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INSIDE

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Respiratory Viruses: A View of Future Pandemics

ABSTRACT & COMMENTARY

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Synopsis: *Healthcare workers who had been actively involved in SARS work were more "positive" in responding to an impending avian influenza epidemic.*

Sources: Tam DK, et al. Impact of SARS on avian influenza preparedness in healthcare workers. *Infection*. 2007;35:320-325; Imai T, et al. SARS risk perceptions in healthcare workers, Japan. *Emerg Infect Dis*. 2005;11:404-410; Koh D, et al. SARS: Health care work can be hazardous to health. *Occup Med (Lond)*. 2003;53:241-243.

THE PERCEPTION OF HEALTH CARE RISKS MOTIVATES BEHAVIORS in healthcare workers as well as patients.[3] Several years after the SARS outbreak in China and Hong Kong, Japanese industrial scientists found that healthcare workers had a high perception of risk for SARS manifest primarily by a desire to avoid patients.[2] At the same time these workers had a low acceptance of risk and felt little personal control. These workers' perceptions were not associated with poor knowledge of preventive measures. Indeed, the workers had a high sense of fear because they felt preventive measures were not effective. When job category was considered, nurses ranked the highest for perception of risk. With regard to gender, women had higher indices of fear than men. Older age correlated with less perception of fear.

Now, two years later comes an article from Hong Kong, an area that was an epicenter of the SARS epidemic. The authors did not ask questions about SARS preparedness and the fear

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therein, but asked questions about a more contemporary perceived threat, avian influenza.[1] The questionnaire modified from one used previously for SARS perceptions was administered in Chinese to 2929 healthcare workers; 999 questionnaires were available for analysis, most from nurses (84.3%). About 30% of respondents had experience in SARS outbreaks. What stood out in the results was the association between the experience with SARS and the sense of needing to remain vigilant for avian influenza. Nurses with experience with SARS were more likely to avoid patients suspected of having avian influenza. The same nurses were less likely to want a change in their job. The nurses who had frequent recall of their SARS experience were the ones more likely to be afraid of becoming ill with avian influenza. A SARS recall on the part of the health care worker did not relate to a positive acceptance of acquiring avian influenza as part of the job, whereas, subjects with SARS recall were slightly, but significantly more likely (54.6 vs 46.8%) to believe there would be a avian influenza outbreak in Hong Kong.

COMMENTARY

Most of the data from this survey support the idea that SARS in Hong Kong better prepared the healthcare society to approach a hypothetical influenza pandemic. While there may have been sampling errors, as the authors caution, this setting was a unique attempt to sample the sense of risk when no standardized instrument exists "to measure attitude and risk perception of health care workers towards an impending avian influenza outbreak."

With this study we move into rarefied level of inquiry: how does memory affect our willingness to provide healthcare? It is known that traumatic memories can affect our behavior, but there is little study of such memories on healthcare delivery. Thus, we have a paradox between the Japanese observation of anxiety about SARS among healthcare workers who had no actual exposure to SARS and the greater acceptance of risk with regard to an acute respiratory pathogen by Hong Kong workers who actually had exposure to SARS.

An American explanation to this paradox may be, well, if you escaped once you have a good chance of escaping again. Still the real reasons may have deeper cultural roots. Indeed the cultural differences among the SARS-unaffected Japanese and SARS affected Chinese may be profound, thus the reason that more studies like this one by Tam et al need repeated in various countries, perhaps with contrasting experiences to other pathogens. For example are nurses with experience with HIV patients more likely to have less anxiety caring for patients with hepatitis C? Are physicians who worked in leper colonies more likely to risk their lives in subsequent exposures to potentially fatal infections? Perhaps the experience with Ebola in Uganda would be another area of study.

These current investigations were not easy to perform and recruitment of subjects can be difficult. In Tam's study only about a fourth of questionnaires were ultimately returned, most of these being from nurses. New studies need pursue a higher enrollment of more physicians, pharmacists and allied healthcare workers so that we can understand the psychologic dynamics among those groups and develop strategies based on the group's response to both perceived and real past exposures.

