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INSIDE

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Virulent Klebsiella Pneumoniae

SPECIAL REPORT

By Dean L. Winslow, MD, FACP, FIDSA

Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor of Medicine, Stanford University School of Medicine

Dr. Winslow serves as a consultant to Siemens Diagnostics and is on the Speakers Bureaus of Boehringer-Ingelheim and GSK.

Synopsis: *An increasing incidence of Klebsiella pneumoniae pyogenic liver abscess complicated by endophthalmitis or central nervous system (CNS) infections has been noted over the last 20 years. This retrospective cohort study demonstrated that genotype K1 was the only significant risk factor for these complications and was independent of underlying disease in the host.*

Source: Fang CT, et al. Klebsiella pneumoniae genotype K1: An emerging pathogen that causes septic ocular or central nervous system complications from pyogenic liver abscess. *Clin Infect Dis* 2007; 45: 284-293.

I HAD PRACTICED CLINICAL INFECTIOUS DISEASES FOR MANY years before starting work fulltime as an attending physician at our county hospital here in San Jose. Here we serve an extremely diverse population of patients, many of whom are immigrants from Latin America, Asia (especially Southeast Asia), and sub-Saharan Africa. During the 4 years I have worked at Santa Clara Valley Medical Center, I have seen more cases of tuberculosis than in my previous 26 years combined. In addition, it seemed like I saw at least one or 2 cases of primary pyogenic liver abscess due to Klebsiella during my frequent monthly rotations on the consult service. All of these cases occurred in patients from China or other countries in Southeast Asia. Several of these patients had widely disseminated pyogenic complications including 2 with endophthalmitis.

This paper presents case summaries of 23 well-studied patients from Taiwan who presented with pyogenic liver abscess due to K. pneumoniae and either endophthalmitis, meningitis, or brain abscess, which were culled from a larger group of 177 patients with

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K. pneumoniae pyogenic liver abscess. Genotyping of the isolates was accomplished by sequencing of the cps gene cluster. Serum resistance was assessed with standard methods.

Key findings from this study included the striking association of genotype K1 with both primary liver abscess (81% of cases vs 42% in secondary liver abscess) and septic ocular or CNS complications (occurred in 19 % of K1 liver abscess vs 5% non-K1 associated liver abscesses). Underlying biliary tract disease, previous abdominal surgery, diabetes, and malignancy were statistically more likely in patients with non-K1 associated liver abscess. High serum resistance of K1 strains (possibly related to K1 capsular polysaccharide structure) was noted and is likely to be the major pathogen-specific virulence factor. These data demonstrate that K2 strains had reduced serum resistance compared to K1 strains, in contrast to previously published data that had suggested similar serum resistance and in vitro resistance to phagocytosis.

This study clearly shows that K. pneumoniae genotype K1 is an important emerging pathogen capable of causing widely metastatic septic disease including endophthalmitis and CNS complications. ■

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Atazanavir-Associated Kidney Stones

SPECIAL REPORT

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *The US FDA Adverse Event Reporting System (AERS) was searched for reports of nephrolithiasis in HIV patients receiving atazanavir (ATV)-containing antiretroviral (ARV) regimens. 30 cases were identified.*

Source: Chan-Tack KM, et al. Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's Adverse Event Reporting System. *AIDS* 2007; 21:1215-1218.

I RECENTLY TREATED A PATIENT AT OUR HIV CLINIC here in San Jose who had, interestingly, developed kidney stones years ago while receiving indinavir. He was subsequently switched to an efavirenz-based regimen and later developed virologic failure with evidence of M184V and K103N substitutions in

reverse transcriptase (RT). After some significant efforts to encourage better ARV adherence, we switched his regimen to tenofovir/FTC plus ritonavir-boosted ATV. This new regimen rapidly suppressed his plasma HIV RNA levels, but approximately 6 months into treatment the patient began developing recurrent kidney stones. Two were eventually spontaneously passed. Both were tan-colored and were sent for chemical stone analysis, which revealed the stones' composition to be of "unknown substance." The patient has done well and has had no recurrence since being switched to a lopinavir/ritonavir-containing ARV regimen.

This report from FDA's Division of Antiviral Drug Products details 30 cases from data submitted to the FDA's Drug Adverse Event Reporting System. Far from being just painful, many of these cases of ATV-associated nephrolithiasis required hospitalization, lithotripsy, stenting and even placement of nephrostomy tubes because of development of hydronephrosis. The mechanism of ATV-induced stone formation is not known.

This report is important for 2 reasons: 1) Clinicians should be aware that nephrolithiasis is a possible complication of ATV therapy. 2) It is critically important for all of us to be diligent in using the FDA's AERS to report unusual medication side effects so that a more complete picture of a drug's side effect profile is developed after a drug receives marketing clearance. ■

A Review of the Effects of Antiretroviral Agents on Lipid Panels of HIV-Positive Patients

SPECIAL REPORT

By Jessica C. Song, MA, Pharm D

Jessica C. Song, MA, PharmD, is Pharmacy Residency Coordinator, Santa Clara Valley Medical Center.

Jessica C. Song and Paul Hsiao report no financial relationships relevant to this field of study.

INTRODUCTION

HUMAN IMMUNODEFICIENCY VIRUS (HIV) infected patients have been shown to experience hypertriglyceridemia and/or hypercholesterolemia as a result of their highly active antiretroviral therapy (HAART), along with natural disease progression.[1,2] In particular, dyslipidemia associated with HAART therapy, has been reported in up to 70-80% of HIV-infected individuals. Hypertriglyceridemia appears to be especially problematic in patients receiving protease-inhibitor-based regimens, with the highest frequencies seen in patients treated with ritonavir-based HAART regimens.[1] Because of the potential pharmacological interactions with certain antiretroviral agents, many clinicians tend to under-treat HAART-associated dyslipidemias. However, recent literature reports have shown that young HIV-positive individuals receiving protease inhibitors may be at increased risk of experiencing premature coronary artery disease.[1] At present, despite the relative lack of treatment recommendations for dyslipidemic HIV-infected patients, most HIV specialists are of the opinion that the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) guidelines could be applicable to their patient population.[2]

The updated NCEP ATP III guidelines highlighted significant changes in the treatment of high-risk patients, as the panel recommended more intensive LDL-C lowering in very high-risk patients to a goal of less than 70 mg/dl.[3] Patients who are classified as very high-risk have established CVD plus one of the following: multiple major risk factors, especially diabetes; severe and poorly controlled risk factors, especially cigarette smoking; multiple risk factors of the metabolic syndrome, especially TG (triglyceride) 200 mg/dl, non-HDL-C 160 mg/dl, and HDL-C (high-density lipoprotein cholesterol) <40 mg/dl; or acute coronary syndrome (ACS).

