Residency Review

WESTERN NEW ENGLAND UNIVERSITY
COLLEGE of PHARMACY and HEALTH SCIENCES

FreeStyle Libre System: Liberated

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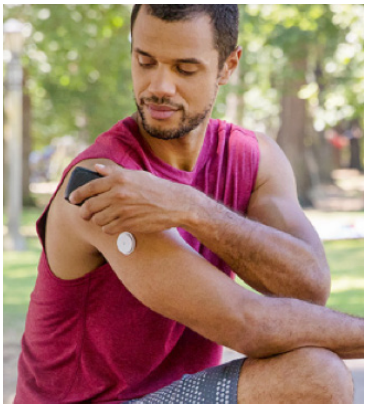
Managing diabetes is multi-dimensional, multi-factorial, and for a person with the condition it can be burdensome. From medication adherence to food choices and physical activity, for some people it is hard to think of anything other than diabetes. The American Diabetes Association (ADA) recommends the use of self-monitoring of blood glucose (SMGB) in an effort to guide treatment and/or self-management in those taking insulin or those on noninsulin therapies. The ADA suggests that continuous glucose monitoring (CGM) may be a useful tool for those on insulin therapy, with hypoglycemia unawareness, and/or frequent hypoglycemic events. According to the American Association of Clinical Endocrinologists (AACE), in a study using CGM, 49% of people with diabetes experienced at least 1 hypoglycemic event (<70 mg/dL) over a 5-day period, and 10% experienced a blood glucose of <50 mg/dL. Hypoglycemia is both common and dangerous. Because of the safety concerns related to hypoglycemia, it is important to prevent the occurrence. CGM systems may provide a safety measure to aid in the reduction of hypoglycemia and provide real time glucose data and alarms for hyper- and hypoglycemic events. Without the added burden of finger sticks, CGM may be a useful tool in managing diabetes.[1,2]

In September 2017 the FDA approved FreeStyle Libre, a CGM system which provides interstitial glucose monitoring. The values measured in this manner may show different readings than the finger stick blood glucose due to the lag time experienced with interstitial readings. The differences in readings may be especially obvious during times of rapidly changing glucose such as after a meal, with physical activity, and after insulin. People with diabetes age 18 and older are eligible for the system, which aids in monitoring trends and patterns while also detecting hyperglycemia and hypoglycemia. The system consists of a sensor worn on the back of the upper arm with a handheld reader. Using an inserted filament, the sensor measures glucose in the interstitial space every minute and records readings every 15 minutes. The system stores glucose data for up to 8 hours. The device is factory calibrated and accuracy is not dependent on finger stick calibration.[3]



In a study by Al Hayek and colleagues aimed at determining the effectiveness of the FreeStyle Libre CGM system on glycemic control, the researchers found that by using the system, HbA1C levels decreased by approximately 1%. Forty-seven patients with type 1 diabetes (T1D) who used finger sticks to test their blood glucose were recruited in the prospective study and continued through to the end of the study. Researchers defined an HbA1C level of <7% as good control of blood glucose. At baseline, participants' HbA1C was 8.5 + 1.07 and these values reduced to 7.84 + 1.06 three months after the study began. The decrease in HbA1C was statistically significant with a p value of <0.05, but because the HbA1C was not within the researchers stated level of good control, it may not be clinically significant.[4]

In the REPLACE study, participants with type 2 diabetes (T2D) on intensive insulin therapy were randomized to either SMBG or the FreeStyle Libre CGM system. Once the 139 participants finished the 6-month treatment phase, they proceeded into the open-access phase. At the end of the open-access phase (at 12 months), there was a 50% reduction in time in hypoglycemia (sensor glucose <70 mg/dL) compared to baseline [-0.7 + 1.85/24 h (mean + standard deviation); p = 0.0002]. People using the FreeStyle Libre system spent approximately 30 minutes less per day with blood glucose values <70 mg/dL and approximately 13 minutes less per day with blood glucose <55 mg/dL compared to SMBG.[5]

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Should the FreeStyle Libre CGM system be an appropriate choice, the prescriber would write 2 prescriptions; the first for '1 FreeStyle Libre reader' and the second for a 30-day supply of 'FreeStyle Libre sensors' which equates to 3 sensors/month. The sensors are changed every 7-10 days. The reader also doubles as a blood glucose monitor and requires the use of Freestyle Neo test strips which are not included. With the reader doubling as a monitor, the patient is able to check blood glucose if the patient feels that the result from the reader does not match how they are feeling.

