TOP TIPS FROM FAMILY PRACTICE

Choosing Wisely XXIII

Recommendations from the American Academy of Pediatrics Section on Endocrinology, American Society of Clinical Pathology, American Association of Gynecologic Laparoscopists

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This is my 23rd article on Choosing Wisely from the Board of Internal Medicine Foundation. As previously noted, each specialty group is developing "Five, Ten, or Fifteen Things that Physicians and Patients Should Know."

I. RECOMMENDATIONS FROM THE AMERICAN ACADEMY OF PEDIATRICS SECTION ON ENDOCRINOLOGY

1. Children with pubic hair and/or body odor (but no other signs of puberty) should not have measurements of LH and FSH, estradiol or testosterone. The diagnosis is usually premature adrenarche, which does not involve activation of the pituitary-gonadal axis but is due to an early increase in adrenal androgens. DHEA-S levels are elevated for age, but do not alter the management of this common and generally benign condition.

2. Healthy children growing at or above the third percentile for height, with a normal growth rate (i.e., not crossing percentiles), and with appropriate weight gain, should not have screening tests looking for chronic illness or an endocrine cause, including CBC, CMP, IGF-1, thyroid tests, and celiac antibodies. The incidence of newly diagnosed pathology is only about 1%, even in children who are below the 3rd percentile for height, if the history and physical exam are normal.

3. Vitamin D concentrations should not be routinely ordered in otherwise healthy children, including children who are overweight or obese.[1] It's been shown that children who are overweight or obese have a greater likelihood of low vitamin D levels. If the history suggests an obese child has insufficient dietary intake of vitamin D (e.g., little milk intake), a vitamin D supplement should be recommended, which is more cost-effective than measuring 25-hydroxyvitamin D, either for screening or monitoring therapy.

Although a 25-hydroxyvitamin D concentration, which reflects both vitamin D synthesis and intake, is the correct screening lab test to monitor vitamin D deficiency, current evidence is insufficient to suggest that screening is necessary or safe in otherwise healthy children who are overweight or obese. The AAP report on Optimizing Bone Health in Children and Adolescents advises screening for vitamin D deficiency only in patients with disorders associated with low-bone mass, such as rickets, or with a history of recurrent, low trauma fractures.

4. Obese children should not have routine measurements of thyroid function and/or insulin levels. TSH levels can be slightly elevated in obesity but this is more likely a consequence of obesity and rarely true hypothyroidism. Free T4 levels are usually normal. There is no proven benefit to treatment when TSH is minimally elevated with normal Free T4 levels. Insulin levels have significant limitations as a marker of insulin resistance. Both the AAP Section on Obesity and the AAP Section on Endocrinology state that it is not necessary to order insulin levels to establish a weight control management plan.

5. Children with simple goiters or autoimmune thyroiditis should not have routine thyroid ultrasounds.[2] Ultrasounds should be limited to children who have asymmetric thyroid enlargement, palpable nodules, or troubling cervical lymphadenopathy. Overuse of ultrasonography results in needless healthcare costs and is time-consuming for families. Ultrasound can detect nodules that elude palpation, and one prospective series found that 31.5% of patients with Hashimoto's thyroiditis indeed had thyroid nodules. However, the majority are not harmful and might lead to additional radiological studies, fine needle aspiration, or aggressive treatment of "pseudo-disease." Although there is a known association between Hashimoto's thyroiditis and thyroid cancer, and a pathologic diagnosis of

papillary carcinoma was made in 3% of patients in a study, there is insufficient evidence to conclude that detecting nodules before they are palpable leads to better outcomes.

II. RECOMMENDATIONS FROM THE AMERICAN SOCIETY OF CLINICAL PATHOLOGY (ASCP)

The ASCP has added five tests to the list it considers unnecessary or potentially harmful. The list has now grown to 20 recommendations; I will only list the first 15, as we have discussed them in the past, and further describe the latest five.