Lipid-lowering treatment options for HIV-infected patients include certain hydroxy-methyl-coenzyme A reductase inhibitors (statins), fibric acid derivatives, niacin, ezetimibe, and fish-oil supplements, either provided as monotherapy, or in combination, depending on the specific lipid disorder.[2] Bile acid-binding resins (cholestyramine, colestipol, colesevelam) should not be used by HIV-infected patients, as absorption of antiretrovirals may be impaired, and these agents have the potential to increase serum triglyceride levels.[2]

Statins are commonly used antihyperlipidemic agents that are well tolerated and relatively safe. The most common adverse effects are headache and gastrointestinal-related (i.e., abdominal pain, dyspepsia, nausea), but myopathy and hepatotoxicity have also been of some concern.[4] Statin-induced myotoxicities

are dose-related and related to the lipophilicity of the drug.[5,6] Other drug-related properties that may increase risk of myopathy are high systemic exposure, high bioavailability, limited protein binding, and potential for drug-drug interactions metabolized by cytochrome p450 (CYP) pathways (particularly CYP 3A4).[6] While myalgia represents the most common myotoxic event[1], myositis and rhabdomyolysis have been reported to cause significant morbidity and mortality worldwide.[5,6]

Fibric acid derivatives represent the most potent triglyceride-lowering agents, but exert variable effects on LDL-C and modest effects in regards to increasing HDL-C. Unlike statins, fibric acid derivatives do not inhibit CYP3A4, but are more likely to inhibit CYP2C8/2C9.[7-10] Niacin derivatives have been shown to be the most potent HDL-raising agents, and also provide moderate reductions in LDL-C and serum triglyceride concentrations.[11-13] However, despite the availability of extended-release products that have improved side effect profiles, the initial flushing reaction associated with niacin use has required the use of a gradual dose-titration process and the use of prophylactic aspirin. Furthermore, because of its potential to increase blood glucose concentrations during the initial stages of dose titration, healthcare providers may need to increase the doses of hypoglycemic agents in patients starting niacin therapy.[14-15] Ezetimibe has been shown to primarily decrease LDL-C, but to a lesser extent than statins and niacin, thereby limiting its use to providing additional LDL-C reductions in patients receiving other LDL-C-lowering agents.[16-17] Fish oil supplements are available as nonprescription products and as a prescription drug. Reductions in serum triglyceride concentrations with fish oil supplements have been shown to be comparable to the reductions associated with fibric acid derivative use, but some patients may experience increases in LDL-C concentrations.[18-19]

The purpose of this two-part review is to (1) review the drug-interaction potential between antiretroviral agents and lipid-lowering agents, (2) review the propensity of antiretroviral agents to cause hyperlipidemia disorders, (3) review the efficacy and safety profiles of lipid-lowering agents, and (4) develop an algorithm for the treatment of various HAART-associated hyperlipidemia disorders. The review featured in this issue will focus on the first 2 objectives.

EFFECTS OF ANTIRETROVIRALS / INTERACTION RISKS

The effects of currently marketed antiretroviral agents on lipid profiles of HIV-positive patients and the risk for interactions with lipid-lowering agents are summarized in **Table 1**.[20-49] Current treatment recommendations from the most recently updated DHHS Guidelines[20] are highlighted in **Tables 2** and **3**. ■

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Table 1.Antiretroviral Agents: Drug Interactions/Propensity for Inducing Dyslipidemias[20-49]

