



CHOOSING WISELY VIII

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This is my eighth article in this journal on the “Choosing Wisely” initiative from the Board of Internal Medicine Foundation. As previously noted, each specialty group has or will be developing “Five Things Physicians and Patients Should Question.”*

The Choosing Wisely items covered in this article include Five Practices to Question in Maternal-Fetal Medicine from The Society for Maternal-Fetal Medicine, along with five more from The American Geriatric Society and five added items from The American Academy of Allergy, Asthma, and Immunology.

Finally, following the Choosing Wisely items I provide a few Top Tips.

RECOMMENDATIONS FROM THE SOCIETY FOR MATERNAL-FETAL MEDICINE

1. Don’t do an evaluation for inherited thrombophilia in women with histories of pregnancy loss, restricted intrauterine growth, preeclampsia, and abruption. Specific testing for antiphospholipid antibodies, when clinically indicated, should be limited to lupus anticoagulant, anticardiolipin antibodies, and beta 2 glycoprotein antibodies. Data do not support a causal association with other polymorphisms or other common inherited thrombophilias.¹

2. Don’t place a cerclage in women with short cervix who are pregnant with twins. These women are at very high risk for delivering preterm but scientific data shows that cerclage in this clinical situation is not only not beneficial, but may in fact be harmful, i.e., associated with an increase in preterm births.

3. Don’t offer noninvasive prenatal testing (NIPT) to low-risk patients, and do not make irreversible decisions based on the results of this NIPT. NIPT has only been adequately evaluated in singleton pregnancies at high risk for chromosomal abnormalities. False positive and false negative results occur with NIPT,

particularly for trisomy 13 and 18. Any positive NIPT results should be confirmed with invasive diagnostic testing prior to a termination of a pregnancy.²

4. Don’t screen for subsequent intrauterine growth restriction (IUGR) with Doppler blood flow studies. Studies that have attempted to screen pregnancies for subsequent occurrence of IUGR have produced inconsistent results. No standards have been established for the optimal definition of an abnormal test, for the best gestation age for performance of the test, or for the technique for its performance. However, once the diagnosis of IUGR is suspected, the use of antenatal fetal surveillance, including umbilical artery Doppler flow studies, is beneficial.

5. Don’t use progestogens for preterm birth prevention in uncomplicated multi-fetal gestations. Progestogens have not been shown to reduce the incidence of preterm birth in women with these uncomplicated multi-fetal gestations.

RECOMMENDATIONS FROM THE AMERICAN SOCIETY OF GERIATRICS

The previous recommendations were:

- Don’t recommend percutaneous feeding tubes in patients with advanced dementia; instead offer oral assisted feeding.
- Don’t use antipsychotics as first choice to treat behavioral and psychological symptoms of dementia.
- Avoid using medications to achieve hemoglobin A1c less than 7.5% in most adults age 65 and older; moderate control is generally better.
- Don’t use benzodiazepines or other sedative-hypnotics in older adults as first choice for insomnia, agitation or delirium.
- Don’t use antimicrobials to treat bacteriuria in older adults unless specific urinary tract symptoms are present.

* Non-physician readers should not use these recommendations as a substitute for consultation with a medical professional. Patients with any specific questions about the items on these lists or their individual situations should consult their physicians.

The five added recommendations are as follows:

1. Don't prescribe cholinesterase inhibitors for dementia without periodic assessment for perceived cognitive benefits and adverse gastrointestinal effects. Clinicians, caregivers, and patients should discuss cognitive, functional, and behavioral goals of treatment prior to beginning a trial of cholinesterase inhibitors. In addition to any consideration of a trial of cholinesterase inhibitors the treatment plan should include advanced care planning, patient and caregiver education about dementia, diet, exercise, and non-pharmacologic approaches to behavioral issues. These measures are all integral to the care of patients with dementia. If goals of treatment are not attained after a reasonable trial of, for example, twelve weeks, then consider discontinuing the medication.

