

“Pediatric Aero-Digestive Disorders in the New Century”

A Valley-Mount Sinai Kravis Children's Hospital educational symposium.



CHILDREN'S HEALTH





Changing Pharmacology of Acid Suppression in Pediatric GERD

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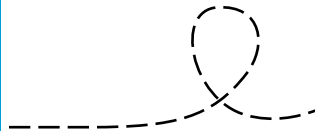
CHILDREN'S HEALTH

Faculty Disclosure

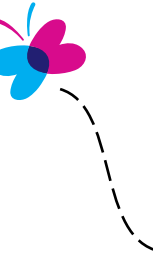
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No financial disclosures

No unlabeled use of a product is being discussed



Objectives



- Know three potential risk factors associated with suppression of gastric acid.
- Describe at least 2 mechanisms to control of acid production in the stomach
- List at least 5 conditions in differential of reported “heartburn”

TREATMENTS
for
GE REFLUX (DISEASE)

Tips on therapy

1. Set the RIGHT expectation
2. Select the right combination of interventions
3. Understand the short and long-term consequences of interventions

Tips on therapy

1. Set the RIGHT expectation

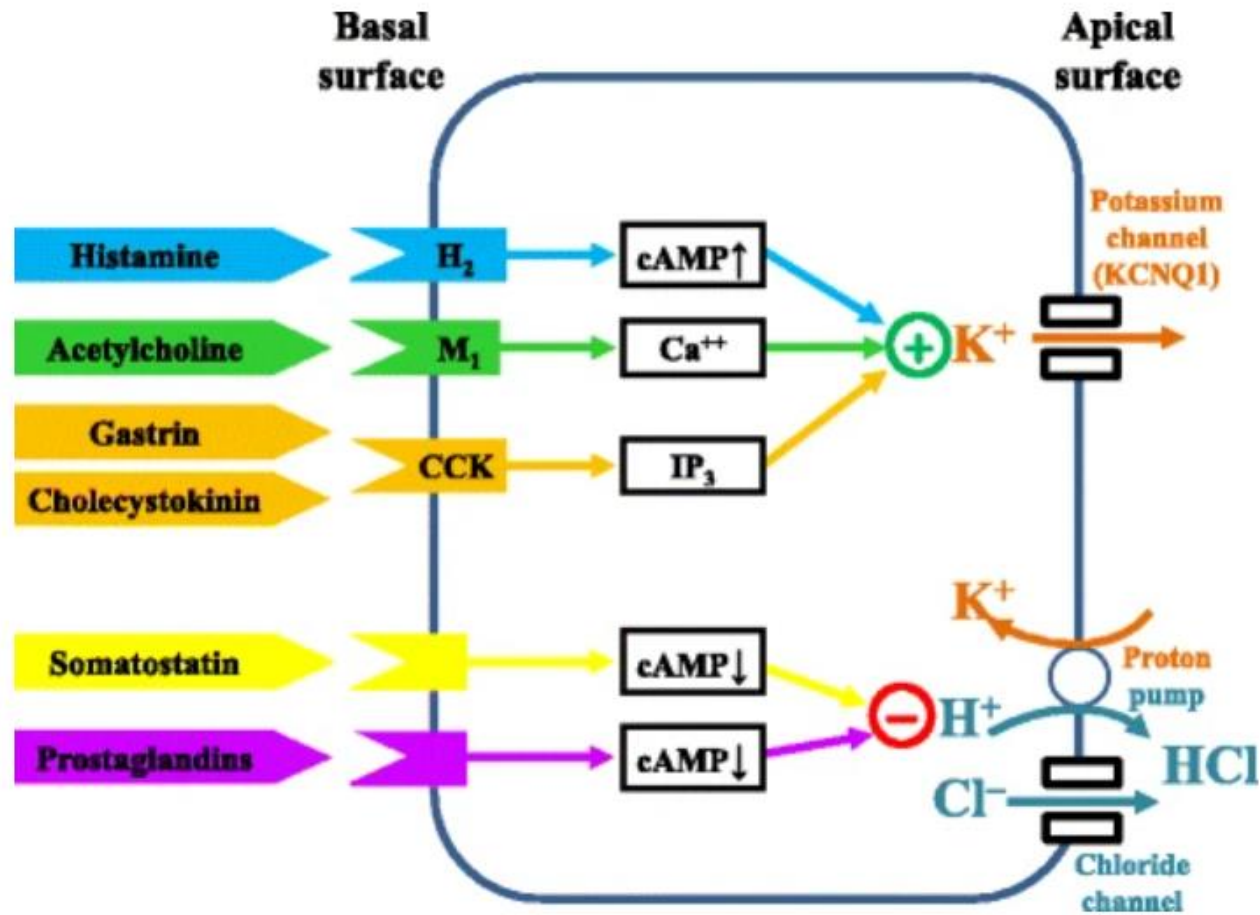
1. In infants fussiness is not always reflux
2. In older kids reflux is not always just “GERD” and further testing might be needed including upper endoscopy.

2. Select the right combination of interventions

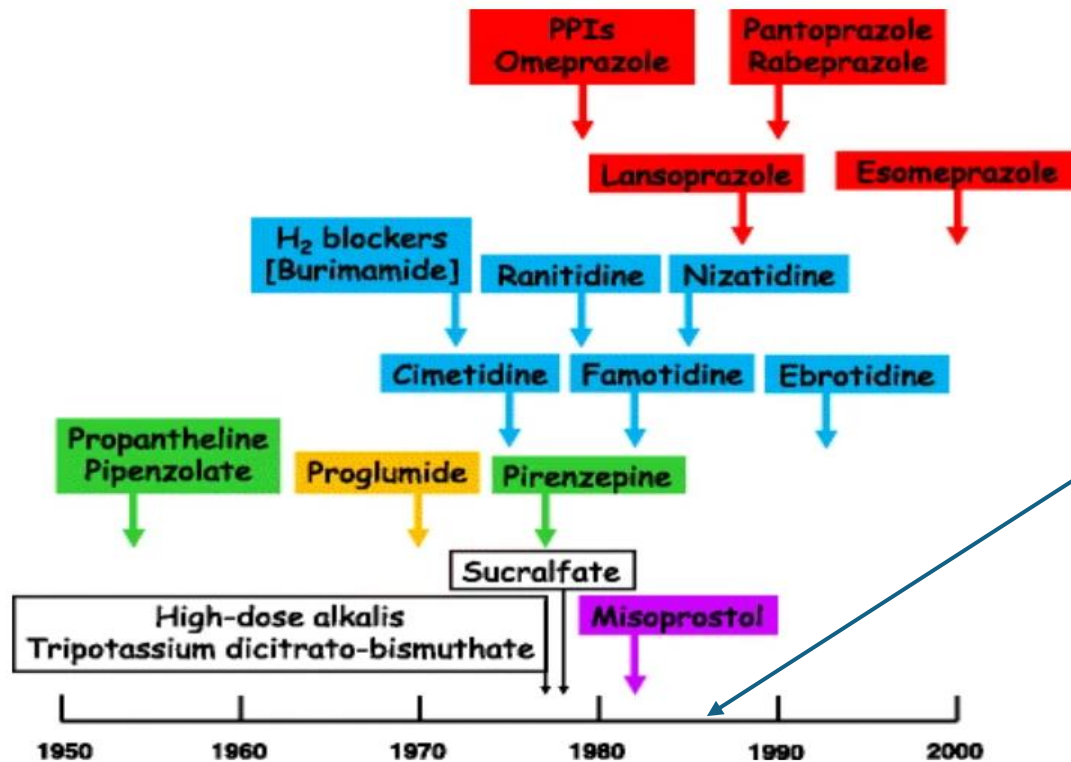
3. Understand the short and long-term consequences of interventions

