New MRSA Treatment Guidelines from IDSA

In February 2011, the Infectious Disease Society of America (IDSA) published its first guideline on the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections for both adults and children. These recommendations contain information regarding a number of different clinical syndromes associated with MRSA, dosing and monitoring of vancomycin, and the treatment of MRSA strains with reduced susceptibility to vancomycin. Daptomycin dosing is indication-specific and noted below; other agents are given in fixed doses.

Skin and Soft Tissue Infections

As a common theme for all MRSA-related infections, the guideline emphasizes the importance of incision and drainage as the primary treatment of skin and soft tissue infections (SSTIs). Antimicrobial therapy is only recommended for SSTIs that are severe or extensive, or in patients with an increased risk of systemic illness (eg, comorbidities, immunosuppression, extremes of age, septic phlebitis) or ineffective incision and drainage.

For outpatient treatment of purulent SSTIs, empiric therapy for community-acquired MRSA (CA-MRSA) is recommended; coverage for β-hemolytic streptococci is likely unnecessary. In contrast, outpatients with non-purulent cellulitis should receive empiric treatment for β-hemolytic streptococci. In both cases, antibiotic therapy should be continued for a total of 5 to 10 days. The following oral antibiotics are recommended for empiric treatment of purulent CA-MRSA SSTIs: clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), a tetracycline (eg, doxycycline or minocycline), or linezolid. Appropriate empiric treatment of β-hemolytic streptococci in non-purulent SSTIs is the same as CA-MRSA except that TMP-SMX, doxycycline, and minocycline should be administered with a β-lactam antibiotic such as amoxicillin.

Complicated SSTIs (cSSTIs) are defined as infected surgical/trauma wounds, burns or ulcers, major abscesses, cellulitis, and deeper tissue infections. Inpatient treatment of a cSSTI should consist of one of the following intravenous (IV) antibiotics for a total duration of 7 to 14 days: vancomycin, linezolid, daptomycin (4 mg/kg IV once daily), telavancin, or clindamycin.

In hospitalized children, vancomycin is the preferred treatment for SSTIs. Clindamycin should only be considered in patients without bacteremia and in hospitals with a clindamycin resistance rate less than 10%. Linezolid is also an alternative therapeutic option in children with cSSTIs. Tetracyclines should not be used in children <8 years of age, and TMP-SMX should not be used in infants <2 months old.

The guideline describes recommendations for the management of recurrent SSTIs, primarily emphasizing the importance of wound care and hygiene. In patients with recurrent SSTIs despite environmental control measures, decolonization may be a consideration but is not strongly recommended. Decolonization may include nasal regimens (eg, mupirocin twice daily for 5 to 10 days), topical body regimens (eg, skin antiseptic solution for 5 to 14 days), or dilute bleach baths; oral antimicrobial therapy should not be routinely used for decolonization.

Bacteremia and Endocarditis

Appropriate therapy for bacteremia is classified based on the severity of the infection. Uncomplicated bacteremia is defined as a positive blood culture, no implanted prostheses (eg, prosthetic valves, cardiac devices, arthroplasties), sustained negative blood cultures 2 to 4 days after an initial set of negative cultures, defervescence within 72 hours of starting effective therapy, and no evidence of metastatic infection (including endocarditis). Complicated bacteremia is defined as a positive blood culture not meeting criteria for uncomplicated bacteremia.
For treatment of uncomplicated bacteremia, vancomycin or daptomycin (6 mg/kg IV once daily) for at least 2 weeks is recommended. In contrast, patients with complicated bacteremia should be treated for 4 to 6 weeks, and some experts recommend a higher dose of daptomycin in such cases (8 to 10 mg/kg IV once daily). In addition, all patients with complicated or uncomplicated MRSA bacteremia should undergo evaluation for endocarditis.

Patients with native-valve endocarditis should receive vancomycin or daptomycin (6 mg/kg IV once daily) for 6 weeks. Similar to other complicated bacteremias, some experts recommend a higher daptomycin dose of 8 to 10 mg/kg IV once daily. Gentamicin and rifampin should not be used in combination with vancomycin in patients with native-valve endocarditis; however, this strategy is recommended for prosthetic valve infective endocarditis in combination with first-line agents. In addition, patients with prosthetic valves should undergo early evaluation for valve replacement surgery.