2. Don't recommend screening for breast or colorectal cancer, nor prostate cancer (with the PSA test) without considering life expectancy and the risks of testing, over diagnosis, and treatment. For prostate cancer, 1,055 men would need to be screened and 37 would need to be treated to avoid 1 death in eleven years. For breast and colorectal cancer, 1,000 patients would need to be screened to prevent one death in ten years. For patients with a life expectancy under ten years, screening for these three cancers exposes them to immediate harms with little chance of benefit.

3. Avoid using prescription appetite stimulants or high-calorie supplements for treatment of anorexia or cachexia in older adults; instead optimize social supports, provide feeding assistants, and clarify patient goals and expectations. Although high-calorie supplements increase weight in older people, there is no evidence that they affect other important clinical outcomes, such as quality of life, mood, functional status, or survival. Use of megestrol acetate results in minimal improvements in appetite and weight, no improvement in quality of life or survival, and increased risk of thrombotic events, fluid retention, and death. In the 2012 American Geriatric Society Beers criteria, megestrol acetate and cyproheptadine are listed as medications to avoid in older adults. Mirtazapine is likely to cause weight gain or increased appetite when used to treat depression, but there is little evidence to support its use to promote appetite and weight gain in the absence of depression.³

4. Don't prescribe a medication without conducting a drug regimen review. The elderly use more prescription and non-prescription drugs than other populations, which increases the potential for side

effects and inappropriate prescribing. Polypharmacy can lead to diminished adherence, adverse drug reactions, and increased risk of cognitive impairment, falls, and functional decline.

5. Avoid physical restraints to manage behavioral symptoms of hospitalized older adults for delirium as there is little evidence to support their effectiveness in these situations. Further, they can lead to serious injury or death or may worsen agitation and delirium. Alternatives include strategies to prevent and treat delirium, identification and management of conditions causing patient discomfort, environment modifications to promote orientation and effective sleep-wake cycles, frequent family contact, and supportive interaction with staff. Nursing educational initiatives and innovative models of practice include continuous observation; trying reorientation once, and discontinuing it if not effective; observing behavior to obtain clues about patients' needs; discontinuing and/or hiding unnecessary medical monitoring devices or IVs; and avoiding questions that test short-term memory to limit patient agitation. If the patient presents harm to him or herself or to others, pharmacological interventions are occasionally utilized after evaluation by a medical provider at the bedside.⁴

RECOMMENDATIONS FROM THE AMERICAN ACADEMY OF ALLERGY, ASTHMA, AND IMMUNOLOGY

This academy has also added five new items.

The previous recommendations were:

- Don't perform unproven diagnostic tests, such as immunoglobulin G (IgG) testing or an indiscriminant battery of immunoglobulin E (IgE) tests, in the evaluation of an allergy.
- Don't order sinus computed tomography (CT) or indiscriminately prescribe antibiotics for uncomplicated acute rhinosinusitis.
- Don't routinely do diagnostic testing in patients with chronic urticaria.
- Don't recommend replacement immunoglobulin therapy for recurrent infections unless impaired antibody responses to vaccines are demonstrated.
- Don't diagnose or manage asthma without spirometry.

The five added recommendations are as follows:

1. Don't rely on antihistamines as first-line treatment in severe allergic reactions. Epinephrine is the first-line treatment for anaphylaxis, which—by definition—has cardiovascular and respiratory manifestations. Antihistamines are second-line supportive

therapy for cutaneous, non-life threatening symptoms (hives). Fatalities during anaphylaxis have been associated with delayed administration of epinephrine.

