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Antiplatelet therapy and GI risk

Strategies for primary and secondary prevention of cardiovascular events constitute a multitude of interventions including use of antiplatelet therapy. Commonly used antiplatelet agents include aspirin (ASA) and clopidogrel. Although their cardiovascular benefits are well known, the gastrointestinal (GI) risks of using antiplatelet therapy with non-steroidal anti-inflammatory drugs (NSAIDs) or in high risk patients are less well recognized and/or addressed. In conjunction with the American College of Gastroenterology (ACG) and the American Heart Association (AHA), the American College of Cardiology (ACC) has published a consensus document on identifying and reducing GI risk associated with antiplatelet therapy.

Identifying risk

As defined by the consensus document, upper gastrointestinal events (UGIE) include symptomatic ulcer (dyspepsia along with an ulcer) or ulcer complications such as bleeding or perforation. For patients receiving antiplatelet therapy, risk factors for UGIE include:

- history of ulcer disease or complications
- dual antiplatelet therapy
- concomitant anticoagulant therapy
- NSAID or cyclo-oxygenase 2 (COX-2) inhibitor use

And/or more than 1 of the following:

- age \geq 60 years
- corticosteroid use
- dyspepsia or gastroesophageal reflux disorder (GERD)

Aspirin and NSAIDs cause local irritation to the GI tract and systemic effects through reduction in the production of GI protective prostaglandins via inhibition of COX-1 and 2 enzymes. A COX-2 inhibitor, such as celecoxib, selectively blocks the COX-2 enzyme leading to the reduction in prostaglandins involved in pain, inflammation and fever and spares the COX-1 enzyme involved in producing GI protective prostaglandins. Some evidence

suggests gastric ulceration may require inhibition of both COX-1 and COX-2 enzymes. Therefore, the addition of aspirin to a COX-2 inhibitor potentially negates any reduced GI risk associated with use of a COX-2 inhibitor. Although clopidogrel does not cause direct injury to the GI mucosa, it does interfere with angiogenesis involved in repair and healing of erosions and ulcers. Similarly, anticoagulants do not cause direct GI ulceration but can exacerbate existing GI lesions caused by aspirin, NSAIDs or *Helicobacter pylori* infection. Table 1 below provides a description of the UGIE and bleeding risks associated with antiplatelet therapy alone and in combination with other agents.

Table 1. Description of UGIE and bleeding risks.

Medication	Description of risk
Aspirin alone	2- to 4- fold increase in UGIE risk with low dose aspirin (\leq 325 mg/day); lower doses are associated with lower risk
Aspirin + NSAID	5.6% annual risk of UGIE; relative risk estimates for UGIE range from 3.8 to 5.6 compared to aspirin alone
Aspirin + COX-2	7.5% annual risk of UGIE
Aspirin + LMWH	50% increase in major bleeds compared to aspirin alone in ACS patients
Aspirin + warfarin	2-fold increase of major extracranial bleeding in ACS patients
Clopidogrel alone	One study demonstrated similar relative risk of upper GI bleeding with aspirin 100 mg/day (RR 2.7), clopidogrel (RR 2.8) and anticoagulants (RR 2.8) 13.6% of clopidogrel patients vs. 0% of aspirin + esomeprazole patients developed recurrent UGIE in patients with a previous history of UGIE due to aspirin
Clopidogrel + NSAID	Odds ratio of 7.4 for developing serious UGIE

UGIE=upper gastrointestinal events, NSAID=non-steroidal anti-inflammatory drug, COX-2=cyclooxygenase 2, LMWH=low molecular weight heparin, ACS=acute coronary syndrome, GI=gastrointestinal, RR=relative risk

Reducing risk

Gastrointestinal risk should be evaluated in all patients deemed to be candidates for antiplatelet therapy. When single antiplatelet therapy is required, aspirin 81 mg per day should generally be the antiplatelet agent and dose of choice unless a patient has a history of aspirin hypersensitivity. Patients on antiplatelet therapy who have a history of UGIE or are receiving concomitant anticoagulant, antiplatelet, NSAID or COX-2 therapy should receive gastroprotection with a proton pump inhibitor (PPI). Although misoprostol may be effective for preventing GI events in patients receiving aspirin plus either an NSAID or COX-2 inhibitor, its side effects (primarily diarrhea) limit its use. The guidelines do not recommend use of clopidogrel alone as an alternative to aspirin in patients with a history of UGIE since the combination of aspirin and a PPI has demonstrated superior efficacy in reducing GI events compared to clopidogrel alone. Prior to initiation of antiplatelet therapy, patients with a GI history should be tested and treated, if infected, for *H. pylori* infection. Other patient populations that qualify for addition of a PPI to antiplatelet therapy include those with 1 or more of the risk factors discussed above (ie, age \geq 60 years, corticosteroid use or dyspepsia). The guidelines also recommend a target International Normalized Ratio (INR) of 2 to 2.5 in patients started on warfarin that are also receiving aspirin and clopidogrel.