Physicians, infectious diseases specialists and infection control professionals need to understand these evolving dynamics of anxiety in healthcare workers. Understanding their fear can help us better address the basic infection control issues of isolation, handwashing and other protective measures during epidemics and pandemics. ■

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Antiretroviral Agents and Lipid Profiles of HIV-Positive Patients: Part 2

SPECIAL FEATURE

By Catherine J. Hill, PharmD Candidate; Crystal T. Kimura, PharmD Candidate; Lian Chang, PharmD Candidate; Jessica C. Song, MA, PharmD

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Catherine Hill, Crystal T. Kimura, Lian Chang, and Jessica C. Song all report no financial relationships relevant to this field of study.

Lipid abnormalities can be problematic in HIV-positive patients receiving highly active antiretroviral therapy (HAART) due to the risk of premature coronary artery disease developing in susceptible patients.[1,2] As discussed in the previous article, the proportion of patients receiving HAART therapy who develop dyslipidemia depends on the type of anti-retroviral agent included in the treatment regimen. In some cases the dyslipidemic condition may be of sufficient severity to warrant treatment. The preferred agents that can be used for the treatment of dyslipidemia in patients on HAART therapy include hydroxyl-methyl-coenzyme A reductase inhibitors (statins), fibric acid derivatives, niacin, ezetimibe, and fish-oil supplements.[2] These agents may be used as monotherapy or in combination. The purpose of this review is to outline treatment guidelines and to discuss the agents used for treatment of dyslipidemia.

NCEP Guidelines

Table 1 defines the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) Guidelines' LDL-C goals and cut-points for therapeutic lifestyle changes (TLC), along with drug therapy in different risk categories.

Therapeutic approaches for persons with hyperlipidemia vary depending on the baseline lipid panel. However, unless triglyceride levels exceed 500 mg/dL, LDL-C is the primary focus of lipid-lowering therapy. An LDL-C goal of < 100mg/dL with a baseline value of > 130mg/dL or between 100-129 mg/dL requires TLC and LDL lowering drugs.[3] Although a baseline LDL-C value of < 100 only requires TLC and controlling of other associated risk factors, some clinicians may recommend the use of LDL-C lowering drugs for very high-risk patients (refer to footnote c, *Table 1*).[3]

Patients with a 10-year Framingham risk of 10-20%, have an LDL-C goal of < 130mg/dL.[3] A baseline LDL-C value of < 130mg/dL requires management of associated risk factors and re-evaluation of the patient in one year.[3] If a patient's baseline value equals or exceeds 130mg/dL, TLC is required, followed by a three-month follow-up assessment. After three months, if a patient's LDL-C value drops below 130mg/dL, TLC is continued and drug therapy initiation can be considered. Likewise, after three months, if the LDL-C exceeds 130mg/dL, TLC should continue and drug therapy must be initiated.[3]

Patients with a 10-year Framingham risk of less than 10% have an LDL-C goal of < 130mg/dL.[3] Treatment recommendations for this subset of patients are generally the same as above with the exception of the time to consider lipid-lowering therapy. After three months of TLC, if the LDL-C value drops below 160mg/dL, the patient should continue TLC. TLC and drug therapy should be initiated if the LDL-C value persists at a level of 160mg/dL or higher after three months of TLC.[3]

Patients displaying a < 10% 10-year risk have an LDL-C goal of <160mg/dL.[3] The most important treatment element for patients with an LDL-C baseline of < 160 is risk factor control with re-evaluation in one year. Patients with a baseline of > 160mg/dL require TLC for three months, and if they have an LDL-C value > 190mg/dL, continuation of TLC along with drug therapy should be undertaken.[3] If LDL-C levels range between < 160mg/dL and 189mg/dL, patients should continue TLC; drug therapy may be an option for patients with severe hypertension and/or continue to smoke cigarettes.[3]

Lipid-Lowering Agents

Since their introduction in the 1980s, there have been at least seven statins approved by the Food and Drug Administration (FDA) for clinical use, with a total of six currently available for use in the United States.[4-10] *Tables 2-6* highlight key pharmacologic properties of the six statins, and *Table 7* highlights the changes in total cholesterol levels.

