American College of Physicians
New Hampshire Chapter
Annual Meeting 2018

Morbidity and Mortality

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Today’s Approach

• Present a clinical story (case)
• Discuss specific decision points in the patient’s care
• Use audience response system to promote introspection and prompt discussion
• Raise additional questions about diagnosis and management for discussion as a group
• Provide a few anchoring didactic points
March 26: Emergency Department

83 year old woman with crampy abdominal pain and diarrhea, with 4 episodes bright red blood per rectum

- Abdominal pain similar to previous IBS; no prior rectal bleeding
- ROS positive for lightheadedness
- ROS negative for fatigue, diaphoresis, headache, lightheadedness, confusion, vision changes, cough, sore throat, SOB, CP, palpitations, vomiting, dysuria, hematuria, myalgias/arthralgias, bleeding/bruises, rashes, numbness/tingling or weakness in extremities
PMH

• MCI, MOCA 22/30
• Fibromyalgia
• Osteoarthritis and spinal stenosis
• Chronic headaches
• Anxiety
• Depression
• Chronic insomnia
• CKD stage 3
• Essential hypertension
• GERD
• IBS-D

Medications

• Diclofenac 1% gel 4 gm qid prn
• Duloxetine 60 mg daily
• Nortriptyline 10 mg qhs
• Clonazepam 0.5 mg qhs
• Lisinopril 10 mg daily
• Omeprazole 20 mg daily
• Multivitamin
• Vitamin D 1000 units daily

PSH

• Cholecystectomy
Family and Social History

- One of 7 children; three siblings died in the past year of cardiac disease; one sister – 10 years her junior – is still living
- Brother died in Vietnam
- Sister died of Alzheimer’s
- CAD and CHF in Mother, 2 sisters, 2 brothers
- Widowed – husband died about 10 years ago of meningitis
- 3 sons, 1 daughter; raised her granddaughter with whom she currently lives; helps care for great grandson
- GED, retired school bus driver
- Never smoker, no alcohol
Physical Exam

- **VS:** T 36.5 °C   BP 150/71   HR 93   RR 20   O2 99 %
- **Constitutional:** Well-developed and well-nourished; no distress
- **HEENT:** NCAT; ears and nose normal; OP clear and moist, Conjunctivae normal
- **Neck:** Supple, normal ROM
- **Cardiovascular:** Normal rate
- **Pulmonary:** Effort normal. No respiratory distress.
- **Abdomen:** Soft, no distention; **endorses diffuse TTP (however endorses diffuse body TTP due to her fibromyalgia);** no rebound or guarding
- **Rectal:** guaiac positive stool
- **Musculoskeletal:** Normal ROM, no edema, tenderness or deformity
- **Neurologic:** Alert and oriented to person, place, and time
- **Skin:** Warm and dry, no rash, diaphoresis or pallor
- **Psychiatric:** Normal mood and affect
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
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<tbody>
<tr>
<td>T protein</td>
<td>7.3</td>
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<td>Alb</td>
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<td>AST</td>
<td>15</td>
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<td>ALT</td>
<td>12</td>
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<tr>
<td>Alk phos</td>
<td>131</td>
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<tr>
<td>T bili</td>
<td>&lt;0.2</td>
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<tr>
<td>D bili</td>
<td>&lt;0.1</td>
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<tr>
<td>Lipase</td>
<td>24</td>
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<tr>
<td>Calcium</td>
<td>9.4</td>
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</table>
Would you recommend diagnostic colonoscopy for this patient?

A. Yes, with confidence!
B. Yes, with reservations
C. No, with ambivalence
D. No, with certainty!

Bar chart showing:
- A: 20%
- B: 28%
- C: 48%
- D: 5%
What are the risks of colonoscopy in the elderly?
Meta-analysis of RCTs and cohort studies of colonoscopy in elderly patients

- Incidence rate for cumulative adverse events 26/1000 in 65+, 35/1000 in patients 80+
- Specific risks in 80 and older:
  - Perforation 1.5/1000
  - GI bleeding 2.4/1000
  - CV/pulmonary adverse events 28.9/1000
- 80+ had 70% higher risk of adverse events compared to younger patients, including 60% higher risk of perforation

Day et al, Gastrointestinal Endoscopy 2011
332K Medicare claims for non-high risk outpatient colonoscopies in patients > 65 at 8140 facilities

- 5412 patients (16.3/1000 colos) had at least one unplanned ED/hospital visit within 7 days after colo
  - 9% GI bleeding/hemorrhage
  - 3% abd pain
  - 3% laceration/perforation