Although a reduction in the risk of UGIE may occur with concomitant use of clopidogrel and PPIs in high GI risk patients, there is some evidence to suggest that omeprazole may reduce the antiplatelet efficacy of clopidogrel. The Omeprazole Clopidogrel Aspirin (OCLA) study compared the effects of clopidogrel on platelet activity in post-stent patients receiving aspirin, clopidogrel and omeprazole to patients receiving aspirin and clopidogrel alone. Clopidogrel's effect on decreasing platelet activity was significantly reduced in patients receiving omeprazole compared to those who did not receive gastroprotection. On the other hand, a recent study found no decrease in clopidogrel's antiplatelet activity in patients undergoing percutaneous coronary intervention (PCI) that received either pantoprazole or esomeprazole. A retrospective review of an Aetna database compared the incidence of myocardial infarction (MI) in clopidogrel treated patients that received a PPI to those that did not receive PPIs. After adjusting for various cardiac risk factors, the MI rates were significantly higher in patients that received PPIs compared to those who did not (11.3% vs. 2.6%, $p < 0.05$). Another review of the Medco Integrated Database presented at a recent AHA meeting also found a greater number of cardiac events in patients receiving both a PPI and clopidogrel compared to patients on clopidogrel alone. In contrast, results of a subgroup analysis of patients from the CREDO (Clopidogrel for the Reduction of Events During Observation) study also presented at an AHA meeting found no increase in cardiac events in patients receiving a PPI and clopidogrel compared to clopidogrel alone. Based on conflicting data presented at the meeting, the ACC, AHA and ACG released a joint

statement suggesting that no changes in clinical practice can be recommended based on the limited and conflicting evidence available.

In late January 2009, the Food and Drug Administration (FDA) released an early communication regarding the need for further studies evaluating effects of genetic factors on clopidogrel efficacy as well as the drug interaction between PPIs and clopidogrel. The FDA at that time suggested clinicians reassess GI risk and the need for PPI use for patients prescribed clopidogrel and a PPI. Several recent reports have provided additional information on the potential interaction between proton PPIs and clopidogrel.

The hospitalization and death rates due to acute coronary syndrome (ACS) were evaluated in a retrospective cohort study of approximately 8200 Veterans Affairs (VA) patients prescribed clopidogrel with or without a PPI. Of the 5244 patients prescribed clopidogrel with a PPI, 1561 (29.8%) experienced death or hospitalization due to ACS compared to 615 of 2961 (20.8%) patients taking clopidogrel without a PPI. After adjusting for multiple variables, the use of clopidogrel and a PPI was found to be associated with an increased risk of hospitalization or death due to ACS compared to use of clopidogrel without a PPI (adjusted odds ratio, 1.25; 95% confidence interval [CI], 1.10 to 1.46). Of the secondary outcomes of all-cause mortality, revascularization procedures, and recurrent hospitalizations, the risk of the latter 2 were found to be significantly higher with concurrent clopidogrel and PPI use. In addition, no significant increased risk in outcomes was detected in patients who received only a PPI. Although close to 60% of the patients who received a PPI were prescribed omeprazole, the study was not designed to detect whether outcomes were related to a specific PPI.

A case control study evaluated the impact of PPI use on recurrent myocardial infarction in patients receiving clopidogrel within 3 days of hospital discharge. Cases were defined as those patients who were hospitalized for recurrent MI within 90 days of the first MI. Controls included patients who did not experience a recurrent event within 90 days. Over 13,000 post-MI patients filled a prescription for clopidogrel within 3 days of discharge. Of these patients, 734 cases and 2057 matched controls were identified. A greater number of cases were current users of a PPI compared to controls (26.4% vs. 20.6%) and PPI use was found to be significantly associated with recurrent MI (adjusted OR 1.27, 95% CI 1.03 to 1.57). No significant association was identified with pantoprazole use and recurrent MI (adjusted OR 1.02, 95% CI 0.70 to 1.47), which is in contrast to the association found with use of other PPIs including omeprazole, lansoprazole, or rabeprazole (adjusted OR 1.40, 95% CI 1.10 to 1.77). The authors explained this difference by the lack of pantoprazole's effect on cytochrome (CYP) 2C19.