Dosing varies depending on the statin used for therapy.[4-10] *Table 2* provides a summary of initial and maximum doses of the six marketed statins. With the exception of atorvastatin4 and fluvastatin,[9] the other statins need to be dose adjusted for renal function.

Table 1

LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in

Risk Category	LDL Goal (mg/dL)	LDL level at which to initiate TLC (mg/dL)	LDL level at which to consider drug therapy[f]
CHD[a] or CHD Risk Equivalentsb; High risk (10-year risk > 20%)	<100 (optional goal < 70 mg/dl)c	100[d]	100 mg/dLe (< 100 mg/dl: consider drug options)[f]
2+ Risk Factorsg; Moderately high risk (10-year risk 10%-20%)[h]	<130i	130[d]	130 mg/dL (100-129; consider drug therapy options)j
2+ Risk Factorsg; moderate risk (10-year risk <10%)[h]	<130	130	160 mg/dL
0-1 Risk Factor; Lower risk	<160	160	190 mg/dL (160-189: LDL-lowering drug therapy optional)

[a] CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia

[b] CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease, abdominal aortic aneurysm, and carotid artery disease (transient ischemic attacks or stroke of carotid origin or > 50% obstruction of a carotid artery)), diabetes, and 2+ risk factors with 10-year risk for hard CHD > 20%

[c] Very high risk favors the optional LDL-C goal of < 70 mg/dl, and in patients with high triglycerides, non HDL-C < 100 mg/dl. Factors placing patients at very high risk include recent acute coronary syndrome, persistent cigarette smoking.

[d] Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated trigylcerides, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level

[e] If baseline LDL-C < 100 mg/dl, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

[f] When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels

[g] Risk factors include cigarette smoking, hypertension (BP 140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (<40 mg/dl), family history of premature CHD (CHD in male first-degree relative < 55 years of age; CHD in female first-degree relative < 65 years of age), and age (men 45 years of age, women 55 years of age)

[h] Electronic 10-year calculators are available at www.nhlbi.nih.gov/guidelines/cholesterol

[i] Optional LDL-C < 100 mg/dl

[j] For moderately high-risk persons, when LDL-C level is 100-129 mg/dl, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level < 100 mg/dl is a therapeutic option on the basis of available clinical trials

[k] Almost all people with zero or 1 risk factor have a 10-year risk < 10%; 10-year risk assessment not necessary

Recommendations for initial doses and maximum doses for renally impaired patients are displayed in *Table 3*.

Of the six currently marketed statins, simvastatin and lovastatin appear to exhibit the highest propensity for interacting with cytochrome p450 (CYP3A4) isoenzymes, whereas pravastatin does not interact with any of the major metabolic CYP450 isoenzymes.[4-10] *Table 3* highlights major drug interactions observed with simvastatin, lovastatin, and other statins.

Statins induce varying degrees of LDL-C- and triglyceride-lowering in dyslipidemic patients.[4-10] As shown in *Tables 4 and* 5, atorvastatin and rosuvastatin appear to possess the most potent LDL-C- and triglyceride-lowering abilities among the six statins.

