) includes polypectomy, endoscopic mucosal resection, and endoscopic submucosal dissection.
- Several societies have recommended the standard indications for endoscopic resection of GPL and intestinal GC.
- *Frontiers in Oncology10.3389/fonc.2023.1226652*

Non-Endoscopic management

- Risk-factor modification

✓ Smoking cessation

✓ Moderation in alcohol intake

✓ Diet

- In patients with ***H pylori*-induced gastritis**

✓ *H pylori* detection and eradication are crucial to halt progression to gastric Cancer

- *CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 91 • NUMBER 1 JANUARY 2024*.

Effects of *H pylori* eradication once GIM occurs

- Undetermined.
- GIM changes may **be irreversible**
- Impact of *H pylori* eradication on cancer progression once GIM is established

✓ May **be minimal**

- **Observational studies** have reported

✓ Partial GIM reversal and decreased progression to stomach cancer

➢ **Aspirin** and nonsteroidal anti-inflamatory drugs such as celecoxib.

❑ More evidence is needed to support their use

- *CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 91 • NUMBER 1 JANUARY 2024.*

Eradicate Hp
Cao et al.

- Eradication of Hp after **early cancer resection**

✓ Can prevent GC

- Eradication **cannot prevent the development of new cancers**
- Can **only prevent cancer** in patients **without GPL** (atrophy, IM, and dysplasia)

Frontiers in Oncology *10.3389/fonc.2023.1226652*

The longest prospective cohort of an H pylori eradication trial in a Hispanic population

- A total of 800 adults with precancerous lesions were randomized to anti– H pylori treatment or placebo. Gastric biopsy samples taken at baseline and 3, 6, 12, 16, and 20 years
- 356 individuals completed 20 years of follow-up.
- *Gastroenterology 2021;160:1106–1117*

The longest prospective cohort ….

Gastroenterology 2021;160:1106–1117

- Protective effect of anti–H pylori therapy (ITT) against the progression of precancerous lesions remains after 20 years.

✓ **41% reduction** of the risk of progression

- **MAG is**

✓ **Reversible to a nonatrophic stage after**

➢ **Minimum of 6 years of being free of infection.**

The longest prospective cohort ….

Gastroenterology 2021;160:1106–1117 3

- **IM is virtually irreversible** to a less advanced diagnosis,
- ✓ Except when the lesion is minimal (eg, focal and complete type).
- These findings support the concept that
- ✓ **The earlier the H pylori clearance, the greater the benefits**.
- In line with previous observations , **our current results support the reversibility of MAG a**nd shed light on controversial findings about the benefits of anti–H pylori therapy on Most of the evidence suggest that IM is largely irreversible by H pylori eradication

The longest prospective cohort ….

Gastroenterology 2021;160:1106–1117

- **40%** of the individuals who attended the 20-year endoscopy were still infected
- Our analysis of the cumulative effect of H pylori status from baseline to 20 years showed that bacterial clearance did not lead to visible histologic changes during the first years of follow-up, **but greater effects were observed subsequently as years free of infection accumulated**

COX-2 expression

- Level of COX-2 expression and the grade of premalignant gastric lesions.
- An important role in the gradual process resulting eventually in gastric cancer.
- *Acta gastroenterol. belg., 2020, 83, 249-254*

COX-2 inhibitors

- Based on the relationship between chronic inflammation and cancer
- ✓ **NSAIDs** are well known cyclooxygenase (COX) inhibitors for the treatment and prevention of cancer
- In spite of the huge list of potential chemopreventive agents, there are
- ✓ **No agents licensed for chemoprevention in adults until now**

TCM treatment

- Manpixiao Decoction can prevent the progress of GPL by improving systemic inflammation in local gastric mucosa and inhibiting EGFR-PI3K-AKT-related EMT pathways
- Banxia Xiexin decoction can hinder the signaling path of the toll-like receptors (TLRs)/nuclear factors- k B(NF- k B).
- Huangqi Jianzhong Decoction combined with acupuncture can reduce high-sensitivity C-reactive protein, IL-6, TNF- a, and Pepsinogen (PG) II level .
- This suggests that Manpixiao decoction, Banxia Xiexin decoction, and Huangqi Jianzhong Decoction may have a specific therapeutic effect on inflammation in GPL

Lamb's tripe extract and vitamin B12 capsule plus celecoxib reverses intestinal metaplasia and atrophy: A retrospective cohort study (on 255 patients)

