

Gastroesophageal Reflux Disease (GERD) and Proton Pump Inhibitors (PPIs)

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Objectives

1. Define Gastroesophageal Reflux Disease (GERD)
2. Discuss epidemiology and pathophysiology of GERD
3. Discuss current treatment recommendations for patients diagnosed with GERD
4. Review current evidence regarding the risks of long-term PPI use
5. Discuss alternative treatment options



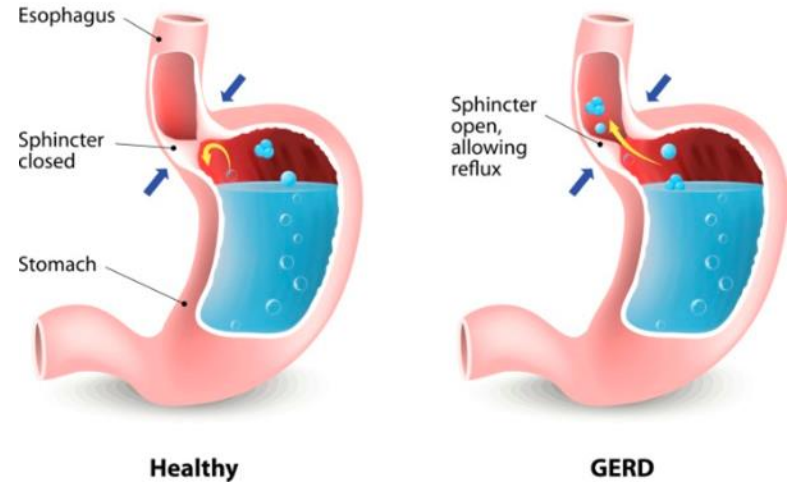
BACKGROUND

What is GERD?

“Condition in which patients have reduced lower esophageal sphincter (LES) pressure allowing acidic gastric contents to backflow into the esophagus”

Pathophysiology

- Involves a poorly functioning esophagogastric junction (composed of the LES and crural diaphragm), impaired esophageal clearance, and alterations in esophageal mucosal integrity
- Refluxed acidic gastric juices trigger release of cytokines and chemokines that attract inflammatory cells



Symptoms

- **Heartburn**
- **Regurgitation**
- Dysphagia
- Chest pain
- Hoarseness
- Chronic cough



Complications of GERD

- **Erosive esophagitis:** erosions and ulcers caused by excessive acid reflux and pepsin leading to degradation of the esophageal mucosa
- **Barrett's esophagus:** result of chronic GERD when the lining of the esophagus changes from squamous epithelium to columnar epithelium, increasing risk for developing esophageal cancer
- **Esophageal strictures:** consequence of the healing esophageal ulcers narrowing the esophagus

TREATMENT

Non-Pharmacological Recommendations

- Weight loss
- Avoid meals within 2-3 hours of bedtime
- Avoid tobacco products/smoking
- Avoid “trigger foods” (i.e. caffeine, acidic/spicy foods, etc.)
- Elevate head of the bed at night

Pharmacological Recommendations

- 8-week course of proton pump inhibitors (PPIs) = 1st line
 - If symptoms have resolved after 8 weeks, discontinue or use PRN
 - Recommend administration 30-60 min before meals
 - PPI should be administered at the lowest effective dose for maintenance therapy

Proton Pump Inhibitors

Generic (BRAND)	OTC/Rx	Dosing	Notes
Pantoprazole (PROTONIX)	Rx	40mg daily	Available IV
Omeprazole (PRILOSEC)	OTC/Rx	OTC: 20mg daily Rx: 15-30mg daily	Do not use with clopidogrel, Can open capsule and mix with applesauce
Esomeprazole (NEXIUM)	OTC/Rx	OTC: 20mg daily Rx: 20-40mg daily	Available IV, Do not use with clopidogrel, Can open capsule and mix with applesauce
Lansoprazole (PREVACID)	OTC/Rx	OTC: 15mg daily Rx: 15-30mg daily	Can open capsule and mix with applesauce
Rabeprazole (ACIPHEX)	Rx	20mg daily	Can open capsule and mix with applesauce
Dexlansoprazole (DEXILANT)	Rx	30-60mg daily	Can open capsule and mix with applesauce

Pharmacological Recommendations

- Antacids and histamine-2 receptor antagonists (H2RAs) may be considered if symptoms are intermittent and relieved with medications
- Prokinetic agents are NOT recommended unless gastroparesis is present
- Sucralfate ONLY recommended in pregnancy

LONG TERM PPI USE

Risks of Long-Term PPI Use

- Increased Risk of Infections
 - *C. difficile*
 - Pneumonia
- Progression of CKD
- Bone Fractures
- Links to Dementia?