- Strongest patient level predictors of unplanned visits:
  - H/O fluid/electrolyte imbalance (OR 1.4)
  - Psychiatric disorders (OR 1.34)
  - Increasing age (OR 1.87 for >85 versus 65-69 years)

Ranasinghe et al, Gastroenterology 2016
3/26 ED Treatment and Course

- 1 L NS
- Hemodynamically stable and no distress during 2 hour ED stay; no diarrhea or rectal bleeding
- Dicyclomine 20 mg q6 hours prn
- Referred for diagnostic colonoscopy
- Recommended follow up with PCP
- Discharge dx: BRBPR
3/29 GIM (ED follow up)

- No recurrent diarrhea
- Abdominal pain substantially improved with dicyclomine
- Reports pain/diarrhea similar to IBS, not worse recently other than the day she went to the ED
- No ongoing rectal bleeding
- Exam notable for generalized abdominal and CVA tenderness with no rebound or guarding
- Plan: soft diet, dicyclomine prn, obtain UA with reflex culture, proceed with colonoscopy next week
Would you recommend that the patient continue dicyclomine for symptomatic relief?

A. Yes, with confidence!
B. Yes, with reservations
C. No, with ambivalence
D. No, with certainty!

- A: 44%
- B: 27%
- C: 27%
- D: 2%
Anticholinergic Risk Scale categorizes anticholinergic potential as: moderate (1), strong (2), or very strong (3)

- Dicyclomine is an ARS 3 medication and nortriptyline is ARS 2
- Adverse CNS effects: cognitive dysfunction and delirium, dizziness and falls, impulsive behavior, loss of independence
- Other adverse effects: dry mouth, dry eyes, constipation
- VA study of 117 primary care patients 65 or older and 132 geriatric clinic patients: ARS of 3 or more was associated with 2 or more adverse anticholinergic effects in >70% of patients in both groups
- 10% of 6.8 million ambulatory care visits for dementia in 2006-7 involved prescribing at least one ARS 2 or 3 drug

Rudolph et al, Arch Int Med 2008
Bhattacharya et al, Am J Geriatr Pharmacother 2011
Dicyclomine: AVOID - anticholinergic effects, uncertain benefit

Tricyclics other than doxepin <6 mg: AVOID - anticholinergic effects, sedation, orthostatic hypotension

Long acting benzodiazepines: MAY BE APPROPRIATE for severe generalized anxiety disorder - increased risk of delirium, cognitive impairment, falls, fracture, MVA

PPI: AVOID SCHEDULED USE > 8 WEEKS (with diagnosis exceptions or demonstrated need for maintenance Rx) - C. diff infection, bone loss, fractures

SSRI/SNRI: USE WITH CAUTION - exacerbate or cause SIADH; increased risk of falls with >/= 2 other CNS drugs
4/5 Colonoscopy

• Fair preparation
• Technically difficulty due to restricted mobility of the colon; switched to pediatric scope
• Blood in rectum, streaks of blood in ascending colon, ? due to barotrauma
• External and internal hemorrhoids
• Sigmoid diverticulosis
• One 7 mm polyp in the cecum
• Limited views of the ileum were normal
• No observed bleeding source, mucosa grossly normal
• Random biopsies for microscopic colitis

Initial ED visit 3/26
4/6 Walk-in Clinic

- Developed “15/10” generalized abdominal pain after returning home from colonoscopy
- Bilateral subscapular pain with inspiration
- ROS: belching, nausea; no vomiting; decreased appetite but tolerated a light snack; no diarrhea, no fevers or chills
- “She wonders if she should just get a script for more Bentyl”
4/6 Physical Exam

- **VS:** T 36.6C   BP 170/64   HR 91   RR 18   O2 98%
- **General:** Appears uncomfortable, rubbing her abdomen; communicative and cooperative
- **HEENT:** anicteric
- **Chest:** clear to A and P, no rub
- **Heart:** no gallop, no rub
- **Abdomen:** not distended, **increased tympany in the upper abdomen; bowel sounds normal pitch throughout;** some guarding, no rebound
4/6 Labs

T Protein  7.7
Albumin  4.3
AST  258
ALT  125
Alk Phos  159
Total Bilirubin  1.7
Direct Bilirubin  1.4
PT 12.5, INR 1.1

