Gastritis – General standpoints

Histologically documented inflammation ~60% in mucosal biopsy specimens.
Heterogeneous etiology.
More than 100 classification system.
Classified based on time course (acute vs. chronic), histology, pathogenic mech., anatomic distribution.
Poor correlation between histology, clinical picture (dyspepsia), endoscopic findings.
There is no typical manifestation of gastritis.
There is virtually no carcinoma in normal mucosa.

Classification of Gastritis

I. Acute gastritis
   A. Acute H.pylori infection
   B. Other acute infections
      (other bacterial, phlegmonous, mycobacterial, syphilitic, viral, parasitic, fungal)
   C. chemical (drugs, NSAIDs, bile), hypoxia (stress, trauma, burns, sepsis)

II. Chronic Gastritis
   - Chronic Nonatrophic gastritis – H.pylori
   - Chronic Atrophic Gastritis:
      Type A: Autoimmune, body-predominant (AMAG)
      Type B: H.pylori-related, antral predominant (EMAG)
   Nonmetaplastic
   - Special Forms:
      Chemical, Radiation
      Lymphocytic, eosinophilic, Crohn’s disease, sarcoidosis, granulomatous ~
Histological description of gastritis

Acute gastritis

- Most common causes are infectious and chemical.
- Protective acidic environment.
- *H. pylori* infection: dyspepsia, nausea, vomiting, mucosal edema, hyperemia, infiltration with neutrophils, hypochlorhydria → chronic infection
- Phlegmonous gastritis: marked, diffuse infiltration of the entire wall, necrosis, life-threatening disorder (alcoholics, immunocompromised individuals, *Streptococci*, *Staphylococci*, *E.coli*, *Proteus*, *Haemophilus*, iatrogen causes: polypectomy, mucosal injection)
Chronic gastritis

- Mucosal infiltration mainly with lymphocytes.
- Early phase is superficial gastritis (lamina propria, intact gastric glands)
- Atrophic gastritis (deeper infiltration, glandular destruction)
- Gastric atrophy (lost glandular structure, endoscopically thin mucosa)
- Intestinal metaplasia: conversion of glands to small intestinal phenotype → predisposing factor for cancer

Type A Chronic Gastritis

- Involves body and fundus (antral sparing)
- Associated with pernicious anaemia (autoimmune gastritis: antibodies against parietal cells and intrinsic factor)
- Autoimmune metaplastic atrophic gastritis (AMAG)
- Autosomal dominant disorder
- Associated autoimmune disorders
- Achlorhydria
- Antral sparing → G-cells → hypergastrinemia → ECL cell hyperplasia (→carcinoid tumor)
- Intestinal metaplasia (risk of adenocarcinoma:3-18x)
Helicobacter pylori

H. pylori is a curved, Gram-negative rod. colonizes the gastric mucosa, and perhaps gastric metaplasia in duodenum secondary to acid production.

Type B Chronic Gastritis

- H. pylori associated, antral-predominant, frequent form

- Environmental metaplastic atrophic gastritis (EMAG)

- Progression toward the body (pan-gastritis), increases with age

- Histology improves after H. pylori eradication.

- H. pylori: independent risk factor (6-9x) for gastric cancer → chronic atrophic gastritis, gastric atrophy, metaplasia, dysplasia, carcinoma
Chronic chemical gastritis

- Drugs, NSAIDs, bile reflux
- Dyspepsia
- Mucosal injury, inflammation, erosions

Chronic atrophic gastritis

antrum

corpus
Clinical significance of the Helicobacter pylori infection


Warren, JR  and  Marshall, BJ


Discovery of the correlation between H. pylori infection and gastroduodenal pathology was a milestone in gastroenterology.
Helicobacter pylori - Epidemiology

- H. pylori is indigenous in the stomach, one of the most common human microorganisms, infects about half of the world population.

- Infection rates vary (40-90%) among developed and developing countries (personal hygiene, community sanitation)

- H.p. does not cause serious illness in most cases (85%).

- The outcome of its acquisition is not predictable, depends on bacterial pathogenic and immunogenic mechanisms, host immune response and environmental factors.

- The infection can lead to chronic gastritis, peptic ulcer disease, gastric cancer, and MALT lymphoma.

