



the PRUDENT prescriber

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IN THIS ISSUE

- The Longer the Fill the Better
- Alternatives to Antibiotics for UTI prophylaxis: Methenamine hippurate, Cranberries and D-mannose
- Guideline Update: Antibiotics for Diverticulitis?

Our lead article this month is from the pen of Zach Kareus, PharmD and Pharmacy Account Manager at UnitedHealthcare

THE LONGER THE FILL THE BETTER

Per the American Medical Association “More than 84% of all office visits to primary care physicians involve medication therapy.” In addition to prescriptions and refills handled during office visits or condition specific phone calls, clinicians refill prescriptions, often for multiple medications, for over 12 patients each day (Baron 2010). This consumes an estimated 55 minutes per day and contributes to interruptions along with a large number of phone calls, inbox messages and faxes, and frustrated patients, team members and pharmacists. When these activities are combined with additional administrative and regulatory burdens, primary care teams experience considerable strain and an increased workload (Arndt et al., 2017).

Writing prescriptions for 90-day fills with a years’ worth of refills (90 x 3) is a potential solution. An extended prescription duration contributes to a more

efficient practice workflow, reduces administrative burden, and increases the time that primary care physicians can spend with their patients. This is even more efficient if the patient's chronic medication refills can be synchronized (see <https://edhub.ama-assn.org/steps-forward/module/2702751>).

Extended prescription duration offers several advantages for your practice and your patients.

- Provider advantages
 - Reduced workload with refills
 - The AMA STEPFORWARD® program estimates that providers can save up to **two hours every day** by writing for 90-day fills with 3 refills and synchronizing all drug refills to one of the patients visits each year
 - Increases patient adherence by 10-20%. This can lead to slower disease progression, fewer drug changes/treatment escalations, and reduce ER visits
 - Decreases patient calls and pharmacy faxes
 - Potentially improved patient satisfaction scores

- Patient advantages
 - Fewer trips to the pharmacy which saves gas and time (mail order pharmacies offered by many insurance plans is an even more convenient option, and may provide additional savings)
 - Potential to save money on copays
 - Increased understanding of what to expect from the treatment plan
 - Facilitates easier automatic refills at the pharmacy (if the patient chooses to enroll) with refill reminders coming from the pharmacy to help with adherence

Most patients are eligible for 90-day prescription fills either through a retail pharmacy or mail order through their insurance. Insurances may offer a copay reduction when prescriptions are filled for 90-days depending on your patient's benefit.

- Consider if your patient may be eligible or may benefit from these extended days' supply if they:
 - Are on a chronic medication at a stable dose
 - Have expressed concern over the cost of their drugs
 - Would be willing and able to fill through mail order if insurance allows or requires it
 - Routinely follow up with scheduled appointments for lab testing and monitoring, if required

- Are not at risk for self-medicating or taking the drug other than prescribed



MY TAKE



- For those patients that are appropriate for 90-day fills with a year's worth of refills, consider writing for 90-day fills with 3 refills.
- Who doesn't need more time?
- Those new to therapy or discontinuing therapy will still need shorter duration fills and more frequent visits.

Alternatives to Antibiotics for UTI prophylaxis: Methenamine hippurate, Cranberries and D-mannose

Long term, low dose daily antibiotic treatment is the current standard of care for prophylaxis in women with recurrent urinary tract infections. The potential adverse effects (including direct toxicities, selection of resistance, alteration of microbiome, and secondary *Clostridioides difficile* infection) often outweigh the benefit of reducing the risk of an infection. ^{[1][5EP]} A British multicenter, open label, randomized, non-inferiority trial (BMJ 2022 March 9) of 240 women over 18 years with recurrent UTIs compared the efficacy of methenamine hippurate (Hiprex) with low dose antibiotics. These women with an average of seven symptomatic UTIs in the previous year were randomly assigned to daily low dose antibiotic (nitrofurantoin, trimethoprim or cephalexin) or methenamine hippurate 1 gram BID for one year.

Results:

More symptomatic UTI infections occurred among the methenamine hippurate group than among the antibiotic group (1.38 vs. 0.89 per patient-year), but the outcome fell within the pre-specified, non-inferiority limit of one UTI per person-year.

During the treatment period, a higher proportion of patients allocated to daily prophylactic antibiotics showed resistance to at least one antibiotic in *E coli* isolates from perineal swabs than patients allocated to methenamine hippurate.

Results from urine cultures revealed higher rates of resistance to trimethoprim and cephalosporins in *E coli* isolated from urine samples from women in the antibiotic arm than in the methenamine hippurate arm. .

- Adverse reactions were reported by 24% of the antibiotic group and 28% of the methenamine group. Most reactions were mild.

Cranberries

- Cranberries (juices, capsules and tablets) have been used to prevent recurrent urinary tract infections. Cranberries contain a substance, proanthocyanidins (PACs), that can prevent bacteria from sticking to the walls of the bladder.
- The original Cochrane review in 2008 suggested a potential role for cranberries in preventing UTIs in young women with recurrent cystitis.
- A later, larger Cochrane review in 2012 identified 24 studies (4473 participants) comparing cranberry products with control or alternative treatments. **There was a small trend towards fewer UTIs in people taking cranberry products compared to placebo or no treatment, but this was not a significant finding.**
- Many people in the studies stopped consuming the cranberry products (0%-55%) suggesting it may not be an acceptable long term intervention.
- **Cranberry juice does not appear to have a significant benefit in preventing UTIs and may be unacceptable to consume in the long term.**

D-mannose

- A natural sugar available online and in health food stores
- Mimics the host uroepithelial receptors use by uropathogens. The postulated mechanism of action for D-mannose is that it competitively binds to bacterial surface ligands and therein decreases the number of bacteria attached to the bladder mucosa.
- The published data for D-mannose in preventing cystitis are scant. In the largest study ([World J Urol 2014Feb; 32\(1\)79-84](#)) 309 women (average age 46) were randomized to 2 g of D-mannose in 200ml of water, 50 mg of nitrofurantoin daily or no prophylaxis. At six months recurrent infections occurred in 15% of the D-mannose group, 20% of the nitrofurantoin group and 60% the women receiving no prophylaxis. Both D-mannose and nitrofurantoin had low rates of side effects (bloating and loose stools for the D-mannose group) that did not necessitate stopping prophylaxis
- Amazon will sell you 120 capsules (1000mg each) for \$14 (\$7/month for 2000mg per day dose).