3/26 ED:
AST 15
ALT 12
Alk Phos  159
Total Bilirubin  1.7
Direct Bilirubin  1.4
T bili <0.2
D bili <0.1
4/7 Early AM Admission Plan

- NPO
- Trend LFTs
- Hepatitis serologies
- GI Consult
- NS at 100 cc/hour
- PT Referral
4/7 LFTs

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<th></th>
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<th>T Bili</th>
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<tr>
<td>4/6</td>
<td>258</td>
<td>125</td>
<td>159</td>
<td>1.7</td>
<td>1.4</td>
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<tr>
<td>4/7</td>
<td>314</td>
<td>211</td>
<td>174</td>
<td>3.5</td>
<td>2.9</td>
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- HCV Ab (-)
- HBV SAg (-)
- HAV Ab (+)
4/7 PM GI Consult

• Her clinical presentation of pain followed by elevated LFTS is suggest of stone disease but thusfar imaging has failed to show either stones or stigmata of recent obstruction and her LFTS are primarily hepatocellular.
• Hep A or E seem unlikely
• There have not been new medications introduced and none of her current meds are likely offenders. At this point would obtain RUQ US to further examine the CBD.

• Recommendations:
• # RUQ US today
• If RUQ US negative and LFTS stable could be discharged with close GI follow up
• # Hep A IgM
• # Daily LFTS
• # Will follow up inpatient if patient remains admitted
The next morning (4/8)…

- Patient remained pain free since admission
- Nursing notes report she ate 100% of her dinner (after diet advanced)
- RUQ US normal (absent gallbladder, 8 mm CBD); Hepatitis A IgM negative
- LFTs trended

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<td>3.5</td>
<td>2.9</td>
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<tr>
<td>4/8</td>
<td>290</td>
<td>247</td>
<td>197</td>
<td>2.3</td>
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The next morning (4/8)…

- Patient remained pain free since admission
- Nursing notes report she ate 100% of her dinner (after diet advanced)
- RUQ US normal (absent gallbladder, 8 mm CBD); Hepatitis A IgM negative
- LFTs trended

- Primary team performed a chart review and noted that the patient had received a prescription for 7 days of nitrofurantoin after her clinic appointment on 3/29
Chart Review: A Look Back to 3/29 (ED follow up)

- UA and reflex culture ordered for bilateral CVA tenderness
- UA: spec grav 1.014, pH 5.0; (-) glu, pro, bili, urobili, nit; (+) leuk
  Micro: 1 RBC, 15 WBC
- Nitrofurantoin 100 mg bid called to pharmacy; patient started 7 day course 3/30
- Culture returned negative

Initial ED visit 3/26
Based on symptoms and signs (diffuse abdominal pain, diarrhea, self-limited hematochezia, CVA tenderness) what is this patient’s probability of UTI before any testing?

A. <10%
B. 10-30%
C. 30-50%
D. 50-70%
E. >70%
How much do her urinalysis results (+ LE, 15 WBC/hpf) change the probability of UTI?

A. Convincingly; these results make UTI much more likely
B. Moderately; these results make UTI somewhat more likely
C. Slightly; these results make UTI minimally more likely
D. Not at all; these results do not change the likelihood that she has a UTI
<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>All specimens</td>
<td></td>
<td></td>
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<tr>
<td>Positive leukocyte esterase test result</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>At least moderate numbers of bacteria</td>
<td>46.4</td>
<td>89</td>
</tr>
<tr>
<td>Both of above results</td>
<td>46.4</td>
<td>94</td>
</tr>
<tr>
<td>Nitrite</td>
<td>19.2</td>
<td>94.9</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
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<tr>
<td>Positive leukocyte esterase test result</td>
<td>54.5</td>
<td>68.2</td>
</tr>
<tr>
<td>At least moderate numbers of bacteria</td>
<td>54.5</td>
<td>93.2</td>
</tr>
<tr>
<td>Both of above results</td>
<td>45.5</td>
<td>95.5</td>
</tr>
<tr>
<td>Nitrite</td>
<td>0.0</td>
<td>93.2</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
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<tr>
<td>Positive leukocyte esterase test result</td>
<td>70.6</td>
<td>69.6</td>
</tr>
<tr>
<td>At least moderate numbers of bacteria</td>
<td>47.1</td>
<td>87.5</td>
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<tr>
<td>Both of above results</td>
<td>47.1</td>
<td>92.9</td>
</tr>
<tr>
<td>Nitrite</td>
<td>26.7</td>
<td>94.6</td>
</tr>
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</table>
A positive test result may not help much:

- Pre-test probability 10% → Post-test probability 21%
- Pre-test probability 30% → Post-test probability 50%
- Pre-test probability 50% → Post-test probability 70%
A negative result could be more helpful with low to intermediate pre-test probability:

Pre-test probability 10% → Post-test probability  4%

Pre-test probability 30% → Post-test probability 15%

Pre-test probability 50% → Post-test probability 30%
Are our patient’s symptoms suggestive of UTI?