Antiretroviral (ARV) Drug	CYP450 inhibitor/Substrate?	Lipid-lowering Agent Interactions with ARV	Potential to Induce Dyslipidemia
	NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		
Efavirenz (Sustiva, EFV)	In vivo: CYP3A4 inducer In vitro: CYP2C9/2C19 inhibitor	Has been shown to decrease effects of: 1) Simvastatin 2) Atorvastatin It may potentially ↑risk of fluvastatin/ rosuvastatin toxicity.	Combination of efavirenz, lamivudine, and zidovudine: ↑ total cholesterol by 20%, ↑ HDL-C by 25%
Nevirapine (Viramune, NVP)	Primarily an inducer of CYP3A4 and CYP2B6.	Prescribing information (PI) did not mention need to avoid statins.	PI did not mention the effects of this drug on lipid panel.
Delavirdine mesylate (Rescriptor, DLV)	CYP3A4 inhibitor (perhaps inhibitis CYP2C9/2C19).	Do not use simvastatin or lovastatin. Use low doses of atorvastatin.	PI did not mention the effects of this drug on lipid panel.
	ONCE-DAILY SINGLE TABLET REGIMEN		
Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (Atripla)	Refer to above information on EFV. No potential CYP450 interactions for tenofovir and emtricitabine components.	Refer to above information on EFV.	Atripla: mean ↑in LDL-C, 13 mg/dl; mean ↑in HDL-C, 6 mg/dl; 4% of patients will have TG > 750 mg/dl.
	PROTEASE INHIBITORS		
Atazanavir Sulfate (Reyataz, ATV)	CYP3A4/CYP2C8 inhibitor.	Do not use simvastatin or lovastatin. Use low doses of atorvastatin. May potentially ↑ toxicity of gemfibrozil and fenofibrate.	Atazanavir: ↓ LDL-C, 10%; HDL-C, 7%, ↓TG, 4%.
Tipranavir (Aptivus, TPV)	Metabolized by CYP3A4.	Since this drug MUST be given with ritonavir, do not use simvastatin or lovastatin. Use low doses of atorvastatin.	Tipranavir/ritonavir: 11.3% have total cholesterol > 300-400 mg/dl; 26.2% have TG of 400-750 mg/dl.
Darunavir (Prezista)	CYP3A4 inhibitor.	This drug is given with ritonavir. Do not use simvastatin or lovastatin. Use **low doses** of atorvastatin and **pravastatin.**	Darunavir/ritonavir: 25% have TG ≥ 400 mg/dl; 9.2% have total cholesterol ? 240 mg/dl.
Lopinavir/Ritonavir (Kaletra, LPV/RTV)	Lopinavir is a substrate of CYP3A4, ritonavir is a CYP3A4 inhibitor.	Do not use simvastatin or lovastatin. Use low doses of atorvastatin.	**Kaletra + D4T + 3TC:** 5.1-10.7% have TG > 750 mg/dl; 6.7-14.3% have total cholesterol > 300 mg/dl. **Kaletra+NRTI+NNRTI** (treatment experienced): 26.2% have TG > 750 mg/dl; 25.7% have total cholesterol > 300 mg/dl.
Fosamprenavir (Lexiva, FPV)	Active metabolite, amprenavir, is CYP3A4 inhibitor.	Do not use simvastatin or lovastatin. Use low doses of atorvastatin.	Lexiva+Ritonavir (treatment experienced): 11% have TG > 750 mg/dl.
Ritonavir (Norvir, RTV)	CYP3A4 inhibitor.	Do not use simvastatin or lovastatin. Use low doses of atorvastatin.	**Ritonavir-based** regimens in treatment-naïve: 17.2% have TG > 800 mg/dl; 44.8% have total cholesterol > 240 mg/dl. **Ritonavir/saquinavir-**based regimens: 23.4% have TG > 800 mg/dl; 65% have total cholesterol > 240 mg/dl.
Saquinavir Mesylate (Invirase, SQV)	Saquinavir is a substrate of CYP3A4.	Since this drug is usually given together with ritonavir, do not use simvastatin or lovastatin. Use low doses of atorvastatin.	Refer to above row for information on lipid panel effects of saquinavir in combination with ritonavir.
Nelfinavir Mesylate (Viracept, NFV)	CYP3A inhibitor (in vitro).	Do not use simvastatin or lovastatin. Use low doses of atorvastatin.	Increases in LDL-C of 19-29 mg/dl shown when nelfinavir added to Combivir or D4T/3TC.
Indinavir Sulfate (Crixivan, IDV)	CYP3A4 inhibitor.	Do not use simvastatin or lovastatin. Use low doses of atorvastatin.	Indinavir + 2NRTIs: ↑ LDL-C, 30 mg/dl; ↑TG, 48 mg/dl from baseline levels.
Stavudine (Zerit, D4T)	No CYP450 interactions.	No drug interactions with lipid-lowering agents.	Change in lipid panel when switching from stavudine to tenofovir: TG ↓ by 35 mg/dl, LDL-C ↓ by 8 mg/dl.
	NUCLEOTIDE/NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		
Emtricitabine/Tenofovir Disoproxil Fumarate (Truvada, FTC/TDF)	No CYP450 interactions.	No drug interactions with lipid-lowering agents.	No effect on lipid panel reported in prescribing information.
Tenofovir Disoproxil Fumarate (Viread, TDF)	No CYP450 interactions.	No drug interactions with lipid-lowering agents.	No effect on lipid panel reported in prescribing information.
Emtricitabine (Emtriva, FTC)	No CYP450 interactions.	No drug interactions with lipid-lowering agents.	No effect on lipid panel reported in prescribing information.
Abacavir Sulfate/Lamivudine (Epzicom, ABC/3TC)	No CYP450 interactions.	No drug interactions with lipid-lowering agents.	Abacavir/Combivir vs. Combivir: 14% more abacavir arm patients had in TG of all grades.
Didanosine (Videx, Videx EC, DDI)	No CYP450 interactions.	No drug interactions with lipid-lowering agents.	No effect on lipid panel reported in prescribing informationl
Abacavir Sulfate (Ziagen, ABC)	No CYP450 interactions.	No drug interactions with lipid-lowering agents.	Abacavir/Combivir vs. Combivir: 14% more abacavir arm had in TG of all grades.
Zidovudine/Lamivudine (Combivir, AZT/ 3TC)	No CYP450 interactions.	No drug interactions with lipid-lowering agents.	No effect on lipid panel reported in prescribing information.
Zidovudine (Retrovir, AZT)	No CYP450 interactions.	No drug interactions with lipid-lowering agents.	No effect on lipid panel reported in prescribing information.
Abacavir Sulfate/Lamivudine/Zidovudine (Trizivir, ABC/3TC/AZT)	No CYP450 interactions.	No drug interactions with lipid-lowering agents.	Trizivir: 2% of patients have TG > 750 mg/dl.
Zalcitabine (Hivid, DDC)	No CYP450 interactions.	No drug interactions with lipid-lowering agents.	No effect on lipid panel reported in prescribing information.
	NUCLEOTIDE/NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		
Enfuvirtide (Fuzeon, T-20)	No CYP450 interactions.	No drug interactions with lipid-lowering agents.	No effect on lipid panel reported in prescribing information.