Previous Recommendations:

1. Population-based screening for 25-hydroxy vitamin D deficiency should not be performed.
2. Low-risk human papillomavirus testing should not be performed.
3. Routine preoperative testing before low-risk surgeries should be avoided unless there is a clinical indication.
4. Methylated Septin #9 should be used to screen for colon cancer only in patients for whom conventional diagnostics are not possible.
5. A bleeding-time test should not be used to guide patient care.
6. An erythrocyte sedimentation rate should not be ordered to look for inflammation in patients with undiagnosed conditions. Order a C-reactive protein level to detect acute-phase inflammation.
7. Do not order vitamin K levels unless the patient has an abnormal INR (International Normalized Ratio) and does not respond to vitamin K therapy.
8. Testosterone therapy should not be prescribed unless there is laboratory evidence of testosterone deficiency.
9. For the diagnosis of acute myocardial infarction, use troponin I or T, not myoglobin or creatine kinase-MB.
10. In the initial evaluation of a patient with suspected non-neoplastic thyroid disease, do not order multiple tests. Rather, order a TSH level, and if abnormal, follow-up with additional evaluation or treatment, depending on the findings.
11. For the evaluation of early, thin melanoma, do not routinely perform a sentinel lymph node biopsy or other diagnostic tests, as they do not improve survival.
12. Expanded lipid panels (particle sizing, nuclear magnetic resonance) should not be ordered routinely as screening tests for cardiovascular disease. A standard lipid profile includes total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride.
13. In cases of suspected acute pancreatitis, test for lipase, not amylase.
14. Do not request serology for Helicobacter pylori. Instead, use the stool antigen or the breath test.
15. When bone marrow samples obtained for cytopenia reveal abnormalities related to myelodysplastic syndrome, do not perform fluorescence in situ hybridization (FISH) if an adequate conventional karyotype is obtained.

New Recommendations:

16. A frozen section should not be requested on a surgical specimen unless the result will immediately affect intraoperative or perioperative patient management. Usefulness of a frozen section may be limited by sampling and technical issues that can hinder interpretation, and it may compromise the integrity of the specimen for the final diagnosis. If it is not going to be used for immediate management, it is preferable to submit the specimen for routine (or "rushed," if necessary) permanent section and histologic evaluation.[3]

17. In patients who have hemoglobin variant levels, but have a prior result and do not require therapeutic intervention or monitoring, do not order hemoglobin electrophoresis (or equivalent). Repeat hemoglobin electrophoresis testing is required only to make a more specific diagnosis, or to monitor the results of interventional therapies in patients with known hemoglobinopathies.

18. Tests for Protein C, Protein S, or Antithrombin (ATIII) levels to diagnose a hereditary deficiency are not analytically accurate during an active clotting event; they should not be done then. These assays may, however, be useful to test for an acquired deficiency (i.e., disseminated intravascular coagulation) in consumptive coagulopathies. Deferral to an outpatient/non-acute setting allows for the testing to be done at a time when the results would not change patient management, i.e., ceasing or continuing anticoagulation. Anticoagulation may also impact the determination of the results (e.g., Protein C and Protein S decrease on warfarin, while ATIII is actually elevated). Testing while on

anticoagulants may also yield misleading results and should be avoided.

19. Red blood cell folate levels should not be ordered at all. In adult patients with macrocytic anemia, consider folate supplementation instead of serum folate testing. Since 1998 when the US and Canada mandated that foods with processed grains be fortified with folic acid, there has been a significant decline in the incidence of folate deficiency. If one suspects a folate deficiency, simply treating with folic acid is a more cost-effective approach than blood testing. While red blood cell folate levels have been used in the past as a surrogate for tissue folate levels, or as a marker of folate status over the lifetime of red blood cells, the results of this test do not, in general, add to the clinical diagnosis or therapeutic plan.[4]

20. Sputum cytology should not be used to evaluate patients with peripheral lung lesions. Consider alternative diagnostic approaches (e.g., image guided needle aspiration).

III. Recommendations from the American Association of Gynecologic Laparoscopists (AAGL)

1. Laparotomy should not be performed when surgical management is indicated for the management of non-malignant gynecologic disease, if a vaginal, laparoscopic, or robotic-assisted approach is feasible and appropriate. The endoscopic approach should consider patient selection, surgeon ability, equipment availability, cost effectiveness, and potential complications.