In children with bacteremia or infective endocarditis, vancomycin for 2 to 6 weeks is recommended. Alternatively, daptomycin 6 to 10 mg/kg IV once daily for 2 to 6 weeks can be used. Clindamycin or linezolid should only be used for uncomplicated bacteremias. Data are lacking regarding combination therapy with first-line agents and rifampin or gentamicin in children.

**Pneumonia**
Empiric MRSA coverage should be provided to patients with severe community-acquired pneumonia, defined as a need for intensive care, necrotizing or cavitary infiltrates, or empyema. Appropriate therapy for both healthcare-associated and CA-MRSA pneumonia includes vancomycin, linezolid, or clindamycin for a total duration of 7 to 21 days. Children with MRSA pneumonia should receive vancomycin; linezolid can also be used. Clindamycin should be reserved for pediatric patients without bacteremia and in hospitals with a clindamycin resistance rate less than 10%.

**Bone and Joint Infections**
As with SSTIs, surgical debridement and drainage of abscesses or joint spaces are the mainstays of therapy for bone and joint infections. Appropriate empiric therapy includes: vancomycin, daptomycin (6 mg/kg IV once daily), linezolid, clindamycin, or combination therapy with TMP-SMX and rifampin. For the treatment of osteomyelitis, a minimum of 8 weeks of therapy is recommended; however, some experts suggest an additional 1 to 3 months or longer of rifampin-combination therapy if debridement is not performed. For the treatment of septic arthritis, a shorter duration of 3 to 4 weeks can be used.

Patients with a device-related joint infection should receive IV antibiotic therapy plus rifampin for 2 weeks, followed by oral rifampin combination therapy for 3 months (prosthetic hips) or 6 months (prosthetic knees). Long-term oral suppressive antibiotics may be considered in certain cases, particularly if device removal is not possible, debridement is not performed, or inflammatory markers (eg, erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) remain elevated. Recommended long-term oral suppressive agents include TMP-SMX, a tetracycline, a fluoroquinolone, or clindamycin. Long-term suppressive agents may also be given in combination with rifampin. When a fluoroquinolone is used, concurrent rifampin is strongly recommended due to the potential for fluoroquinolone resistance.

For children with hematogenous MRSA osteomyelitis or septic arthritis, vancomycin is recommended; however, clindamycin may also be used if the incidence of clindamycin resistance is low (eg, <10%) and the patient is clinically stable. Duration of therapy is individualized, but a minimum of 3 to 4 weeks for septic arthritis or 4 to 6 weeks for osteomyelitis is typical.

**Central Nervous System Infections**
The IDSA MRSA guideline recommends vancomycin with or without rifampin for a total duration of 2 weeks for meningitis, or 4 to 6 weeks for central nervous system abscesses or septic thrombi. Alternative therapies include linezolid or IV TMP-SMX. As with other infections, foreign materials such as shunts should be removed and not be replaced until cerebrospinal fluid cultures are negative.

**Vancomycin Dosing and Monitoring**
The recommendations for vancomycin dosing and monitoring are based on the consensus statement published by the American Society of Health-System Pharmacists, IDSA, and the Society of Infectious Disease Pharmacists. Although controversial, monitoring of serum vancomycin concentrations is advocated to predict and prevent drug-induced toxicity and to ensure appropriate dosing.

For patients with normal renal function, the guideline recommends vancomycin 15 to 20 mg/kg (based on actual body weight) every 8 to 12 hours, not to exceed 2000 mg per dose. In seriously ill patients (eg, those with sepsis, meningitis, pneumonia, and infective endocarditis), a loading dose of 25 to 30 mg/kg (actual body weight) with a prolonged, 2-hour infusion may be considered. Additionally, an antihistamine may be used prior to the administration of a loading dose to reduce the risk of red man syndrome and possible anaphylaxis. Pediatric patients with serious or invasive disease should receive vancomycin 15 mg/kg every 6 hours.

The guideline recommends monitoring a vancomycin trough concentration prior to the fourth or fifth dose after initiation or a dosage change. Peak concentrations should not be routinely monitored. For less severe infections, the goal trough is 10 to 15 mcg/mL. For severe MRSA infections (eg, bacteremia, endocarditis,
osteomyelitis, meningitis, pneumonia, and severe SSTI), a goal trough concentration of 15 to 20 mcg/mL is recommended in order to improve tissue penetration and minimize selection of resistant bacterial strains. Trough concentrations may be especially important in patients with severe infections, morbid obesity, renal dysfunction, fluctuating volumes of distribution, or those receiving dialysis. Although not well studied, a goal trough concentration of 15 to 20 mcg/mL should also be considered in pediatric patients with severe infections.