2. Don't perform food IgE testing without a history consistent with an allergy mediated by IgE. False or clinically irrelevant positive allergy tests for foods occur frequently. IgE testing for specific foods must be driven by a history of signs or symptoms consistent with an IgE-mediated reaction after eating a particular food. Skin testing or serum testing for specific IgE to food antigens has excellent sensitivity and high negative predictive value, but has low specificity and low positive predictive value. Fifty to ninety percent of presumed cases of food allergy do not reflect IgE-mediated (allergic) pathogenesis and may reflect food intolerance or symptoms not causally associated with food consumption.

3. Don't routinely order low or iso-osmolar radiocontrast media or pretreat with corticosteroids and antihistamines for patients with a history of seafood allergy, who require radiocontrast media. There is no cause/effect connection with seafood allergy and radiocontrast media. Patients with a history of seafood allergy are not at elevated risk for anaphylaxis from iodinated contrast media. Similarly, patients who have had anaphylaxis from contrast media should not be told that they are allergic to seafood. If patients with a history of seafood allergy are labeled as being at a greater risk from contrast infusions, they can experience considerable morbidity from unnecessary precautions. The mechanism for anaphylaxis to radio-iodinated contrast media relates to the physiochemical properties of these media and is unrelated to its iodine content. However, a prior history of anaphylaxis to contrast media is an indication to use low- or iso-osmolar agents and to pretreat with corticosteroids and antihistamines. Patients with asthma or cardiovascular disease, or who are taking beta blockers, are at increased risk for serious anaphylaxis from radiographic contrast media.⁵

4. Don't routinely avoid influenza vaccination in egg-allergic patients. Of the vaccines that may contain egg protein (measles, mumps, rabies, influenza, and yellow fever), measles, mumps, and rabies vaccines have, at most, negligible egg protein; consequently no special precautions need to be followed in egg-allergic patients for these vaccines. Studies in egg-allergic patients receiving egg-based inactivated influenza vaccine have not

reported reactions;** consequently egg-allergic patients should be given either egg-free influenza vaccine or should receive egg-based influenza vaccine with a 30-minute post-vaccine observation period. Egg-allergic patients receiving the yellow fever vaccine should be skin tested with the vaccine and receive the vaccine with a 30-minute observation period if the skin test is negative.

The Advisory Committee on Immunization Practices recommends that egg-allergic persons receive inactivated influenza vaccine as a single dose without prior vaccine skin testing and be observed for 30 minutes afterwards for possible allergic reaction. If the reaction to the ingestion of eggs was only hives, the vaccine can be administered in a primary care setting. There are 2 new inactivated influenza vaccines not grown in eggs that have been approved for patients 18 and older. These are called Flublok[®] and Flucelvax[®]. Measles and mumps vaccines (and Purified Chick Embryo Cell [PCEC] Rabies vaccine) are grown in chick embryo fibroblast cultures and contain negligible or no egg protein, thus MMR and PCEC Rabies vaccine can be administered to egg-allergic recipients in the usual manner.⁶

5. Don't overuse non-beta lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation. About 10% of the population reports a history of penicillin allergy but studies show that 90% or more of these patients are not allergic to penicillins and are able to take these antibiotics safely. The main reason is that penicillin allergy is often misdiagnosed and when it is present it wanes over time in most individuals. If one is labeled as penicillin-allergic, alternative antibiotics are utilized with higher medical costs, longer hospital stays, and more likelihood of developing complications such as infections with vancomycin-resistant enterococcus (VRE) and *Clostridium difficile*. There are also possible cardiovascular side effects from the use of certain antibiotics such as Azythromycin and the Quinolones.

Evaluation for specific IgE to penicillin can be carried out by skin testing. Ideally, penicillin skin testing should be performed with both major and minor determinants. The negative predictive value of penicillin skin testing for immediate reactions approaches 100%, whereas the positive predictive value is between 40 and 100%. In vitro tests are not suitable substitutes for penicillin skin testing.⁷

** In 27 published studies, 4,172 patients with egg allergy received 4,729 doses of egg-based inactivated influenza vaccine with no cases of anaphylaxis, including 513 with severe egg allergy who uneventfully received 597 doses.