2. Do not perform routine oophorectomy in premenopausal women undergoing hysterectomy for non-malignant indications who are at low risk for ovarian cancer. Except in high-risk populations, there is a substantial association between oophorectomy and increased mortality in the general population, particularly regarding higher rates of coronary artery disease and cardiovascular death. Long term risks associated with salpingo-oophorectomy are most pronounced in women who are younger than 45-50 years who were not treated with estrogen.

3. Do not give prophylactic antibiotics routinely for low-risk laparoscopic procedures. Although there are many appropriate uses of antibiotic prophylaxis for hysterectomy, they are increasingly being administered to women who are less likely to receive benefit. This practice can, of course, increase not only antimicrobial resistance in the facility, but also cost and possible allergic complications.[5]

4. Unaided removal of endometrial polyps without direct visualization should be avoided when hysteroscopic guidance is available and can be safely performed. Conservative management may be appropriate in some patients, but hysteroscopic polypectomy is the mainstay of treatment. Without the aid of direct visualization, removal should be avoided due to its low sensitivity and negative predictive value of successful removal, compared with hysteroscopy and guided biopsy.

5. Opioid misuse in the patient with chronic pelvic pain can be avoided without compromising care by proper education, responsible opioid prescribing, and advocacy. Opioid misuse has become a public health crisis. Patients have a right to appropriate assessment and management of pain, and providers should become familiar with published FDA and CDC plans and guidelines. Education of patients and screening for risk factors for opioid misuse must be accomplished. Patients on chronic opioid therapy must be followed carefully for any signs of misuse.[6]

Top Tips

Association between rainfall and diagnoses of joint or back pain

How many times have you or someone around you said, "Boy, I'm really achy today, it must be because of the rain, or barometric pressure, or humidity?" A group from Harvard looked at U.S. Medicare insurance claims linked to rainfall data from U.S. weather stations.[7] The cohort included over a million and a half adults, aged 65 and over, who had a total of more than 11 million outpatient visits with a general internist from 2008 through 2012.

The outpatient visits for joint or back pain included diagnoses of rheumatoid arthritis, osteoarthritis, spondylosis, intervertebral disc disorders, and other non-traumatic joint disorders. The number of visits was compared between rainy days and non-rainy days, adjusting for patient characteristics, chronic conditions, and geographic fixed effects. The latter adjustment allowed comparisons of rates of joint or back pain-related outpatient visits on rainy days versus non-rainy days within the same area.

No statistically significant relation was found between the proportion of claims for joint or back pain and the number of rainy days in the week of the outpatient visit. Nonetheless, the authors do say that a relation may still exist, and therefore a larger, more detailed study on disease severity and pain would be useful to support the validity of this commonly held belief.*

POST-APPROVAL SAFETY CHECKS ON MEDICINES

An analysis in the New England Journal of Medicine concluded that, in many cases, safety checks on medicines are not being done.[8] Woloshin and colleagues at the Dartmouth Institute for Health Policy and Clinical Practice, looked at federal records and found that among the 614 post-approval studies mandated in 2009 and 2010, 20% were never started and 9% were delayed.

With the present administration in Washington vowing to speed up the FDA approval process, "Drug approval is likely to become increasingly rapid and rely on looser evidence standards," according to the Woloshin team.

Obviously, as physicians, we would like to have important questions that are unanswered at the time of approval resolved as quickly as possible. The investigators supplied the following examples of missed deadlines.