Clopidogrel is a prodrug that requires activation by CYP P450 enzymes including the isoenzyme CYP2C19. Certain forms of the genes encoding for CYP2C19 have been shown to cause reduced function of this isoenzyme. This would theoretically lead to reduced enzymatic conversion of clopidogrel to its active form and, therefore, decreased antiplatelet activity. A recent study by Mega and colleagues reported approximately 30% of healthy subjects (n=162) administered clopidogrel carried a reduced function allele for CYP2C19. These patients demonstrated a 32% relative risk reduction in plasma exposure to the active form of clopidogrel compared to subjects who did not carry the reduced function allele (p<0.001). In addition, maximal platelet aggregation decreased by 9% in patients who carried the reduced function allele compared to non-carriers (p<0.001). The study also evaluated clinical outcomes in ACS patients who were randomized to receive clopidogrel in the TRITON-TIMI 38 study and who carried the reduced function allele. Of 1477 subjects in whom a sample was obtained, approximately 27% carried a CYP2C19 reduced function allele. Death from cardiovascular causes, myocardial infarction, or stroke was significantly higher in these patients compared to non-carriers (12.1% vs. 8%; hazard ratio for carriers 1.53, 95% CI 1.07 to 2.19; p=0.01).

A second study by Simon and colleagues further demonstrated a reduced response to clopidogrel in patients that carry variant alleles for genes involved in clopidogrel metabolism (CYP2C19). In this study, the 1 year rates of death, nonfatal MI, or stroke were determined for over 2200 French patients who were admitted for MI and discharged on clopidogrel. Two hundred ninety four patients experienced the primary outcome. Patients with 2 reduced function alleles of CYP2C19 had a higher rate of events compared to those who did not carry the alleles (21.5% vs. 13.3%; adjusted hazard ratio, 1.98; 95% CI, 1.10 to 3.58). However, outcomes were not significantly increased by concomitant PPI use.

The suggestion is that PPIs, such as omeprazole, that are also CYP2C19 inhibitors, may diminish the activation of clopidogrel and therefore, reduce plasma exposure to the active form of clopidogrel as well as its antiplatelet effect. However, what has not been confirmed in randomized controlled trials is whether CYP2C19 inhibition by PPIs or presence of reduced function alleles of CYP2C19 result in similar adverse clinical outcomes in patients who are taking clopidogrel. Although an increasing amount of data suggests a potential interaction between PPIs and clopidogrel, caution is still advised in interpreting these results due to limitations of retrospective and case control studies.

Summary

Assessment and management of GI risk are recommended when antiplatelet therapy for primary or

secondary cardiovascular disease prevention is initiated. Patients determined to be at risk for GI events should receive gastroprotection, preferably with a PPI. The antiplatelet agent of choice is low dose aspirin (81 mg per day). Clopidogrel alone is not sufficient at reducing GI risk in high-risk patients and is not considered an acceptable alternative to aspirin in patients with previous GI events. The addition of a PPI to aspirin is considered to have greater efficacy in reducing GI events compared to clopidogrel alone. Similarly, the use of a COX-2 inhibitor instead of an NSAID in patients receiving aspirin does not lower GI risk and gastroprotection is still recommended for patients receiving both aspirin and a COX-2 inhibitor. The guidelines do not specifically address the GI risk of concomitant clopidogrel and COX-2 inhibitor therapy or whether gastroprotection is required with such a regimen.

Preliminary evidence suggests a potential reduction in antiplatelet activity of clopidogrel when combined with certain PPIs. If patients receiving clopidogrel are determined to be at high risk for GI events and a PPI is deemed necessary, selection of a PPI such as pantoprazole may be preferred as it does not exhibit inhibition of the CYP2C19 enzyme. This recommendation, however, is based on the limited data available and the lack of pantoprazole on adverse clinical outcomes in patients who are receiving clopidogrel needs to be further studied. Histamine receptor antagonists (H2 receptor antagonists), with the exception of cimetidine, can also be considered. Cimetidine, similar to PPIs, is a CYP2C19 inhibitor. Clinicians, however, should be aware that H2 receptor antagonists do not confer similar protection against GI ulcers and bleeding as do PPIs in patients taking clopidogrel.

Update to “Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents”: A summary of major changes in 2009

In April 2009, the Centers for Disease Control and Prevention (CDC), in conjunction with the National Institutes of Health (NIH) and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA), published updated guidelines for the prevention and treatment of opportunistic infections (OIs) in adults and adolescents (13-17 years of age) infected with human immunodeficiency virus (HIV). These guidelines provide information on epidemiology and clinical presentation and offer recommendations for making a diagnosis, preventing exposure/disease, treating disease, handling treatment failure, and monitoring of OIs. Specific information for treating pregnant patients is outlined in the guidelines as well. A section on OIs of “geographical interest” is also provided to aid clinicians in preventing and treating OIs in patients traveling to high-risk areas. The document also contains several tables that offer concise treatment

and prophylaxis recommendations, as well as specific drug information. The authors cited several major changes to the guidelines. The following is a summary of these changes. For specific diagnosis, treatment and prophylaxis recommendations, the complete guidelines should be consulted.