Adverse effects associated with statin therapy are generally minor and include abdominal pain, flatulence, constipation and headache, but myopathy and hepatotoxicity represent the most serious toxicities associated with this lipid-lowering drug class.[11-13] The true incidence of severe myopathy reported in clinical trials was probably underestimated compared with actual rates in nonstudy situations. Patients in clinical trials represent a select group of individuals with no known contraindications to statins and were monitored closely for appearance of adverse effects. Patient factors that increase the risk of statin-induced myopathy include advanced age, female gender, renal insufficiency, hepatic dysfunction, hypothyroidism, diet (grapefruit juice), and polypharmacy.[11-33]

Treatment of statin-induced myopathy depends on the severity of signs and symptoms. If a patient presents with an elevated CK level (3-10 times upper limit of normal), weekly CK monitoring should be conducted while continuing the same dose. Patients presenting

Table 2

Usual Dosage and Administration[4-10]

Drug (generic name)	Brand name	FDA-Approved Daily Dosage	Timing of dose
Atorvastatin	Lipitor (Pfizer)	Initial: 10mg once daily Maximum: 80mg once daily	Any time of the day
Fluvastatin	Lescol (Novartis)	Initial: 40mg once daily (use 20mg dose if < 25% LDL reduction needed) Maximum: 40mg twice daily	Take at bedtime
	Lescol XL (Novartis)	80mg once daily	Take at bedtime
Lovastatin	Generic Available	Initial: 20mg once daily (start with 10mg dose if <20% LDL reduction is needed) Maximum: 40mg twice daily or 80mg qday	Should be taken with dinner meal
	Altocor (Andrx)	Initial: 20mg once daily (can start with 10mg dose with lower baseline LDL-C) Maximum: 60mg once daily	Take at bedtime
Pravastatin	Generic Available Pravachol (Bristol-Myers-Squibb)	Initial: 40mg once daily Maximum: 80mg once daily (FDA-approved for 80mg dose)	Any time of the day
Rosuvastatin	Crestor (AstraZeneca)	Initial:10 mg once daily (use 20 mg dose if LDL-C > 190 mg/dl) Maximum: 40mg once daily	Any time of the day
Simvastatin	Generic Available Zocor (Merck)	Initial: 20mg once daily (use 40mg dose if >45% LDL reduction is needed or *if patient has diabetes, peripheral vascular disease, history of stroke, or CAD)* Maximum: 80mg once daily	Take at bedtime

with CK elevations in excess of 10 times the upper limit of normal should have their statin therapy discontinued and then consider rechallenge, dose reduction, or a switch to another more hydrophilic statin, such as pravastatin.[11-13]

Hepatotoxicity is a rare adverse effect associated with statins that appears to be a dose-related phenomenon.34-36 Clinically significant ALT elevations (> 3 times upper limit of normal) rarely leads to acute hepatic failure, the rate of which is 1 in one million patient-treatment years.[36] The majority of transaminase elevations due to statins usually present within 12-16 weeks from the start of treatment.[36] The monitoring plan and treatment of statin-induced elevations in ALT depend on the particular agent and the degree of biochemical abnormality observed in the patient. *Table 6* summarizes key liver function monitoring recommendations from the manufacturers of the six marketed statins.

Fibric acid derivatives represent the most effective lipid lowering agents for decreasing triglyceride levels.[37-40] Gemfibrozil and micronized fenofibrates decrease triglyceride levels by 33% and 28.9%, respectively.

Drug interactions implicated with fibric acid derivatives include potentiating warfarin effects and increased nephrotoxicity risk associated with concomitant administration of fenofibrate and cyclosporine.[39,40] Rhabdomyolysis associated with co-administration of fibrates (especially gemfibrozil) with statins has been well-documented in the medical literature.[14,17,24,27,31]

The most common adverse effects associated with fibric acid derivatives include: rash, nausea, vomiting, diarrhea and dyspepsia.[37-40] A dose-related hepatotoxicity associated with fenofibrate therapy can occur, causing an increase of transaminases of three times the upper limit of normal in 5.3% of patients.[39,40]

Other lipid-lowering agents, such as niacin, are not currently indicated for metabolic changes related to antiretroviral therapy because they can potentially induce acute insulin resistance, a risk equivalent for CHD. 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.[41-44] *Table 8* summarizes the effects of various niacin formulations on LDL-C, HDL-C, and on triglyceride levels.