- Indivior's Suboxone® is a combination of buprenorphine and naloxone used to treat opioid dependence. The FDA and others wanted to know the risk of prolonged QT intervals. The sponsor was given more than a year to submit the trial protocol and five years to complete the trial. As of July 2017, the final protocol apparently had not been submitted.
- Novartis' new drug for multiple sclerosis (Gilenya® - fingolimod) costs $72,000/ year, and the FDA asked for tests at a lower and less expensive daily dose. More than six years after approval, the trial has not been completed despite the manufacturer reporting $2.8 billion in sales.
- Victoza® is Novo Nordisk's widely used drug for type 2 diabetes. Animal tests show that it might cause thyroid cancer, so the FDA ordered the company to keep a 15-year registry concerning thyroid cancer among those taking the drug. The deadline for submitting the rules for running the registry was July 2010. As of September 2017, no protocol for the registry had been submitted.
- The schedule for a one-year pediatric safety and efficacy study for Welchol® (colesevelam) to assess its effects on type 2 diabetes in children was allowed six years for completion. An additional four-year extension was also granted.

The Dartmouth team believes that the FDA should set shorter deadlines and impose penalties when companies miss these deadlines. That sounds reasonable to me and I'm sure to most other physicians.

EXPERT CONSENSUS PATHWAY FOR MANAGEMENT OF BLEEDING ON ORAL ANTICOAGULANTS (OACS)

This new decision pathway for management of acute bleeding in patients treated with direct OACs (DOACs) and vitamin K antagonists (VKAs) was published December 1st in the Journal of The American College of Cardiology.[9] (This is a supplement to the 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in patients with nonvalvular atrial fibrillation, which I reported as one of my Top Tips in the Fall issue of JLGH.)

The DOACs are the "newer" drugs indicated for the management of clotting risk in many clinical situations such as non-valvular atrial fibrillation and DVT/ PE. Any practitioner that has a patient on any of these drugs will want to keep this guide handy in case your patient experiences bleeding.

The document is extremely complete with

* **Editor's note:** Most clichés have roots in actual life experiences. The expression "I can feel it in my bones" is no exception. Due to an old rib fracture I have personal experience with this phenomenon, and for me it is real. I suspect that none of the authors personally experienced these symptoms, or they might have avoided several problems with this study's design:

1. It only dealt with non-traumatic conditions, whereas – based on my experience, and as confirmed to me by Bruce Brewer, M.D., then chair of orthopedics at my previous employer, the Medical College of Wisconsin – healed fractures are a common source of these symptoms.
2. People with such aches recognize them as a chronic and somewhat distracting, but hardly disabling, part of their lives. They are unlikely to seek a doctor's appointment for a transient discomfort.
3. If, as is likely, aches are related to drops in barometric pressure, they occur one to two days before it rains, so it's off the mark to expect doctor visits (if they occur at all) to be on rainy days. Better to have subjects record the days with aches, and correlate these symptoms with barometric pressure readings.

algorithms, tables, and figures in its 20 pages. Some of the items that it includes are:

- Defining and assessing bleed severity
- Laboratory measures of the DOACs based on specialized assay availability
- Caring for major and non-major bleeds
- Options for reversal of VKAs (the most common is warfarin), dabigatran and Factor Xa inhibitors
- Prescribing reversal agents based on the OAC prescribed
- Duration of withholding DOACs based on the bleed risk
- Available reversal agents and indications for each of the OACs
- When and whether a patient should resume anticoagulation
- Indications for anticoagulation with high-thrombotic risk
- Cases in which it is recommended that the patient restart anticoagulation
- Situations where it is recommended that a patient delay restart of anticoagulation
- Important discussion points with patients prior to restarting anticoagulation

Obviously, as more DOACs come forth and more evidence is generated from research and clinical practice, further refinement will be needed.

WHY DOCTORS SHOULD BE CONCERNED ABOUT GUN VIOLENCE

In the last issue of the JLGH, Dr. Chet Morrison wrote an excellent article on firearm violence.[10] The editors of the top medical journals in the United States have come together to denounce the epidemic of gun violence and offer steps that health care professionals can take. An average of almost 100 people die each day in the U.S. from gun violence. In 2015, the number of deaths from firearms exceeded the number of deaths from motor vehicle accidents. Also, that same year the CDC reported that five people died from terrorism. Since 1968, more have died in the U.S. from gun violence than in all the wars we have fought since 1776!

It is often forgotten that most gun deaths in the U.S. (60.7% in 2015) are suicides. Guns do not make us safer; they cause far more deaths to our loved ones, than from an intruder intending to cause harm.