TOP TIPS

PERSONALIZED ESTIMATES OF BENEFITS FROM PREVENTIVE CARE GUIDELINES

The US Preventive Services Task Force (USPSTF) makes recommendations for 60 distinct clinical services, but do many clinicians really have time to evaluate and implement the recommendations in an individual patient? This is, of course, what we are trying to do with the concept of the Patient Centered Medical Home. Although the receipt of preventive health care services has improved, it is estimated that only about one half of the recommended services are provided. Utilization remains low for some services, for example, 48% of persons are not screened for colorectal cancer. Disparities in utilization may contribute to health outcomes. For example, 62% of white persons but only 37% of black persons aged 65 years or over receive pneumococcal vaccinations.

The amount of time it would take to fully evaluate and implement all relevant recommendations from the USPSTF is widely considered to be unrealistic: it is estimated that it would require more than 7 hours each day for a typical practice panel of 2,500 patients, thus making prioritization essential.

Many of us do not know which USPSTF recommendations have the greatest benefit for each individual patient. Accordingly, a recent study followed a mathematical model to rank screening and preventive services according to increases in life expectancy, and demonstrated how the order changes with differences in demographic characteristics, medical conditions, and life style choices.⁸ Increases in life expectancy varied more than 100-fold across USPSTF recommendations.

The rank order of benefits varied considerably among patients. For example, for an obese man age 62 years who smoked and had hypercholesterolemia, hypertension, and a family history of colorectal cancer, the model's top three recommendations (from most to least gain in life expectancy) were tobacco cessation (adding 2.8 life-years), weight loss (adding 1.6 life-years), and blood pressure control (adding 0.8 life-years). Lower-ranked recommendations were a healthier diet, aspirin use, cholesterol reduction, colonoscopy, screening for abdominal aortic aneurysm, and HIV testing (each adding 0.1 to 0.3 life-years). For a person with the same characteristics plus uncontrolled type II diabetes mellitus, the model's top three recommendations were diabetes control, tobacco cessation, and weight

loss (each adding 1.4 to 1.8 life-years). Generally across various hypothetical patients, tobacco cessation, diabetes control, weight loss, and blood pressure reduction were consistently among the highest-ranked guidelines.

To improve clinical relevance, future versions of this framework must address several limitations. Patient-level adherence rates should be incorporated into the decision support. To improve patient-centeredness, metrics other than life expectancy (such as quality of life and patient preferences) should be included. To the degree that racial differences in life expectancy are influenced by socioeconomic status, variables such as income and education should be incorporated into the equation. An ideal model should consider interaction among recommendations. For example, the effect of weight loss at a patient's current blood pressure is estimated, but not how much blood pressure may decrease because of weight loss. Also the model would benefit from confidence intervals surrounding several sources of data. Baseline life expectancy should consider dominant comorbid conditions that substantially affect mortality risk, such as previous diagnosis of cancer.

Models of personalized preventive care may help clinicians prioritize USPSTF recommendations at the patient level and especially in our new Patient Centered Medical Home offices.

WHAT ABOUT THE BENEFITS AND RISKS OF ELECTRONIC CIGARETTES (E-CIGS)

E-cigs, the smokeless, battery-powered devices that resemble cigarettes, seem to be the latest craze. They contain small cartridges that hold a liquid mixture typically comprised of propylene glycol, vegetable glycerin, nicotine, and special flavorings. Heat produced by a battery vaporizes the liquid, which is then inhaled through a mouthpiece and exhaled as a fine mist. In 2013 retail sales exceeded \$1 billion in the United States alone.

ARE E-CIGS ANY HEALTHIER THAN CIGARETTES?

"Vaping," as inhaling e-cig vapors is called, does not burn tobacco or paper. But does it help smokers to quit and is it healthy? One study concluded that e-cigs are as effective as other proven forms of nicotine reduction therapy, such as nicotine patches, at helping smokers transition off cigarettes. But does this promising benefit outweigh the potential harms of using e-cigs?