Role of Anti-retroviral Therapy

A greater importance is placed on the use of anti-retroviral therapy (ART) to reconstitute the immune system as a method for preventing and treating OIs. This is of particular importance in those infections that lack specific anti-infective therapy recommendations. For example, the guidelines recommend ART to restore CD4+ cell counts to greater than 100 cells/μL as the treatment of choice for cryptosporidiosis and microsporidiosis. Initiating or optimizing ART is also the recommendation for treatment of progressive multifocal leukoencephalopathy (PML). Early initiation of ART will ideally increase natural immune function and the infection will likely resolve quicker and the patient may be less likely to experience an additional opportunistic infection. However, the authors also caution that beginning ART during active opportunistic infection may have some inherent risks. For infections that require specific treatment, there is the risk of drug interactions that must be managed. Also, during acute illness, some organs may not be functioning normally. This can lead to sub-therapeutic absorption, or difficulty in accurately dosing ART medications with respect to renal or hepatic function. Patients are then at risk of acquiring resistance to or experiencing toxicity from the ART drugs. There is also the risk of adverse effects mimicking disease and vice-versa. Immune reconstitution inflammatory syndromes (IRIS) may also arise and, due to its non-descript nature, be mistaken for exacerbation of an existing OI or occurrence of a new OI, drug toxicity or other condition. In general, reconstitution of the immune system is recommended for HIV patients with low CD4+ counts to aid in resolution and prevention of OIs.

Immune Reconstitution Inflammatory Syndromes

The new guidelines explore the diagnosis and management of IRIS, both in general and with respect to the different OIs. Immune reconstitution inflammatory syndrome is associated with increases in immune function following the initiation of ART. It often manifests as an exacerbation of the previously diagnosed opportunistic infection, but could also reveal another infection that was present against which the body was previously unable to mount a reaction. Patients who experience IRIS often do so within the first 2 months of ART initiation, but this can vary and the exact syndrome experienced by each patient can be unique. Immune reconstitution inflammatory syndrome has been associated with low CD4+ counts and high viral load. This phenomenon has not been reported with all opportunistic infections. Specifically, cryptosporidiosis, microsporidiosis, bacterial respiratory or enteric infections, bartonellosis, syphilis, mucocutaneous candidiasis, coccidioidomycosis, human herpesviruses 6 and 7, and the human papillomavirus have not been

associated with an IRIS. *Toxoplasma gondii* encephalitis has had unverified reports of a neurologic IRIS, while IRIS with histoplasmosis is uncommon and not described. Specific to each OI with known IRIS, table 2 provides a synopsis of what to expect in terms of symptoms, time to onset, and management recommendations.

Table 2. Onset, symptoms, and management of IRIS.

Disease	Onset	Symptoms	Management
<i>Pneumocystis pneumonia</i> (PCP)	Within weeks	Not described	Unknown optimal time to initiate ART
<i>Mycobacterium tuberculosis</i>	Within 1-3 months of initiating ART	High fevers, respiratory decline, new/worsening lymphadenopathy, breakthrough meningitis, new/growing central nervous system lesions, worsening of pulmonary infiltrates, increased pleural effusions	Usually self-limiting; Non-severe IRIS can be symptomatically treated with NSAIDs; Severe IRIS may be symptomatically treated with systemic corticosteroids
Disseminated <i>Mycobacterium avium</i> Complex	Not specified	Specific symptoms not described	NSAIDs for moderate to severe symptoms; If inadequate 20-40 mg daily prednisone for 4-8 weeks may be helpful
Cryptococcosis	Not specified	Not described, but occurs in 30% of patients initiating or reinitiating ART	Continue ART and antifungal; severe IRIS symptoms may warrant short-course corticosteroids; In severe cryptococcosis with elevated intracranial pressure, initiating ART may be postponed for the first 2 weeks of treatment
Cytomegalovirus	Within 4-12 weeks of initiating ART	Immune recovery uveitis with inflammation of anterior chamber of eye or vitreous	Periocular or short-course systemic corticosteroids

Table 2. Continued

Disease	Onset	Symptoms	Management
Herpes Simplex Virus	Not specified	Atypical cutaneous lesions	May be resistant to treatment, specific management not provided
Varicella-Zoster Virus (VZV)	4-16 weeks after ART initiation	Increased frequency of VZV reactivation	Same as any herpes zoster episode
Human Herpesvirus-8	Not specified	Not described	ART should not be delayed; Fatal reports in patients with pre-existing Kaposi's Sarcoma or Multicentric Castleman's Disease
Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV)	Within first 6-12 weeks of ART initiation	Large increases in serum aminotransferases; Similar presentation to acute hepatitis	Always use ART and HBV treatment in concert to prevent fatal IRIS; Attempt to differentiate IRIS from acute hepatitis A, B or C, or drug-induced hepatotoxicity; only discontinue ART if serum aminotransferase levels exceed 10-times upper limit of normal, or patient experiences symptomatic hypersensitivity or hepatitis
Progressive Multifocal Leukoencephalopathy/ JC Virus Infection	Not specified	Not described	Determine if IRIS is helpful or harmful (may cause greater injury leading to brain displacement/herniation); In patients with progressive symptoms, shortest possible duration of corticosteroids may help control inflammation and cerebral edema; Discontinuing ART is not recommended