- Symptoms matter
- 16-18% of women over 70 have asymptomatic bacteria; up to 50% in longitudinal studies
- 90% of elderly patients with asymptomatic bacteriuria also have pyuria
- CVA tenderness is among the signs and symptoms considered consistent with symptomatic UTI (in the presence of pyuria and bacteriuria)
- In a study of 551 non-catheterized nursing home residents with clinically suspected UTI, flank pain as an indication for testing for UTI had a RR of 0.95 (0.5 to 1.5) for pyuria and positive culture
- Acute dysuria was the most powerful predictor, with RR 1.51

Mody and Juthani-Mehta, JAMA 2014
Juthani-Mehta, JAGS 2009
Are Antibiotics Over-prescribed for UTI?

- Difficult to measure – what is the gold standard?
- Antibiotics are overprescribed in general; of 182,032 ambulatory visits in 2010-2011:
  - Antibiotics were prescribed in 12.6% of visits
  - 30% of prescriptions were inappropriate
- Retrospective study of 153 elderly women diagnosed with UTI in an ED:
  - 66 (43%) had negative cultures (<10K cfu)
  - Only 18% had a chief complaint of urinary symptoms; 20% reported urinary symptoms on ROS.
- Asymptomatic bacteriuria does not benefit from treatment

Fleming et al JAMA 2016
Gordon et al JAGS 2013
A Complication of Unnecessary Treatment

Based on the temporal association of nitrofurantoin and the onset of liver test abnormalities, our patient was diagnosed with drug induced liver injury secondary to nitrofurantoin.
What proportion of cases of idiosyncratic drug induced liver injury are attributable to antimicrobial medications?

A. 10-20%
B. 20-30%
C. 30-40%
D. 40-50%
Idiosyncratic DILI

- Annual incidence 14-19 cases per 100,000
- Drug Induced Liver Injury Network (DILIN) – multicenter prospective observational longitudinal study of idiosyncratic DILI:
  - Started enrolling in 2004
  - As of May 2013, 899 patients with probable, likely, or definite DILI
  - 54% hepatocellular, 23% cholestatic, 23% mixed
  - 6% six month mortality; 3% directly attributed to DILI
  - Additional 4% had liver transplant within six months
  - 17.5% had ongoing liver injury after six months

Chalasani et al, Gastroenterology 2015
DILI and Antibiotics

- 408 of 899 (45%) cases attributed to antibiotics
- Top 9 causes were antimicrobials, including 8 antibiotics
- 52% of the nitrofurantoin associated cases had a high-titer ANA

Chalasani et al, Gastroenterology 2015

<table>
<thead>
<tr>
<th>Drug</th>
<th>#(%) of Cases</th>
<th>Rank in Prescription Frequency</th>
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</thead>
<tbody>
<tr>
<td>Amox-clav</td>
<td>91 (10)</td>
<td>78</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>48 (5)</td>
<td>&gt;300</td>
</tr>
<tr>
<td><strong>Nitrofurantoin</strong></td>
<td>42 (5)</td>
<td>180</td>
</tr>
<tr>
<td>Trimeth/sulfa</td>
<td>31 (3)</td>
<td>73</td>
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<tr>
<td>Minocycline</td>
<td>28 (3)</td>
<td>253</td>
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<tr>
<td>Cefazolin</td>
<td>20 (2)</td>
<td>&gt;300</td>
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<tr>
<td>Azithromycin</td>
<td>18 (2)</td>
<td>15 → 53</td>
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<tr>
<td>Ciprofloxacin</td>
<td>16 (2)</td>
<td>93</td>
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<tr>
<td>Levofloxacin</td>
<td>13 (1)</td>
<td>161</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>12 (1)</td>
<td>84</td>
</tr>
</tbody>
</table>
Nitrofurantoin