- LTEVB12 initial therapy and celecoxib rescue therapy significantly increase the regression effect.
- IM may not be the point of no return among gastric precancerous lesions.
- Celecoxib rescue therapy, the effective rates for IM and AG were **56.25% and 51.56%, respectively.**
- The IM regression rate of complete therapy was up **to 85.03%.**

World J Clin Cases 2021 December 6; 9(34): 10472-10483

Other treatments
Vitamins A, C, E , Folic acid

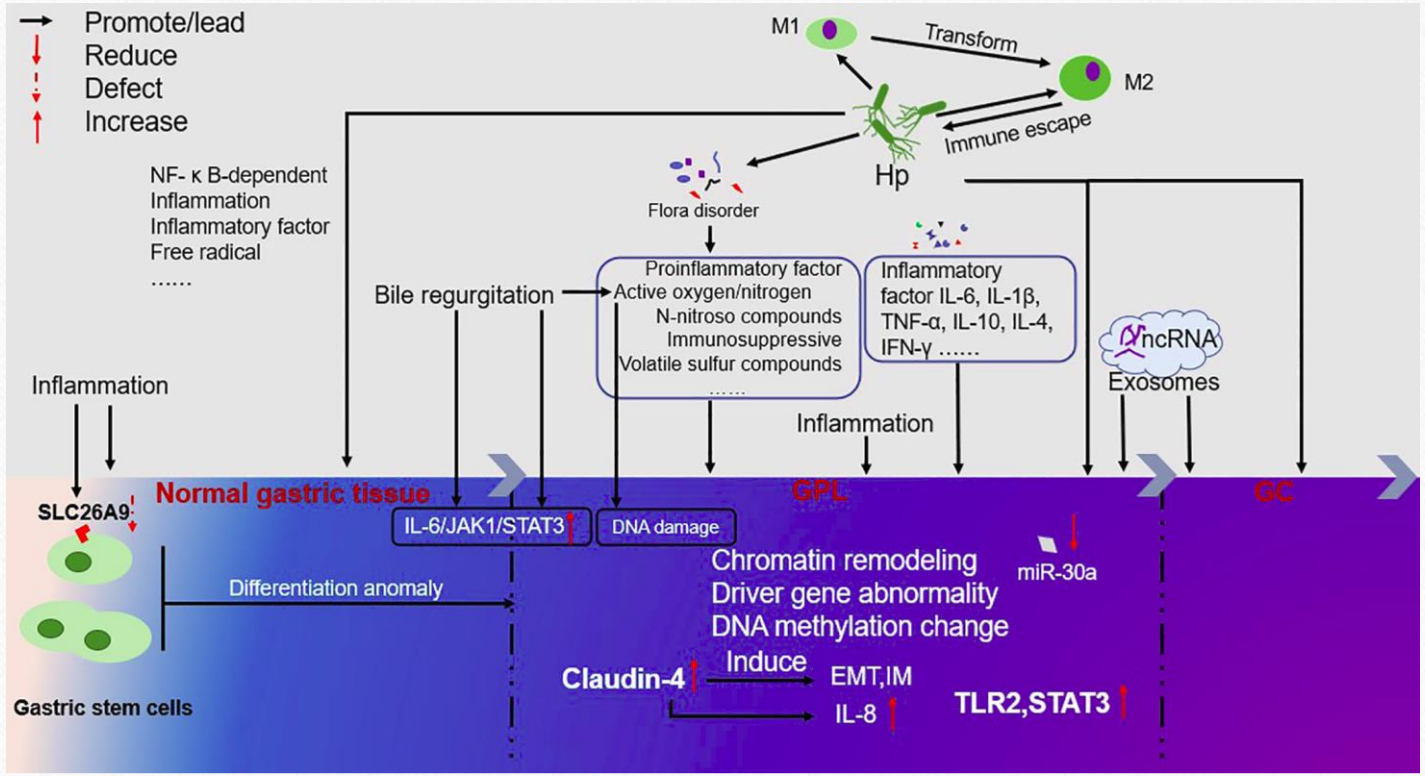
- A recent study found that daily dosages of 1.5 mg, 100 mg, and 10 mg of vitamins A, C, and E, respectively, could effectively lower the **incidence** of **GPL by about one-third**
- However, high doses of vitamin A and vitamin E supplements were associated with **increased GC mortality**.
- In contrast, the risk of death from GC was found to be lowered in a trial including the use **of low-dose dietary vitamins** (physiological rather than pharmaceutical dosages)
- A recent study on the reversal of GPL with **folic acid supplementation** found that folic acid can help heal atrophic gastric mucosal lesions and **reverse intestinal metaplasia** in GPL patients
- *Frontiers in Oncology10.3389/fonc.2023.1226652*