PREFERRED HAART REGIMENS FOR TREATMENT-NAÏVE HIV (+) PATIENTS (DHHS)20

Table 2.Preferred HAART Regimens: Select One Choice (Each) from Columns A + B

DHHS Ranking of ARVs	Column A	Column B
Preferred	Efavirenz OR	Tenofovir + Emtricitabine OR
Preferred	Atazanavir + Ritonavir OR	Zidovudine + Lamivudine
Preferred	Fosamprenavir + Ritonavir OR	
Preferred	Lopinavir + Ritonavir	

DHHS TREATMENT RECOMMENDATIONS FOR FIRST VIROLOGIC FAILURE ON HAART20

Table 3. Treatment Options for First Virologic Failure on Antiretroviral Regimens

Antiretroviral Class	Initial Regimen	Recommended Change
NNRTI	2 NRTIs + NNRTI	2 NRTIs (based on resistance patterns) + PI (± low-dose ritonavir)
PI	2 NRTIs + PI (±low-dose ritonavir)	1) 2 NRTIs (based on resistance patterns) + NNRTI 2) 2 NRTIs (based on resistance patterns) + alternative PI (with low-dose ritonavir, based on resistance patterns) 3) NRTI(s) (based on resistance patterns) + NNRTI + alternative PI (low-dose ritonavir, based on resistance pattern)
Triple-NRTI	3 Nucleosides	1) 2 NRTIs (based on resistance patterns) + NNRTI + PI (± low-dose ritonavir) 2) NNRTI + PI (± ritonavir) 3) NRTI(s) (based on resistance patterns) + NNRTI + PI (± low-dose ritonavir)

NRTI = Nucleoside Reverse Transcriptase Inhibitor; NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor; PI = Protease Inhibitor

Say No to Norovirus

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Source: Johnston CP, et al. Outbreak management and implications of a nosocomial norovirus outbreak. *Clin Infect Dis* 2007; 45:534-540.

Synopsis: *Norovirus outbreaks, many caused by newly emerged strains, are increasing in frequency in healthcare facilities and other settings, are difficult to control and are costly.*

In the midst of multiple outbreaks of norovirus infection in Maryland in 2004, infection control personnel at Johns Hopkins Hospital were notified that 2 healthcare workers (HCW) had acute gastroenteritis, resulting in the initiation of active surveillance of gastrointestinal illness among patients and staff. Between January 7th and May 1st, 265 HCW and 90 patients had the new onset of vomiting and/or diarrhea, thus meeting the case definition. Clustering of cases occurred in the coronary care unit (CCU) and psychiatry units. It was noted that one of the first affected HCWs in the CCU had vomited in the bathroom used by the entire staff, while another and vomited into a trash basket on the unit. The attack rate was 5.3% (7 of 133) among patients and 29.9% among HCWs in the CCU, where the outbreak had a bimodal temporal distribution and lasted a total of 8 weeks. In

the psychiatry units, the attack rates were 16.7% (29 of 233) for patients and 38.0% (76 of 200) among HCWs; the outbreak continued on these units for 16 weeks. Norovirus was identified in 2 of 10 samples tested by the Maryland Department of Health and one of 6 tested at the National Institutes of Health. The virus belonged to genogroup II.4 and had 98%-99% nucleotide sequence identity with the Farmington Hills and other new-variant viruses that first circulated in the U.S. and Europe in 2002-2004. The prolonged transmission eventually succumbed to the implementation of aggressive infection control measures, which included unit closures and disinfection with sodium hypochlorite. An economic analysis estimated the total cost of the outbreak to be $657,644.

COMMENTARY

Norovirus has become a scourge of healthcare facilities in the U.S.[1] The CDC received notices toward the end of 2006 suggesting an increase in the number of outbreaks of acute gastroenteritis (AGE), particularly in long-term care facilities. Although baseline data was not available since acute gastroenteritis is not reportable, further investigation confirmed this apparent increase. More detailed information indicated that the North Carolina Division of Public Health received 17 reports of outbreaks consistent with norovirus infection in 2006 compared to only 6 in 2005 and 3 in 2004. Wisconsin had 106 AGE outbreaks reported in 2006, a more than 4-fold increase from the previous year while New York also reported a 4-fold increase from 76 to 333. Molecular confirmation confirmed norovirus as the cause of outbreaks in cruise ships, long-term care and assisted living facilities, restaurants, catered events, parties, and a variety of other settings. Three-fourths of the noroviruses studied belonged to 2 new GII.4 variants, Minerva and Laurens.

Noroviruses may be foodborne, but are also transmitted directly from person-to-person. In addition, transmission may result from contact with contaminated environmental surfaces, on which the virus can persist for a prolonged period. The infectious dose is < 10 viral particles, while patients shed the virus in very high concentrations and may continue to shed for relatively prolonged periods. Shedding, perhaps at lower levels is also prolonged. Furthermore, fecal shedding is reported to be frequent in asymptomatic individuals during outbreaks, having been found in 26% of clinically unaffected HCW and 33% of unaffected patients.[2]

The prolonged duration of the Johns Hopkins outbreak is not unusual. I can vouch from personal experience at one institution with which I am affiliated that it can be very frustrating to have implemented aggressive control measures, such as those in the accompanying BOX, and to have the outbreak continue, nonetheless. The optimal approach is early recognition and to immediately dealing with the affected units as if they were cruise ships, extending this approach to the entire healthcare facility and to do so sooner rather than later. I can also confirm that these outbreaks are enormously costly to institutions especially because of the need to close units to further admissions and because the high frequency of involvement of healthcare workers. ■

Recommended Measures for the Prevention and Control of Norovirus Infection

1. Practice good hand hygiene.
   - Wash hands frequently with soap and water.
   - Alcohol-based sanitizing hand gels (≥62% ethanol content) may be used to complement hand washing with soap and water.
2. Disinfect contaminated surfaces with either of the following methods:
   - Use a chlorine bleach solution with a concentration of 1,000–5,000 ppm (1:50-1:10 dilution of household bleach [5.25%]) for hard, nonporous surfaces.
   - Use disinfectants registered as effective against norovirus by the Environmental Protection Agency (EPA)* in accordance with the manufacturers' instructions.
3. Do not return to work or school until 24-72 hours after symptoms resolve and practice good hand hygiene after returning.
4. Additional measures for outbreaks in health-care and long-term care facilities include the following:
   - Use contact precautions for preventing gastroenteritis.
   - Avoid sharing staff members between units or facilities with affected patients and units or facilities that are not affected.
   - Group symptomatic patients and provide separate toilet facilities for ill and well persons.
   - Instruct visitors on appropriate hand hygiene and monitor compliance with contact isolation precautions.
   - Close affected units to new admissions and transfers.

* List of EPA-approved products available at http://www.epa.gov/oppad001/list_g_norovirrus.pdf. Evidence for efficacy against norovirus is usually based on studies feline calicivirus (FCV) as a substitute for norovirus. FCV and norovirus have different physiochemical properties, and whether inactivation of FCV reflects efficacy against norovirus is unclear.