TREATMENTS:
ACID SUPPRESSION

Parietal cell physiology



History of our attempts to manage acid



K competitive channel blockers (1st reported in 1986)

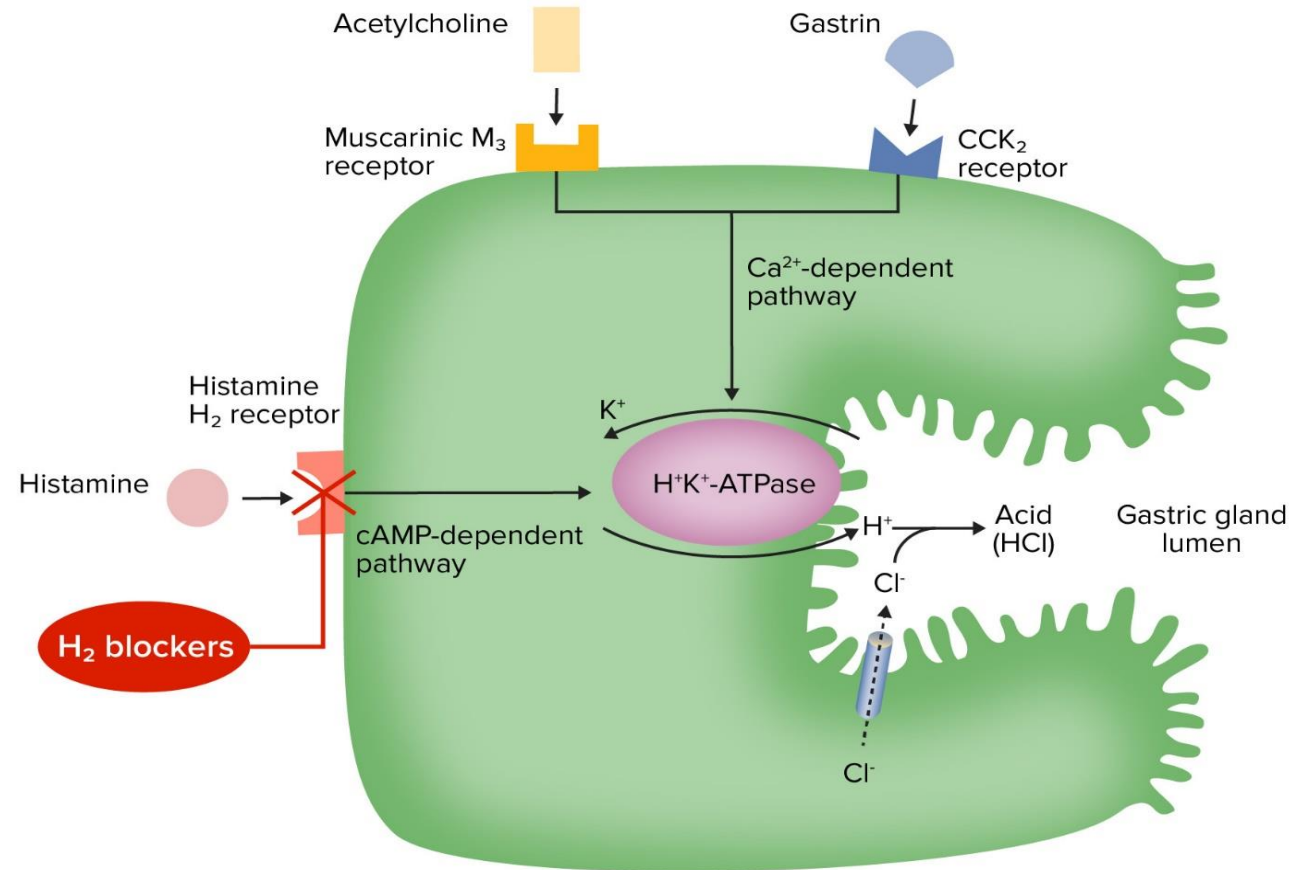
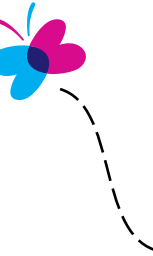
Valsartan FDA approved in 2018