Table 3

Doses in Patients with Impaired Renal Function and/or Taking Certain Medications[4-10]

HMG CoA Reductase Inhibitor	Impaired renal function dosage adjustment	Concomitant medication/food/ethnicity
Atorvastatin	No dose adjustment	**Use low doses with protease inhibitors.**
Fluvastatin	No dose adjustment; doses above 40mg/d have not been studied in patients with significant renal dysfunction	
Lovastatin *Avoid taking protease inhibitors, clarithromycin, erythromycin, nefazodone, telithromycin, 1 quart grapefruit juice, ketoconazole, itraconazole*	If CrCl<30ml/min, patients on doses > 20mg/d should be carefully monitored	Cyclosporine: do not exceed 20mg/d 1g/d niacin: do not exceed 20mg/d Gemfibrozil, Danazol: do not exceed 20mg/d Amiodarone: do not exceed 40mg/d Verapamil: do not exceed 40mg/d
Pravastatin	Patients with significant renal dysfunction should receive an initial dose of 10mg/d	Cyclosporine: do not exceed 5mg/d Gemfibrozil: do not exceed 10mg/d Asians: start with 5 mg qday, don't exceed 20 mg qday
Rosuvastatin	If CrCl<30ml/min/1.73m^2, patients should receive an initial dose of 5mg/d; 10mg once daily dose should not be exceeded	
Simvastatin *Avoid taking protease inhibitors, clarithromycin, erythromycin, nefazodone, telithromycin, 1 quart grapefruit juice, ketoconazole, itraconazole*	Patients with significant renal dysfunction should receive an initial dose of 5mg/d	Cyclosporine: do not exceed 10mg/d 1g/d niacin: do not exceed 10mg/d Gemfibrozil: do not exceed 10mg/d Danazol: do not exceed 10mg/d Amiodarone: do not exceed 20mg/d Verapamil: do not exceed 20mg/d

Table 4

Mean Reductions in LDL Cholesterol (Primary Hypercholesterolemia Patients)[4-10]

↓ LDL <25%	↓ LDL 25-35%	↓ LDL 35-45%	↓ LDL 45-50%	↓ LDL > 50%
Fluvastatin 20mg Lovastatin 10mg Lovastatin ER 10mg Pravastatin 10mg Simvastatin 5mg	Fluvastatin 40-80mg Fluvastatin ER 80mg Lovastatin 20-40mg Lovastatin ER 20mg Pravastatin 20-40mg Simvastatin 10-20mg	Atorvastatin 10-20mg Lovastatin 80mg Lovastatin ER 40-60mg Pravastatin 80mg Rosuvastatin 5mg Simvastatin 40mg	Atorvastatin 40mg Rosuvastatin 10mg Simvastatin 80mg	Atorvastatin 80mg Rosuvastatin 20-40 mg (LDL by ~ 53-62% in some studies)

Note: In general, a doubling of the HMG CoA Reductase Inhibitor dose results in an additional 5%-8% reduction in LDL levels

Table 5

Mean Percent Reductions in TGs (Primary Hypercholesterolemia Patients)[4-10]

↓ TG 0-5%	↓ TG 5-10%	↓ TG 10-20%	↓ TG 20-30%
Fluvastatin 20mg Pravastatin 10mg	Fluvastatin 40-80mg Lovastatin 10mg Pravastatin 20-40mg	Atorvastatin 10-20mg Fluvastatin ER 80mg Lovastatin 20-40mg Lovastatin ER 10-40mg Pravastatin 80mg Rosuvastatin 5mg Simvastatin 10-40mg	Atorvastatin 40-80mg Lovastatin 80mg Lovastatin ER 60mg Rosuvastatin 10-40mg Simvastatin 80mg

Table 6

Frequency of Liver Function Test Monitoring[4-10]

