

# A Patient with GI Bleeding

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AT DALLAS

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*This is to acknowledge that Dr. Peterson has disclosed financial interests or other relationships with commercial concerns related directly to this program. Dr. Peterson will be discussing off-label uses in his presentation.*

Dr. Peterson is Professor of Medicine in the division of gastroenterology and hepatology at UTSW. He retired from the Dallas VAMC in July, 2004 and now resides in Breckenridge, Colorado. His interests remain in teaching and evidence based medicine.

### Case Presentation

- S.S. is a 55 y/o man with a three year history of osteoarthritis.
- Past history is negative except for a "small stroke" two years ago for which he now takes 325mg of aspirin a day.

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### Case Presentation

- His osteoarthritis was treated initially with Tylenol and acupuncture, but this now provides him scant relief of his symptoms.
- His physician decides to begin the patient on an NSAID – naproxen is prescribed.

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### Case Presentation

- The patient does well for the first three weeks and tells of no joint pains, although he does tell of periodic dyspepsia.
- On day 22, he awakens and feels light-headed.
- Shortly thereafter, he passes four melenic stools.

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## Case Presentation

- The patient's wife calls 911; the EMS team takes S.S. to the Parkland ER.
- In the ER, his BP is 95/50 and his heart rate is 120.
- Appropriate resuscitation is begun and a nasogastric tube is inserted.
- The NG aspirate reveals bright red blood that turns pink on lavage but does not clear.

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## Case Presentation

- The patient is transferred to the MICU where he is met by the GI fellow on call.
- Following resuscitation, an EGD is performed.
- What is found?

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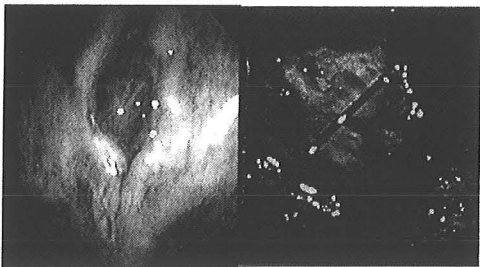
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**Visible Vessel**

**Spurting**



Laine and Peterson NEJM 1994

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## Case Presentation

- The lesion is injected with epinephrine, following which thermal therapy is applied. The bleeding stops and the patient is stable.
- A biopsy is taken for rapid urease testing and is negative.

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## Case Presentation

- What do you do next?
  - Begin an IV infusion of pantoprazole?
    - To be discussed
  - Begin the oral PPI *de jour*?
    - Not yet
  - Order a *Helicobacter pylori* antibody test?
    - Yes
  - Plan discharge the next day?
    - No

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## Mucosal Urease Testing for *H. pylori* in the Presence of Gastric Blood

Lee. Am J Gastroenterol 2000;95:1166-70

- 55 patients with bleeding DU and 69 with non-bleeding DU were studied
- *H. pylori* was sought by rapid urease test, histology, and microbiology
- The sensitivity of the rapid urease test was 75% in bleeders vs. 98% in non-bleeders

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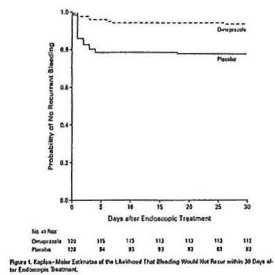
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## 30 Day Rebleeding

(Lau et al. NEJM 2000;343:310-6)



## PPI Therapy for Acute Bleeding Peptic Ulcer

- Results from three systematic reviews

## Why Use A Systematic Review?

- Volume of medical literature is exploding
- Systematic Review provides :
  - comprehensive search & summary of literature
  - data presentation with minimal bias

## Narrative Reviews vs. Systematic Reviews

### Narrative Review

- No Focused Question
- Author of Narrative Review selects Trials
- No Criteria for Searching for Articles

### Systematic Review

- Focused Question
- Explicit Criteria for Inclusion of Trials
- Comprehensive Literature Search
- +/-Quantitative summary

Oxman A. JAMA 1994; 272: 1367-71

## EBM Approach to Systematic Review

- Focused Clinical Question
- Explicit Criteria for Inclusion of Articles
- Comprehensive Literature Search
- Assessment of Validity of Individual Articles
- Assessment of Articles Reproducible
- No Heterogeneity Among Articles

