What's new in drug therapy

DRUG INTERACTIONS

Biotin may interfere with the results of troponin testing (December 2017)

Biotin, which is contained in varying amounts in many vitamins and dietary supplements, may impact the results of high-sensitivity troponin assays. In general, the reported troponin values are decreased [1,2]. A safety warning from the US Food and Drug Administration has been issued. There is insufficient information to guide the formulation of firm recommendations regarding this clinical scenario; our approach is presented. Clinicians should be aware of this issue and query patients about biotin or vitamin intake. When troponin results are unexpected, it is reasonable to further observe the patient and repeat the troponin test. (See "Troponin testing: Clinical use".)

Thyroid hormone assay interference with biotin supplements (October 2017)

A growing number of reports have noted that ingestion of 5 to 10 mg of biotin (marketed over the counter to prevent hair loss) can cause artifactually low serum thyroid stimulating hormone (TSH) and high triiodothyronine (T3) and thyroxine (T4) in assays using biotin-streptavidin affinity systems in their design [3,4]. Thyroid tests should be repeated at least two days after discontinuation of biotin supplements. (See "Laboratory assessment of thyroid function", section on 'Assay interference with biotin ingestion'.)

RECENT APPROVALS - ANTIMICROBIALS

Monoclonal antibody for multidrug-resistant HIV (March 2018)

For patients with multidrug-resistant HIV infection who are failing antiretroviral therapy, it can be difficult to construct a regimen that leads to virologic suppression. In March 2018, the US Food and Drug Administration approved the use of the monoclonal antibody ibalizumab-uiyk for treatment of such patients [5]. This agent is administered intravenously every two weeks and must be used in combination with other antiretroviral agents. In one small trial, approximately 50 percent of those who received ibalizumab-uiyk in addition to an optimized background regimen achieved a viral load <200 copies/mL by six months [6]. The decision to initiate ibalizumab-uiyk should be made by or in consultation with a provider experienced in managing patients with drug-resistant HIV. (See "Selecting an antiretroviral regimen for treatment-experienced HIV-infected patients who are failing therapy", section on 'If a fully active PI is NOT available'.)

Meropenem-vaborbactam in complicated urinary tract infection (March 2018)

Meropenem-vaborbactam is a novel antibiotic combination of a carbapenem with a broad-spectrum beta-lactamase inhibitor that potently inhibits certain carbapenemases. In a randomized trial of patients with complicated urinary tract infection, including pyelonephritis, clinical and microbiologic outcomes were comparable between meropenem-vaborbactam and piperacillin-tazobactam [7]. The main role of meropenem-vaborbactam is for treatment of

infections with highly resistant, *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacteriaceae; data evaluating outcomes with such organisms are limited but emerging. (See "Combination beta-lactamase inhibitors, carbapenems, and monobactams", section on 'Meropenem-vaborbactam' and "Overview of carbapenemase-producing gram-negative bacilli", section on 'Serious infections'.)

RECENT APPROVALS - HEMATOLOGIC AND ANTICOAGULANT

Denosumab in multiple myeloma (February 2018)

New guidelines from the American Society of Clinical Oncology (ASCO) include denosumab as a bone-modifying agent option for patients with multiple myeloma (MM) [20]. We consider denosumab a reasonable alternative to intravenous pamidronate or zoledronic acid for patients with renal impairment who are not on chronic dialysis and for those with ongoing acute phase reactions after repeated dosing with bisphosphonates. Its use in other patients with MM is less attractive given its markedly higher cost and lack of an efficacy advantage over intravenous zoledronic acid in two randomized trials. Importantly, if denosumab is discontinued, at least one dose of intravenous bisphosphonates must be given to prevent rebound osteoclast activity which can lead to rapid bone loss and increased risk of fractures. Denosumab was recently approved by the US Food and Drug Administration for the prevention of skeletal-related events in patients with MM. (See "The use of osteoclast inhibitors in patients with multiple myeloma", section on 'Denosumab'.)

RECENT APPROVALS - ONCOLOGIC

Adjuvant therapy for cutaneous melanoma (January 2018)

Patients with cutaneous melanoma and positive lymph nodes (stage III) at initial definitive surgery and those with distant metastases (stage IV) who undergo definitive resection of all sites of metastatic disease stage are at increased risk for recurrence and subsequent death due to metastatic melanoma (table 1A-B). In a phase III trial, nivolumab, a checkpoint inhibitor targeting programmed cell death protein 1 (PD-1), increased progression-free survival compared with ipilimumab and was associated with decreased toxicity [32]. Based upon these results, nivolumab was approved by the US Food and Drug Administration as adjuvant therapy for cutaneous melanoma [33]. Nivolumab is now our preferred agent for adjuvant therapy in most patients with stage III cutaneous melanoma and those with stage IV disease who have undergone definitive resection of all metastatic sites; targeted therapy is also an option in patients with *BRAF*-mutant melanoma. (See "Adjuvant therapy for cutaneous melanoma", section on 'Nivolumab'.)