References:

1. CDC. Norovirus activity - United States, 2006-2007. *MMWR Morb Mortal Wkly Rep* 2007; 56:842-846.
2. Gallimore CI, Cubitt D, du Plessis N, Gray JJ. Asymptomatic and symptomatic excretion of noroviruses during a hospital outbreak of gastroenteritis. *J Clin Microbiol* 2004; 42:2271-2274.

Malaria and Travelers

ABSTRACT & COMMENTARY

By Philip Fischer, MD, DTM&H

Dr. Fischer is Professor of Pediatrics, Division of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

Dr. Fischer reports no financial relationship relevant to this field of study. This article originally appeared in the August 2007 issue of Travel Medicine Advisor. *It was edited by Frank Bia, MD, MPH, who receives funds from Johnson & Johnson. It was peer reviewed by Lin Chen, MD, who reports no financial relationships relevant to this field of study.*

Synopsis: *Helpful summary information can guide travel medicine practitioners through a maze of controversy toward appropriate use of incompletely understood malaria chemoprophylactic agents as well as toward evidence-based treatment of patients with malaria.*

Sources: Chen LH, et al. Controversies and misconceptions in malaria chemoprophylaxis for travelers. *JAMA* 2007; 297:2251-2263.
Griffith KS, et al. Treatment of malaria in the United States: . *JAMA* 2007; 297:2264-2277.

THE MAY 23/30, 2007, ISSUE OF *JAMA* WAS DEVOTED to malaria and contained an informative selection of papers. In particular, 2 articles were of particular interest to practitioners of travel medicine. *Travel Medicine Advisor* associate editor, Lin Chen, joined with collaborators on each side of the Atlantic to discuss myths and controversies about malaria chemoprophylaxis. While the prevention of malaria in travelers requires detailed knowledge of malaria epidemiology and host-vector-parasite interactions, they wrote, decisions are also complicated by lack of standardized recommendations. The Centers for Disease Control and Prevention's (CDC's) Monica Parise MD and some of her public health colleagues suggested that U.S. clinicians' unfamiliarity with malaria and drug resistance patterns have contributed to delays in diagnosis and treatment with resulting poor outcomes. Then, with text, tables, and a helpful algorithm, they systematically reviewed the details of medications used in the treatment of malaria.

COMMENTARY

Chemoprophylaxis: Data are not complete, and various national groups have offered differing recommendations in regard to the use of chemoprophylaxis for travelers. In addition, travelers and public media sometimes share misconceptions. Thus, health care providers providing pre-travel care must be aware of factual material while being ready to discuss controversies — particularly in regard to mefloquine and to primaquine.

Since it became available in Europe in 1985, mefloquine has been used by more than 30 million individuals. Many individual reports document both serious and minor adverse events, but larger studies are not completely comparable due to variations in design, methods, and study populations. Some studies have shown similar rates of abnormal dreams and insomnia between travelers taking mefloquine and those taking other antimalarials such as chloroquine. Recent studies, however, show more sleep trouble, headache, and psychological disturbance in travelers, especially women, taking mefloquine. While disabling adverse reactions are uncommon (less than 1%) with mefloquine, they are even less common for individuals taking other medications. Mefloquine does not cause difficulty with driving, concentration, balance, or diving.

Malaria chemoprophylaxis is designed to prevent life-threatening disease but does not effectively prevent later illness due to recrudescence of *Plasmodium vivax*. Even atovaquone-proguanil, which has some activity against liver stages of malaria, does not prevent hypnozoites from causing later bouts of vivax malaria. Primaquine also offers the potential for providing both primary and post-exposure prevention of malaria and is effective against all species of human malaria. Prior to even prophylactic treatment with primaquine, however, glucose-6-phosphate dehydrogenase (G6PD) deficiency must be ruled out. Until primaquine becomes routinely recommended, travelers to areas endemic for *Plasmodium vivax* or *ovale* must be warned that febrile illness, even up to a year or more after return from the endemic area, should prompt a diagnostic evaluation for malaria.

Treatment

Prompt diagnosis of malaria is the key to effective treatment, and clinicians in all settings should consider the diagnosis of malaria in febrile patients who have visited malaria endemic areas within the past year. Blood smears should be obtained and examined promptly; the CDC provides a telediagnosis service as well as physician consultation (770-488-7788 during regular working hours and 770-488-7100 after normal working hours).

Oral quinine (in combination with either tetracycline, doxycycline, or clindamycin), atovaquone-proguanil, and mefloquine are effective in most cases of uncomplicated malaria. Mefloquine use is limited by resistance of malaria parasites originating in some parts of southeast Asia and by its association, in treatment doses, with adverse neuropsychiatric events. Resistance to atovaquone-proguanil has only been reported in 12 patients, but is certainly possible. The combination of atovaquone and proguanil is also probably the best choice for treatment of chloroquine-resistant *P. vivax* malaria from Papua New Guinea and Indonesia. Primaquine can prevent *P. vivax* relapses and is now recommended in a dose of 0.5 mg primaquine base/kg by mouth daily for 14 days with a maximum daily dose of 30 mg. Because of either resistance or toxicity, the use of sulfadoxine-pyrimethamine, amodiaquine, and halofantrine is not recommended in the United States.

Treatment of severe malaria should be initiated with parenteral therapy, and quinidine is the only parenteral product available in the U.S. Artemisinin derivatives are effective in cases of severe malaria and will likely be available in the U.S. through the CDC by later this year. Exchange transfusions seem beneficial in some cases of severe malaria. Other treatment modalities including prophylactic phenobarbital, dexamethasone, heparin, and iron chelators are either unproven or harmful and are not recommended.

Children less than 8 years of age should not receive doxycycline or tetracycline due to effects on bone and teeth. Clindamycin is, however, effective in combination with quinine and can replace tetracycline for the treatment of young children. Mefloquine is adequately tolerated in children as small as 5 kg. Primaquine can be used at any age, as long as G6PD testing has been normal.