## Systematic Review and Meta-Analysis of Proton Pump Inhibitor Therapy in Peptic Ulcer Bleeding

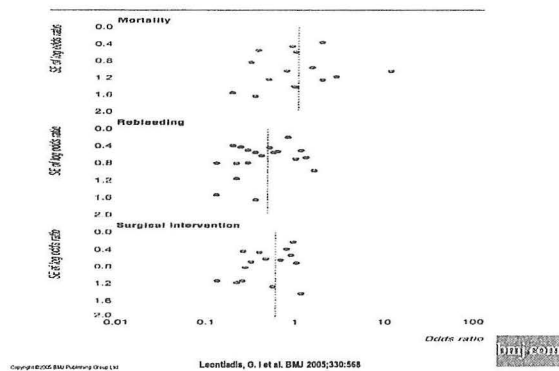
Leontiadis BMJ 2005;330:568-75

- RCTs comparing PPI with placebo or H2 receptor antagonist
- Concealed allocation graded for each study
- Pre-specified sensitivity analyses

## Systematic Review and Meta-Analysis of Proton Pump Inhibitor Therapy in Peptic Ulcer Bleeding

- 21 publications
  - 18 papers
  - 3 abstracts
- Possible publication bias

Funnel plots of included trials for mortality, rebleeding, and surgical intervention rates



## Number Needed to Treat

$$NNT = 1/ARR$$

- The number of patients that need to be treated with the experimental drug instead of the control drug to prevent one bad event



# Systematic Review and Meta-Analysis of Proton Pump Inhibitor Therapy in Peptic Ulcer Bleeding

Outcome @ 30days	No. of Trials	Heterogeneity	% PPI Patients	% Control Patients	NNT
Mortality	18	No	5.2	4.6	NSD
Recurrent Bleeding	19	Yes (p=0.05)	10.6	18.7	12
Need for Surgery	17	No	8.4	13.0	20

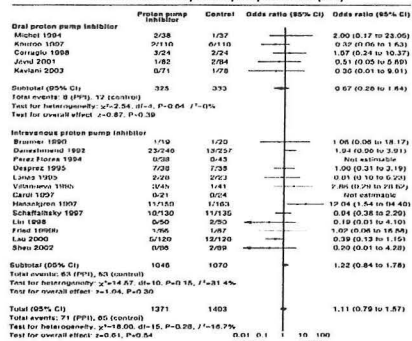
Leontiadis BMJ 2005;330:568-75

## Odds Ratio

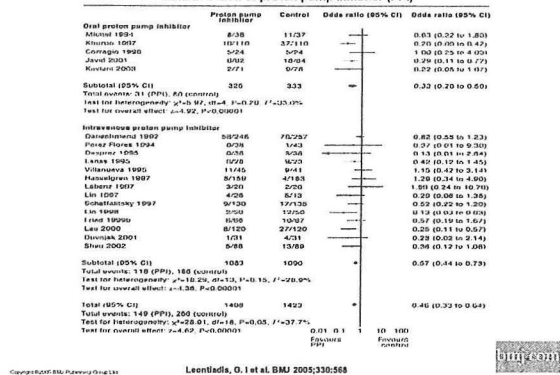
	PPI +	PPI -
Outcome +	a	b
Outcome -	c	d

$$OR = \frac{a/c}{b/d} = \frac{ad}{bc}$$

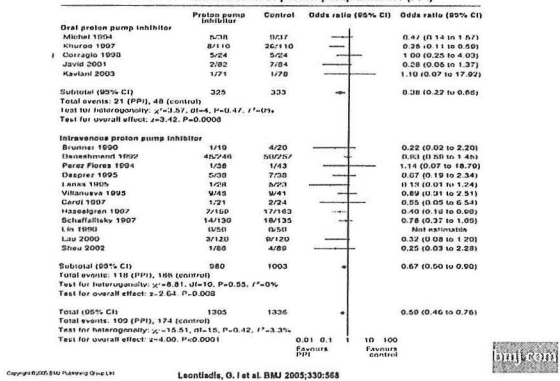
Odds ratios for individual trials and pooled data for mortality, according to route of administration of proton pump inhibitor (PPI)



Odds ratios for individual trials and pooled data for rebleeding, according to route of administration of proton pump inhibitor (PPI)



Odds ratios for individual trials and pooled data for rates of surgical intervention, according to route of administration of proton pump inhibitor (PPI)



## Systematic Review and Meta-Analysis of Proton Pump Inhibitor Therapy in Peptic Ulcer Bleeding

- Sensitivity analyses did not change results:
  - Type of control
  - Quality score
  - Administration means or dose of PPI
  - SRH at endoscopy
  - Use of endoscopic therapy

