




Upper GI Update

2022

MICHIGAN STATE UNIVERSITY College of Human Medicine

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Objectives

- Highlights from recent consensus documents on *H. pylori*
 - H. pylori* is the major risk factor for gastric cancer (GC)
 - Eradication of HP is associated with less risk for GC
- Updates on GERD management
- Presentation and treatment for eosinophilic esophagitis (EoE)

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H Pylori Consensus Reports

- Bottom line:** All *H. pylori* infections should be considered pathogenic and should be eradicated

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Kyoto Global Consensus report (2015)
Maastricht V/Florence Consensus Report (2017)
American College of Gastroenterology (2017)
Taipei Global Consensus (2020)

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H Pylori Consensus Reports

- H. pylori* infection is a common bacterial infection of the human stomach that affects more than half the world population (e.g., ~80% Africa, 55% Asia, 37% N America).
- Most *H. pylori* infections are acquired before the age of 10 producing a chronic infection that may remain clinically unapparent or evolve into severe complications.
- The rate of progression is unpredictable and most patients with chronic gastritis may remain asymptomatic until the appearance of severe complications.

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Kyoto Global Consensus report (2015)
Maastricht V/Florence Consensus Report (2017)
American College of Gastroenterology (2017)
Taipei Global Consensus (2020)

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H Pylori Consensus Reports

- H. pylori* is a class 1 human carcinogen, responsible for ~90% of human gastric cancers worldwide
- Gastric cancer is the 5th most common cancer and 3rd leading cause of cancer deaths worldwide
- Importantly, it is now established that eradication of *H. pylori* reduces the risk of gastric cancer development

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Kyoto Global Consensus report (2015)
Maastricht V/Florence Consensus Report (2017)
American College of Gastroenterology (2017)
Taipei Global Consensus (2020)

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H Pylori Prevalence = High | Abstract 1

- 183 studies | 410,879 participants | 73 countries | Meta-analysis
- Overall prevalence of *H. pylori* is 44% worldwide
 - 34.7% developed countries
 - 50.8% developing countries
 - 48.6% adults | 32.6% children

According to the AGA "it is often difficult to know what the *H. pylori* prevalence is in the local population"

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Systematic review with meta-analysis: the worldwide prevalence of *Helicobacter pylori* infection

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H Pylori & Gastric CA | Abstract 2

Objective: To address the effect of *H. pylori* eradication on GC incidence

Methods: Systematic review and meta-analysis of 28 studies reporting GC incidence between *H. pylori* eradication and control groups.

Results:

- *H. pylori* eradication was assoc with a significantly lower risk of GC (OR = 0.46)
- > 5 years of follow up (OR = 0.32) ↓ 45 – 68%
- < 5 years follow up (OR = 0.55)

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Cohort Study | Effect of Helicobacter pylori eradication on the incidence of gastric cancer: a systematic review and meta-analysis

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H Pylori & Gastric CA | Abstract 3

Objective: To evaluate the effectiveness of *H. pylori* eradication for the primary prevention of gastric cancer and tertiary prevention of GC (patients with early gastric cancer)

Methods: Systematic review and meta-analysis of 19 studies

Results: *H. pylori* eradication was assoc with a significantly lower risk of GC

- Primary prevention: (OR = 0.34) ↓ 58 – 66%
- Tertiary prevention: (OR = 0.42)

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Cohort Study | Effects of Helicobacter pylori eradication on gastric cancer incidence in the Japanese population: a systematic evidence review

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H Pylori & Gastric CA | Abstract 5

Objective: To evaluate the effectiveness of mass eradication of *H. pylori* on the incidence of, and mortality rates from GA

Methods: Mass eradication of HP 2004 – 2018 in Taiwanese population (7616 adults) who tested positive for HP by the urea breath test | rates compared to historical controls

Results:

- *H. pylori* prevalence rates decreased from 64.2% to 15.0%
- Reinfection rates < 1% per year
- GC incidence & mortality ↓ 53 and 25% | no change in incidence of other GI cancers

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Cohort Study | Mass eradication of Helicobacter pylori to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands

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H Pylori & Gastric CA | Abstract 4

Objective: To evaluate the effectiveness of *H. pylori* eradication in decreasing the rate of histological progression in patients with precancerous lesions and *H. pylori*

Methods: 800 adults with precancerous lesions; randomized to HP eradication Rx or placebo & 356 had gastric biopsies taken 5 x in 20 years

Results: *H. pylori* eradication was assoc with a significantly lower risk of histological progression

- Primary prevention: (OR = 0.59)

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RCT Study | The Colombian Chemoprevention Trial: 20-Year Follow-Up of a Cohort of Patients With Gastric Precancerous Lesions

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H Pylori & Gastric CA | Abstract 6

Objective: To evaluate the effectiveness of eradication of *H. pylori* on recurrence rates among patients with early GC

Methods: DB RCT of 396 patients with endoscopic resection of early GC or high-grade adenoma.