ART=antiretroviral therapy, IRIS=immune reconstitution inflammatory syndrome, NSAID=non-steroidal anti-inflammatory drug

Tuberculosis

New information is presented regarding the use of interferon-gamma release assays (IGRAs), such as the QuantiFERON®-TB Gold and the T-SPOT™ TB test, for the detection of latent *Mycobacterium tuberculosis* (TB) infection. At the University of Illinois Medical Center (UIMC), the QuantiFERON-TB Gold test or the tuberculin skin test are used to detect latent TB. For UIMC HIV patients, who need to be tested at diagnosis and then yearly if they are at high-risk of exposure, either test is

appropriate. The authors suggest that the IGRAs are more specific and consistent for identifying latent disease when compared to the skin test. Also, the skin test may cross react with prior mycobacterium exposure, including Bacillus Calmette-Guerin vaccination. However, the IGRAs can be cost prohibitive and the optimal utilization in HIV-infected persons is not yet known. While more data are forthcoming, a positive result from any test for latent TB infection warrants evaluation for active TB.

The authors also state this update to the guidelines provides more specific information on drug interactions occurring with rifampin and rifabutin. Both drugs induce CYP3A hepatic enzymes, though rifabutin to a lesser extent. Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based anti-HIV regimens are preferred in the setting of rifampin- or rifabutin-based TB therapy due to fewer drug interactions when compared to protease inhibitor (PI)-based therapy. Rifampin should not be used with PI-based treatment, but appropriate dosage adjustments may allow concomitant use of rifabutin with PIs. Correct dosage adjustments will help avoid viral resistance and drug toxicities, but therapeutic drug monitoring may be needed. If ART is to be initiated in a patient currently being treated for active TB, efavirenz or nevirapine based regimens can be given concurrently with rifampin. In addition, nucleoside or nucleotide analogs are acceptable for use with both rifampin and rifabutin, but maraviroc, raltegravir and elvitegravir should be avoided until current drug interaction studies are completed. Tables are provided in the guideline document for specific dose adjustment recommendations and drug interactions.

Hepatitis B

A completely new section on hepatitis B virus (HBV) infection is also presented in the updated guidelines. The strength of most of the treatment recommendations is rated such that the efficacy data is insufficient or the risk to benefit is such that a recommendation for or against treatment cannot definitively be made. Recommendations of this strength are considered “optional” by the authors. However, strong recommendations are made in the areas of preventing exposure and preventing disease.

The risk for HBV infection in HIV patients should not be overlooked as it is transmitted more readily in this population. As many as 90% of HIV patients have had prior exposure to HBV based on serology testing. Ten percent of HIV patients have chronic HBV infection. While patients are often asymptomatic, acute infection could present with right upper quadrant pain, nausea/vomiting, fever, arthralgia, and/or jaundice. Chronic infection can cause hepatitis that may progress to cirrhosis and portal hypertension. As well, hepatocellular carcinoma (HCC) may complicate HBV infection at any point. Upon HIV diagnosis, all patients should be tested to determine if HBV infection exists, or if the patient would benefit from vaccination. Since HIV patients have a higher incidence of

positive serology for hepatitis B core antibody (anti-HBc), patients presenting this way should have HBV DNA testing before clinical decisions are made.

Exposure to HBV can be prevented by avoiding intravenous drug use, or at the very least, eliminating the sharing of needles. Also patients are at risk during procedures like tattooing or body-piercing if the artist does not follow proper sterilization procedures or practices for stopping infection. All HIV patients should be thoroughly educated on the importance of safe sex practices to prevent exposure to HBV and other sexually transmitted diseases. If HIV-patients have been successful at avoiding exposure, the next step is to prevent disease. All such patients should receive HBV vaccination as soon as possible, but antibody-titers must be drawn 1 month after completion of the series. This is because HIV patients are less likely to acquire immunity than non-HIV adults and a decreased response occurs more often when the CD4+ count falls below 350 cells/ μ L. The authors do stress, however, that low CD4+ count is not an acceptable reason to delay or withhold vaccination. Patients not exhibiting immunity with titers 1 month after the first vaccination should be revaccinated.