Revealing the role of metformin in GIM treatment Ruoyu Hu et al,

- Therapeutic effect on IM in Atp4a−/− mice. Combining the results of network pharmacology and molecular docking, it regulates the expressions of predicted core targets and related factors.
- Reduces inflammation and inhibits the PI3K/AKT/mTOR/HIF-1α signaling pathway, which eventually slows down the IM process in inflammation and apoptosis.
- *Frontiers in Pharmacology 10.3389/fphar.2024.1340309*



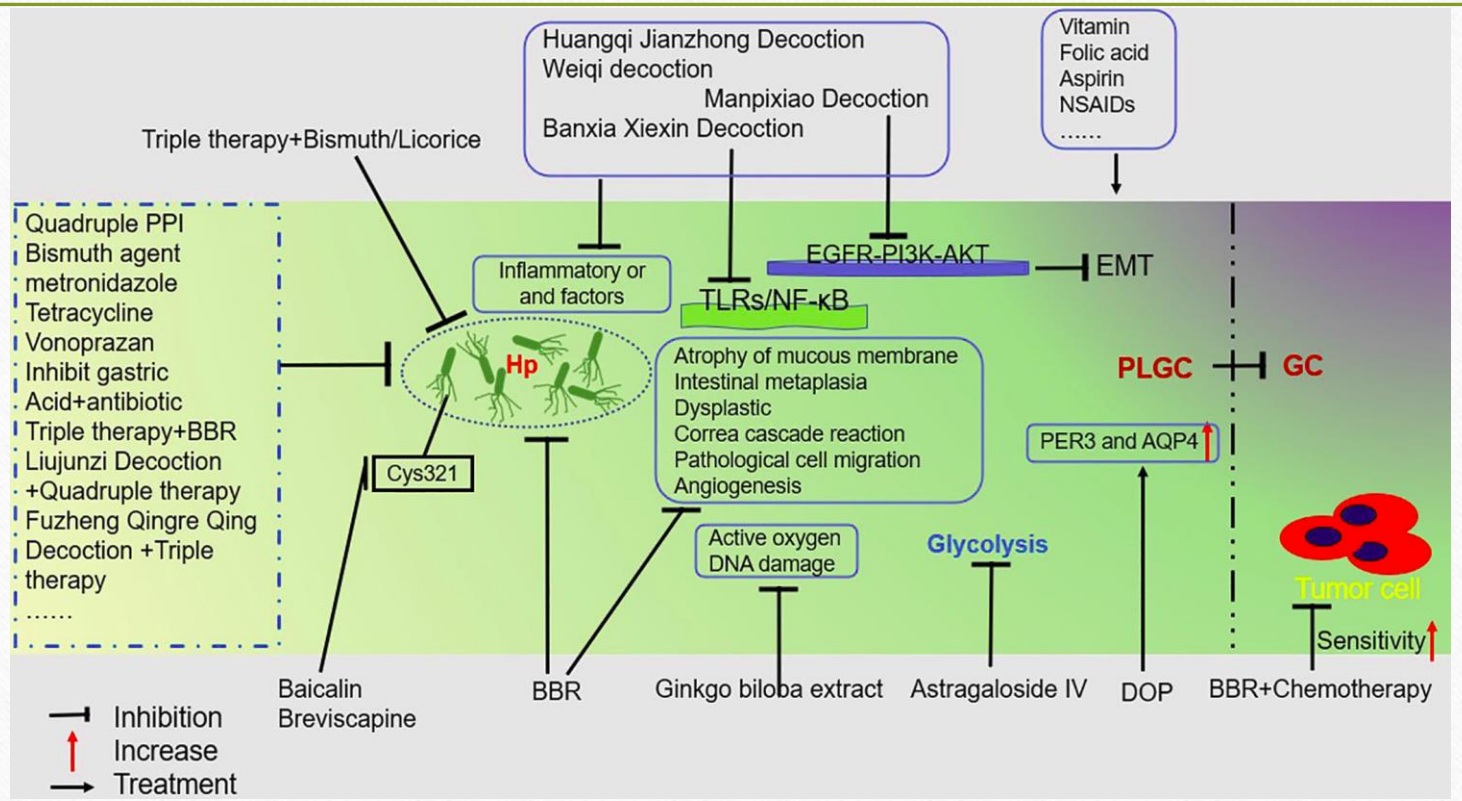
Overview of the occurrence and development of GPL