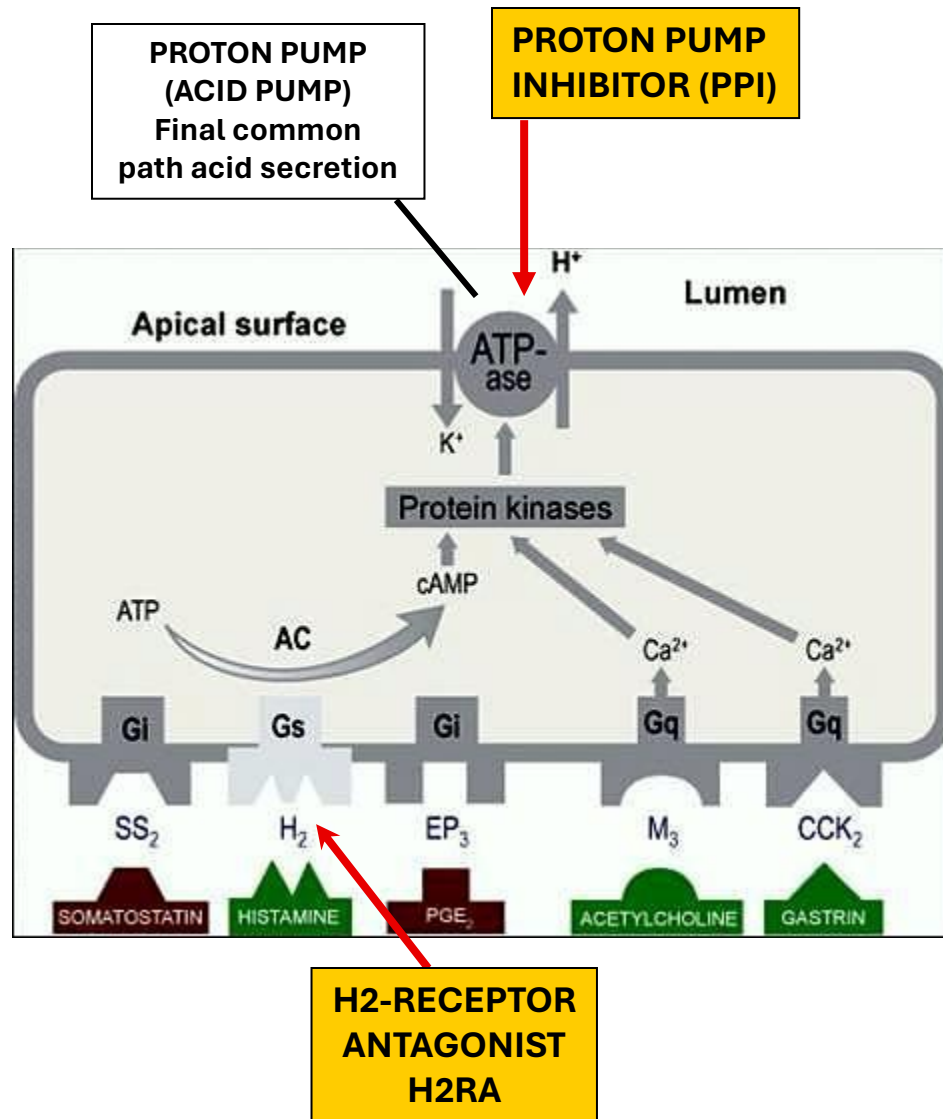
Treatment: Role of Acid Suppression

- Histamine₂-receptor antagonists (H₂RAs) produce relief of symptoms and mucosal healing. Grade A
- PPIs are superior to H₂RAs in relieving symptoms and healing esophagitis. Grade A

H2 Blockers Mechanism of Action



HCL Acid Suppression: Parietal Cell



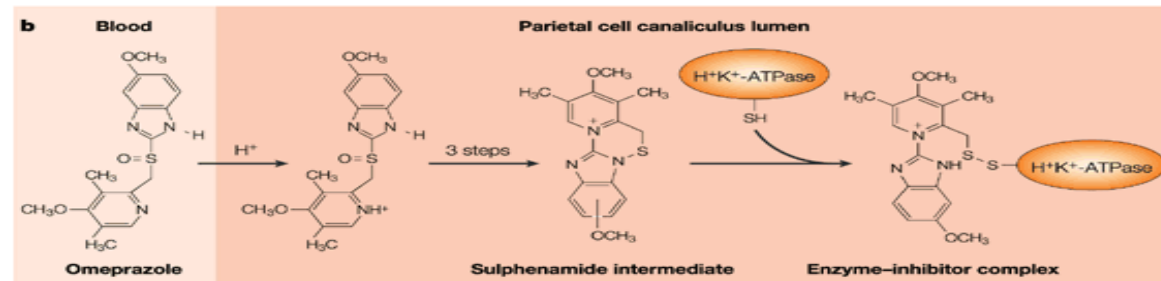
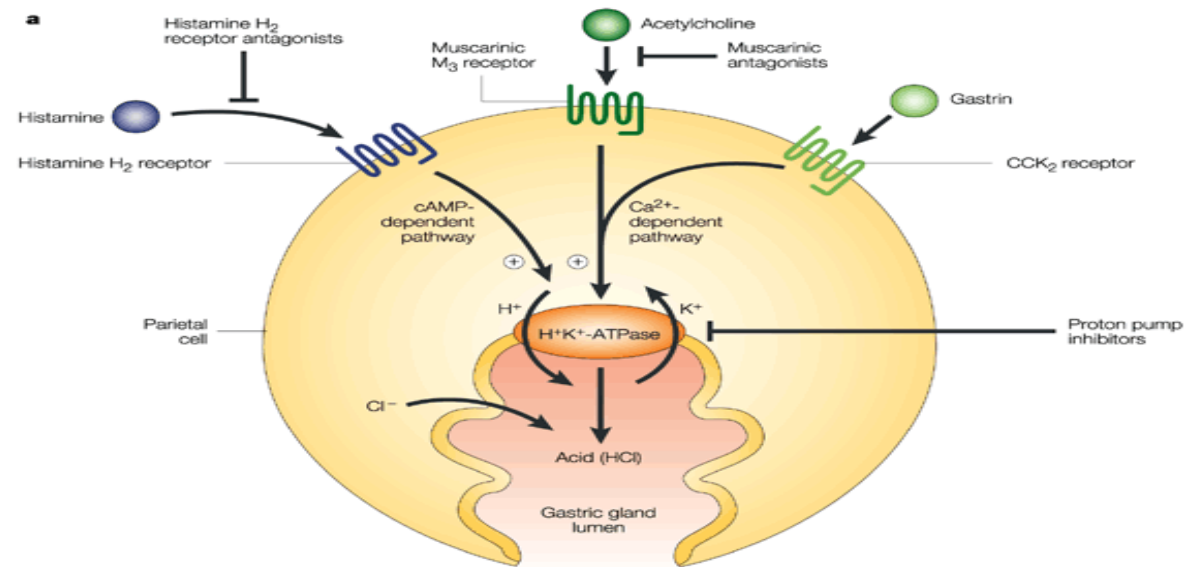
H₂RA

- Active drug available to block receptor soon after absorption
‘On-demand’ use
- Tachyphylaxis
- Fail to block meal-stimulated acid secretion