Atovaquone-proguanil and mefloquine are not currently recommended at treatment doses during pregnancy but can be considered if quinine and clindamycin are not available or are not tolerated. Primaquine should not be used during pregnancy due to the potential risk of undiagnosed G6PD deficiency in the preborn child. ■

CME Questions

1. Which is correct with regard to norovirus?

A. It may survive for prolonged times on environmental surfaces.
B. It has been demonstrated to be transmitted by the bloodborne route.
C. Vomiting is uncommon in patients with infection.
D. Hospital outbreaks of infection are short-lived, almost always lasting less than a week

2. Which of the following is correct?

A. Atazanavir has been reported to cause nephrolithiasis.
B. Atazanavir does not interact with simvastatin
C. Atazanavir does not interact with lovastatin.
D. Atazanavir is an inducer of cytochrome P450 enzymes.

3. Which of the following does not affect the metabolism of statin drugs?

A. Ritonavir.
B. Darunavir
C. Tipranavir
D. Tenofovir

Answers: 1.(a) 2.(a) 3.(d)

CME Objectives

The objectives of *Infectious Disease Alert* are:

• To discuss the diagnosis and treatment of infectious diseases;

• To present current data regarding use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• To present the latest information regarding the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• To discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy. ■

In Future Issues:

Treatment of *C. difficile* associated diarrhea

UPDATES

By Carol A. Kemper, MD, FACP

Teen Survives Rabies —And Doing Well 3 Years Later

Source: Hu WT, et al. Long-term follow-up after treatment of rabies by induction of coma. N Engl J Med *2007; 357:945-946.*

NOTHING SHORT OF A MEDICAL miracle occurred in 2004, when a 15-year old Wisconsin girl survived rabies encephalitis following a therapeutically induced coma, using a novel combination of ketamine, ribavirin, and amantadine. How and why she survived is not clear. Only 5 other humans have been reported to have survived rabies; most were presumed to have some degree of pre-existing immunity. An interesting question raised in the young woman's case was whether she had been infected with a less virulent or variant lyssavirus (there is speculation that other lyssaviruses may cause a rabies-like condition), but efforts to recover virus were unsuccessful. And, sadly, since this case was published in 2005,[1] a similar therapeutic effort failed in a young man who died from rabies in Texas.[2]

Hu and colleagues report on her remarkable recovery over the past 3 years. Her initial recovery was complicated by generalized choreoathetosis, and speech and gait abnormalities. A trial of therapeutic carbidopa-levodopa worsened her gait. With intensive physical therapy, her speech and gait abnormalities significantly improved by 18 months post-rabies exposure, and her choreoathetosis completely resolved by 2006. MRI of the brain showed resolution of the earlier hyperintensities seen in the basal ganglia during her acute illness. Cerebrospinal fluid analysis showed 6 unique oligoclonal bands, mildly elevated levels of neopterin, and decreased levels of homovanillic acid and 5-hyroxyindoleacetic acid, suggestive of decreased turnover of dopamine and serotonin.

Twenty-seven months after exposure, she continued to have mild dysarthria and intermittent dysesthesias. She had no evidence of attention deficit, memory problems, or mood disorder. She took college-level math and physics in high school, scored above average on a national college achievement test, and is now attending college. ■

References:

1. Willoughby RE Jr, et al. Survival after treatment of rabies with induction of coma. *N Engl J Med* 2005; 352:2508-2514.
2. Hemachudha T, et al. Failure of therapeutic coma and ketamine for therapy of human rabies. *J Neurovirol* 2006; 12(5):407-409.

Antibiotic-Impregnated Urinary Catheters Reduce Infection Risk

Source: Stensballe J, et al. Infection risk with nitrofurazone-impregnated urinary catheters in trauma patients. Ann Intern Med *2007; 147:285-293.*

ANTIBIOTIC IMPREGNATED CATHETERS can reduce biofilm formation, bacterial colonization, and have the potential to reduce the frequency of UTI in hospitalized patients. However, their use has not met with broad acceptance. This may, in part, be due to a lack of convincing data from larger randomized clinical trials and proven cost-effectiveness. The cost of the newer antibiotic- or silver-impregnated catheters is 2 to 4 times as much as a standard silicone catheter.

These authors examined the risk of UTI in a large, randomized, double-blind, controlled clinical trial of 212 consecutive trauma patients requiring urinary catheterization. Patients were randomly assigned to receive a nitrofurazone-impregnated (Rochester Medical Corporation. Stewartville, Minnesota) or standard silicone catheter (nitrofurazone is a nitrofuran drug, similar to nitrofurantoin). Urine specimens were obtained immediately after insertion of the catheter and then daily until its removal. The primary end-point was the incidence of catheter-associated bacteruria or fungeria with at least 103 colony forming units/mL with ≥ 1 isolate; post-hoc analysis were also done using a cut-off $\geq 10^5$ CFU/mL. Subjective symptoms could not be readily assessed as most patients had altered mental status and/or required ventilatory assistance. Patients who did not qualify for enrollment included those who were pregnant, HIV+, burn victims, or those with baseline bacteriuria. Most of the patients were hospitalized with blunt trauma or penetration injuries from car accidents (49%) or falls (32%).

A total of 1190 urine cultures were obtained over 1001 catheter days. Patients with nitrofurazone-catheters had a significantly lower incidence of catheter-associated bacteriuria and funguria compared with the control group (9.1% vs. 24.7%, adjusted relative risk 0.31, *P* -0.005). The incidence per 1000 catheter days was 13.8% vs 38.6, respectively, for the nitrofurazone vs. the control group. In the post-hoc analysis, using the cut-off of at least 105 CFU/mL, bacteriuria and funguria were still significantly lower in the nitrofurazone group (6.5% vs 19.5%, $P = 0.014$).

The presence of bacteriuria/funguria led to a change in or initiation of antimicrobial therapy in 5 of 7 patients (71%) in the nitrofurazone group compared with 18 of 19 patients in the control group (95%). Thus, the proportion of patients specifically treated for a UTI was 4.8% vs 17.5% of nitrofurazone vs. control subjects, respectively ($P = 0.006$). In addition, the onset of catheter-associated bacteriuria/funguria was significantly delayed in the nitrofurazone group ($P = 0.01$).