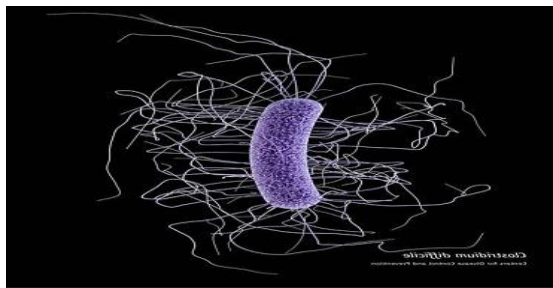
PPIs and Infection Risk

- *Clostridium Difficile*

- Healthcare associated infection leading to infectious diarrhea
- PPIs associated with increased risk of developing infection¹
 - Proposed Mechanism: chronic acid suppression → bacterial proliferation
 - ≈ 38% greater risk with PPI vs H2RA²

“Association Between Proton Pump Inhibitor Therapy and *Clostridium difficile* Infection in a Meta-Analysis”¹

- Meta-analysis of 30 observational studies (n=202,965)
- PPI use associated with ≈ 2-fold increased risk of CDI (OR 2.15, 95% CI 1.81-2.55)
- Analysis remained consistent even when stratifying studies based on amount of antibiotic usage



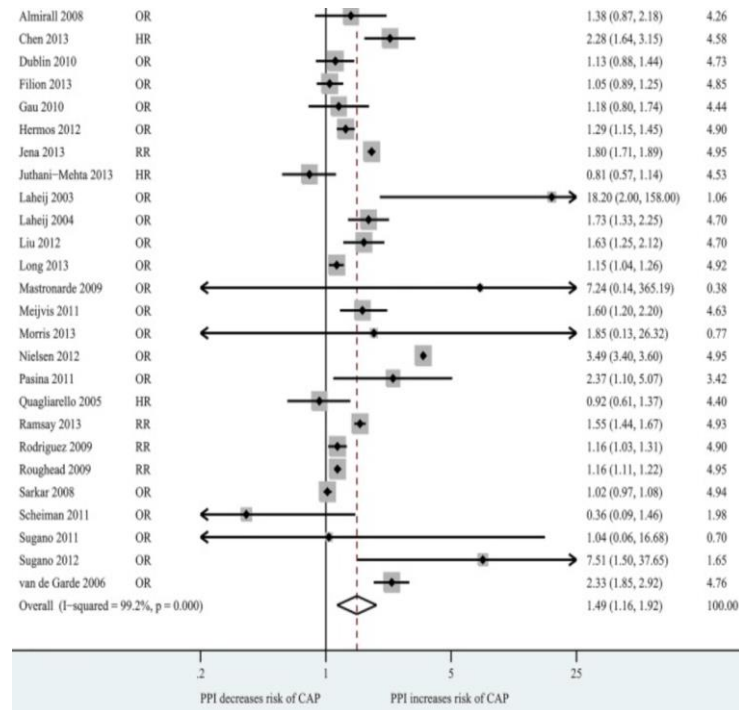
PPIs and Infection Risk

● Pneumonia

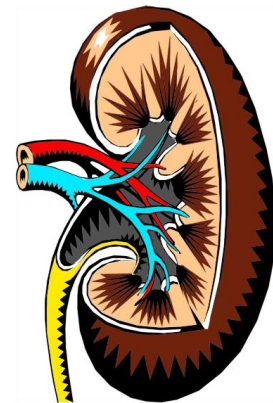
- Use of PPIs is associated with increased risk of CAP³
- Several studies have found an association with PPIs and HAP/VAP, but confounding is too high to draw conclusions⁴
- Proposed mechanism: chronic acid suppression → alteration of respiratory flora⁵

“Risk of Community-Acquired Pneumonia with Outpatient Proton-Pump Inhibitor Therapy: A Systematic Review and Meta-Analysis”³

- Meta-analysis of 26 studies including 4 RCTs (n=6,351,656)
- PPI use led to a pooled relative risk of 1.49 (95% CI, 1.16-1.92)
- Secondary analysis with H2RAs was not associated with increased CAP risk
 - (RR 1.00, 95% CI, 0.9-1.12)



Renal Effects of PPI Use



- Risk of CKD
 - Mechanism is unknown
 - Acute interstitial nephritis has been documented (extremely rare)
 - No dosage adjustments necessary

“Proton Pump Inhibitor Use and Risk of Chronic Kidney Disease”⁶

- Prospective cohort study (n=10,482) with a follow-up period from 1996-2011
- Participants begin trial with eGFR > 60mL/min/1.73m²
- Baseline PPI users were at greater risk of incident CKD (HR 1.45, 95% CI, 1.11-1.90)
 - Similar results found when adjusted for demographics, comorbidities, and concomitant medications
 - Results were validated with a replication cohort (n=248,751) with comparable results
- H2RA use was not associated with statistically significant risk of incident CKD