Although trough monitoring is recommended in most cases, non-obese patients with an SSTI and normal renal function may receive a traditional dose of 1 g every 12 hours without trough concentration monitoring.

**Vancomycin Susceptibility Testing**

In patients with poor clinical or microbiological responses to vancomycin despite debridement and removal of other foci of infection, an alternative therapeutic agent should be used regardless of the vancomycin minimum inhibitory concentration (MIC). For isolates with a vancomycin MIC >2 mcg/mL, an alternative to vancomycin should be used empirically.

**Summary**

The 2011 IDSA MRSA guideline presents a wide variety of recommended antimicrobial therapies. Due to the increasing incidence of MRSA infections, appropriate treatment is especially relevant. Clinicians should be aware of these new recommendations, as well as the clinical evidence supporting each recommendation, in order to provide optimal antimicrobial therapy to patients with MRSA infections.

**Atrial Fibrillation Update: Guidelines, Dronedarone, and Dabigatran**

Recently, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) published a focused update to their 2006 guidelines for the management of atrial fibrillation (AF). The 2011 focused update provides clinicians with the most recent data from the 2009 annual scientific meetings of the ACC, AHA, and European Society of Cardiology, as well as more recent data available through April 2010. The major drug-related changes from the focused update are summarized below.

**Combining Clopidogrel with Aspirin for Thromboembolism Prophylaxis**

Historically, warfarin has been the drug of choice for preventing thromboembolism in patients with AF and has proven to be superior to aspirin in clinical trials. Two recent trials evaluated the effectiveness of clopidogrel plus aspirin for stroke prevention.

The ACTIVE-W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) trial was a noninferiority study that compared clopidogrel plus aspirin versus warfarin for prevention of vascular events in patients with AF and an average of 2 stroke risk factors. The primary outcome was the first occurrence of stroke, non-central nervous system systemic embolism, myocardial infarction, or vascular death. The relative risk (RR) of achieving the primary endpoint with clopidogrel plus aspirin was 1.44 (95% confidence interval [CI] 1.18 to 1.76; p=0.0003; number needed to treat [NNT] 47). Rates of major hemorrhage were similar between groups; however, significantly more minor and total bleeds occurred in the clopidogrel plus aspirin group. The trial was stopped early due to overwhelming evidence showing the superiority of warfarin over clopidogrel plus aspirin.

The ACTIVE-A (Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation) trial investigated the potential benefit of adding clopidogrel to aspirin in patients considered unsuitable for warfarin therapy. Reasons patients were deemed unsuitable for warfarin included a specific risk of bleeding (22.9%), patient preference (26%), or physician preference (49.7%). The primary outcome was a composite of stroke, myocardial infarction, non-central nervous system systemic embolism, or death from vascular causes. Patients in this study were 70 years of age, had a mean CHADS2 score of 2, and the majority had permanent AF with a duration >2 years. Major vascular events occurred at a rate of 6.8% per year in the clopidogrel group and 7.6% per year in the placebo group after a median follow-up period of 3.6 years (RR with clopidogrel 0.89; 95% CI 0.81 to 0.98; p=0.01). The benefit seen with clopidogrel was largely due to its reduction in strokes. Major hemorrhage occurred in 251 patients (2% per year) in the clopidogrel group and 162 patients (1.3% per year) in the aspirin group. Treating 143 patients with clopidogrel for 1 year will result in 1 major hemorrhage (severe or fatal) and treating 200 patients will prevent 1 disabling or fatal stroke.

Overall, the addition of clopidogrel to aspirin to reduce the risk of major vascular events, including stroke, might be considered in patients with AF in whom oral anticoagulation with warfarin is considered unsuitable due to patient preference or the physician’s assessment of the patient’s ability to safely sustain anticoagulation.