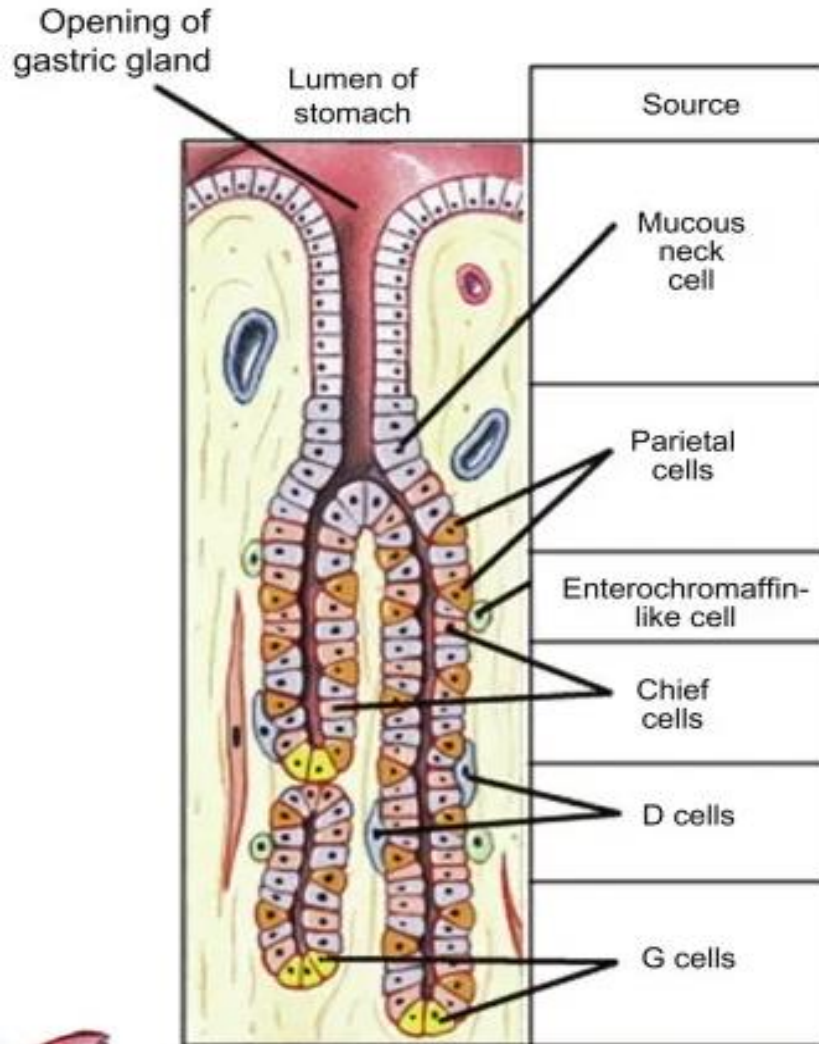
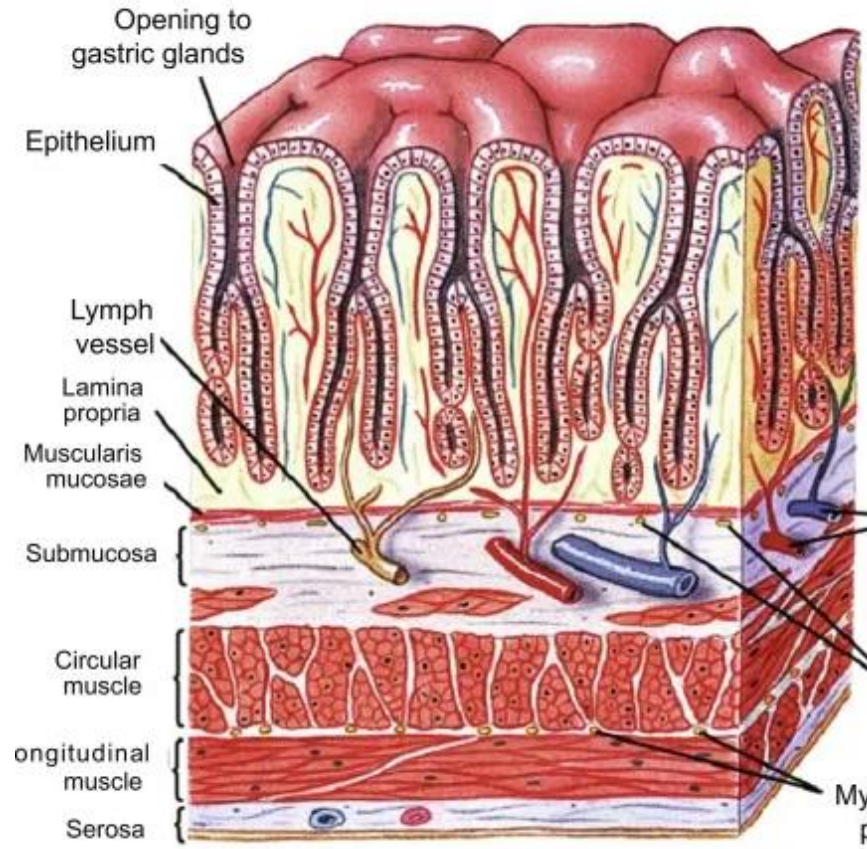
PPI

- Coated: protect v gastric acid
- Absorbed small bowel
- Pro-drug to active sulfenamide
- Secreted into lumen, binds only new/active acid pumps: take before breakfast
Delayed action