“Association Between Proton Pump Inhibitor Use and Risk of Progression of Chronic Kidney Disease”⁷

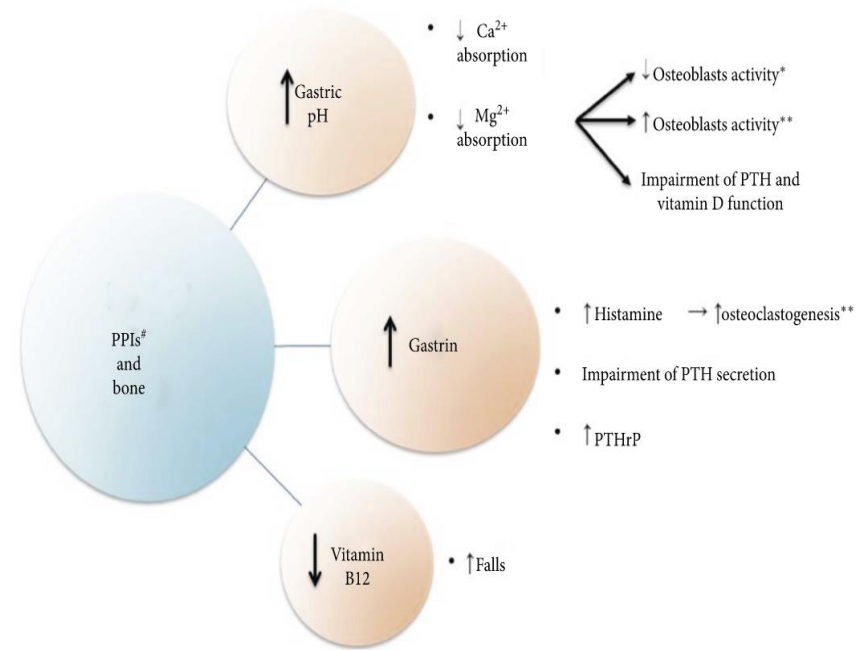
- Retrospective cohort study of new users of PPIs (n=105,305) versus H2RAs (n=9578)
- PPIs associated with increased risk progression of CKD
 - Risk of of doubled Scr (HR 1.26, 95% CI, 1.05-1.51)
 - Risk of 30% or greater decline in eGFR (HR 1.26, 95% CI, 1.16-1.36)

Bone Health and PPIs

- PPIs are associated with micronutrient deficiencies⁴
 - Magnesium
 - Calcium
 - Vitamin B12
- Mechanisms and link to osteoporosis are not fully understood
- Currently no recommendations exist for increased monitoring or supplementation for patients on a PPI

“Proton pump inhibitors and risk of hip fracture: a meta-analysis of observational studies”⁸

- Meta analysis of 24 observational studies (n=2,103,800)
- PPI use was associated with greater risk of hip fracture
 - RR 1.2 (95% CI, 1.14-1.28)
- Relative risk increased with higher doses and longer durations



Briganti, S. I., Naciu, A. M., Tabacco, G., Cesareo, R., Napoli, N., Trimboli, P., Castellana, M., Manfrini, S., & Palermo, A. (2021). Proton pump inhibitors and fractures in adults: A critical appraisal and review of the literature. *International Journal of Endocrinology*, 2021, 1–15. <https://doi.org/10.1155/2021/8902367>

PPIs and Dementia

- Association between PPI use and dementia are highly debated
- Proposed mechanism: interference with amyloid plaque degradation⁴
- Potential link to dementia is based on two German epidemiological studies
 - “Association of Proton Pump Inhibitors With Risk of Dementia A Pharmacoepidemiological Claims Data Analysis”⁹
 - “Risk of dementia in elderly patients with the use of proton pump inhibitors”¹⁰
- Most recent studies have not been able to establish a positive correlation between PPI use and dementia



- Evaluate patients individually on risks and benefits of PPI use
 - How severe are the patients GERD symptoms?
 - What are the patient's goals and concerns?
 - Is the patient frequently hospitalized or at risk of nosocomial infections?
 - What is the patient's renal function and electrolyte levels?
 - Is the patient at a high risk for falls?