- There are studies underway to identify compounds related to D-mannose that are well absorbed and have high affinity for the bacterial surface ligand.



MY TAKE



- Although the methenamine hippurate study suffers from a relatively small “n” and no treatment blinding, methenamine hippurate appears to be a reasonable alternative (Think Antibiotic Stewardship!) to low dose antibiotics. Both treatments work--reducing the average number of annual UTIs in this group of women from seven to one.
 - Methenamine costs about \$30 per month while nitrofurantoin (\$9/mo), trimethoprim (\$10/mo) and cephalexin (\$5/mo) are cheaper.
- If you decide to recommend or support use of a cranberry product (patient is convinced it works) ConsumersLab’s top picks are:
 - Ocean Spray Pure Unsweetened Cranberry Juice (2.7 ounces contains 36 PACs and costs \$0.43/daily dose, \$13/month)
 - Theralogix TheraCrane One capsule contains 36mg of PACs and costs \$0.92-\$0.97/daily dose, \$28-\$29/month)
- With limited data, it appears that D-mannose might work, has an apparent benign side effect profile and is dirt cheap.
- And perhaps, part of the answer is NOT always a drug. Although the behavioral approaches suggested below have not been well studied, the interventions are mostly innocuous and at times dearly held by some patients:
 - Increasing fluid intake: 2-3 quarts/day
 - Early post-coital voiding
 - Avoiding spermicides
 - Wiping from front to back to avoid perineal contamination
 - Considering topical estrogen for postmenopausal women

Guideline Update: Antibiotics for Diverticulitis?

In the February 2021 issue of Gastroenterology, the American Gastroenterological Association (AGA) updated their practice guidelines for

management of diverticulitis.

General Care

- The AGA continues to recommend CT scans whenever diverticulitis is suspected, as alternative diagnoses are identified in about half of cases.
- When symptoms persist after an episode of acute diverticulitis, CT scan and colonoscopy are recommended to exclude ongoing inflammation.
- Clinicians should be hesitant to recommend partial colectomy based solely on the number of episodes of diverticulitis. Colectomy decisions should be based on an individual patient's disease severity, operative risks and their preferences.

Antibiotics

- Antibiotics should be used “selectively rather than routinely” for mild cases of diverticulitis. Indications for antibiotic use in uncomplicated diverticulitis include presence of comorbidities or immunosuppression, C-reactive protein level >140 mg/L, white blood count greater than 15,000/ml, presence of a fluid collection, or a long segment of inflammation on imaging.
- Three studies support these recommendations:
 - In two studies involving inpatients with acute uncomplicated diverticulitis who were randomized to receive antibiotics or not: outcome data confirmed NO differences in pain levels, complications requiring surgery, duration of hospitalizations or readmission rates. (Br J Surg 2017 Jan;104:52 and Br J Surg 2012 Apr; 99:532)
 - In the DINAMO RCT (Ann Surg 2021; 274) of 480 patients with imaged-confirmed uncomplicated acute diverticulitis who met criteria for outpatient management, supportive treatment with pain control and liquid diet with amoxicillin/clavulanic acid 875/125 mg every 8 hours or without antibiotics resulted in similarly low rates of unscheduled return visits (6.7% vs 7%) and hospitalizations (6% vs 3%).
- And if you decide to go with antibiotics...

Traditionally clinicians have used either metronidazole plus a quinolone or amoxicillin-clavulanate for outpatient management of acute diverticulitis. Gaber et al (Ann Intern Med 2021 Feb 23) analyzed two large insurance databases of ~120,000 immunocompetent adults with uncomplicated diverticulitis who were treated with either of these regimens.

Results:

- There were no significant differences in 1-year admission risk (risk difference, 0.1 percentage points).
- 1-year urgent surgery risk (risk difference, 0.0 percentage points).
- 1-year Clostridioides difficile infection risk (risk difference, 0.0 percentage points).
- In Medicare patients, users of metronidazole with fluoroquinolone ($n = 17,639$) and amoxicillin-clavulanate ($n = 2709$) were identified. There were no differences admission risks or surgical risks between groups. The 1-year Clostridium difficile infection risk was higher for metronidazole-with-fluoroquinolone than for amoxicillin-clavulanate (risk difference, 0.6 percentage points).



MY TAKE



- Another one bites the dust. The data supporting NOT using antibiotics at all in mild, uncomplicated diverticulitis are strong.
- And if you decide to prescribe antibiotics, the evidence leans toward amoxicillin-clavulanate.
- Even often conservative UpToDate until recently had supported using antibiotics in all patients with diverticulitis. Now UpToDate initially recommends pain management and a liquid diet for mild disease. Their algorithm suggests that if after two to three days, patients who have persistent or recurrent abdominal pain, fever, or inability to tolerate oral fluids should be admitted for inpatient treatment.

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