People with Medicare may qualify for the FreeStyle Libre system following an eligibility check. Most commercially-insured patients will pay $40 to $75 per month for eligible FreeStyle Libre sensor prescriptions at retail pharmacies. The amount any patient may pay is subject to variability due to insurance plans.[3]

Following the prescription for FreeStyle Libre, a user adheres the sensor to the outer, upper arm. Using the handheld reader, the sensor may be scanned. The sensor should be replaced every 7-10 days and is water resistant. While the system may replace regular finger sticks, it is important to remind users that a finger stick should be taken before any treatment decisions are made or if the 'Check Blood Glucose' symbol appears on the handheld reader.[3] Due to the sensor needing to be in place for 12 hours before readings are taken, the ideal time to place the sensor each time is before bedtime. After 12 hours the sensor may be "read" with the handheld reader device.

It is important to instruct users to remove the sensor before MRI, CT scan, X-ray, or diathermy treatment. The system is not intended for use in pregnancy, dialysis, or critically-ill individuals; specifically people who are dehydrated, hypotensive, or in shock.[3]

While living with diabetes can be overwhelming and time-consuming, the advent of CGM systems such as the FreeStyle Libre provide accurate, real-time glucose readings. Through this system, therapy modifications may be made and trends in glucose may be observed to optimize outcomes in diabetes.

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Sharing the News on Shingrix®

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In the fall of 2017, Shingrix®, a recombinant, adjuvanted zoster vaccine (RZV), was FDA approved and shortly thereafter named the preferred vaccine for the prevention of herpes zoster by the Advisory Committee on Immunization Practices (ACIP). There are key features the vaccine offers that led to a preferred recommendation over the herpes zoster live-attenuated Zostavax® vaccine (ZVL) including age recommendations and efficacy.[1]

Shingrix® is a 2-dose, subunit vaccine, administered 2-6 months apart, containing recombinant glycoprotein E in combination with a unique adjuvant (AS01B).[1] RZV is not live and is stored in the refrigerator prior to reconstitution. Its vaccine efficacy and safety was compared to that of the live zoster vaccine by the ACIP in the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Recombinant Zoster Vaccine (RZV) and Herpes Zoster Live-Attenuated Vaccine (ZVL). For ages 50-59 years, the RZV 2-dose series was 96.9% effective at preventing herpes zoster compared to ZVL which was 70% effective. Due to its' efficacy, the FDA recommends patients receive the RZV starting at age 50, compared to 60 years old for ZVL vaccine. Considering age further, the ZVL efficacy for prevention of herpes zoster decreases with increasing age. At 60-69 years old, ZVL is 64% effective; ages 70-79, ZVL is 41% effective; above 80 years old, ZVL is 18% effective. In contrast, RZV is 97.4% effective at ages 60-69 and 91.3% effective for people 70 years of age and older.[2]

In addition to the benefits at age of administration, the RZV also has a substantial duration of protection against herpes zoster at 85% compared to ZVL at <40%, up to 4 years post vaccination. Moreover, the efficacy of RZV on preventing post-herpetic neuralgia was 91.2% at >50 years old and 88.8% at >70 years old. The efficacy of ZVL on preventing post-herpetic neuralgia was 65.7 % for ages 60-69 years old and 66.8% over the age of 70 years old. From the GRADE analysis performed by ACIP, RZV is more efficacious overall and remains more efficacious 4 years following administration when compared to ZVL. Data beyond 4 years has not been published at this time for RZV.[2]