Research on gun violence is obviously crucial, yet in the last two decades Congress has limited the amount of research that can be conducted. The suppression of research resulted in a 64% decline in the number of firearms studies per million citations in SCOPUS between 1998 and 2012.

In the "old days," when I did complete physicals on my patients (I know those days are fleeting now), one of the preventive health questions I posed was about guns in the home and whether they were kept in a locked site for safe storage from children and others. Also, was the ammunition kept separate from the weapon? Safe storage does reduce misuse. I feel that we should continue appropriate screening and early intervention to prevent suicide and accidental violence from gun deaths.

As the editorial in *JAMA* concluded, "But the key to reducing firearm deaths in the United States is to understand and reduce exposure to the cause, just like in any epidemic, and in this case, that is guns."

I'LL TAKE A FEW MORE CHEMICALS…….IN MY DRINKING WATER?

A class of chemicals, known as perfluorinated chemicals has been linked to illnesses including cancer, high cholesterol, and developmental problems in young children. This finding has prompted the EPA to issue a health advisory about "safe limits" in drinking water.

Although the EPA does not formally regulate the chemicals, some states have started imposing their own restrictions. In New Jersey, last month scientists recommended strict limits on perfluorooctane sulfonate (PFOS), a type of perfluorinated chemical whose health effects – according to an EPA advisory – may include low birth weight in infants, kidney and testicular cancer, liver damage, and impaired immune system function. Other effects can be increased uric acid levels, and hypertension.

The proposed New Jersey limit for PFOS is 13 parts/trillion (PPT), which is much lower than the EPA's recommendation of 70 PPT for combined PFOS and perfluorooctanoic acid (PFOAN). Vermont also regulates these chemicals, and the NJ limit is lower than Vermont's limit.

These chemicals are extremely persistent in the environment and they can seriously impact human health at extremely low concentrations. They were used in consumer products for about 50 years, until their manufacture was phased out in the United States early in this century because of health concerns. Foreign manufacturers overseas still use these chemicals and they are present in other sources such as dust that

results from the breakdown of certain consumer products. Other sources include water treatment plants, landfills, and military bases that have used firefighting foam containing PFOS and other perfluorinated chemicals. Recreational fishermen who eat fish caught in waters contaminated by these chemicals may be at particular risk for health problems.

Other sources of these chemicals include cookware (Teflon®, Nonstick), carpets, clothing, fabrics for furniture, paper packaging for food, and other materials that are made to be resistant to water, grease, or stains. Food packaging materials such as microwave popcorn bags, fast food containers, candy wrappers, and pizza boxes have been found to have these chemicals. (Don't recycle them.)

Also, they are used for industrial purposes in photo imaging, metal plating, semiconductor coatings, aviation hydraulic fluids, medical devices, insect baits, printer and copy machine parts, chemically driven oil production, rubber and plastic industries.

These chemicals have been detected in 95-100% of samples of people's blood in the years 1999–2000 and 2003–2004. Average blood levels of PFOS from 2011–2012 were 6.3 parts/billion (PPB), with 95% of the general population at or below 21.7 PPB. These chemicals leave the body mainly through the urine, and it takes nearly four years for the level in the body to decrease by half.

People can reduce the risk of exposure by choosing consumer products that do not contain any perfluorochemicals. People whose well water contains these chemicals above the EPA's advisory levels for drinking water may choose bottled water for drinking and cooking, or may install an activated carbon filtration system or reverse osmosis system. Certainly, if one lives near a present or past industrial facility or a military facility, there is more reason to be concerned and to check the level in the water.

The EPA issued a health advisory for these chemicals in May of 2016, based on the agency's assessment of the latest peer-reviewed science. Here in Pennsylvania, the state has the authority to set maximum contaminant levels (MCLs), but the Department of Environmental Protection (DEP) has never established a state MCL, apparently due to a lack of state funding and resources. We must look to states like New Jersey and Vermont, which seem to be more concerned about their citizens' environmental health.

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