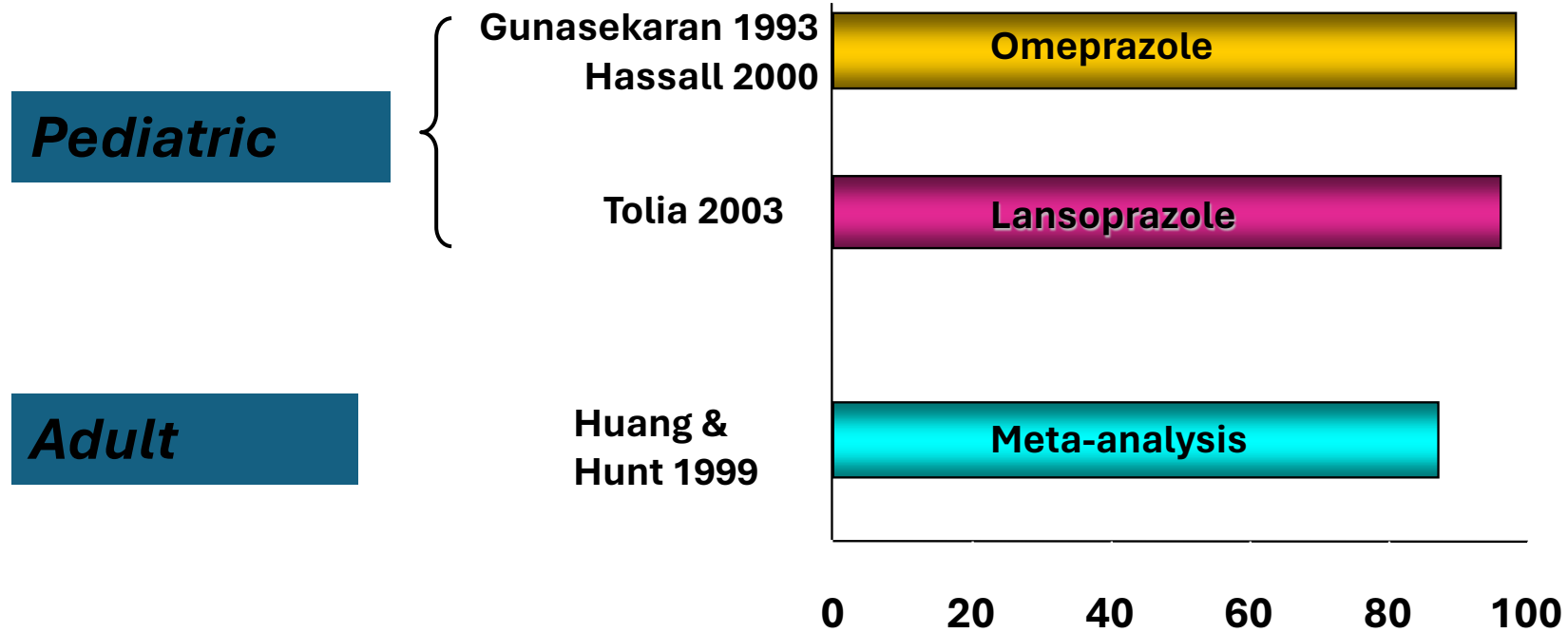
PPI (omeprazole) mechanism of action



PPI excretion image

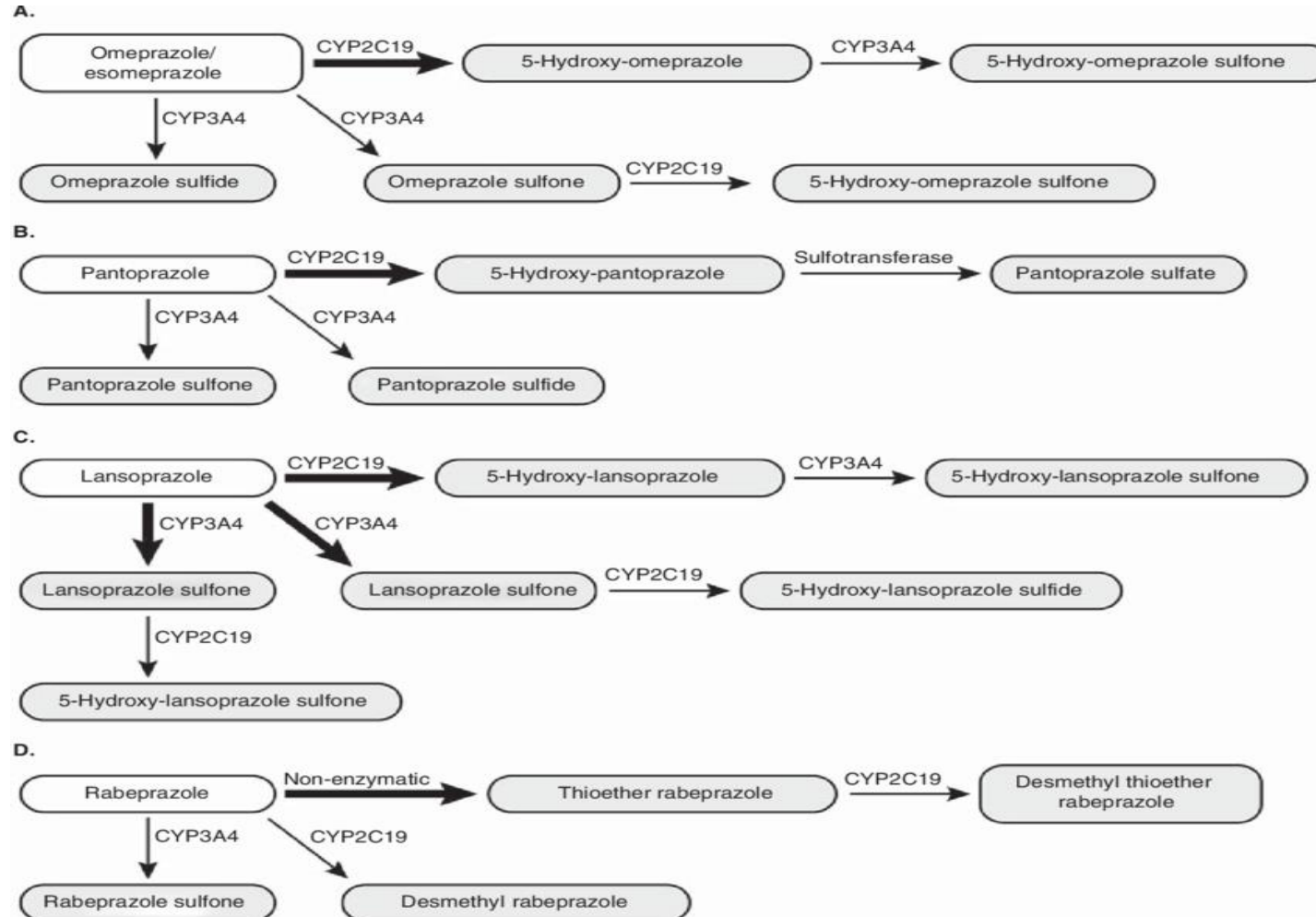


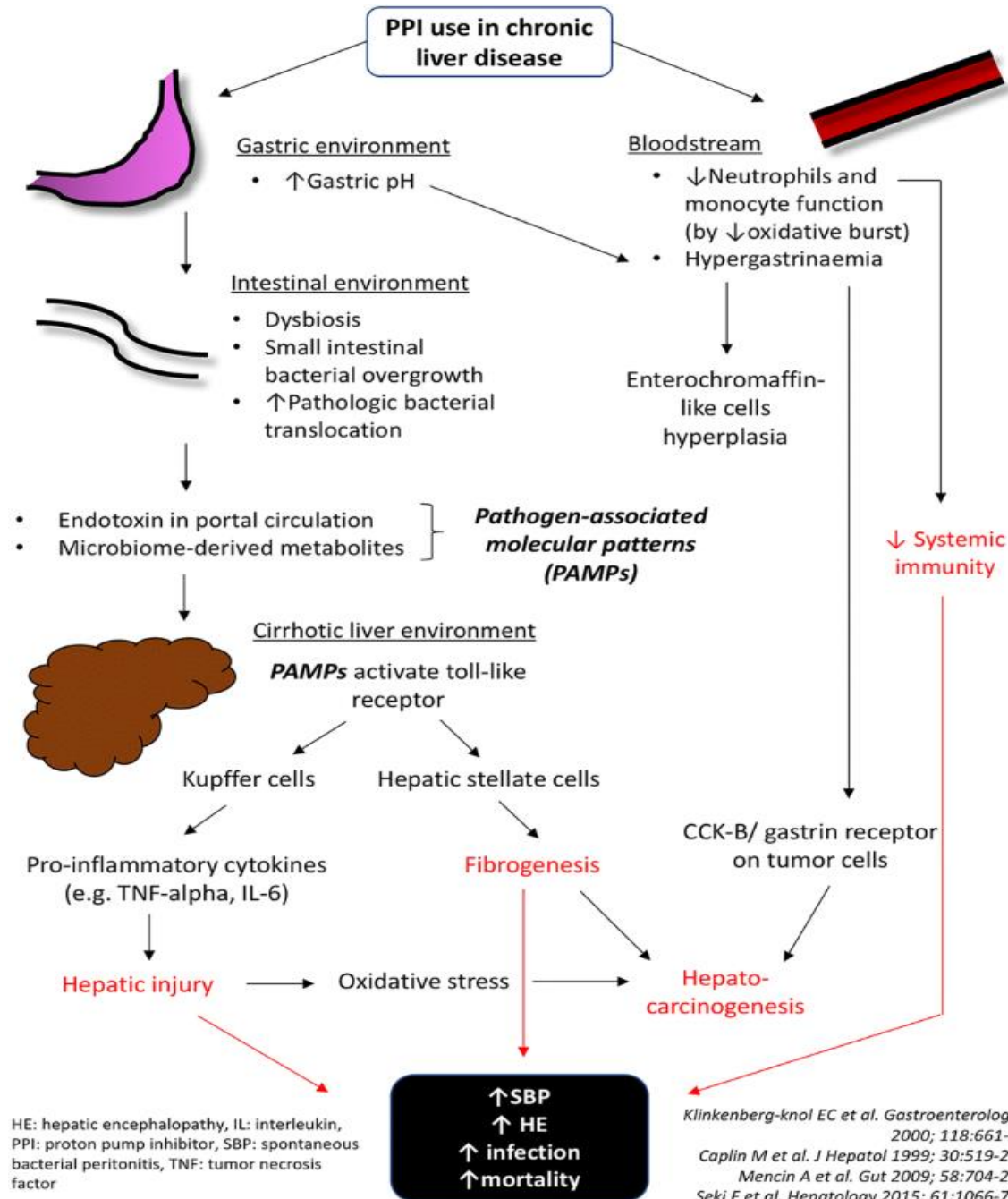
Similar PPI Healing Rates In Adults & Children: Short-term Erosive esophagitis