Results:

- HP eradication ↓ 50% metachronous GC incidence after 5.9 years
- Improvement in "atrophy grade" (48.4% with active treatment vs 15% with placebo)

H. pylori eradication is still effective in patients with advanced preneoplastic lesions.

Metachronous GC = recurrence of GC detected on endoscopy on follow up ≥ 1 y after eradication Rx
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RCT | Helicobacter pylori Therapy for the Prevention of Metachronous Gastric Cancer

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H Pylori & Family Hx of GC | Abstract 7

Objective: To evaluate the effectiveness of eradication of *H. pylori* among 1st degree relatives on the incidence of GA

Methods: 1676 participants with a family hx of GC & *H. Pylori* positive randomized to eradication therapy vs placebo 9.2 years of follow up

Results:


- GC developed in 1.2% (treatment) vs 2.7% (placebo)
 - 50% of the GC in the treatment group had persistent HP
 - GC developed in 0.8% who had HP eradicated vs 2.9% with persistent infection

Among persons with *H. pylori* infection who had a family history of gastric cancer in first-degree relatives, *H. pylori* eradication treatment reduced the risk of gastric cancer.

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RCT | Family History of Gastric Cancer and Helicobacter pylori Treatment

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Evidence from cohort studies and RCTS demonstrate that HP eradication decreases the risk of histological progression, the development of gastric cancer & GC mortality by at ~ 50%



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H Pylori Testing Options

- Testing options
 - Urea breath test (UBT) is the most investigated and best recommended non-invasive test in the context of a 'test-and-treat strategy'.
 - Stool antigen tests (SATs) may be less acceptable but have high sensitivity and specificity
 - PPIs should be discontinued for 2 weeks prior to testing (UBT & SAT) as PPIs have anti-H. pylori activity leading to false negative tests.
 - No need to discontinue H2 blockers or antacids (aside from bismuth)
- Confirmation of eradication
 - UBT is the best option for confirmation of H. pylori eradication & SAT is an alternative. It should be performed at least 4 weeks after completion of therapy. (Same PPI recommendations as above)



Kyoto Global Consensus report (2015)
Maastricht V/Florence Consensus Report (2017)
American College of Gastroenterology (2017)
Taipei Global Consensus (2020)

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Retesting for H Pylori = Rare | Abstract 8

Objective: To evaluate factors associated with retesting for H pylori in a large, nationwide cohort.

Methods: Retesting rates among 27,185 veterans who were prescribed anti-HP therapy between 1994 – 2018

Results: 23.9% were retested 67.1% not retested for HP for "test-of-cure"

Low rates of retesting exists after eradication treatment for HP.



Low Rates of Retesting for Eradication of Helicobacter pylori Infection After Treatment in the Veterans Health Administration <https://pubmed.ncbi.nlm.nih.gov/34124141/>

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GC rates only ↓ if eradication = successful | Abstract 9

Objective: To evaluate how successful eradication affects cancer risk


Methods: 371,813 patients (median age 62 years; 92.3% male) who received a diagnosis of H pylori infection from January 1, 1994, through December 31, 2018.

Results:

- Confirmed H pylori eradication after treatment reduced risk of gastric cancer (SHR, 0.24; 95% CI, 0.15-0.41; P < .001) vs no confirmation.

Treatment of H pylori infection decreased risk only if eradication was successful

? In part associated with antibiotic resistance



Risk Factors and Incidence of Gastric Cancer After Detection of Helicobacter pylori Infection: A Large Cohort Study <https://pubmed.ncbi.nlm.nih.gov/36014111/>


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HP Antibiotic Resistance

Geographical distribution of antimicrobial resistance patterns per U.S. region, 2017-2018

6-44% antimicrobial resistance rates among antimicrobials commonly used to Rx HP

Antibiotic	All isolates n=345	West n=108	Central n=96	East n=151	P-value
Amoxicillin	6.4% (22)	8.3% (9)	5.8% (5)	5.3% (8)	0.6
Clarithromycin	17.4% (60)	11.1% (12)	15.1% (13)	23.2% (35)	0.03
Metronidazole	43.6% (150)	35.5% (38)	43.0% (37)	49.7% (75)	0.08
Rifabutin	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	ND
Limited Analysis n=71					
Tetracycline	2.8% (2)	5.3% (1)	5.3% (1)	0 (0.0%)	0.3
Levofloxacin	57.8% (41)	57.8% (11)	68.4% (13)	17 (51.5%)	0.5