The GRADE analysis gathered information regarding safety and reactogenicity. While the safety results are similar between vaccines, reactogenicity differed. Randomized control trials of ZVL vs. placebo demonstrated no differences in serious adverse events between vaccinated and placebo groups. Reactogenicity data showed injection-site reactions as the most common adverse reaction related to ZVL. As reported in the package insert for RZL, solicited local adverse reactions in people aged 50 years and older were pain (78.0%), redness (38.1%), and swelling (25.9%). Solicited general adverse reactions in people aged 50 years and older were myalgia (44.7%), fatigue (44.5%), headache (37.7%), shivering (26.8%), fever (20.5%), and gastrointestinal symptoms (17.3%).[4] For RZL, there were no differences in the proportion of study participants reporting grade 3 (reactions that are severe enough to prevent normal activities) local reactions between dose 1 and dose 2. Headache and shivering were reported at a greater rate after dose 2 (28.2% and 21.4%) compared with dose 1 (24.4% and 13.8%), respectively. Grade 3 solicited general adverse events (headache, shivering, myalgia, and fatigue) were reported at a greater rate after dose 2 (2.3%, 3.1%, 3.6%, and 3.5%, respectively) compared with dose 1 (1.4%, 1.4%, 2.3%, and 2.4%, respectively).[4] For precautionary measures, educate the patient of the probability of pain at the injection site and offer over-the-counter pain relief medications, if necessary. By advising patients appropriately, patients may be more likely to return for the second dose to complete the series and increase efficacy.[2]

Overall, RZV is more effective at preventing herpes zoster and post-herpetic neuralgia than the ZVL vaccine, although the side effect profile of RZV showed a greater incidence of systemic and injection-site reactions. Due to its superior effectiveness, RZV is the current CDC and ACIP preferred vaccine for the prevention of herpes zoster.

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Sharing the News on Shingrix®

By Jasmine Rivera, Pharm.D.

Vaccine Characteristics of Recombinant Zoster Vaccine and Herpes Zoster Live-Attenuated Vaccine [1-3]

	Recombinant Zoster Vaccine (RZV)	Herpes Zoster Live-Attenuated Vaccine (ZVL)
Brand name	Shingrix®	Zostavax®
Doses/route of administration	2/ intramuscular	1/ subcutaneous
Effective at preventing herpes zoster age 50-59 years old	96.9%	70%
Effective at preventing herpes zoster 60-69 years old	97.4%	64%
Effective at preventing herpes zoster 70-79 years old	91.3%	41%
Effective at preventing herpes zoster > 70 years old	91.3%	18%
Efficacy at age of administration (up to 4 years post vaccination)	85%	<40%
Efficacy of preventing post-herpetic neuralgia	91.2% (> 50 years old) 88.8% (> 70 years old)	65.7 % (age 60-69) 66.8% (> 70 years old)
Serious adverse events between vaccine and placebo	No difference	No difference
Reactogenicity	Grade 3 reactions: 16.5% RZV vs 3.1% placebo Grade 3 injection-site reactions: 9.4% RZV vs 0.3% placebo Grade 3 systemic reactions: 10.8% RZV vs 2.4% placebo	Serious adverse events: 0.6% ZVL vs 0.5% placebo Moderate/severe grade 3 injection-site reactions: 0%-4% of ZVL Systemic reactions: Headache: 9.4% ZVL vs 8.2% placebo Pain in the extremity: 1.3% ZVL vs 0.8% placebo

Old Dogs Same Tricks: Treatment Options for Uncomplicated Cystitis

By Michael Lorenzo, Pharm.D., AAHIVP
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Urinary tract infections (UTIs) are one of the most common infections and indications for antibiotic use in the United States and internationally.[1] UTIs represent a spectrum of disease, ranging from uncomplicated cystitis (UC) to pyelonephritis with concurrent bacteremia, often termed 'urosepsis'.[1] The focus of this commentary will be on 'uncomplicated' cystitis, which can be a misleading term as the increasing trends of resistance to agents commonly prescribed and recommended by guidelines makes treating these infections anything but uncomplicated.

Current guidelines by the Infectious Diseases Society of America recommend the use of nitrofurantoin, trimethoprim/sulfamethoxazole (TMP/SMZ), or fosfomycin as first line options in UC.[2] These guidelines, published 7 years ago, recommended these options due to their low risk of collateral damage, robust coverage of the most common uropathogens, and outstanding track record of safety and tolerability.[2] Beyond these options, the guidelines recommend fluoroquinolones and β-lactams as alternatives, owing to their higher risk for collateral damage, and risk of resistance in some areas (see figure 1).[2] While some of this information remains the same, there have been some important changes to the landscape of microbiology in UC that warrant consideration.