**Dabigatran for Thromboembolism Prophylaxis**

In October 2010, the Food and Drug Administration (FDA) approved dabigatran (Pradaxa), a new oral direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular AF. Therefore, dabigatran is the first oral direct thrombin inhibitor to reach the market since the failure of ximelagatran because of its associated serious liver toxicity. Dabigatran etexilate is a prodrug that is rapidly absorbed and converted to its active moiety, dabigatran, by esterase-catalyzed hydrolysis in the plasma and liver. After administration, the drug reaches peak plasma levels within 1 to 2 hours; maximum prolongation of blood coagulation activity occurs once the peak concentration is achieved. Dabigatran is minimally protein bound (35%),
is not a substrate, inhibitor, or inducer of CYP enzymes and is primarily excreted renally (80%). Although drug interactions via the cytochrome (CYP) system do not appear to be an issue with this agent, dabigatran is an efflux P-glycoprotein substrate, so agents that impact this pathway may be a concern. There are no dietary interactions with the drug.

Dabigatran is given as a fixed-dose with no titration, and does not require any special monitoring. It is dosed at 150 mg twice daily for patients with a creatinine clearance (CrCl) >30 mL/min, and the agent needs to be dose adjusted for patients with a CrCl between 15 and 30 mL/min (75 mg twice daily). There are no dosing recommendations for patients with a CrCl <15 mL/min or for patients receiving dialysis. The prescribing information has specific guidance on how to convert patients from warfarin to dabigatran and from dabigatran to warfarin. Patients can be converted to dabigatran from warfarin once the international normalized ratio (INR) is <2. When converting from dabigatran to warfarin, the initiation of warfarin is dependent upon CrCl. Dabigatran should be discontinued 1 to 2 days (CrCl ≥50 mL/min) or 3 to 5 days (CrCl <50 mL/min) before an invasive or surgical procedure. The prescribing information also has specific information on converting patients to or from parenteral anticoagulants.

Dabigatran is contraindicated in patients with active pathological bleeding or in those with a history of a serious hypersensitivity reaction to the drug. In addition, dabigatran increases the risk of bleeding, especially when used in combination with other medications that increase this risk such as antiplatelet agents, heparin, and non-steroidal anti-inflammatory drugs (NSAIDs).

The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial was the largest trial conducted with dabigatran in patients with AF. The trial randomized 18,113 patients with AF who were at high risk for stroke to 1 of 3 treatment groups: dabigatran 110 mg twice daily, dabigatran 150 mg twice daily, or unblinded, adjusted-dose warfarin to maintain an INR between 2 and 3. Patients were followed for a median duration of 2 years, and during the study period the INR was within therapeutic range 64% of the time in patients treated with dose-adjusted warfarin. Baseline characteristics were similar between groups with patients having a mean age of 71.5 years, majority being male (63.6%), and having a mean CHADS2 score of 2.1.

The primary outcome of stroke or systemic embolism occurred at a similar rate for the dabigatran 110 mg (1.53% annually) and warfarin groups (1.69% annually), but was lower in the dabigatran 150 mg group (1.11% annually). Statistically, both dabigatran doses were noninferior to warfarin for the primary outcome, and the dabigatran 150 mg dose was also superior to warfarin (RR 0.66; 95% CI 0.53 to 0.82; p<0.001). Rates of hemorrhagic stroke were lower in both dabigatran groups (0.12% annually for 110 mg and 0.10% annually for 150 mg) compared with the warfarin group (0.38% annually, p<0.001 for both dabigatran doses); however, mortality was similar among the groups (range 3.64% to 4.13% annually).

Major bleeding occurred at a similar rate for the dabigatran 150 mg and warfarin groups (3.11% and 3.36% annually, respectively, p=0.31) but was lower in the dabigatran 110 mg group (2.71% annually, p=0.003 compared to warfarin). Dyspepsia occurred more frequently in dabigatran-treated patients, occurring in 11.8% of the 110 mg and 11.3% of the 150 mg groups compared with 5.8% of patients in the warfarin group. The annual rate of myocardial infarction was also higher in the dabigatran groups (0.72% for 110 mg [p=0.07], 0.74% for 150 mg [p=0.048]) compared with warfarin (0.53%). The investigators concluded that dabigatran, administered at a dose of 150 mg twice daily was associated with lower rates of stroke and systemic embolism compared to warfarin, and had a similar rate of major bleeding.