Gunasekaran, J Pediatr 1993
Hassall, J Pediatr 2000
Tolia, JPGN 2003
Huang & Hunt, Gut 1999

Metabolism of PPIs

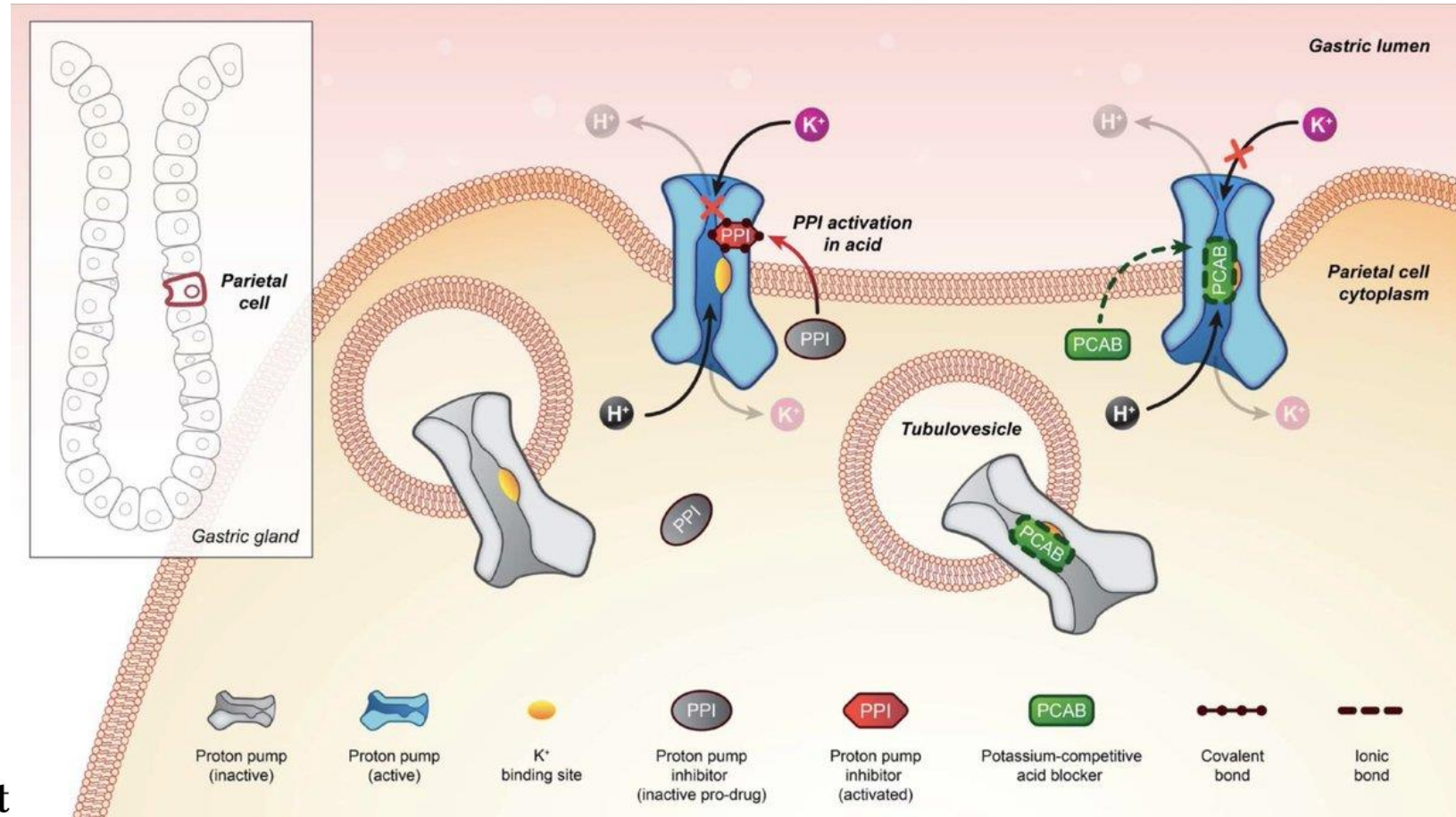




HE: hepatic encephalopathy, IL: interleukin, PPI: proton pump inhibitor, SBP: spontaneous bacterial peritonitis, TNF: tumor necrosis factor

Klinkenberg-knol EC et al. *Gastroenterology* 2000; 118:661-9
 Caplin M et al. *J Hepatol* 1999; 30:519-26
 Mencin A et al. *Gut* 2009; 58:704-20
 Seki E et al. *Hepatology* 2015; 61:1066-79