- 2022 ACG Guideline Recommendation
 - "We recommend attempting to discontinue the PPIs in patients whose classic GERD symptoms respond to an 8-wk empiric trial of PPIs"¹¹
 - PPIs may end up being necessary, but potential risks should be considered

Alternative Treatments for GERD

- **Non-Pharmacological options should be recommended in all patients**
 - Avoiding dietary triggers
 - Weight loss
 - Elevating the head of the bed
- Antacids
 - No preferred agent
 - Only for occasional, on-demand relief of symptoms
- H2RAs
 - Famotidine (Pepcid) 20 mg twice daily
 - Nizatidine (Axid) 75 mg twice daily
 - Cimetidine: not recommended due to potential for drug interactions

Conclusions

- GERD is bothersome condition that can potentially lead to serious downstream consequences if untreated
- PPIs are the most effective treatment for GERD, but should be used judiciously
- There is growing evidence that long-term use of PPIs is associated with undesirable effects
- Current ACG recommendations are to attempt to discontinue PPIs if symptoms resolve after 8 weeks
- Alternative treatment with H2RAs may be a better long-term option in certain patients

References

1. Deshpande, A., Pant, C., Pasupuleti, V., Rolston, D. D. K., Jain, A., Deshpande, N., Thota, P., Sferri, T. J., & Hernandez, A. V. (2012). Association between proton pump inhibitor therapy and clostridium difficile infection in a meta-analysis. *Clinical Gastroenterology and Hepatology*, 10(3), 225–233. <https://doi.org/10.1016/j.cgh.2011.09.030>
2. Azab, M., Doo, L., Doo, D. H., Elmofti, Y., Ahmed, M., Cadavona, J. J., Liu, X. B., Shafi, A., Joo, M. K., & Yoo, J. W. (2017). Comparison of the hospital-acquired *clostridium difficile* infection risk of using proton pump inhibitors versus histamine-2 receptor antagonists for prophylaxis and treatment of stress ulcers: A systematic review and meta-analysis. *Gut and Liver*, 11(6), 781–788. <https://doi.org/10.5009/gnl16568>
3. Lambert, A. A., Lam, J. O., Paik, J. J., Ugarte-Gil, C., Drummond, M. B., & Crowell, T. A. (2015). Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: A systematic review and meta-analysis. *PLOS ONE*, 10(6). <https://doi.org/10.1371/journal.pone.0128004>
4. Jaynes, M., & Kumar, A. B. (2018). The risks of long-term use of Proton Pump Inhibitors: A critical review. *Therapeutic Advances in Drug Safety*, 10, 204209861880992. <https://doi.org/10.1177/2042098618809927>
5. Fohl, A. L. (2011). Proton pump inhibitor-associated pneumonia: Not a breath of fresh air after all? *World Journal of Gastrointestinal Pharmacology and Therapeutics*, 2(3), 17. <https://doi.org/10.4292/wjgpt.v2.i3.17>
6. Lazarus, B., Chen, Y., Wilson, F. P., Sang, Y., Chang, A. R., Coresh, J., & Grams, M. E. (2016). Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Internal Medicine*, 176(2), 238. <https://doi.org/10.1001/jamainternmed.2015.7193>
7. Klatte, D. C. F., Gasparini, A., Xu, H., de Deco, P., Trevisan, M., Johansson, A. L. V., Wettermark, B., Ärnlov, J., Janmaat, C. J., Lindholm, B., Dekker, F. W., Coresh, J., Grams, M. E., & Carrero, J. J. (2017). Association between Proton Pump inhibitor use and risk of progression of chronic kidney disease. *Gastroenterology*, 153(3), 702–710. <https://doi.org/10.1053/j.gastro.2017.05.046>
8. Poly, T. N., Islam, M. M., Yang, H.-C., Wu, C. C., & Li, Y.-C. J. (2018). Proton pump inhibitors and risk of hip fracture: A meta-analysis of observational studies. *Osteoporosis International*, 30(1), 103–114. <https://doi.org/10.1007/s00198-018-4788-y>
9. Gomm, W., von Holt, K., Thomé, F., Broich, K., Maier, W., Fink, A., Doblhammer, G., & Haenisch, B. (2016). Association of Proton Pump inhibitors with risk of dementia. *JAMA Neurology*, 73(4), 410. <https://doi.org/10.1001/jamaneurol.2015.4791>
10. Haenisch, B., von Holt, K., Wiese, B. *et al.* Risk of dementia in elderly patients with the use of proton pump inhibitors. *Eur Arch Psychiatry Clin Neurosci* 265, 419–428 (2015). <https://doi.org/10.1007/s00406-014-0554-0>
11. Katz, P. O., Dunbar, K. B., Schnoll-Sussman, F. H., Greer, K. B., Yadlapati, R., & Spechler, S. J. (2021). ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. *American Journal of Gastroenterology*, 117(1), 27–56. <https://doi.org/10.14309/ajg.0000000000001538>



Thank you!
Questions?

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