RECENT APPROVALS - OTHER

Gene therapy for a congenital form of retinitis pigmentosa (December 2017)

Leber congenital amaurosis (LCA) is a form of retinitis pigmentosa present at birth. Some patients with LCA have a mutation in *RPE65* that prevents the production of 11-cis retinal, an essential photopigment. In a randomized trial in 31 patients aged ≥3 years with *RPE65*-mediated LCA, bilateral subretinal delivery of voretigene neparvovec-rzyl (adeno-associated

virus type 2 [AAV2] vector containing human *RPE65*) improved the ability to navigate independently in low-to-moderate light conditions compared with untreated controls at one-year follow-up [35]. Nearly all treated patients showed improved light sensitivity, visual fields, and functional vision under dim lighting conditions. Voretigene neparvovec-rzyl received approval by the US Food and Drug Administration (FDA) in December 2017 for biallelic *RPE65* mutation-associated retinal dystrophy [36]. Long-term follow-up studies will be necessary to determine whether the beneficial effects are durable. This represents the first gene therapy approved by the FDA for an inherited disorder. (See "Retinitis pigmentosa: Treatment", section on 'Leber congenital amaurosis'.)

DRUG WITHDRAWALS

Daclizumab withdrawn from the market (March 2018)

Daclizumab, an injectable disease-modifying therapy for relapsing-remitting multiple sclerosis (RRMS), was withdrawn from the market worldwide in early March 2018 due to reports of severe adverse effects including hepatotoxicity, encephalitis, and meningoencephalitis [41]. The efficacy of daclizumab for reducing relapse rates in patients with RRMS led to regulatory approval in 2016 [42-44]. However, even during its short period of availability, it was considered a second- or third-line agent for RRMS due to the risk of hepatotoxicity and serious infection. (See "Disease-modifying treatment of relapsing-remitting multiple sclerosis in adults", section on 'Daclizumab'.)

ADVERSE REACTIONS AND WARNINGS

Oral estrogen-progestin contraceptives and breast cancer risk (March 2018)

Data on breast cancer risk with combined estrogen-progestin oral contraceptive use have been variable with some epidemiologic studies reporting no association, and others observing an increase in risk with current, but not past use. In a prospective cohort study of nearly 2 million women followed on average for 11 years, the relative risk of breast cancer in oral contraceptive (OC) users compared with never users was 1.19 [45]. However, the overall absolute increase in breast cancers was small, 13 per 100,000 person years (approximately 1 additional case per 7690 women per year). In women under age 35 years, the risk was only 2 per 100,000 person years (1 additional case per 50,000 women per year). This small risk needs to be balanced against some of the important benefits of OC use: contraception, and the reduction in endometrial and ovarian cancer risks that persist for at least 30 years. (See "Risks and side effects associated with estrogen-progestin contraceptives", section on 'Breast cancer'.)

Digoxin levels and mortality in patients with atrial fibrillation (March 2018)

The role of digoxin for rate control of atrial fibrillation (AF) has been questioned for years based on a concern about an increase in mortality. In a well-performed, post-hoc subgroup analysis of the ARISTOTLE trial (which compared anticoagulant therapies in approximately 18,000 patients with AF), digoxin use was significantly associated with an increased risk of death at levels ≥1.2 ng/mL [46]. We almost never use digoxin as the first rate-controlling drug and rarely add it to other rate-controlling drugs. (See "Control of ventricular rate in atrial fibrillation: Pharmacologic therapy", section on 'Digoxin'.)