## Meta-analysis: Proton-pump Inhibition in High-risk Patients with Acute Peptic Ulcer Bleeding

Bardou Aliment Pharmacol Ther 2005;21:677-86

- All RCTs which included high-risk bleeding ulcers
- Only studies in which endoscopic therapy delivered first
- No abstracts
- 18 publications
  - 11 also used in Leontiadis meta-analysis
  - 10 from Leontiadis not used

## Absolute Risk Reduction

$$ARR = CER - EER$$

- ARR retains the baseline risks involved

Study 1  $.80 - .40 = .40$

Study 2  $.08 - .04 = .04$

## Meta-analysis: Proton-pump Inhibition in High-risk Patients with Acute Peptic Ulcer Bleeding

### Mortality

PPI	N	Control	No. of Studies	ARR	Signif?	NNT
HD IV	4	Placebo	2	-2.7	No	-
		H2RA	1	-2.4	No	-
HD Oral	4	Placebo	2	-1.4	No	-
		H2RA	2	+2.1	No	-
Non HD	10	Placebo	1	-3.5	Yes	29
		H2RA	4	+0.8	No	-

Meta-analysis: Proton-pump Inhibition in High-risk Patients with Acute Peptic Ulcer Bleeding

Rebleeding

PPI	N	Control	No. of Studies	ARR	Signif?	NNT
HD IV	4	Placebo	2	-14.6	Yes	7
		H2RA	1	-20.6	Yes	5
HD Oral	4	Placebo	2	-15.3	Yes	7
		H2RA	2	+1.7	No	-
Non HD	10	Placebo	1	-25	Yes	4
		H2RA	4	-14.4	Yes	7

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Meta-analysis: Proton-pump Inhibition in High-risk Patients with Acute Peptic Ulcer Bleeding

Surgery

PPI	N	Control	No. of Studies	ARR	Signif?	NNT
HD IV	4	Placebo	2	-5.4	Yes	19
		H2RA	1	-1.0	No	-
HD Oral	4	Placebo	2	-3.3	No	-
		H2RA	2	-1.6	No	-
Non HD	10	Placebo	1	-16.2	Yes	6
		H2RA	4	+0.1	No	-

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Enhanced Efficacy of Proton-Pump Inhibitor Therapy for Peptic Ulcer Bleeding in Asia ...

Leontiadis Aliment Pharmacol Ther 2005; In Press

- *Post hoc* updated analysis of previous meta-analysis
- 16 RCTs from Europe and N. America were pooled and analyzed separately from 7 RCTs from Asia
- No significant heterogeneity

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### Enhanced Efficacy of Proton-Pump Inhibitor Therapy for Peptic Ulcer Bleeding in Asia ...

Outcome	Location	Rate on PPI (%)	Rate on control (%)	OR (95% CI)	NNT
Mortality	Asian	1.5	4.7	0.35 (0.16-0.74)	31
	Non-Asian	4.8	3.6	1.36 (0.94-1.96)	-
Recurrent Bleeding	Asian	6.8	22.2	0.24 (0.16-0.36)	6
	Non-Asian	11.9	15.5	0.72 (0.58-0.89)	27
Need for Surgery	Asian	2.9	9.2	0.29 (0.16-0.53)	16
	Non-Asian	7.5	9.8	0.74 (0.56-0.97)	43

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### The Effect of Endoscopic Therapy in Patients Receiving Omeprazole for Bleeding Ulcers with NBVV or Clots

Sung Ann Intern Med 2003;139:237-43

- 156 patients randomized to IV omeprazole infusion alone or after endoscopic therapy
- Recurrent bleeding within 30 days was:
  - 9/78 (11.6%) omeprazole alone
  - 1/78 ( 1.1%) omeprazole after endoscopic therapy

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### Case Presentation

- An IV infusion of pantoprazole is begun.
- A *Helicobacter pylori* antibody test is negative.
- Discharge is planned for the morning of day 4.

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## Case Presentation

- On Day 4 the patient has not re-bled and is ready for discharge; an oral PPI will be given for four weeks to ensure healing of the duodenal ulcer.
- He asks about therapy for his osteoarthritis.
- What do you recommend?

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## Case Presentation

- Therapeutic options for osteoarthritis
  - Resume therapy with naproxen?
  - Change to another non-selective NSAID?
    - Not unless you want another lawsuit
  - Change to celecoxib?
- Resume therapy with naproxen but add a concomitant PPI?