Existing research into their health effects is inconclusive. Studies on vaping and nicotine absorption have drawn varying conclusions about effects on blood nicotine levels. Among new e-cig users, vaping appears to

have a minimal effect on blood nicotine. Experienced vapers, on the other hand, can obtain significantly higher blood levels that more closely match the nicotine absorption levels obtained via cigarette smoking.¹⁰

WHAT ABOUT THE DEEPER ISSUE OF NICOTINE ADDICTION?

Some vapers report that e-cigs actually increase their desire to smoke tobacco, thus perpetuating the cycle of craving and consumption. This might be why some of the major companies of Big Tobacco have gotten into the game and purchased or have started some e-cig companies themselves.

E-cig opponents fear that rather than reducing cigarette dependence, e-cigs may instead act as a gateway to tobacco use by encouraging curious non-smokers to experiment with cigarettes and other tobacco products. The Centers for Disease Control showed that between 2011 and 2013, e-cig experimentation doubled among middle and high school students, and that an estimated 1.78 million students had used e-cigs as of 2012. Of those, an alarming 160,000 youth who reported e-cig use had never smoked conventional cigarettes. The growing numbers of young vapers raises questions also about potentially harmful effects of nicotine on adolescent brain development.

E-cigarettes are available in pharmacies, gas stations, "Vape Shops", and on-line. The internet market is virtually unregulated. Despite legislative efforts to curb use among minors, some manufacturers appear to be intentionally targeting adolescents with flavored "e-juices" that cater to young tastes. Nearly all also contain artificial food flavorings, colors, and sweeteners. The health consequences of long-term inhalation of these ingredients are not known.

E-cig liquid can also contain "detectable levels of known carcinogens and toxic chemicals to which users could potentially be exposed," according to an FDA analysis. Among those are diethylene glycol—an ingredient used in antifreeze—as well as tobacco-specific carcinogenic nitrosamines and other impurities including anabasine, myosmine, and L-nicotyrine that are suspected of being harmful to humans, again according to the FDA.

In a more recent study it was demonstrated that the vapor mist exhaled by these users releases volatile organic compounds and ultrafine particles into the environment—although these are in lower concentrations than cigarette smoke. This suggests that the e-cig users may negatively impact not only their health but also contribute to second hand toxin exposure and air

pollution. Numerous technical flaws including leaking liquid and mislabeled nicotine have been reported.

As these problems become an increasingly hot-button topic, further research will be required to weigh their value as a tool that reduces harm against their potentially damaging health effects. The FDA is expected to issue regulations soon but there is currently no federal oversight of this industry. In the meantime, we should look at this as a huge social and public health experiment and hope that further studies illuminate the long-term safety and/or risks of this new technology.

OPPOSITION GROWING AGAINST AZITHROMYCIN

Recent treatment guidelines are recommending that certain antibiotics no longer be used to treat certain infections.

Azithromycin was developed in 1980 and has been marketed in the United States since 1991. As of 2011, it was considered the most commonly prescribed antibiotic. Just last year the Canadian Pediatric Society strongly recommended that a Z-Pack (Azithromycin) not be used to treat acute sore throats, ear infections, or community-acquired pneumonia. That article did not simply suggest that clinicians consider not using it; rather, its recommendation is "do not use." The article's only exception for use of a Z-Pack is in cases of life-threatening allergy to certain antibiotics, and pneumonia caused by atypical bacteria. One of the problems with Azithromycin is that its long half-life contributes to the emergence of resistance. In fact, resistance has been documented in people up to several months after they have finished a course of the antibiotic.