In 2011, the guidelines cited that *E. coli* is the dominant uropathogen, causing between 75-95% of episodes of UC.[2] The frequency of *E. coli* in UC remains relatively unchanged with recent reports estimating it as a causative pathogen in up to 75% of cases, however trends of resistance in *E. coli* have not been as steadfast.[1] In the early 2000's, there was an underappreciation of the now well-characterized sequence type (ST) of 131 *E. coli*. This particular clade of *E. coli* has now been shown to represent the majority of pathogenic *E. coli* in the United States.[3] Concerningly, this ST is characterized by resistance to quinolones (to which less than 5% will typically be susceptible), carriage of extended-spectrum β-lactamases (ESBLs, 10-20%), and resistance to TMP/SMZ (up to 25% of isolates can be resistant).[3] Importantly, nitrofurantoin and fosfomycin have remained largely unaffected by recent trends of resistance in *E. coli*, with over 90% of *E. coli* in the United States maintaining susceptibility to these agents.[4,5] Because of the predominance of this type of *E. coli*, the durability of fluoroquinolones and TMP/SMZ, but not nitrofurantoin and fosfomycin, have been dramatically impacted, and their use in empiric therapy of UC can lead to an increased risk of failure and subsequent hospitalization when resistant isolates are present.[6] For these reasons it is critical to obtain high quality clean catch urine samples for culturing in patients presenting with urinary symptoms. Furthermore, empiric therapy can be guided by using regional antibiograms, such data is available from the Massachusetts Department of Health. This data can be limited however, as urinary active agents are not commonly reported in the same way as systemic antibiotics, and are often excluded from antibiograms to avoid erroneous decision making.[7] For non-*E. coli* UC, treatment options can become even more challenging, as nitrofurantoin and fosfomycin become less reliable for infections caused by Klebsiella spp. and P. mirabilis. However, outside of *E. coli*, no single bacterial species is responsible for >6% of UC episodes in the Unites States, meaning that for the overwhelming majority of patients, nitrofurantoin and fosfomycin still rightfully hold their guideline recommended first line therapy status.[1,2]

A second consideration in the use of antibiotics for UC is the collateral damage caused by certain antibiotics. Collateral damage can represent a large variety of unintended effects of antibiotic use including side effects of the antibiotics, associated adverse events, the selection of resistant bacteria, and the facilitation of *C. difficile* associated diarrhea.[2] As nitrofurantoin and fosfomycin administered orally have minimal systemic absorption, their collateral damage is relatively limited to the side effects related to their administration such as nausea, vomiting, and in the case of nitrofurantoin, peripheral neuropathy if used in patients with severe renal dysfunction.[4,2] TMP/SMZ applies a low degree of selection pressure due to its relatively narrow spectrum of activity and minimal activity against many commensal organisms. While it is absorbed systemically, its collateral damage can be considered to be relatively limited to its common side effects and adverse events such as potential photosensitivity, transient hyperkalemia (although unlikely with the low doses used for UC), and development of a rash more commonly seen with long term use.[2] The minimal collateral damage of the guideline recommended first line options is not shared by the alternatives, fluoroquinolones and β-lactams. Fluoroquinolones represent the single most common cause of antibiotic associated adverse events, and the list of adverse events seems to be ever increasing, with dysglycemia, seizure, optic neuritis/neuropathy, tendon rupture, and neuropathy being reported with increasing rates.[8] Similarly, if not more concerning, these antibiotics represent one of the highest risk antibiotics for acquiring *C. difficile* associated diarrhea, and apply tremendous selection pressure for the development of resistant bacteria.[9] While β-lactams have a longstanding track record of safety, in general they represent an unnecessarily broad spectrum antibiotic for treating UC, as the near ubiquitous coverage of *S. aureus* and *Streptococcus* spp. is unwarranted in UC. Some β-lactams, particularly amoxicillin containing regimens, may also have poorer associated outcomes in UC due to increasing rates of resistance.[2] For these reasons, fluoroquinolones and β-lactams are best reserved as alternatives in specific scenarios for the treatment of UC.

In summary, the current antibiotic management of UC remains unchanged since the 2010 guideline updates. Providing efficacious antibiotic therapy is dependent upon understanding local resistance patterns, and reviewing culture data to support or guide changes in therapy. An often forgotten principal of using antibiotics is the minimization of collateral damage, as can be seen by the high prescribing rate in the US of fluoroquinolones with 32.8 million prescriptions written in 2014.[8] It seems relatively clear however, these agents are well deserving of their second line treatment classification due to increasing rates of resistance and high collateral damage.