A lack of nitrofurazone susceptibility was found in 3 isolates (2 yeast and 1 *Pseudomonas aeruginosa*) in the nitrofurazone group, compared with 7 isolates in the control group (5 yeast and 2 Enterobacter spp).

There were no instances of bacteremia related to catheter-associated bacteriuria. There was no apparent affect on length of stay in the ICU, duration of stay in hospital, or 30-day mortality. Elevations of white blood counts, increased heart rate, or temperature did not significantly differ between groups. A large number of patients (n = 52) were not included in the per-protocol analysis, and a number of patients had missing values. However, examination of the data by intent-to-treat and sensitivity analyses (best case/worse case scenarios) did not appear to affect the conclusions.

There are some intriguing aspects to this study, and several limitations. One of the more compelling findings of this study is the less frequent administration of antibiotics specifically for "UTI" in the nitrofurazone group compared with controls. Presumably physicians prescribed antibiotics for what they believed was symptomatic urinary tract infection, and not just asymptomatic colonization. However, there is no evidence for this, and none of the patients evaluated had documentation of temperature greater than 38.2° C. The more frequent (daily) monitoring of urine specimens may have led to more frequent recognition of colonization and treatment than would have occurred in the clinical setting. Should physicians have been blinded to those results, except for those instances where urinary specimens were requested by the treating physicians, different results may have been obtained. In addition, most of the patients enrolled in this study were young (median age early 40s), and few had complicating conditions, such as diabetes, heart disease, or urologic disease. Thus, this data may not be generalizable to older, chronically ill patients in a critical care setting, or to those requiring non-critical hospital care, where the use of a catheter may be limited to a couple of days. ■

Direct Consumer Advertising — Is There Adequate Oversite?

Source: Donohue JM, et al. A decade of direct-to-consumer advertising of prescription drugs. N Engl J Med *2007, 357:673-681.*

DIRECT CONSUMER ADVERTISING was first approved by the Food and Drug Administration in 1996. Since then, direct pharmaceutical promotions within the United States, either through print, radio, or television ads, has increased from $985 million to more than $4 billion in 2005, and now accounts for 2.6% of drug sales. Almost every drug class has been affected, although drugs that are advertised to consumers tend to be new (expensive) agents for chronic conditions. For certain agents, such as the protocol pump inhibitors, erythropoietin, and the statins, about one-third of their marketing budget is designated for direct consumer advertising. In contrast, professional promotion to health care workers during this same period of time dropped 23%, although it still represents 4.4% of total drug costs (including $429,000 for journal advertising). In total, marketing dollars account for 18.2% of drug sales, and are heavily focused on newer agents.

As I scanned through the list of the top 20 pharmaceutical drugs in terms of spending, I breathed a sigh of relief; only 2 were antimicrobials (Valtrex and terbenafine). Total direct consumer advertising dollars for terbenafine alone was $110 million. Notably, Medical (California's version of Medicaid) pays for neither of these agents; and at the Santa Clara County hospital we've decided our limited ADAP budget can not afford them. (We'd happily take the $110 million to pay for other more necessary drugs). And yet, I am sure every ID physician has had their share of requests for other drugs on the top 20 list, including lunesta, ambien, Viagra and cialis, and even humara and neulasta (!).

This survey found that while the budget for consumer advertising continues to grow every year, adequate FDA regulation of those ads is not keeping pace. From 1999 to 2004, the number of ads reviewed prior to being aired decreased from 64% to 32%. Three FDA staff members were assigned in 2002 to review direct-to-consumers ads, but only 4 staff members were assigned in 2006, although the budget for consumer advertising grew 45% during that period of time, to a current value of 4.2 billion dollars.

The total number of letters for violating regulations for prescription advertising sent by the FDA to pharmaceutical manufacturers dropped 86% from 1997 to 2006 (only 21 letters were issued in 2006). Nearly half were for direct consumer advertising, 84% of which cited companies for minimizing risk, exaggerating effectiveness, or unsubstantiated claims of superiority, or all of the above.

Most direct consumer drug campaigns for the top 20 most heavily advertised agents all started within one year of FDA approval of the drug. This raises concerns that adequate regulatory oversite of these campaigns is not occurring (or possible) in this time frame, and that drugs are being heavily marketed even before there is much consumer experience with them or, for that matter, even before physicians have experience with them. Complicating the timely intervention of misleading or false advertising was a new policy instituted in 2002 whereby the FDA general counsel must first review and approve all FDA letters related to advertising violations. As a result, the number of letters issued by the FDA in 2002 dropped by half compared with one year earlier, many of which were issued after the advertising campaign had run its course. Several authorities have called for restrictions in advertising until at least one year after FDA approval, and perhaps even after regulatory bodies have had the opportunity to at least review the advertisements.

Obviously, pharmaceutical companies do not spend heavily without achieving their aims. But the next time a pharmaceutical company protests that drug development and research are responsible for high drug costs, you can suggest they could cut their marketing budgets for the top 20 drugs alone and save a bundle. ■

Thought for the day….

Are you aware that tap water is much more heavily regulated than bottled water, and is not only cheaper but cleaner? That is because tap water is regulated by the EPA, with fairly strict standards. Bottled water is monitored by the FDA. ■

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Stopping Statins in At-Risk Patients — Just Too Risky

In this issue: *Make sure your patients don't stop statins after a stroke or surgery; MRSA is becoming more resistant to mupirocin; new asthma treatment guidelines; and FDA approvals and warnings.*

Stopping statins, even briefly, after stroke or cardiovascular surgery increases vascular complications according to 3 new studies. Spanish investigators looked at 89 patients who were on chronic statin therapy and were admitted with acute stroke. Half were randomized to statin withdrawal for the first 3 days after admission, while the other half immediately received atorvastatin 20 mg/day. After 4 days, the statin withdrawal group was also started on atorvastatin. The primary outcome was death or dependence after 3 months as defined by modified Rankin scale of 2 or more. After 3 months, 60% of those in the statin withdraw group were disabled to the point of dependence compared with 39% of those that continued statin therapy (P = 0.043). Early neurologic deterioration was also far greater in the statin withdrawal group (65.2% versus 20.9%; $P < 0.0001$). Statin withdrawal patients also had greater infarct volume (P = 0.002). The authors conclude that statin withdrawal in the first few days after stroke is associated with a markedly increased risk of death or dependency at 90 days; hence, treatment should continue the acute phase of an ischemic stroke (*Neurology* 2007; 69:904-910).