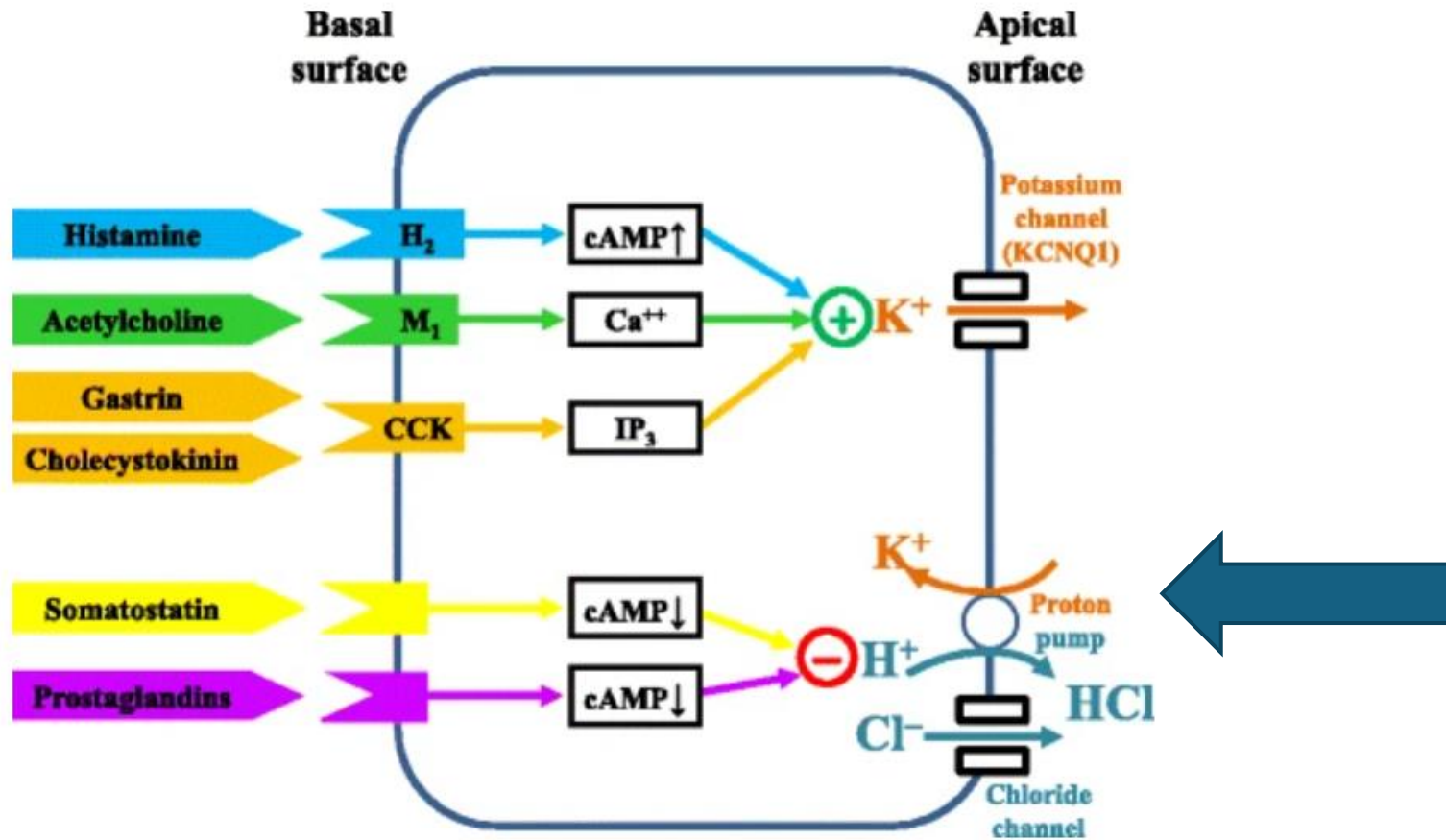
PCAB mechanism of action



Characteristics of Children Receiving PPIs for up to 11 years Duration

- 1989-2004, 166 children Rx PPIs continuously
(median 3yr, max 11yr)
- 79% had at least 1 GERD-predisposing condition
 - neuromotor, esophageal atresia
- 15% failed fundoplication before or after starting PPI
- Barrett's 10%, hiatal hernia 40%
- Side-effects: headache, constipation, diarrhea, agitation
- Safe and effective in preventing relapse

Potassium Competitive Channel Blockers



Treatment: Role of Acid Suppression

- For the treatment of chronic heartburn in *older children or adolescents*, lifestyle changes with a 4-week PPI trial are recommended. Grade A
- If symptoms resolve, continue PPI for 3 months. If chronic heartburn persists or recurs after treatment, it is recommended that the patient be referred to a ped gastroenterologist. Grade C

Tips on therapy

1. Set the RIGHT expectation
- 2. Select the right combination of interventions**
 1. Relief of acute symptoms is different than long term acid suppression
 2. Delayed gastric emptying due to other factors needs to be always kept in mind.
 3. Value important of “lifestyle” changes at home.
3. Understand the short and long-term consequences of interventions

Range of approaches to GER/D: Infants

- Doing nothing: watch & wait
 - Positioning
 - Eliminate exposure to smoke
 - 'Non-nutritive sucking' (pacifier)
 - Thickened feedings
 - Trial of hypoallergenic formula
 - Longer feed infusion/transpyloric
-

Range of approaches to GER/D: Older children/adults

- Weight loss
 - Decrease fatty foods/raw onions/caffeine
 - Don't eat within 2-3 hours of bedtime
 - Elevate head of bed on 6" blocks
 - Antacids, eg, Gaviscon, Maalox, Mylanta, Tums, etc
 - Prokinetics: metoclopramide, domperidone, Erythromycin
 - Acid suppressing agents
 - Surgery
-

Tips on therapy

1. Set the RIGHT expectation
2. Select the right combination of interventions
- 3. Understand the short and long-term consequences of interventions**
 1. Risks of asthma with acid suppression use in infants a concerning development
 2. Dysbiosis needs to be considered for complaints in child with long term use of acid suppression therapy.
 3. Consider all the options for treatment (including surgery).

Adverse effects of acid suppression: H2RA *or* PPI

- Acute gastro & community-acquired pneumonia. *Canani. Peds '06*
- Necrotizing enterocolitis. *Guillet. Peds 2006*
- *Candida* in NICU. *Saiman. Ped Infect Dis J 2001*
- *C. difficile*-associated disease. *Dial S. JAMA 2005*
- Community-acquired pneumonia. *Laheij. JAMA 2004*
- Bacterial gastroenteritis. *Garcia Rodriguez. Clin Gastro Hep 2007*
- B12 deficiency in older adults. *Valuck. J Clin Epidemiol 2004*
- Hip fracture. *Yang. JAMA 2006*
- Vitamin B12 in elderly individuals: refuted. *den Elzen. APT 2008*

Gastric acid has purpose - suppression may cause problems
Risk / Benefit

Risks associated with long term PPI use


Digestive Diseases and Sciences (2018) 63:2940–2949

<https://doi.org/10.1007/s10620-018-5122-4>

ORIGINAL ARTICLE



Gut Microbiota Composition Before and After Use of Proton Pump Inhibitors

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Normal microbiota

Oral cavity

Streptococcaceae
Neisseriaceae
Prevotellaceae
Veillonellaceae
Carnobacteriaceae
Pasteurellaceae
Micrococcaceae
Fusobacteriaceae

Esophagus

Streptococcaceae
Prevotellaceae
Veillonellaceae

Stomach

Prevotellaceae
Streptococcaceae
Veillonellaceae
Micrococcaceae
Lactobacillaceae

Small intestine

Streptococcaceae
Pasteurellaceae
Enterobacteriaceae
Moraxellaceae
Pseudomonadaceae
Actinomycetaceae
Lactobacillaceae
Veillonellaceae
Fusobacteriaceae
Bacteroidaceae
Enterococcaceae
Clostridiaceae

Colon

Bacteroidaceae
Ruminococcaceae
Prevotellaceae
Bifidobacteriaceae
Streptococcaceae
Enterobacteriaceae
Enterococcaceae
Clostridiaceae
Lactobacillaceae
Eubacteriaceae
Fusobacteriaceae
Peptostreptococcaceae

PPI treatment

Oral cavity

↑ *Fusobacteriaceae*
Leptotrichiaceae
↓ *Neisseriaceae*
Veillonellaceae

Esophagus

↑ *Micrococcaceae*
Actinomycetaceae
Clostridiaceae
↓ *Comamonadaceae*

Stomach

↑ *Streptococcaceae*
↓ *Prevotellaceae*

Small intestine

↑ *Streptococcaceae*
Staphylococcaceae
Enterobacteriaceae
Bacteroidaceae
Lactobacillaceae
Veillonellaceae
Clostridiaceae
↓ *Bifidobacteriaceae*

Colon

↑ *Enterobacteriaceae*
Enterococcaceae
Lactobacillaceae
↓ *Ruminococcaceae*
Bifidobacteriaceae