National and Regional United States Antibiotic Resistance to Helicobacter pylori Resistance to Helicobacter pylori, Lessons from a Clinical Trial <https://pubmed.ncbi.nlm.nih.gov/34124141/>

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H Pylori Antibiotic Resistance


Treatment is limited by the fact that antibiotic sensitivity testing is not routinely available, forcing clinicians to use empirical therapies

Given the prevalence of HP resistance to clarithromycin, metronidazole, & levofloxacin ... these antibiotics are not considered appropriate for empirical use in triple therapies

In 2019, the FDA approved a 3-in-1 combination product of omeprazole, amoxicillin, and rifabutin for the treatment of *H. pylori* infection in adults

Talicia® contains 12.5 mg of rifabutin, 250 mg of amoxicillin, & 10 mg of omeprazole

- 4 capsules every 8 hours per day for 14 days with food | Goodrx.com ~ \$ 700 for 168 capsules



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HP Antibiotic Resistance | Abstract 10

Objective: To assess the effectiveness of rifabutin-based therapy for *H pylori* eradication

Methods: 455 treatment-naive adults with epigastric discomfort and confirmed *H pylori* infection randomized to amoxicillin (3 g); omeprazole (120 mg); and rifabutin (150 mg) vs amoxicillin (3 g), and omeprazole (120 mg), given as 4 capsules every 8 hours for 14 days.

Outcome: *H pylori* eradication rate, demonstrated by ¹³C urea breath test 4 weeks after treatment

Results:

- Eradication rates: 83.8% vs. 57.7% ($P < 0.001$).

These findings suggest potential for rifabutin as first-line empirical *H pylori* therapy

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Rifabutin-based triple therapy (RFB-150) for Helicobacter pylori eradication: A double-blind, randomized, controlled trial

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Screening Criteria for Any Condition

- There is a significant burden of suffering related to the target condition or disease.
- There is a detectable pre-clinical phase of the condition or disease.
- Early intervention must be helpful.
- There must be a test with adequate sensitivity and specificity.
- The test must be acceptable to the general population.
 - Cheap
 - Non-invasive
- The harms of screening and intervention are minimal

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Frame and Carlson

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H Pylori Consensus Reports

- "There is evidence linking *H. pylori* to unexplained iron deficiency anemia (IDA), idiopathic thrombocytopenic purpura (ITP), and vitamin B12 deficiency. In these disorders, *H. pylori* should be sought and eradicated"

Other conditions linked to HP infection

Kyoto Global Consensus report (2015)
Maastricht V/Florence Consensus Report (2017)
American College of Gastroenterology (2017)
Taipei Global Consensus (2020)

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H Pylori & Chronic Urticaria | Abstract 11

Objective: To assess the association between *H pylori* & chronic spontaneous urticaria (CSU)

Methods: Twenty-seven of 72 patients with CSU who were positive for *H pylori* stool antigen and PCR in gastric biopsy specimens were randomized to receive either anti-*H pylori* treatment or placebo.

Results:

	UAS-7 Score Before Rx		UAS-7 Score After Rx	
	Moderate (16-27)	Severe (28-42)	Moderate (16-27)	Severe (28-42)
Eradication Gp	71.4%	21.4%	21.4%	0
Placebo Gp	61.5%	30.8%	70.9%	15.4%

UAS7, urticaria activity score (score 0 - 42)

Treatment of *H pylori* can significantly improve the symptoms of CSU.

Positive Effect of Helicobacter pylori Treatment on Outcome of Patients With Chronic Spontaneous Urticaria

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GERD

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GERD | Rx

- Classic GERD & regurgitation no alarm symptoms, 8-wk trial of empiric PPIs once daily 30-60 minutes before a meal.
- Discontinue PPIs in patients whose symptoms respond after 8 weeks
- Elevating head of bed for nighttime
- Do no use:
 - Baclofen in the absence of objective evidence of GERD
 - Prokinetic agents of any kind for GERD therapy unless there is objective evidence of gastroparesis
 - Sucralfate for GERD therapy except during pregnancy.
- We suggest on-demand/intermittent PPI therapy for heartburn symptom control in patients with non-erosive reflux disease (NERD).

New guideline published January 2022

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ACG Clinical Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease

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GERD | Assessment

- Classic GERD & regurgitation without alarm symptoms, 8-wk trial of empiric PPIs once daily 30-60 minutes before a meal.