In addition to patients with AF, dabigatran has also been evaluated in numerous trials for prevention of venous thromboembolism (VTE) after orthopedic surgery and treatment of acute VTE. The data showed that dabigatran was noninferior to enoxaparin in 2 prevention trials (RE-MODEL and RE-NOVATE), but inferior to enoxaparin in a third trial (RE-MOBILIZE). For treatment of acute VTE, dabigatran was found to be noninferior to warfarin with a similar safety profile (RE-COVER).

The ACCF/AHA 2011 focused guideline update was modified on February 15, 2011. The modified update states that dabigatran is a useful alternative to warfarin for prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (defined as a CrCl of <15 mL/min), or advanced liver disease (characterized as impaired baseline clotting function). Because of the twice-daily dosing and greater risk of nonhemorrhagic adverse events with dabigatran, patients receiving warfarin with “excellent” INR control may have little to gain by switching to this agent. Overall, the guidelines recommend that numerous factors be considered before switching from warfarin to dabigatran, such as individual clinical features, adherence to twice-daily dosing with dabigatran versus routine INR monitoring visits for warfarin, patient preference, and cost.

**Dronedarone for the Prevention of Recurrent AF**
Dronedarone (Multaq) is a new antiarrhythmic agent that received FDA approval in July 2009. Dronedarone was developed in hopes of having a similar efficacy profile but an improved safety profile compared to amiodarone. Structural modifications made to the dronedarone molecule include the removal of the iodine moiety and the addition of a methyl sulfonylamyl group. These modifications result
in a decreased lipophilicity and thus shorter half life (13 to 19 hours versus 58 days with amiodarone) and less tissue accumulation than amiodarone. Its metabolism via CYP 3A4 has potential for drug-drug interactions. The pharmacologic action of dronedarone is due to inhibition of the L-type calcium current, the inward sodium current, multiple potassium currents, and antiadrenergic actions. In clinical trials, dronedarone has been shown to decrease ventricular rate in AF by 11 to 13 beats per minute. Spontaneous conversion to sinus rhythm with dronedarone is a dose dependent effect.

The DIONYSOS (Efficacy and Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Persistent Atrial Fibrillation) study found dronedarone to be less effective than amiodarone. The composite primary endpoint was recurrence of AF (including unsuccessful electrical cardioversion, no spontaneous conversion, and no electrical cardioversion) or premature study discontinuation which was achieved in 75.1% of study subjects in the dronedarone group versus 58.8% in the amiodarone group at 12 months (hazard ratio 1.59; 95% CI 1.28 to 1.98; p<0.0001). The study found no significant differences in the main safety endpoints; however, there were fewer thyroid, neurologic, dermatologic, and ocular events in the dronedarone group.

The ATHENA trial (a placebo-controlled, double-blind, parallel arm trial to assess the efficacy of dronedarone 400 mg twice daily in patients with AF/atrial flutter) found dronedarone to be superior in reducing the primary composite endpoint of death and cardiovascular hospitalizations. It should be noted that the effectiveness of dronedarone in this trial was mainly due to its reduction in hospitalizations due to AF and cardiovascular death, not all-cause death or maintenance of sinus rhythm.

The ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease) found that dronedarone increased mortality in patients with recently decompensated heart failure and depressed LV function. Based on these data, dronedarone now has a boxed warning restricting its use in patients with New York Heart Association (NYHA) class IV heart failure or class II to III heart failure with a recent decompensation.

Other safety issues with dronedarone include the major cardiac adverse effects of bradycardia and QT prolongation. Torsades de pointes has been reported as well. Like amiodarone, dronedarone is associated with increases in serum creatinine due to inhibition of renal tubular secretion of creatinine, although glomerular filtration rate is unaffected. Concurrent administration with warfarin does not alter the INR; however, concurrent administration with digoxin results in 1.7 to 2.5-fold increased digoxin levels. Although not mentioned in the 2011 focused update, the FDA Medwatch program recently issued a drug safety communication on January 14, 2011 concerning dronedarone and 2 case reports of liver failure leading to transplantation.

The ACCF/AHA 2011 focused guideline update states that use of dronedarone is reasonable to decrease the need for hospitalization for cardiovascular events in patients with paroxysmal AF or after conversion of persistent AF. Dronedarone can be initiated during outpatient therapy. Dronedarone should not be administered to patients with NYHA class IV heart failure or patients who have had an episode of decompensated heart failure in the past 4 weeks, especially if they have depressed left ventricular function (left ventricular ejection fraction ≤35%).