Risks of PPI use and RAD

Analysis	PPI initiators			Noninitiators			Hazard ratio (95% CI)	PPI decreases risk	PPI increases risk
	No. of patients	No. of events	Incidence rate, events per 1000 person-years	No. of patients	No. of events	Incidence rate, events per 1000 person-years			
Primary result	80 870	4428	21.8	80 870	2818	14.0	1.57 (1.49-1.64)		■
Alternative asthma definition									
Primary diagnosis of asthma OR 2 asthmatic prescriptions within 90 d	80 870	4331	21.3	80 870	2764	13.7	1.56 (1.49-1.64)		■
Primary diagnosis of asthma OR 2 asthmatic prescriptions within 60 d	80 870	4160	20.5	80 870	2653	13.1	1.56 (1.49-1.64)		■
Any asthma diagnosis AND asthmatic prescription within 60 d	80 870	1438	6.9	80 870	861	4.2	1.65 (1.52-1.80)		■
Restriction to asthma event without short-acting inhaled bronchodilators	80 870	4428	21.8	80 870	2818	14.0	1.57 (1.49-1.64)		■
As-treated analysis	80 870	222	24.9	80 870	2783	13.9	1.46 (1.24-1.73)		■
Adopted high-dimensional propensity score matching	78 695	4104	20.7	78 695	2757	14.0	1.48 (1.41-1.55)		■
Analysis for H ₂ RA use vs nonuse	15 680	1325	32.8	15 680	858	21.0	1.56 (1.43-1.70)		■
Excluded any asthma diagnosis and asthmatic prescription before index date ^a	68 449	3446	19.7	69 531	2115	11.9	1.65 (1.56-1.74)		■
Restricted to patients without PPI combined therapy at index date	77 134	4238	21.9	80 870	2818	14.0	1.57 (1.50-1.65)		■
Redefined length of follow-up to a maximum 1 y	80 870	2163	27.6	80 870	1343	17.1	1.61 (1.51-1.72)		■

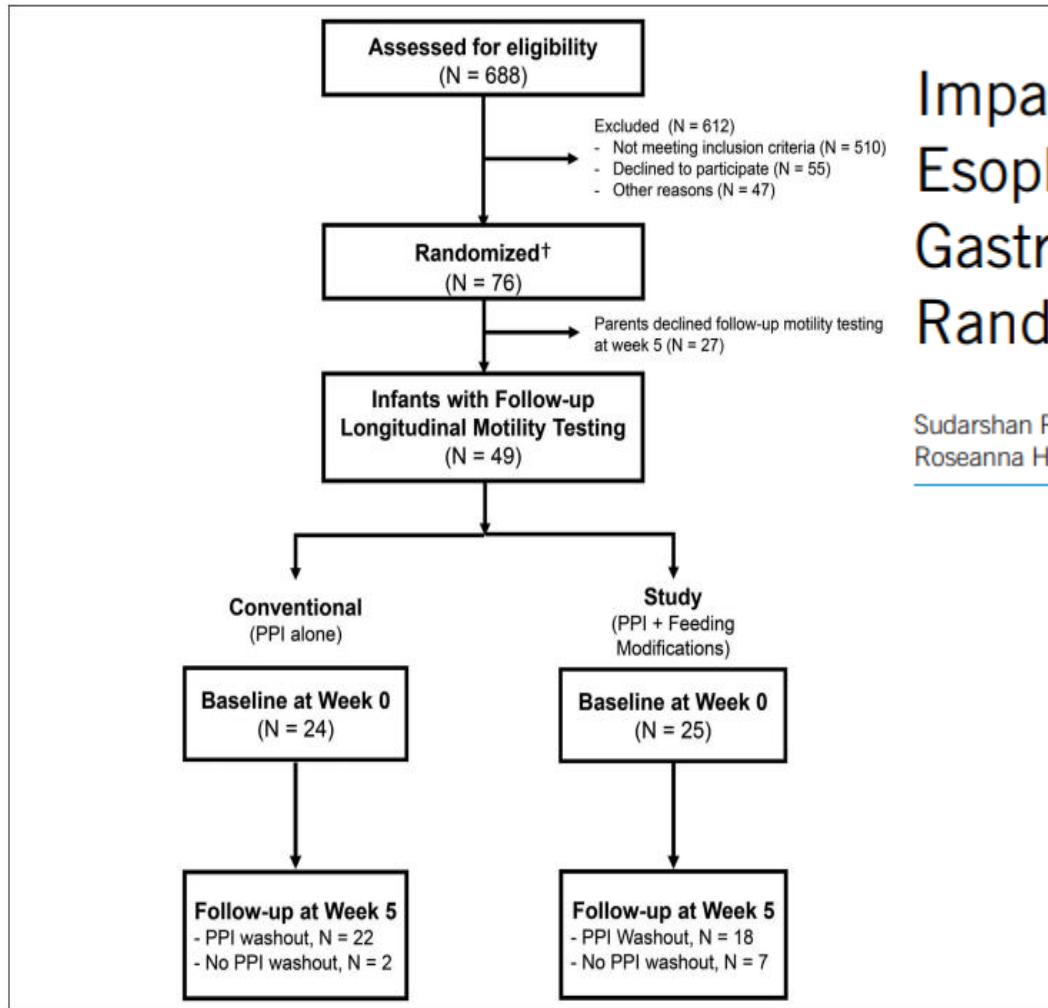
H₂RA indicates histamine 2 receptor antagonist; HR, hazard ratio.

^a Excluded any asthma diagnosis or prescription in all available look-back before index date.

Treatment: Role of Acid Suppression in Infants

- In otherwise normal infants with unexplained crying, irritability, or distressed behavior, there is no evidence to support acid suppression.
Grade A

Acid suppression trial in infant dysphagia?



Impact of Feeding Strategies With Acid Suppression on Esophageal Reflexes in Human Neonates With Gastroesophageal Reflux Disease: A Single-Blinded Randomized Clinical Trial

Sudarshan R. Jadcherla, MD, FRCPI, DCH, AGAF^{1,2,3,4}, Kathryn A. Hasenstab, BS, BME^{1,2}, Ish K. Gulati, MD^{1,2,3}, Roseanna Helmick, BS, BME^{1,2}, Haluk Ipek, BS, BME^{1,2}, Vedat Yildiz, MS^{5,6} and Lai Wei, PhD⁵

SUMMARY

- Certain groups children predisposed to chronic, relapsing GERD
- In otherwise healthy children, GERD often not chronic
- Infants: GERD is infrequent cause of unexplained crying / 'irritability' in otherwise healthy children
 - consider colic, milk protein allergy, constipation, UTI
 - nonpharmacologic first-line approach, rather than acid suppression
- Eosinophilic esophagitis and GERD have similar symptoms
 - don't treat empirically with steroids: EoE is not a clinical diagnosis
 - partial treatment makes diagnosis more difficult
- Symptoms severe/ atypical/dysphagia - don't treat empirically:
Get diagnosis



SUMMARY

- If empiric trial acid suppression: *time-limited*, taper off drug:
Get diagnosis
- On-demand therapy: antacids, H2RA (PCCB?)
- PPIs longer-term Rx: once daily, 15-30mins before breakfast
Routine BID dosage unnecessary
- PPIs: don't stop them abruptly – taper
- Acid suppression in general (H2RA, PPI and PCCB) may have adverse effects that are not immediately apparent
- Antireflux surgery
 - significant morbidity,
 - high failure rates, often early
 - STILL, indicated in selected patients
- Established chronic, relapsing GERD: surgery v long-term PPI





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