Treating HBV in the setting of HIV can be complicated, but HBV-infected individuals should limit or eliminate alcohol use. FDA-approved anti-HBV drugs include lamivudine, adefovir, entecavir, tenofovir, interferon- α , pegylated interferon- α and telbivudine. While they are not approved for this indication, other HIV medications, like emtricitabine, may have anti-HBV activity. Treatment with some HBV drugs may lead to HIV resistance. For this reason, the guidelines state that neither lamivudine, emtricitabine, tenofovir nor entecavir should be used as the sole agent for HBV treatment in patients not receiving combination ART for their HIV. On the other hand, adefovir may be a reasonable option whether or not patients are receiving ART for their HIV. Telbivudine, as a single agent, and famciclovir, in any circumstance, are not recommended due to lack of efficacy against lamivudine-resistant HBV.

When patients are diagnosed with HIV and HBV at the same time, the decision must be made if the patient is to initiate ART for their HIV. It is recommended that if HBV treatment is needed, ART should be initiated as well. If this is the case, the HBV should be covered by at least 2 drugs in the anti-HIV regimen. A feasible regimen would include emtricitabine and tenofovir. Entecavir may also be an option in patients with suppressed HIV if they lack a specific HBV DNA mutation associated with entecavir resistance. If patients are also infected with hepatitis C virus (HCV), anti-HBV therapy should be included as part of the ART regimen. Anti-HCV therapy can then be added as needed. Specific to triple-infected patients who are not starting ART therapy, treatment with an interferon should be effective for both HBV and HCV. Patients should continue anti-HBV treatment as long as they are on ART.

If the decision is made not to begin ART, the decision to treat HBV is made by the same criteria as patients without HIV. Agents that are active against HBV, but not HIV,

should be used. An acceptable treatment may be adefovir or 48-weeks of pegylated interferon. Care should be taken to monitor HBV DNA levels and loss of hepatitis B core antigen (HBcAg). Patients who “seroconvert”, or lose HBcAg and gain anti-HBc, should continue anti-HBV therapy for at least 6 to 12 months after conversion. Patients who respond with HBV suppression, but do not develop anti-HBc levels, should continue therapy indefinitely. Also, treatment with lamivudine should be indefinite in HBcAg-negative patients to avoid relapse.

Treatment efficacy, measured by seroconversion and declines in HBV DNA, should be monitored every 3 months. In addition to monitoring for adverse drug reactions, it is important to monitor patients for exacerbation of liver disease, especially upon discontinuation of HBV treatment with lamivudine, adefovir or tenofovir. In these patients, resuming HBV treatment is recommended and may be life-saving. In patients starting ART, monitoring for liver dysfunction is critical as reactivation of HBV-associated liver disease may occur. This includes monthly liver function tests for 6 months, followed by every 3 months. If lamivudine treatment failure occurs, or is suspected, adefovir or tenofovir should be added and lamivudine should be continued.

Patients with end stage liver disease (ESLD) should be managed in the same manner as non-HIV patients. This includes management of ascites and primary and secondary prophylaxis of spontaneous bacterial peritonitis. Due to an increased risk of HCC, HIV patients with HBV and cirrhosis should be screened for HCC every 6 to 12 months. Early transplant referral is recommended for patients with well-controlled HIV with specified liver dysfunction cut-offs or early HCC.

Malaria

Recommendations for malaria prevention and treatment have also been added to the geographic interests section. Malaria is especially prevalent in Africa and patients traveling there are at risk of contracting malaria. Obviously, avoiding exposure is the easiest way to prevent malaria. When forgoing the trip is not an option, standard drug prophylaxis and mosquito bite avoidance education should be offered. Recommended prophylactic drugs include atovaquone/proguanil, mefloquine, or doxycycline. While there is some evidence that cotrimoxazole may have some efficacy for malaria prophylaxis, it should not be relied on in patients using it for prophylaxis for other opportunistic infections. In

general, prophylaxis is the same as in non-HIV infected patients. Treatment is the same as well, but can be species specific. Drug interactions become important when preventing or treating malaria in HIV patients. The authors refer practitioners to the CDC malaria website (<http://www.cdc.gov/malaria>) for specifics.

Conclusion

The updated guidelines for OIs in HIV patients are similar in format to the previous version. However, several major and some minor changes are present. This review of the major changes discussed the benefit of ART with respect to OI management, recognizing IRIS and the use of newer techniques for recognizing latent TB infection. A brief summary of 2 new sections, HBV and malaria, were also provided. Opportunistic infections remain a life-threatening concern for HIV patients. While treatment should always be patient-specific, the guidelines offer a good resource with which clinicians can begin the decision-making process.

Aspirin for the primary prevention of cardiovascular events: An update of the evidence for the US Preventive Services Task Force

Cardiovascular disease (CVD) is linked to 58% of deaths in the United States and 30% of deaths globally. Its prevalence is rising, with one-third of Americans having CVD and 20 million deaths projected to occur by 2015. Risk factors for developing CVD include cigarette smoking, abnormal lipid panel, increased fasting blood glucose, and family history of premature death due to cardiovascular (CV) causes. Further, patients with blood pressure $\geq 140/90$ mmHg or who are taking an antihypertensive medication experience a doubled incidence of CVD for every 20 mmHg or 10 mmHg increase in systolic or diastolic blood pressure, respectively.