• > 3 million prescriptions per year in US
• Multiple proposed mechanisms of action:
  • Activated by bacterial flavoproteins (nitrofuran reductase) to intermediates that modulate and damage ribosomal proteins and other macromolecules, inhibiting DNA, RNA, protein, and cell wall synthesis.
  • Inhibits multiple other bacterial enzyme systems.
• Antibacterial resistance rare
• Good oral absorption
• Rapid urinary excretion – high concentrations in urine relative to blood

http://clincalc.com/DrugStats/Drugs/Nitrofurantoin
Nitrofurantoin in the Elderly

- Beers recommends against nitrofurantoin for long term suppression due to risk of lung injury, and for treatment of UTI with creatinine clearance <30 due to lower efficacy
- Subsequent studies have not confirmed lower efficacy in reduced GFR
- How risky is it?
  - 5 year retrospective review identified 3400 patients >65 (mean 76.5) who were prescribed nitrofurantoin
  - 25 (0.7%) had a serious pulmonary or hepatic event possibly related to nitrofurantoin; NNH =136
  - 4 pulmonary toxicity and 1 hepatic toxicity case were deemed highly likely due to drug; 4 of the 5 were associated with chronic use

Santos et al, JAGS 2016
Case Conclusion

• Discharged home with diagnosis of drug induced liver injury, most likely secondary to nitrofurantoin
• Repeat LFTs in one week: T bili 0.4, alk phos 157, AST 17, ALT 37
• Path from random biopsies of colon: Reactive colonic mucosa with subtle, focal features of chronic injury and repair (paneth cell metaplasia).
• No recurrent abdominal pain or rectal bleeding
• Granddaughter seeking support to provide home care given increased dependence and mild cognitive decline
• Nitrofurantoin added to ADR list
## Unnecessary and Low Value Care

<table>
<thead>
<tr>
<th>Low Value Care</th>
<th>Driver(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED visit (versus primary care)</td>
<td>Limited access; limited patient awareness of options</td>
</tr>
<tr>
<td>Dicyclomine in elderly patient with cognitive impairment (initial rx, continued at follow up)</td>
<td>Medical culture favoring treatment over observation, pharmaceuticals over non-pharm strategies; deference to decisions of colleagues</td>
</tr>
<tr>
<td>UA/culture in absence of typical UTI symptoms</td>
<td>Tendency to consider and work up familiar problems rather than unfamiliar or poorly understood diagnoses</td>
</tr>
<tr>
<td>Antibiotic for low grade pyuria with negative culture</td>
<td>Tendency to favor risks of inappropriate treatment over risks of delayed treatment; poor mechanisms to follow up after negative test result</td>
</tr>
<tr>
<td>Colonoscopy after self limited episode of minor hematochezia</td>
<td>Tendency to favor testing over watchful waiting</td>
</tr>
<tr>
<td>Failure to recognize previous nitrofurantoin use and connect it to abnormal LFTs</td>
<td>Information overload in EMR masks important details; possible other cognitive and workflow factors</td>
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### Unnecessary and Low Value Care

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<td>UA/culture</td>
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<td>Antibiotics</td>
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<tr>
<td>with nitrofurantoin use and connect it to abnormal LFTs</td>
<td>possible other cognitive and workflow factors</td>
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<tr>
<td>Colon length episodes</td>
<td></td>
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**Downstream consequences:**

- 2 day hospitalization for elevated LFTs and abdominal pain
- Xrays, CT scan
- Multiple lab tests
- GI and PT consults
- Costs of all of the above
Learning Objectives

• Recognize the potential harms of anticholinergic medications in the elderly

• Consider strategies to reduce inappropriate antibiotic prescribing for patients in whom UTI is considered but clinically unlikely

• Recognize nitrofurantoin as a common cause of drug-induced liver injury

• Appreciate the potential harms inherent to a health care system that favors early (sometimes invasive) evaluation and empiric intervention over observation and individualized diagnostic and treatment decisions
An 83 year old woman with early dementia and IBS-D presented with acute on chronic abdominal pain and diarrhea associated with self-limited episodes of bright red blood per rectum. She was hemodynamically stable and was discharged with a prescription for dicyclomine.

On follow up in her PCP’s office she was prescribed a 7 day course of nitrofurantoin due to CVA tenderness and pyuria; urine culture was negative.

Colonoscopy to work up the rectal bleeding was technically difficult and unrevealing.

She presented to the ED hours after colonoscopy with abdominal pain and LFT abnormalities. The abdominal pain resolved spontaneously. LFT abnormalities were ultimately attributed to drug induced liver disease caused by nitrofurantoin and resolved within several days.

She has had no recurrence of rectal bleeding or severe abdominal pain.

Summary