Helicobacter pylori infection - Epidemiology

- H.p. infection is usually acquired during childhood
- Transmission by fecal-oral (gastro-oral, oro-oral) routes (family members, endoscopy personnel, positive stool cultures, contaminated water, food)
- The acute infection often run inapparently (dyspepsia, vomiting, gastritis)
- Chronic infection lasts during lifetime, spontaneous clearing rate is very low (1%/year)
- Koch’s postulates fulfilled
- WHO classified H.p. infection as a group I carcinogenic exposure
Helicobacter pylori infection

Helicobacter pylori -virulence factors

- Flagellum (migration)
- Urease enzyme (urea + H2O → NH4 + bicarbonate), cyotoxic effect, protective microenvironment (pH↑)
- protease, phospholipase, catalase, superoxide dismutase (mucus and membrane desintegration, invasion, protection)
- adherence factors (adhesins) for the epithelial adhesion
- „blood group (Lewis B) antigen-binding adhesion”(adhesin babA2)
- „cag-pathogenicity island”(cag PAI)
- CagA, encoded by „cytotoxin-associated gene”(cagA) in cagPAI
- cagE gene (interleukin-8 secretion, neutrophil activation)
- vacA gene, - „vacuolating cytotoxin” (VacA: production depends on cagA +)
- „protein induced by contact with epithelium”(iceA)
- neutrophil activation protein (HP-NAP)
- „outer inflammatory protein A”(oipA) – predictor of peptic ulcer (?)
Helicobacter pylori infection –Pathology

- Chronic gastritis (obligate)
- Peptic ulcer (lifetime risk is 15% among infected pts)
- Gastric cancer (lifetime risk is 1.0% among infected pts)
- Relative risk of peptic ulcer and cancer 2-10x
- Transition of chronic H.p. gastritis to atrophic gastritis (incidence 1-2%/year) (role of maintenance PPI- treatment of GERD ?)
- Chronic gastritis 1: pan-gastritis: → atrophic gastritis with reduced acid production → intestinal metaplasia → dysplasia → cancer. 2.: antral-predominant gastritis with high acid production and duodenal ulcer
- Differences in host, immune response, environment and bacterial factors

Clinical significance of Helicobacter pylori infection

- After the eradication of H.p. the relapse rate of peptic ulcer remains low
- Regression of low-grade MALT-lymphoma may occur after H.p. is eradicated
- H.p. may be a predisposing factor for developing gastric adenocarcinoma
- Eradication of H.p. has the potential to reduce the risk of gastric cancer development
- Cancers of the cardia are not associated with H.p.
### Helicobacter pylori testing

<table>
<thead>
<tr>
<th>Method</th>
<th>Sample</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comment</th>
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<tr>
<td>quick-test</td>
<td>blood</td>
<td>75-85%</td>
<td>85-93%</td>
<td>qualitative</td>
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<tr>
<td>ELISA</td>
<td>Serum</td>
<td>80-95%</td>
<td>80-95%</td>
<td>quantitative</td>
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<td>Breath</td>
<td>90-100%</td>
<td>98%</td>
<td>gold standard</td>
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<td>Biopsy</td>
<td>95%</td>
<td>98%</td>
<td>endoscopy</td>
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<td>Biopsy</td>
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<td>98%</td>
<td>Dg.etalon inv.</td>
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<tr>
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<td>80-90%</td>
<td>A.b.resistance</td>
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<td>Biopsy</td>
<td>95-100%</td>
<td>95-100%</td>
<td>research</td>
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<tr>
<td>Stool AG</td>
<td>Feces</td>
<td>89-98%</td>
<td>95%</td>
<td>Noninv.</td>
</tr>
</tbody>
</table>

#### Diagnosis of H.p. infection – Urea breath test (\(^{13}\)C)

\[
\text{\( \text{NH}_2 \)} + \text{\( \text{C} - \text{O} + 2 \text{H}_2\text{O} + \text{H}^+ \rightarrow 2 \text{NH}_3^+ + \text{HCO}_3^- \) ureáz}
\]

\[\text{\( ^{14}\text{CO}_2 \) kilégzés} \]

\[
\text{\( \text{NH}_2 \) ureáz} \quad ^{13}\text{CO}_2 \text{vér} \quad \text{H. pylori} \quad \text{NH}_2
\]
Management of H.pylori infection – indications of testing

• „Test and treat” strategy: dyspeptic patients under the age of (40) 45 years, without alarm symptoms, (patients with familiar history of gastric cancer, NSAID users and reflux symptoms excluded)

• „Search and treat” strategy: peptic ulcer patients (acute or chronic phases, with or without symptoms) intermittently treated with antisecretory drugs; symptomless first degree relatives of patients with distal gastric cancer

• Do not test if there is no indication of eradication
• Screening of asymptomatic individuals at average risk of serious gastroduodenal pathology is not indicated

• Alarm symptoms and dyspepsia above the age of (40) 45 years indicate endoscopy!