Age and gender are also significant contributors to CVD. Men have an increased risk compared to women, and experience events at a younger age. After age 40, the lifetime risk for developing CVD is 49% for men and 32% for women. However, mortality due to myocardial infarction (MI) occurs more often in women (38% vs. 25% of men after 1 year). Further, lifetime risk for stroke is greater in women than men (17% to 18% for women compared to 13% to 14% for men). These gender-based differences are believed to be due to the increased life expectancy of women.

Due to the high risk and potentially devastating consequences of CVD, primary prevention is essential for at-risk individuals. Daily aspirin is a key intervention, as it decreases platelet aggregation and reduces the incidence of MI and stroke with chronic use.

The US Preventive Services Task Force (USPSTF) recently updated its 2002 recommendations for aspirin

as primary prevention against CVD. The purpose of the document is to identify individuals without known CVD who would benefit from aspirin through reduced incidence of MI, stroke, and mortality. The guidelines also weigh the risk of gastrointestinal (GI) bleed with the potential benefits of aspirin use. The updated guidelines incorporate new data focusing on the benefits for women, allowing gender-specific recommendations to be made for the first time. The authors stress that the recommendations are only applicable for primary prevention in patients without a history of stroke or MI.

The guidelines are based on a literature search conducted between January 1, 2001 and August 18, 2008. The authors evaluated studies for quality and generalizability to the US population. Evidence incorporated into the guidelines was obtained from 1 good quality randomized controlled trial (RCT), 1 good quality meta-analysis, and 2 fair-quality sub-analyses of RCTs.

Highlights from the 2009 update guidelines regarding aspirin for the primary prevention of cardiovascular events are summarized below. The goal of the guidelines was to answer 2 key questions:

1. Does aspirin use in men and women without known CVD decrease coronary heart events, strokes, death from coronary heart events or strokes, or all-cause mortality?
2. Does aspirin use in men and women increase GI bleeding or hemorrhagic strokes?

Key question 1 – cardiovascular benefits of preventive aspirin use

Since the publication of the 2002 guidelines, new data from the Women's Health Study (WHS) has contributed to the understanding of gender-based differences in the preventive role of aspirin therapy. The WHS was a large, double-blind, RCT comparing aspirin 100 mg every other day to placebo in 39,876 women age 45 or older over a period of 10 years. Importantly, aspirin was found to be beneficial in reducing the risk of ischemic stroke by 24% (relative risk [RR] 0.83, 95% confidence interval [CI] 0.63 to 0.93) and overall stroke by 17% (RR 0.83, 95% CI 0.69 to 0.99). Subgroup analyses demonstrated that greater risk reduction for ischemic strokes occurred in non-smokers. Surprisingly, aspirin use did not correspond with a significant difference in combined CV events, MI, or death from CVD or all causes in women. However, age may factor into this potential benefit, as women over the age of 65 did experience a significantly reduced risk for CV events by 26% (95% CI 0.08 to 0.41), ischemic strokes (RR 0.70), and MI (RR 0.66).

A meta-analysis of 6 primary prevention trials evaluated data from 51,342 women and 44,114 men. The results indicated that the benefits of aspirin in men were a decreased incidence of MI (odds ratio [OR] 0.68, 95% CI 0.54 to 0.86) and CV events (OR 0.86, 95% CI 0.78 to

0.94). Women had a lowered incidence of ischemic stroke (OR 0.76, 95% CI 0.63 to 0.93) and CV events (OR 0.88, 95% CI 0.63 to 0.93). The authors were unable to identify statistically significant reductions in total or CV mortality in either men or women. Further, significant preventive benefits for ischemic stroke in men or MI in women were not found.

The optimal dose of preventive aspirin was not recommended by the guidelines. The doses used in the primary prevention trials ranged from 75 mg daily to 500 mg daily. However, lower doses of 75 mg to 100 mg have been shown to be equally effective to higher doses in preventing CV events, consistent with previous guidelines.

It is currently unknown if any population would receive a greater benefit from aspirin than the general population, based on sub-analyses of RCTs included in the guidelines. Subgroup analysis of the Primary Prevention Project related no benefit of aspirin in the reduction of CV endpoints in patients with diabetes, but a high crossover rate between groups of patients taking or not taking aspirin limits the study's value. A fair-quality subgroup analysis of the Hypertension Optimal Treatment study conveyed an above average MI reduction in subgroups with elevated systolic or diastolic blood pressure.