↑

Important point – PPIs usually only work if taken on an empty stomach 30 – 60 minutes before a meal (usually the patient's largest meal)

MICHIGAN STATE UNIVERSITY College of Human Medicine ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease

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GERD HOB Elevation | Abstract 12

Objective: Evaluate the effect of head-of-bed elevation on relieving symptoms of GERD in adults.

Methods: Systematic review of five trials (four cross-over & one factorial) with 228 patients. Of five trials, two used 'bed blocks' under the bed legs; one used 'sleeping on a wedge' pillow, and two used both.

Outcome: HOB elevation associated with 2.1x higher rate of improved symptoms & intraesophageal pH measurement

Conclusions: "...head-of-bed elevation could be still considered as a cheap and safe alternative to drug interventions ..."

MICHIGAN STATE UNIVERSITY College of Human Medicine Head of bed elevation to relieve gastroesophageal reflux symptoms: a systematic review

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GERD Diaphragmatic Breathing | Abstract 13

Objective: To determine the effects of DB on reflux, lower esophageal sphincter (LES), and gastric pressures in patients with upright GERD and controls.

Methods: 23 patients with pH proven upright GERD compared to 10 controls taught DB or sham

MICHIGAN STATE UNIVERSITY College of Human Medicine DB = Diaphragmatic breathing Effects of Diaphragmatic Breathing on the Pathophysiology and Treatment of Upright Gastroesophageal Reflux: A Randomized Controlled Trial

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GERD Diaphragmatic Breathing | Abstract 13


Relaxed breathing steps:

1. Loosen tight clothing around your belly (abdomen) and waist and sit comfortably with your feet flat on the floor. You may place your hands in your lap or at your side.
2. Place one hand on your chest and another across your abdomen while you breathe. This helps you become aware of your breathing.
3. Breathe in (inhale) slowly through your nose. Notice your abdomen expand as you breathe in (Figure 2).
4. Breathe out (exhale) at your normal rate or slower (Figure 3).

Make a goal to practice this breathing three times a day for 10-15 minutes each time. After regular practice this breathing becomes natural and you can use it as needed.

If you cannot feel your abdomen expand as you breathe in:

- Breathe in first and gently push your abdomen with your hand.
- Breathe in, noticing how your abdomen expands against your hand.



MICHIGAN STATE UNIVERSITY College of Human Medicine Effects of Diaphragmatic Breathing on the Pathophysiology and Treatment of Upright Gastroesophageal Reflux: A Randomized Controlled Trial

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GERD Diaphragmatic Breathing | Abstract 13

Objective: To determine the effects of DB on reflux, lower esophageal sphincter (LES), and gastric pressures in patients with upright GERD and controls.

Methods: 23 patients with pH proven upright GERD compared to 10 controls taught DB or sham

Outcome:

- Post prandial gastric pressure: patients > controls (12 v 7 mmHg)
- Valsalva maneuver → reflux in 65.2% of patient's vs 44.4% of controls (P = 0.035)
- LES pressure ↑ during the inspiratory portion of DB (42.2 vs 23.1 mm Hg, P < 0.001) in patients and healthy persons.
- Postprandial DB reduced the number of postprandial reflux events in patients (0.36 vs 2.60, P < 0.001) and healthy subjects (0.00 vs 1.75, P < 0.001) compared with observation, assoc with ↓ 2 hr postprandial esophageal acid exposure.

These data further encourage studying DB as therapy for GERD.

MICHIGAN STATE UNIVERSITY College of Human Medicine Effects of Diaphragmatic Breathing on the Pathophysiology and Treatment of Upright Gastroesophageal Reflux: A Randomized Controlled Trial

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PPI for Throat Sx | Abstract 14

Objective: To assess the use of PPIs to treat persistent throat symptoms

Throat symptoms = hoarseness, throat pain, globus sensation, throat clearing, postnasal secretions or excess mucus, cough or choking sensation, with persistent throat sx;

Methods: DBRCT of 346 patients (cough or choking sensation) with persistent throat sx; randomized to 30 mg lansoprazole BID vs matching placebo for 16 weeks

Outcome: Total reflux symptom score (RSI) & sx response at 12 months, QOL and throat appearance

Results: RSI scores 22 vs 21.7 | no difference in secondary outcomes


No evidence was found of benefit from PPI treatment in patients with persistent throat symptoms

RSI = 9 items scored 0 – 5; total possible score = 45 (45 = most severe symptoms)