FIGURE

- Overview of the occurrence and development of GPL. The color change from left to right represents the process of GPL development.
- Inflammation runs through the occurrence and development of GPL. At the same time, it will lead to the loss of gastric stem cells SLC26A9, which will lead to the occurrence of GPL and GC. The multi-directional differentiation of gastric stem cells may also be the source of GPL and GC. Inflammatory factor IL- 6, IL-1 in patients with GPL b, TNF- a, IL-10, IL-4, IFN- g The formation of GC will be accelerated.
- Bile regeneration will cause the occurrence and development of GPL through the IL-6/JAK1/STAT3 signal pathway, and the active oxygen/nitrogen generated will cause DNA damage.
- The high expression of Claudin-4 will induce the formation of EMT and IM, and the induced IL-8 will accelerate the formation of GC.
- The ncRNA in Exosomes can also promote the development of GPL and the formation of GC. From the occurrence of GPL to the formation of GC, under the influence of various factors, chromatin modeling, driver gene abnormality, DNA metabolism change, etc. are phenomena that occur in this process, but they are also the driving force for GPL to develop towards GC

Treatment Overview



GPL Treatment Overview

- Therapeutic drugs that inhibit Inflammatory or and factors
- Drugs that inhibit DNA damage caused by reactive oxygen species
- Drugs that inhibit glycolysis in PLGC
- Drugs that treat PGLC by upregulating PER3 and AQP4; By inhibiting TLRs/NF-k B pathway and EGFR-PI3K-AKT pathway to treat PGLC drugs
- A regimen that helps increase the sensitivity of tumor cells to chemotherapy.

Challenges and future perspectives

- Inflammatory microenvironment in GPL
- ✓ Understanding of this complex process
- Develop effective prevention and treatment strategies.
- *Zhang et al. 10.3389/fimmu.2023.1297101 Frontiers in immunology*

Challenges and future perspectives

Zhang et al. 10.3389/fimmu.2023.1297101 Frontiers in immunology

- Interplay between **immune cells and inflammation** in GPL progression
- Immune cells and cytokines play

✓ An important role in the transformation of GPL

- Their interactions and communication, along with their specific contributions to GPL development,

✓ **Remain unclear**

Challenges and future perspectives88

- **Inflammatory microenvironments**
- ✓ Consists of a complex network of cells, molecules, and signaling pathways
- ✓ Abnormal activation of inflammatory microenvironment in GPL
- Targeting inflammatory microenvironment by chemical interventions may
- ✓ Disrupt the delicate balance necessary for normal physiological functions, leading to potential side effects and toxicity.
- Proper target should be rigorously validation in vivo before implementing any intervention strategies
- *Zhang et al. 10.3389/fimmu.2023.1297101 Frontiers in immunology*

The role of **non-*Helicobacter pylori*** **bacteria** in the pathogenesis of gastroduodenal diseases

- Chronic Helicobacter pylori infection is a critical risk factor for gastric cancer (GC).
- Only 1–3 % of people with H. pylori develop GC.
- In gastric carcinogenesis,

✓ Non-H. pylori bacteria in the stomach might interact with H. pylori.

- **Bacterial dysbiosis** in the stomach can strengthen gastric neoplasia development

✓ Generating tumor promoting metabolites, DNA damaging, suppressing antitumor immunity, and activating oncogenic signaling pathways.

- *Bakhti and Latifi-Navid BMC Microbiology (2021*

The role of non-*Helicobacter pylori* bacteria in the pathogenesis of gastroduodenal diseases

- The involvement of *H. pylori* in the development of gastroduodenal diseases is an indisputable factor.
- *H. pylori* may

✓Not be the only pathogen responsible for the pathogenesis of the disease.

- *Waskito et al. Gut Pathogens (2022) 14:19*

Roles and action mechanisms of bile acid-induced gastric intestinal metaplasia: a review

Matsuhisa et al

- **High concentrations** of bile acid appeared to be associated with an **elevated risk of IM**, regardless of H. pylori infection
- Another study demonstrated that the incidence of **GC** was

✓ **High rate of 41%** in a rat model of bile reflux

- *Cell Death Discovery (2022) 8:158*