Cardiovascular risk of febuxostat versus allopurinol in adults with gout (January 2018, Modified March 2018)

The US Food and Drug Administration (FDA) has issued a drug safety communication on febuxostat, a xanthine oxidase inhibitor used in the treatment of gout [47]. The alert was based upon the preliminary results of a randomized trial of over 6000 patients with gout and a history of major cardiovascular disease; the full report of the trial has now been published [48]. The rates of cardiovascular and all-cause mortality were greater with febuxostat than with allopurinol, with differences in the absolute risks, respectively, of 1.2 and 1.4 percent. The safety trial was not placebo controlled; thus, it remains unclear whether allopurinol had beneficial effects on mortality or whether febuxostat had deleterious effects. These findings reinforce our preference for allopurinol as the initial urate-lowering drug for most patients with gout, especially those with high cardiovascular risk. Until further information is available, treatment decisions in patients already taking febuxostat should be individualized and include discussion of safety concerns raised by the FDA, the availability and risks of alternative therapies, and the patient's cardiovascular risk. (See "Pharmacologic urate-lowering therapy and treatment of tophi in patients with gout", section on 'Adverse effects'.)

DOACs in management of heparin-induced thrombocytopenia (HIT) (February 2018)

Heparin-induced thrombocytopenia (HIT) is a life-threatening condition that usually occurs as an adverse reaction to unfractionated or low molecular weight heparin and affects up to 5 percent of patients, regardless of the dose, schedule, or route of administration. Patients with HIT require anticoagulation with a non-heparin agent. Accumulating evidence from observational studies suggests that direct oral anticoagulants (DOACs; eg, dabigatran, apixaban, edoxaban, rivaroxaban) reduce thrombosis risk in HIT without stimulating HIT antibodies [49,50]. We now consider these agents among the options for individuals with HIT, either in the acute setting or if anticoagulation is needed in the future. The choice among these and other anticoagulants takes into account a number of factors including the urgency of anticoagulation, possible need for urgent reversal, and renal and hepatic function. (See "Management of heparin-induced thrombocytopenia", section on 'Direct oral anticoagulants'.)

Association between opioid prescription for postsurgical pain and opioid misuse (February 2018)

Multiple studies have reported an increased risk of new persistent opioid use in opioid-naïve patients prescribed opioids for acute pain. Adding to this body of literature, a retrospective database study of over one million surgical patients without a history of opioid misuse or ongoing opioid use identified opioid misuse (ie, opioid dependence, abuse, or overdose) in 0.6 percent of patients after surgery [52]. The total duration of opioid prescription was the strongest predictor of misuse. Each prescription refill was associated with a 44 percent increase in the rate of misuse, and each additional week of opioid use increased the risk of misuse by 20 percent. While the risk of opioid misuse after surgery is low, the absolute number of patients affected is large because of the volume of surgery performed. (See "Prescription of opioids for acute pain in opioid naïve patients", section on 'Risk of long-term opioid use'.)

Hypersensitivity reactions with rolapitant (January 2018)

Rolapitant is a neurokinin-1 receptor antagonist used, in combination with other antiemetic agents, to prevent delayed nausea and vomiting associated with cancer chemotherapy. Postmarketing reports have surfaced about anaphylaxis, anaphylactic shock, and other serious

hypersensitivity reactions in patients receiving intravenous rolapitant emulsion, which is in soybean oil, occurring during or soon after drug infusion [55]. Clinicians are advised to watch for signs of hypersensitivity or anaphylaxis during and following administration of rolapitant, and to ask patients prior to the first dose if they are allergic to legumes. Patients with known allergies to soybeans, legumes, or other related allergens (including peanuts) should be monitored especially closely. If any serious reaction occurs, rolapitant should be immediately and permanently discontinued. (See "Prevention and treatment of chemotherapy-induced nausea and vomiting in adults", section on 'Rolapitant'.)

Perioperative timing of infliximab and risk of infection (December 2017)

There have been conflicting data regarding the increased risk of postoperative infection associated with perioperative use of tumor necrosis factor (TNF) inhibitors. One of the largest retrospective reviews to evaluate the association between the timing of infliximab infusion and rates of serious infection after elective hip or knee arthroplasties included over 4200 patients with autoimmune diseases [56]. Administration of infliximab within four weeks before surgery was not associated with a higher risk of postoperative infection or prosthetic joint infection within one year when compared with no administration for 8 to 12 weeks prior to surgery. However, until more data are available confirming the relative safety of these agents in the perioperative period, we generally suggest withholding TNF inhibitors as close to one dosing cycle as scheduling permits prior to elective surgery. (See "Preoperative evaluation and perioperative management of patients with rheumatic diseases", section on 'Biologic DMARDs'.)