Old Dogs Same Tricks: Treatment Options for Uncomplicated Cystitis

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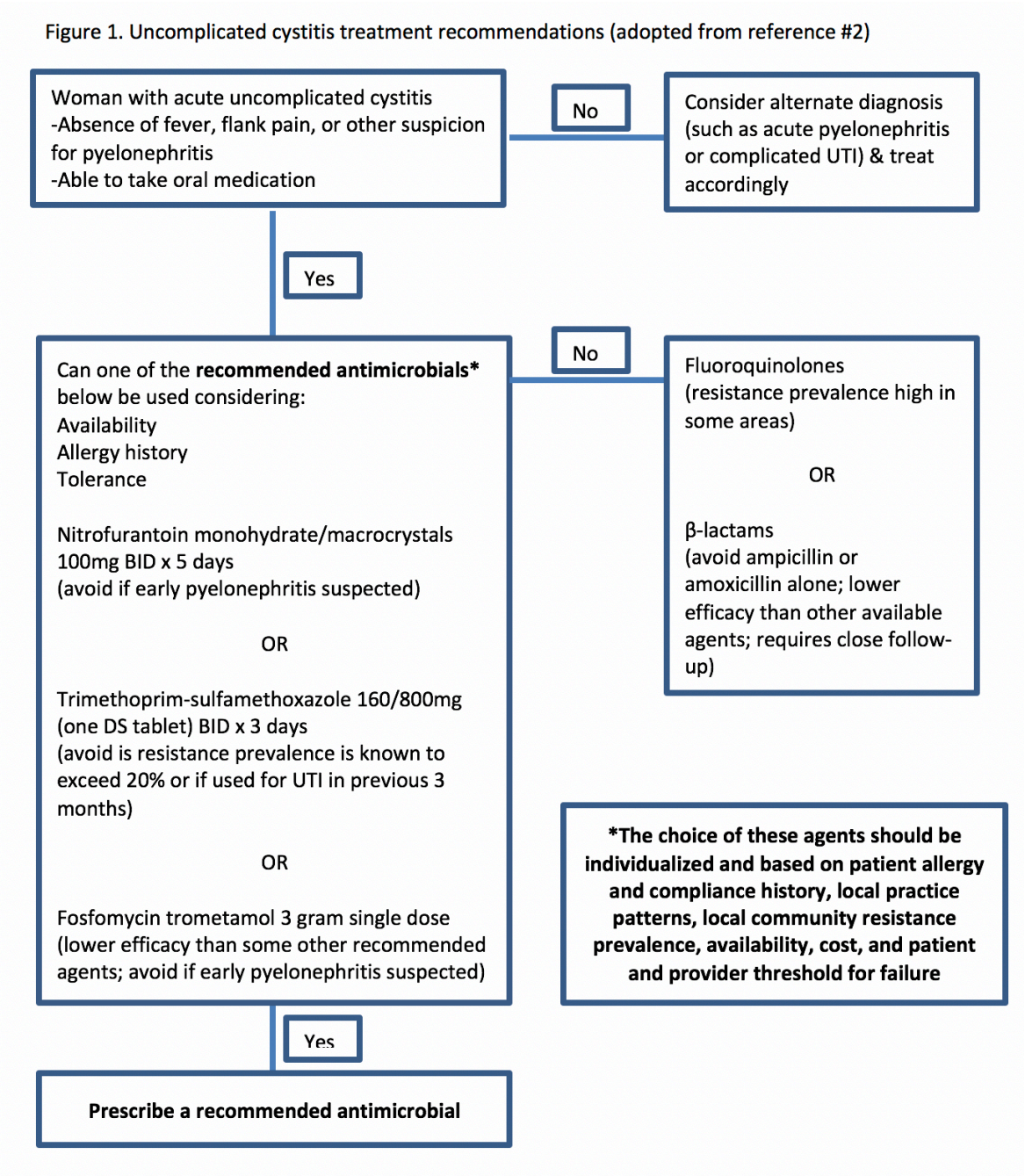
Figure 1. Uncomplicated cystitis treatment recommendations (adopted from reference #2)



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