**Summary**

The 2011 ACCF/AHA guideline update on management of AF provides recommendations for several drug therapy options. Thromboembolism prophylaxis with clopidogrel and aspirin appears to be inferior to warfarin but can be considered in patients for whom warfarin therapy is clinically inappropriate. Dabigatran, a recently-approved oral direct thrombin inhibitor, was superior to warfarin in the RE-LY study for prevention of thromboembolic events in patients with AF when given at a dose of 150 mg twice daily, resulted in fewer hemorrhagic strokes, and had a similar incidence of major bleeding. Dabigatran is a promising alternative to warfarin for thromboembolism prophylaxis in patients with AF who do not have significant valvular disease/valve replacement, CrCl <15 mL/min, or coagulopathy due to liver disease. Dronedarone was less effective when compared to amiodarone in the DIONYSOS study and was associated with fewer adverse effects; however, recent reports of liver toxicity have brought dronedarone’s safety and place in therapy into question.

**FDA Limit of 325 mg for Acetaminophen-containing Products**

In January 2011 the FDA issued a notice to healthcare providers regarding its decision to limit the amount of acetaminophen in prescription products, including combination products with opioids, to 325 mg per dosage form. In addition, a boxed warning discussing the potential for liver injury with acetaminophen use will be added to the product labeling, and a warning will be added regarding the risk of allergic reactions including anaphylaxis. Prescription product manufacturers must comply with these changes within 3 years of the original notice (eg, by January 2014). Over-the-counter (OTC) acetaminophen products will not be affected, since the approved OTC labeling already contains a warning about the risk of hepatotoxicity and OTC manufacturers will not be required to limit acetaminophen content of their formulations.

According to the FDA, although the amount of acetaminophen included in each tablet or capsule may decrease (eg, from 500 mg to 325 mg), the number of dosage forms per dose and the recommended dosing intervals will not change. For example, a product given as 1 to 2 tablets every 4 to 6 hours will have the same
directions after the formulation change. The maximum daily acetaminophen dose will continue to be 4 grams.

The goal of limiting the amount of acetaminophen in prescription products is to maintain patient access to acetaminophen-containing analgesic medications while minimizing the potential for liver injury. Several factors may contribute to the development of liver injury with acetaminophen therapy, including availability of both prescription and OTC formulations, multiple dosage forms with a variety of dosing instructions, and inconsistent labeling of the active ingredient (eg, APAP versus acetaminophen). Patients may inadvertently take multiple acetaminophen-containing products, or take a single product incorrectly, resulting in a supratherapeutic dose. Combination products with opioid analgesics may be most likely to contribute to toxicity if patients self-titrate doses with a desire for better pain relief from the opioid without realizing the product also contains acetaminophen. Limiting the amount of acetaminophen in these combination products to 325 mg may prevent unintended supratherapeutic exposures; however, OTC products with higher doses will be available and could still contribute to misuse.

**Risk of Liver Injury with Acetaminophen: Clinical Evidence**

The FDA’s concern about the potential for liver toxicity with acetaminophen therapy is based on several cohort studies in patients with acute liver failure. Nourjah and colleagues published an estimated prevalence of acetaminophen overdoses in 2006 which was based on compiled data from several national surveillance reports (National Hospital Ambulatory Medical Care Survey, National Electronic Injury Surveillance System All Injury Program, National Hospital Discharge Survey, National Multiple Cause of Death File, Toxic Exposure Surveillance System, and the FDA Adverse Event Reporting System). Acetaminophen-related data included poisonings reported to poison control centers, emergency department (ED) visits for overdose, hospital discharges for overdose, and deaths due to overdose. Annually, acetaminophen overdose accounted for 56,000 ED visits, more than 26,000 hospital admissions, 112,000 calls to poison control centers, and 450 deaths. Of the overdoses that resulted in an ED visit, 23% were unintentional and 56% were intentional; the intention could not be determined in 20% of cases. Similarly, 26% of cases resulting in death were unintentional and 55% of cases results in death were intentional overdoses. Of the 198 cases of unintentional overdose reported to the FDA between 1998 and 2001, 55 (27%) occurred after ingestion of more than one acetaminophen product, usually a non-prescription product and an opioid combination product. Formulations containing 500 mg acetaminophen were implicated with double the frequency of those containing 325 mg.