MICHIGAN STATE UNIVERSITY College of Human Medicine Use of proton pump inhibitors to treat persistent throat symptoms: double blind, randomized, placebo-controlled trial

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Eosinophilic Esophagitis (EoE)




- Eosinophilic esophagitis (EoE) is a chronic, immune-mediated, esophageal-restricted disease, characterized clinically by symptoms of esophageal dysfunction and histologically by an eosinophil-predominant inflammation

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Gastroenterology 2020/Nov-15K/1472-1485.d

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Eosinophilic Esophagitis (EoE)




- Adults:
 - Dysphagia = predominant symptom (including food bolus impaction)
 - Heartburn uncommon
 - Sx present for ~ 3 years before dx
 - High rate of atopy present
- Kids
 - Feeding dysfunction/failure to thrive
 - Abdominal pain/vomiting/regurgitation/reflux
 - High rate of atopy present
 - Long duration of symptoms prior to diagnosis,
- EGD
 - Esophageal changes: exudates, rings, edema, furrows, strictures, narrowing, and crêpe-paper mucosa
 - Only a minority have an endoscopically normal-appearing esophagus.
- Histology
 - Esophageal eosinophilia ≥ 15 eos/hpf (approximately 60 eos/mm²)

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Gastroenterology 2020/Nov-15K/1472-1485.d

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Eosinophilic Esophagitis (EoE)




- Prognosis
 - Natural history = chronic.
 - EoE can progress from inflammatory-predominant to a fibrostenotic predominant disease.
- Rx:
 - There is no current known cure.
 - It is rare for children to "grow out of" EoE.
 - Topical steroids and esophageal dilation.

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Gastroenterology 2020/Nov-15K/1472-1485.d

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Topical Corticosteroids for EoE in Adults | Abstract 15



Objective: Are swallowed topical-acting corticosteroids effective for maintenance of EoE

Methods: 204 adults with EoE with clinical & histological remission randomized to topical budesonide (0.5 or 1.0 mg twice daily) vs placebo for 48 weeks

Outcome: Clinical and histological remission

Results:

- 73.5% with 0.5 mg BID
- 75.0% with 1.0 mg BID
- 4.4% with placebo


No ADE differences | time to relapse 87 d in placebo group | no differences in AM cortisol | suspected candidiasis in 11 – 16% of active treatment group

Conclusion: Budesonide was superior to placebo in maintaining remission in EoE

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Budesonide Ointment/Topical Tablets Maintain Remission in a Randomized, Placebo-Controlled Trial of Patients With Eosinophilic Esophagitis

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Topical Corticosteroids for EoE in Kids | Abstract 16



Objective: To evaluate the histologic and clinical effectiveness of the use of corticosteroids in pediatric patients with a diagnosis of EoE.

Methods: Meta-analysis of 5 studies with 206 patients

Outcome: Clinical and histological effectiveness

Results:


- Histological response: 49.2% vs 4.2%
- Symptomatic response: 33.6% vs 21.8%
- No ADE differences

Conclusion: Histological response is improved in children with EoE with topical corticosteroids versus placebo

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Budesonide Ointment/Topical Tablets Maintain Remission in a Randomized, Placebo-Controlled Trial of Patients With Eosinophilic Esophagitis

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Bottom-Lines



- H pylori is the major risk factor for gastric cancer
- All H pylori infections should be considered pathogenic and should be eradicated
- Test for eradication success for HP
- Antibiotic resistance for HP exists
- HP infection is linked to ITP, B12 & Iron deficiency and chronic urticaria
- HOB elevation in patients with nocturnal GERD is effective
- Empiric PP treatment for patient with nonspecific throat dysphagia is not
- Consider eosinophilic esophagitis (EoE) in adults with dysphagia (esp food bolus impaction) and in kids with failure to thrive
- Topical swallowed corticosteroids are effective in treating EoE in children and adults

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END

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GERD | General Points

- Reflux of gastric contents into the esophagus → symptoms of heart burn, regurgitation and/or complications.
- Extraesophageal manifestations of GERD can include laryngeal & pulmonary symptoms such as hoarseness, throat clearing & chronic cough & conditions such as laryngitis, pharyngitis, & pulmonary fibrosis.
- There is no gold standard for the diagnosis of GERD.
- The diagnosis is based on a combination of symptom presentation, endoscopic evaluation of esophageal mucosa, reflux monitoring, and response to therapeutic intervention.

New guideline published last month

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ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease [https://www.gastrojournal.org/article/S0016-5052\(22\)00000-0](https://www.gastrojournal.org/article/S0016-5052(22)00000-0)

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