In another study, researchers in Italy looked at stroke patients who discontinued statins after discharge from the hospital. The study population included 631 stroke patients (322 men, 309 women) without evidence of heart disease. All patients were discharged on a statin, but 38.9% discontinued the drug within 12 months. In the 12 months of follow-up, 116 patients died. After adjustment for all confounders and interactions, the hazard ratio for mortality in patients who quit a statin was 2.78 (95%CI, 1.96-3.72; P = 0.003) or nearly 3 times higher risk of death (*Stroke* 2007, published online ahead of print 8/30/07).

Another study from the Netherlands looked at a brief interruption in statin therapy associated with major vascular surgery. Nearly 300 patients on statins underwent major vascular surgery, and statin therapy was interrupted in the perioperative period in 70 patients for mean duration of 3 days. An association was observed between statin discontinuation and an increase risk of postoperative troponin release (HR 4.6) and the combination of MI and cardiovascular death combined (HR 7.5). Because many surgical patients are NPO and unable to take oral statins, and there's no intravenous statin available, the only extended release statin was tried on a subset of patients preoperatively. Patients receiving extended-release fluvastatin had fewer perioperative cardiac events compared to other statins (*Am J Cardiol* 2007; 100:316-320). The message of these studies is that statin interruption, even for a brief period during hospitalization, may lead to serious adverse events in patients at risk.

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

Mupirocin Less Effective Against MRSA

Mupirocin (Bactroban) is becoming less and less effective against MRSA, even in hospitals with low levels of mupirocin use. Researchers from Washington University in St. Louis performed nasal swab cultures for MRSA in all patients admitted to their surgical intensive care unit (SICU) on admission, weekly during hospitalization, and at discharge. Of the 302 positive MRSA isolates, 13.2% were resistant to mupirocin, with 8.6% having high-level resistance. Patients with mupirocin-resistant MRSA were more likely to be older, have a history of a previous admission in last year, and had higher in-hospital mortality. The authors conclude that patients carrying mupirocin-resistant MRSA acquired it through contact with the health-care system; the strains were probably not acquired in the SICU (*Clin Infect Dis* 2007; 45:541-547). Mupirocin is commonly used to decolonize patients who are *staph aureus* carriers or have nasal colonization with MRSA. With resistance patterns increasing nationwide, this strategy may need to change.

New Guideline for Asthma Diagnosis/Management

The National Asthma Education and Prevention Program has issued an update to their clinical practice guidelines for diagnosis and management of asthma (Expert Panel Report 3 [EPR-3]). The new guideline emphasizes the importance of asthma control and highlights 4 areas of emphasis including assessment and monitoring, patient education, control of environmental factors and other asthma triggers, and pharmacotherapy. The new guideline recommends continued use of a stepwise approach to asthma control in which medication doses or types are stepped up or down as needed based on asthma control. Recommendations now are based on 3 age groups, 0-4 years, 5-11 years (a new category), and 12 years and older.. The new age group was added because of evidence that children respond differently to medications than adults. The entire guideline can be found at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf .

FDA Actions

The FDA announced on August 14 that manufacturers of rosiglitazone (Avandia) pioglitazone (Actos), and other combination medications containing the 2 drugs will be required to add a "black box" warning to their labeling to reflect the risk of heart failure associated with the 2 drugs. Both drugs have been associated with reports of significant weight gain and edema, and some cases continuation of therapy has lead to poor outcomes including death. The black box warning advises health-care professionals to carefully observe patients taking these drugs for signs and symptoms of heart failure including rapid weight gain, shortness of breath, edema. The warning also recommends not starting either drug in patients with a history of congestive heart failure. The agency continues to review rosiglitazone for the possible increase risk of myocardial infarction associated with use of the drug.

The FDA has approved a new indication for zoledronic acid (Reclast) as a once-a-year treatment for postmenopausal osteoporosis. Reclast is administered as an annual 15-minute intravenous infusion. The drug is a bisphosphonate similar to oral bisphosphonates such as alendronate and risedronate.

Anesiva has received approval to market lidocaine topical powder intradermal injection system (Zingo) to provide local analgesic prior to venipuncture or peripheral intravenous cannulation in children ages 3-18. Zingo is a single-use helium powered system that is administered 1-3 minutes prior to needle insertion. The system is also being studied in trials of adults.

The FDA has approved a new combination of carbidopa, levodopa, entacapone (50 mg/200 mg/200 mg) for the treatment of Parkinson's disease. The new preparation helps reduce the pill burden for Parkinson's patients on multiple medications. Carbidopa/levodopa/entacapone will be marketed by Orion Corporation as Stalevo.

Omrix Biopharmaceuticals has received approval to market human thrombin (Evithrom) to promote blood clotting and control bleeding during surgery. Evithrom is the first human thrombin approved since 1954 and the only product currently available for this indication. It is applied to the surface of bleeding tissue during surgery and may be used in conjunction with absorbable gelatin sponge. Other thrombins currently on the market are derived from cattle plasma.

Nursing mothers who were taking codeine may put their babies at risk of morphine overdose if they are "ultra-rapid metabolizers of codeine," a condition that may affect up to 28% of the population. Codeine is generally recommended for nursing mothers as a cough suppressant and pain medication; however, ultra-rapid metabolizers quickly convert codeine to morphine and excrete it in breast milk. At least one infant death has been associated with this condition. The FDA has issued warning regarding codeine use by nursing mothers, recommending that mothers observe their infants closely while taking the medication for signs of morphine overdose including sleepiness, difficulty breast feeding, breathing difficulties or limpness. ■