Acetaminophen use in pregnancy and risk of attention-deficit/hyperactivity disorder (November 2017)

Epidemiologic studies have reported an association between in utero acetaminophen exposure and subsequent development of attention-deficit/hyperactivity disorder (ADHD)-like behaviors, but data are inconclusive. Now, a study from Norway that adjusted for maternal use of acetaminophen before pregnancy, familial risk of ADHD, and indications for using acetaminophen reported no association between ADHD and use <8 days, but an increased risk with use >29 days [58]. Moreover, paternal and maternal use of acetaminophen were similarly associated with ADHD risk. The authors hypothesized that paternal acetaminophen use before pregnancy may have male germ-line epigenetic effects. These data may reassure pregnant women with fever or pain who are considering short-term use of acetaminophen. (See "Prenatal care: Patient education, health promotion, and safety of commonly used drugs", section on 'Acetaminophen'.)

Acetylcysteine does not prevent contrast nephropathy (November 2017)

Radiocontrast media may cause acute kidney injury (AKI) among high-risk patients. Earlier studies have been inconsistent but indicated that the administration of oral acetylcysteine may decrease the risk of AKI, and led to our previous suggestion to administer acetylcysteine before and the day of angiography to patients at risk of contrast nephropathy. A recent randomized trial in over 5000 patients at increased risk for nephropathy who were undergoing scheduled angiography found that oral acetylcysteine, compared with placebo, did not prevent death, need for dialysis, or decline in kidney function [60]. The trial was a 2 by 2 factorial design and also compared intravenous sodium bicarbonate with isotonic saline, finding no benefit for sodium bicarbonate. UpToDate recommends giving isotonic saline rather than sodium bicarbonate and now suggests not giving acetylcysteine prior to angiography. (See "Prevention of contrast nephropathy associated with angiography", section on 'Acetylcysteine'.)

Frequency for dosing of oral iron (November 2017)

For many years, iron deficiency has been treated with oral iron given at least once per day, despite significant gastrointestinal side effects in the majority of individuals. A small, unblinded randomized trial has now demonstrated that giving oral iron every other day rather than every day resulted in greater iron absorption and fewer gastrointestinal side effects [61]. Alternate-day dosing is also supported by mechanistic studies that showed favorable effects on hepcidin, a negative regulator of intestinal iron absorption and iron release from macrophages. We now suggest that patients treated with oral iron for iron deficiency take the iron every other day rather than daily. (See "Treatment of iron deficiency anemia in adults", section on 'Dosing and administration (oral iron)'.) (Listen to UpToDate Talk podcast.)

VACCINES

Follow-up of infants born to women with chronic hepatitis B virus infection (February 2018)

Some infants born to women with chronic hepatitis B virus (HBV) infection remain susceptible to HBV at age 9 to 12 months despite perinatal immunoprophylaxis (table 4A-B). The Advisory Committee on Immunization Practices now suggests revaccination of these infants with a single dose of hepatitis B vaccine rather than a complete three-dose series, and then repeat serology (algorithm 1) [63]. This recommendation is supported by observational studies demonstrating that one additional dose induces protection in >94 percent of infants. Recommendations in UpToDate have been revised to reflect this change. (See "Hepatitis B virus immunization in infants, children, and adolescents", section on 'Infants'.)

Influenza vaccination in individuals with egg allergy (December 2017)

Numerous studies have demonstrated that egg-based influenza vaccines are safe in individuals with egg allergy, resolving longstanding concerns about an increased risk of allergic reactions to the vaccine in this population. Accordingly, the 2017 update of guidelines from the American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma, and Immunology (ACAAI) Joint Task Force on Practice Parameters no longer recommends inquiring about egg allergy before influenza vaccine administration [70]. Individuals with egg allergy of any severity should undergo yearly influenza vaccination administered in the usual manner according to standard indications and contraindications, without special precautions. Our approach is consistent with these guidelines. (See "Influenza vaccination in individuals with egg allergy", section on 'Vaccine choice'.)

New adjuvanted recombinant hepatitis B vaccine (November 2017)

Hepatitis B vaccination is the best way to prevent hepatitis B virus transmission. Available nonadjuvanted recombinant vaccines are effective and extremely safe, although they require three doses and 5 to 10 percent of patients do not respond. In November 2017, the US Food and Drug Administration granted conditional approval of a new adjuvanted vaccine (HEPLISAV-B) for adults 18 years and older [71]. This vaccine, given in two doses, appears more

immunogenic than the nonadjuvanted vaccines and is generally well tolerated. However, there are ongoing safety concerns regarding a potentially increased risk of acute myocardial infarction and immune-mediated disorders, which will be further evaluated in a phase 4 study. The optimal use of this vaccine is thus still to be determined. (See "Hepatitis B virus vaccination".)