Key Question #2 – risks associated with aspirin use

The harms of aspirin are well-documented. Four recent studies confirm that aspirin increases the risk of major bleeding events, particularly of GI origin, in both men and women. Also, limited data conclude that hemorrhagic strokes are significantly increased in men but not women.

In the WHS, bleeding requiring transfusion was more common in subjects assigned to the aspirin group (RR 1.40, 95% CI 1.07 to 1.83). Three women in the placebo group and 2 in the aspirin group expired due to GI bleeding. Further, peptic ulcer, hematuria, easy bruising, and epistaxis occurred significantly more often in the aspirin group. However, hemorrhagic stroke differences were not significantly different (RR 1.24, 95% CI 0.82 to 1.87).

The meta-analysis discussed in the previous section reported significantly increased incidence of major bleeding events in 301 women (OR 1.68, 95% CI 1.13 to 2.52) and 288 men (OR 1.72, 95% CI 1.35 to 2.20). The risk of hemorrhagic stroke was significantly higher for men (OR 1.69, 95% CI 1.04 to 2.72) but not for women.

Recommendations

The USPSTF guidelines state that aspirin is effective at reducing the incidence of MI and stroke, and is indicated for primary prevention of CVD. However, to date, aspirin has not been linked to decreased mortality in either men or women. The guidelines recommend that men between the ages of 45 and 79 and women age 55 to 79 receive aspirin. These age recommendations are based on estimated Framingham scores, where patients within these

age ranges have a 10-year CVD risk of 3% to 12%, and the benefit of aspirin outweighs potential harm. The updated guidelines clarify the gender-based differences of aspirin. In the previous guidelines, aspirin had been recommended as prophylaxis for MI in both men and women. However, new evidence illustrates that in women, aspirin has a greater effect on stroke prevention than on MI prevention. The guidelines reaffirm the benefit of aspirin for primary MI prevention in men. The explanation for these differences is unknown, although speculated to be the result of differences in aspirin metabolism and rates of CVD events.

While evidence backing aspirin use is convincing, it is not indicated as primary prevention in all patients. In cases where the potential harm outweighs the expected benefit, aspirin use is not recommended. Individuals at high risk for bleed include those taking a non-steroidal anti-inflammatory drug (NSAID), which quadruples the risk of serious GI bleeding when combined with aspirin, and patients with a history of GI ulcer, who have a 2 to 3 times higher risk of serious bleeding. Also, a careful medication history should be taken to identify patients with an allergy to aspirin. Further, younger individuals are not candidates for preventive aspirin, due to the lack of data in men <45 years old and women <55 years old, and lower CVD risk for these age groups. Table 3 lists the current recommendations regarding the use of aspirin for the prevention of CVD.

Table 3. Current recommendations for aspirin use for CVD prevention.

Men: 45 to 79 years	Encourage aspirin use when potential CVD benefit (MIs prevented) outweighs potential harm of GI hemorrhage.
Men: < 45 years	Do not encourage aspirin use for MI prevention.
Women: 55 to 79 years	Encourage aspirin use when potential CVD benefit (strokes prevented) outweighs potential harm of GI hemorrhage.
Women:< 55 years	Do not encourage aspirin use for stroke prevention.
Men & Women: ≥ 80 years	No recommendation (insufficient evidence)

CVD=cardiovascular disease, MI=myocardial infarction, GI=gastrointestinal

UPDATE ON PPI and CLOPIDOGREL INTERACTION

Recent information presented at the 2009 Society for Cardiovascular Angiography and Interventions (SCAI) Scientific Sessions Meeting suggest a possible class effect of the PPIs on clopidogrel therapy. A retrospective cohort study of over 16,000 post-stent patients, the Clopidogrel Medco Study demonstrated a significantly higher risk of major adverse cardiovascular events (MACE) in patients who received a PPI along with clopidogrel (25.1%) compared to patients who received a PPI alone (17.9%; hazard ratio [HR] 1.41, 95% CI 1.39-1.64, p<0.0001).

When evaluated separately, omeprazole (25.1%, HR 1.39), lansoprazole (24.3%, HR 1.39), esomeprazole (24.9%, HR 1.57) and pantoprazole (29.2, HR 1.61) were all associated with a significantly higher incidence and risk of MACE, respectively, compared to no PPI.

Data from the recent SCAI meeting suggests that the effects of PPIs on clopidogrel therapy may be a class effect. Therefore, SCAI recommends consultation with the patient's primary care provider or gastroenterologist to determine alternatives to PPI use when a PPI is deemed necessary in high GI risk patients. Otherwise, H2 receptor antagonists or antacids can be used for treatment of GI symptoms in post-stent patients.

P&T Committee Formulary Action

Additions

- None

Line extensions

- Ethinyl Estradiol - Norgestimate (Sprintec)

Deletions

- Heparin 20,000 units/mL

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