Management of H.pylori infection: indications of H.p. eradication

• Eradication of H.p. is strongly recommended (based on evidences):
  Peptic ulcer (in every stage, acute, chr., asymptomatic or complicated, etc.).
  Low-grade gastric MALT lymphoma (El. St.)
  Atrophic gastritis
  After gastric resection because cancer
  In first-degree relatives of gastric cancer patients
  At the request of the patient

• Eradication is also recommended:
  In functional dyspepsia
  Before long-term PPI treatment of GERD
  If long-term NSAID-, or aspirin treatment is planned in high risk patients
  In unexplained iron deficiency anemia

Eradication is not recommended in extragastrointestinal diseases.
Medical treatment of Helicobacter pylori infection

- First line therapy for H.p. eradication: PPI or RBC based combinations:
  2 x PPI, or 2 x RBC + AMO (2x1000 mg) + CLA (2x500 mg) for min.7 day. In the case of penicilline allergy AMO can be replaced by MET (2x500 mg)
- In the case of failure, the second line therapy is bizmuth-based quadruple th:
  2 x PPI + BIZ (4x120 mg) + MET (3x500 mg) + TET (4 x 500 mg), for min.7 day
- In the case of subsequent failure the rescue therapy should be based on antimicrobial susceptibility testing
- Success of eradication therapy must be tested after 6-8 weeks

AMO= amoxicillin, BIZ= bismuth, CLA= clarythromycin, MET= metronidazole, PPI= proton pump inhibitor, RBC= ranitidin bismuth citrate, TET= tetracycline

Peptic ulcer disease (PUD)

Definition:

- tissue defect usually larger than 5 mm in diameter, spreading beyond the muscularis mucosae of the gastrointestinal tract in sites exposed to acid-pepsin effect
Peptic ulcer disease (PUD)

Etiology:

- Helicobacter pylori
- NSAID
- Zollinger-Ellison syndrome
- Stress - ulcer
- „idiopathic” ulcer

Pathogenesis of peptic ulcer

Balance between aggressive and defensive factors
(questions: why in that pts, why in that time, why at that point ?)

„No acid – no ulcer” (Schwartz’s postulate)
- Pro: 1. there is no peptic ulcer in achlorhydria (cancer!)
- 2. Zolliger-Ellison sy. (multiple ulcers)
- 3. acid suppression: main target of therapy

Contra: hypersecretion is necessary but not sufficient
condition of ulceration (rare cases of Z-E syndrome)

Helicobacter pylori (increase of H.p. –ve cases)
NSAIDs
Disturbed microcirculation, hypoxia, stress
Life style (tobacco, alcohol, diet ?)
Peptic ulcer disease - Symptoms

- Dyspepsia in 80-90% (low sensitivity and specificity)
- Positive familiar history, nocturnal pain, relieving effect of antacids and eating
- Complaints often show periodicity
- Vomiting, loss of appetite and weight, abdominal defense, haemorrhage, anaemia (alarm symptoms) refer to suspicion of complications or malignancy
- Complications can occur in 10-20% of cases without preliminary symptoms
- Usually normal physical examination, sometimes epigastrial tenderness

Complications of peptic ulcer

- bleeding
- perforation, (penetration)
- pyloric stenosis (obstruction)
Main standpoints in diagnosis of PUD

- History, symptoms
- Endoscopy: preferred diagnostic tool
- Air-contrast upper GI barium radiography: complementary method, alternative (disorders of gastric emptying, motility, at pt's request)
- Endoscopy can not replaced with H.pylori testing
- Indications of repeated endoscopy: gastric ulcer with biopsy, duodenal ulcer with alarm symptoms and complications, refractory ulcers

Ulcus ventriculi

Forrest II/A
Forrest II/B
Forrest III.
Aims of peptic ulcer therapy

• Healing of peptic ulcer
• Relieving of complaints, improvement of quality of life
• Preventing, and therapy of complications
• Preventing of relapses

Main tools of therapy of peptic ulcer

• Medical therapy
• Endoscopic therapy (bleeding)
• Surgical therapy (complications)
• Lifestyle modification (diet, tobacco, alcohol, stress)
**Regulation of acid secretion**