ALTERNATIVES

Data show that Azithromycin-type drugs have limited efficacy against two of the most common bacterial pathogens associated with ear infections. The 2012 guidelines for sinusitis from the Infectious Disease Society of America recommend considering antibiotics if symptoms persist beyond ten days, are severe or worsening, or if there is high fever and nasal discharge for at least three days. Azithromycin-type drugs are not recommended at all for this group; about 30% of these cases will be resistant. The clinical practice guidelines from The American Academy of Pediatrics for acute bacterial sinusitis recommend amoxicillin with or without clavulanate (Augmentin®) for patients 1-18 years of age. Once again there is no recommendation for Azithromycin. For "strep throat" guidelines

recommend first-line treatment with Penicillin, and Azithromycin only for patients allergic to Penicillin. In the United States 5%-8% of positive strep patients are resistant to Azithromycin.

For children older than 2 years of age with bacterial pediatric pneumonia, guidelines recommend first-line treatment with amoxicillin with or without clavulanate as mentioned above. *Eighty percent of pediatric pneumonia under the age of two years is viral.* Azithromycin has no activity against any virus. For community-acquired pneumonia in adults, macrolides in combination with doxycycline can be considered in previously healthy adults who have not recently taken an antibiotic. This guideline was issued in 2007 before the emergence of our current concerns about widespread macrolide overuse. Notably, the guidelines are still not recommending the use of Azithromycin alone.

Part of the reason for the overuse of Azithromycin is not only the fact that doctors have gotten into a habit

of using it, but there is now pressure from patients. Combine both of these pressures and you have greatly increased bacterial resistance to Azithromycin and decreased improvement in the patient's condition.

Some of the other complications that can occur with antibiotics, of course, include antibiotic-associated diarrhea or yeast infections. Any antibiotic, of course, can cause rashes, hives, and GI upset. Recently more data have shown an increased risk of cardiac death with the use of Azithromycin or Levofloxacin. This is a small number but statistically significant, and is associated with the fact that Azithromycin can cause arrhythmias and prolongation of the QT interval.

So we all (medical providers, as well as patients) need to take antibiotic resistance seriously. Otherwise these precious resources of antibiotics will vanish before our eyes and there will be rising mortality from bacterial diseases that were once easily treated.

REFERENCES

1. Dizon-Townson, E et al. The Relationship of factor V Leiden Mutation and Pregnancy Outcomes for Mother and Fetus. *Obstet Gynecol.* 2005 Sep;106(3):517-24.
2. American College of Obstetricians and Gynecologists Committee on Genetics Noninvasive Testing for Fetal Aneuploidy. Committee Opinion No. 545. *Obstet Gynecol.* 2012 Dec;120(6):1532-4.
3. American Geriatric Society 2012 Beers Criteria Update Expert Panel. American Geriatric Society updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2012 Apr;60(4):616-31.
4. Flaherty, JH et al. Matching the Environment to Patients With Delirium: Lessons Learned From the Delirium Room, a Restraint-Free Environment for Older Hospitalized Patients With Delirium. *J Am Geriatr Soc.* 2011 Nov; 59 Suppl 2:S295-300.
5. Solensky, R et al. Drug Allergy: An Updated Parameter. *Ann Allergy Asthma and Immunol.* 2010 Oct; 105(4):259-73.
6. Des Roches, A et al. Egg-Allergic Patients Can Be Safely Vaccinated Against Influenza. *J Allergy Clin Immunol.* 2012 Nov; 130(5):1213-1216.
7. Solensky, R. Penicillin Allergy is a Public Health Measure. *J Allergy and Clin Immunol.* 2014 Mar; 133(3):797-798.
8. Taklser, GB et al. Personalized Estimates of Benefit From Preventative Guidelines. *Ann Int. Med.* 2013 Aug; 159(3):161-168.
9. *Lancet* 2013;382 (9905):1629-1637).
10. *Int J Clin Pract* 2011;65(10):1037-1042.
11. *Indoor Air.*2013;23:25-31.
12. American Academy of Emergency Medicine 20th Annual Scientific Assembly Feb. 14, 2014.

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