In 2002, the US Acute Liver Failure Study Group published a prospective observational study of 308 patients with acute liver failure admitted to 17 liver centers between 1998 and 2001. The study aim was to describe the causes and outcomes of patients with acute liver failure in the U.S. Acute liver failure was defined as prothrombin time >15 seconds or INR ≥1.5 and evidence of encephalopathy within 26 weeks of the first symptoms. In contrast to historical trends that identified hepatitis as the most common cause of acute liver failure, this study found that acetaminophen overdose was the most prevalent etiology, accounting for 120 (39%) cases. Of these cases, 37% reportedly overdosed on acetaminophen with suicidal intent and 57% inadvertently took supratherapeutic doses. Ninety nine patients (83%) who experienced an acetaminophen overdose were taking more than the maximum dose of 4 g/day; the median dose ingested was 13.2 g/day. A majority of patients with acute liver failure attributed to acetaminophen survived without transplant (68%), which was much higher than the survival in other groups (17% to 33%). The authors concluded that acetaminophen is implicated in a large number of acute liver failure cases in the U.S., and is more common than any other etiology; however, the validity of this conclusion has been questioned based on the study’s broad inclusion criteria and the potential sample bias of patients admitted to tertiary care liver centers with liver transplant programs.

The Acute Liver Failure Study Group published another multicenter cohort study in 2005 of 275 patients with acetaminophen-induced liver failure enrolled in the group’s registry from 1998 to 2003. The proportion of acute liver failure cases attributed to acetaminophen increased during the study period from 28% to 51%. Cases were stratified by reason for ingestion: suicidal intent (44%) and unintentional ingestion (48%). Detailed evaluation of patient records revealed that 56% of patients had a potentially toxic acetaminophen ingestion and 77% had detectable serum acetaminophen levels. About half (53%) reported only ingesting non-prescription acetaminophen products, and 44% ingested opioid-acetaminophen combination products. Use of combination prescription products was more common in the unintentional ingestion group than the group with suicidal intent (63% vs. 18%, p<0.0001). Most patients (65%) survived without transplant. The authors concluded that cases of acute liver failure due to acetaminophen have dramatically increased, and that many cases are due to potentially preventable unintentional ingestions. Since the definition of acute liver failure used in this study was the same as in the 2002 study, the validity of this conclusion may also be limited.

The first population-based observational study of acute liver failure was published by Bower and colleagues in 2007. Medical records of patients admitted for acute liver failure during a 3-year period to tertiary care centers and community hospitals were reviewed. Using the same definition of acute liver failure reported in the Acute Liver Failure Study Group studies, 65 patients (49 adults and 16 children) were identified. Acetaminophen was the most common cause of liver failure in adult patients (46%).
and the second most common cause in pediatric patients (25%) after undetermined causes (38%). Of the adult overdoses, 45% were reported as intentional and 55% were unintentional. Seventy two percent of patients were admitted to tertiary care centers, with the large majority of these (91%) transferred from community hospitals. Based on the total number of acute liver failure cases observed during the study, the authors estimated that 1600 cases of acute liver failure occur annually in the U.S., with acetaminophen accounting for almost half of adult cases.

Summary
It has been estimated that 100 million Americans (36% of the population) ingest an acetaminophen-containing product every month. Although potentially fatal liver toxicity has been reported with both intentional and unintentional supratherapeutic acetaminophen ingestion, the small number of documented cases compared to the large number of patients exposed to this drug highlight the safety of acetaminophen in the general population. Factors that may place a patient at risk for acetaminophen-related liver toxicity include alcohol abuse, concurrent hepatitis infection or existing liver disease, advanced age, limited dietary glutathione intake, and concurrent use of other hepatotoxic medications. Regardless of the acetaminophen content of the product used, clinicians should ensure that patients understand the dosing directions, are aware of the maximum daily dose recommendations to minimize the potential for liver toxicity, and are instructed to avoid concurrent alcohol use.

P&T Committee Formulary Action

Additions
- Dabigatran - Use restricted to prevention of thromboembolic disorder in patients with non-valvular A.fib at a dose of 150 mg BID for patients with CrCl >30 mL/min and patients on dabigatran prior to admission.

Deletions
- Thiopental

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