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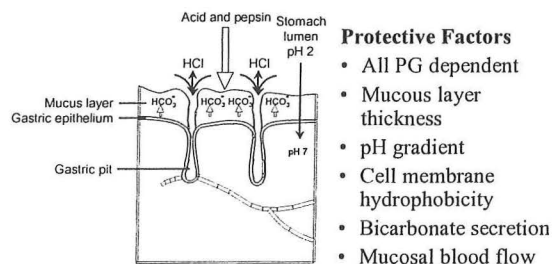
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## Gastric Protective Mechanisms



Scheiman. *Gastroenterol Clin North Am.* 1996;25:279-298.

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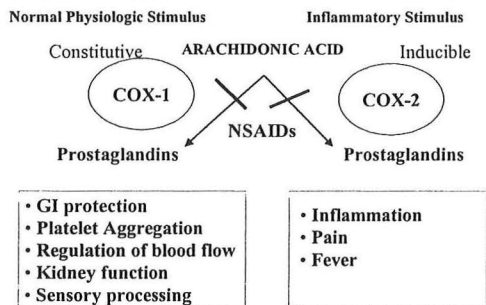
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## Cyclooxygenase (COX) Pathways




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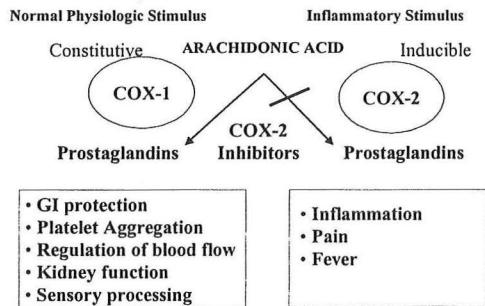
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## Cyclooxygenase (COX) Pathways




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## Problems with the COX-1 Sparing Agents

- Celecoxib may not prevent ulcer complications
- Co-therapy with ASA negates the salutary effects of Cox-1 sparing agents
- Cox-1 sparing agents were overused
- Rofecoxib, and higher dose celecoxib, increase the incidence of CV events
- In animals, **Cox-1** specific antagonists are not ulcerogenic

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Ulcer Formation with Low-Dose Enteric Coated  
Aspirin and the Effect of COX-2 Selective  
Inhibition: A Double-blind Trial  
Laine, Gastroenterology 2004;127:395

- OA patients were randomly assigned to placebo, LD-ASA alone, LD-ASA plus rofecoxib 25 mg/d, or ibuprofen 800 mg tid
- End points were endoscopic ulcers at 6 & 12 wks
- 12 week cumulative incidence of ulcers was:
  - Placebo 5.8%
  - LD-ASA 7.3%
  - LD-ASA + Rofecoxib 16.1%
  - Ibuprofen 17.1%

Celecoxib Versus Diclofenac Plus Omeprazole in  
High-Risk Arthritis Patients: Results of a  
Randomized, Double-Blind Trial  
Chan, Gastroenterology 2004;127:1038

- Patients who had NSAID-related ulcer bleeds, whose ulcer healed, and who were Hp- were randomly assigned to:
  - Celecoxib 200 mg bid OR
  - Diclofenac 75 mg bid + omeprazole 20 mg/d
- Recurrent bleeding occurred in 4.9% of the celecoxib group and 6.4% of the diclofenac+omeprazole group (Chan, N Engl J Med 2002)

Celecoxib Versus Diclofenac Plus Omeprazole in  
High-Risk Arthritis Patients: Results of a  
Randomized, Double-Blind Trial  
Chan, Gastroenterology 2004;127:1038

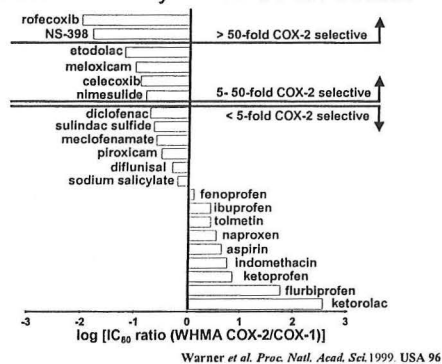
- 222 patients in whom rebleeding did not occur were endoscoped at their last follow-up visit
- Endoscopic ulcers occurred in 18.7% of the celecoxib group and 25.6% of the other
- Neither regimen adequately prevented ulcer recurrence



# Risks of Clinically Significant Upper Gastrointestinal (CSUGI) Events with Etodolac and Naproxen: A Historical Cohort Analysis Weideman, Gastroenterology 2004;127:1322

- Historical cohorts of veterans who received either etodolac or naproxen were assessed for CSUGI events during a 3-year period
- The incidence of events was 0.78% with naproxen and 0.24% with etodolac
- Concomitant use of LD-ASA negated this difference
- Effect of etodolac on CV system not known

## In Vitro Selectivity: COX-2/COX-1 Ratio



## Case Presentation

- What about the aspirin?
  - Change to clopidogrel?