![Diagram of acid secretion](image)

**Main groups of drugs in peptic ulcer therapy**

- Drugs neutralizing gastric acid and/or suppressing acid secretion: antacids, H2-receptor blockers, proton pump inhibitors
- Cytoprotective agents (fortifying defensive factors, increase prostaglandin and bicarbonate release, mucus production): sucralfate, bismuth, (misoprostol)
- Antibiotics: treating Helicobacter pylori infection (eradication)
NSAID-related peptic ulcer

15-40% of NSAID-users develop dyspepsia, 30-50% erosions, 10-30% ulcers, and 2-4% serious complications

30% of peptic ulcer bleeding cases are NSAID-related

First event is the serious complication in 60% of cases (without preliminary symptoms)

700 deaths/year attributed to NSAID-related complications in Hungary, 20,000 deaths/year in USA

Complications (ulcer, bleeding, perforation, stenosis) not only in the upper GI tract

Risk factors of NSAID-related peptic ulcers

• Low, or average risk: <65 of age, no ASA th., dyspepsia, or peptic ulcer in history

• Increased risk: >65 of age, male gender, serious associated disorders, dyspepsia, peptic ulcer in history, coexistent ASA, steroid, anticoagulant, cytostatic therapy, alcohol, tobacco use

• Very high risk: multiple coexistent risk factors
Prevention of NSAID-related complications
How treat the patients with NSAIDs?

- Avoiding continuous NSAID-therapy
- Identifying risk groups (history !)
- Lowest effective dose, shortest treatment period, individual treatment
- Avoiding high risk combinations
- H.pylori testing and eradication in positive history of PUD
- Prophylaxis in high risk groups with proton pump inhibitors (PPI)

Prevention of NSAID-related complications

Treatment strategies:

- Low risk patients: traditional NSAIDs
- Increased risk patients: PPI-prophylaxis and traditional NSAID, or coxibs
- Very high risk patients: PPI-prophylaxis and coxibs
Stress ulcers

- ICU patients with serious illnesses (hypotension, hypoperfusion, hypoxia)
- Hypoxia, metabolic troubles of gastric mucosa
- Acid rediffusion, erosions, dysfunction of regenerative processes
- Low intramucosal pH

Treatment:
Prophylaxis of the tissue hypoxia, mucosal lesions
Early PPI-therapy (2x40 mg PAN, or OME i.v., or 8 mg/h with perfusor, 72 hrs)

Management of PUD

- Endoscopy, biopsy in gastric ulcer!
- H.pylori testing and eradication
- 4-5 weeks antisecretory treatment
- Repeated endoscopy and biopsy of gastric ulcer, second line treatment of H.p. if +ve, 2 months antisecretory treatment afterwards
- UBT control 6-8 weeks after the eradication in DU (H2RA, PPI be held for 2 weeks prior the test)
- Repeated (second line) eradication (if H.p.+ve), or 3-6 months maintenance antisecretory treatment
- UBT control, H.pylori culture and antimicrobial susceptibility testing, if necessary
- Repeated endoscopy and biopsy of gastric ulcer 3 months later, surgery if no healing detected (refractory ulcer, cancer!)
Refractory ulcers

- Defined if 8 weeks of therapy fail to heal duodenal ulcers, and 12 weeks of therapy fail to heal gastric ulcers

Causes:

Ulcerogen factors (NSAID, Hp., lifestyle, tobacco)
Patient noncompliance
Malignancy! (lymphoma, carcinoma)
Crohn-disease
Zollinger-Ellison syndroma
Amyloidosis, sarcoidosis, eosinophil gastritis, infections (CMV, TBC, syphilis)
Injectios vérzéscsillapítás eszközei

Endoszkópos injectios terápia duodenalis ulcusvérzésben
Indications for surgery of PUD

- Perforation
- Pyloric stenosis, obstruction
- Bleeding (after complex endoscopic and medical therapy failed)
- Intractable ulcer
- Malignancy
Medical treatment in ulcer bleeding

**Aims:** primary hemostasis, preventing rebleeding, promoting ulcer healing

Antisecretory treatment: increase thrombocyte aggregation, clot stabilization (in-vitro)

**H2-receptor blockers:**
no effect on rebleeding, emergency surgery, and mortality

**High dose PPI + Endoscopic therapy:** decrease rebleeding rate and mortality (contra ET + placebo/H2RA) (Bardou, 2003)

80 mg (Ome or Pan.) i.v. → 8 mg/h inf. 72h