## Clopidogrel versus Aspirin and Esomeprazole to Prevent Recurrent Ulcer Bleeding

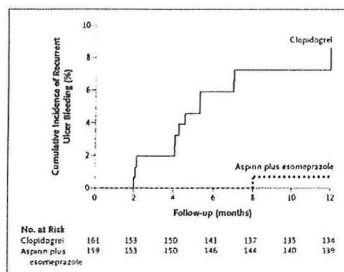
Chan N Engl J Med 2005;352:238-44

- 320 patients who had bled from aspirin-associated peptic ulcers and required continued anti-platelet therapy were enrolled
- All ulcers were healed and patients were *H. pylori* negative

## Clopidogrel versus Aspirin and Esomeprazole to Prevent Recurrent Ulcer Bleeding

- Patients were randomly assigned to clopidogrel (75mg/d) or aspirin (80mg/d) plus esomeprazole (20mg bid)
- During 12 mos F/U, bleeding occurred in:
  - 8.6% (4.1-13.1) with clopidogrel
  - 0.7% (0-2.0) with aspirin + esomeprazole

Cumulative Incidence of Recurrent Ulcer Bleeding in the Group Receiving Clopidogrel and the Group Receiving Aspirin plus Esomeprazole



Chan, F. et al. N Engl J Med 2005;352:238-44



### One Approach to the Use of NSAIDs

- Stratify for CV risk; use LD-ASA as necessary
- Try non-NSAID approach if at all possible; if you must use NSAIDs,
- Stratify for GI risk
  - If low, use cheap, non-selective NSAID
  - If moderate, use lowest dose possible of COX-1 sparing NSAID OR use inexpensive NSAID + PPI
  - If high, use lowest dose possible of COX-1 sparing NSAID + PPI and hope for the best

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### Case Presentation

- The patient is treated with etodolac, aspirin, and a PPI twice daily.
- His arthritis is well-controlled and he has had no more episodes of UGI bleeding.
- However, he tells his physician that he can no longer do his 5 mile runs without becoming winded.

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### Case Presentation

- Examination discloses pale conjunctivae and a + FOBT.
- A CBC is ordered:
  - Hgb: 8.5
  - Hct: 25
  - Platelets: 450,000
  - Ferritin: 5

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### Case Presentation

- A gastroenterologist is consulted and decides to do lower and upper endoscopies, both of which are negative.
- What is your diagnosis?

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### Case Presentation

- A gastroenterologist is consulted and decides to do lower and upper endoscopies, both of which are negative.
- What is your diagnosis?
- How do you proceed?

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### Management of Iron Deficiency Anemia

- Exclude cancer:
  - upper and lower endoscopy
  - SBFT if symptoms of SBO
- Begin iron supplements
  - Oral
  - Parenteral +/- erythropoietin

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## Management of Iron Deficiency Anemia

- Exclude cancer:
  - upper and lower endoscopy
  - SBFT if symptoms of SBO
- Begin iron supplements
- Keep your fingers crossed
- Do further workup only if anemia persists

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## Further Diagnostic Testing for Obscure GI Bleeding

### The Past

- Repeat upper and lower endoscopy
- Push enteroscopy
- Enteroclysis
- Tagged RBC scan
- Angiogram
- Surgical exploration with intra-operative endoscopy

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## Further Diagnostic Testing for Obscure GI Bleeding

### The Present

- Repeat endoscopy
- Push enteroscopy
- Enteroclysis
- Wireless capsule endoscopy
- Surgical exploration

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### Capsule Endoscopy vs. Push Enteroscopy: Rates of Diagnosis

- Push enteroscopy finds lesions about 30% of the time
- Capsule endoscopy finds lesions about twice as often
- Patients with evidence of recent bleeding are more likely to have lesions found

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### Capsule Endoscopy: The Problems

- The capsule gets stuck ("non-natural excretion")
- The capsule is not therapeutic
- The test is time-consuming

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### Case Presentation

- The patient undergoes colonoscopy and push enteroscopy, both of which are negative
- He is begun on oral iron supplements
- 3 months later his lab results are:
  - Hgb = 14.5
  - Ferritin = 130

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