HMG CoA RI	When to perform LFT	Comments
Atorvastatin	Perform LFTs prior to initiating therapy and 12 weeks following initiation of therapy and after any dose increase; twice yearly thereafter.	If the LFTs are elevated, perform a second LFT to confirm the abnormality. Patient work-up should be done if LFTs 1.5 X UNL. Perform more frequent LFTs until normalization occurs. If the LFTs are persistently 3X UNL, discontinue HMG CoA RI.
Fluvastatin	Perform LFTs prior to initiating therapy and 12 weeks following initiation of therapy and after any dose increase; twice yearly thereafter.	Same as above
Lovastatin	Perform LFTs prior to initiating therapy and 12 weeks following initiation of therapy with the 40 mg dose; twice yearly thereafter.	Same as above
Pravastatin	Perform LFTs prior to initiating therapy and before any dose increase.	Same as above
Rosuvastatin	Perform LFTs prior to initiating therapy and 12 weeks following initiation of therapy and after any dose increase; twice yearly thereafter.	Same as above
Simvastatin	Perform LFT prior to initiating therapy, then semi-annually during the first year; patients titrated to the 80mg dose should receive an additional test at 3 months.	Same as above

Table 7

Percent Changes in Total Cholesterol, HDL, LDL, and Triglycerides with Fibrates[37-40]

Drug	Dose (mg)	Total cholesterol	HDL	LDL	Triglyceride	Renal Dose
Gemfibrozil[1] 600 bid	600 bid	-4%	+6%	+2%	-33%	Avoid if SCr>2 mg/dl
Micronized Fenofibrate[2]	145 qd	-18.7%	+11%	-20.6%	-28.9%	Start with 48 mg po qday if CrCl < 50 ml/min
Micronized Fenofibrate[3]	145 qd	-17 to -22%	10-15%	-20 to -31%	-23 to -36%	

[1] Data from 1185 patients on gemfibrozil in VA-HIT trial
[2] Data from package insert (patients with hypercholesterolemia)
[3] Data from package insert (patients with mixed dyslipidemia)

The most common adverse effects of niacin derivatives include tingling, itching, rash, headache, and flushing that usually begins 10 to 15 minutes within ingestion and can last up to an hour.[42] Recently, extended-release products have been formulated to improve the flushing that is associated with immediate-release formulations.[43] Initial treatment with aspirin and a gradual dose-titration can be used to minimize the initial flushing effects of niacin.[42]

As mentioned earlier, niacin derivatives have the potential to increase insulin resistance during the initial stages of dose titration. In the ADMIT trial45, the mean change in glucose concentration was found to be +8.1mg/dl in diabetic patients receiving immediate-release niacin, while the Hemoglobin A1c remained unchanged. The largest increase in glucose levels (~20mg/dL) occurred during weeks 12 to 18, before declining down to baseline levels. Similarly, a differ-

Table 8

Percent Changes in LDL, HDL, and Triglycerides with Niacin Products[41,43]

Drug	Dose (mg/d)	LDL (%)	HDL (%)	Triglyceride (%)
Immediate-release	3000	20-25	25-30	30
Niaspan	1000	3	10	5
Niaspan	1500	9	15	11
Niaspan	2000	14	22	28
		17	26	35

Table 9

Drugs Affecting Lipid Panel: Combination Therapy[51-55]

Drug Class	LDL-C	HDL-C	TG
Statins + Bile Acid Resins or Ezetimibe	++++++	+++	+
Statins and niacin*	++++++	++++++	+++++
Statins and fibric acid derivative	++++	+++++	+++++
Niacin and Bile Acid Sequestrant	++++	++++++	+++
Ezetimibe + Fenofibrate**	++++	+++++	+++++

*The COMPELL study showed that atorvastatin or rosuvastatin combined with niacin resulted in LDL-C reductions of 51-56%, HDL-C increases of 22-24%, and TG reductions of 40-47%.
**This combination results in LDL-C reductions of 20%, TG reduction of 44%, and HDL-C increase of 19%

ent clinical trial with extended-release niacin[46] showed a minor increase in Hemoglobin A1c of approximately 0.3% in patients receiving doses of at least 1500 mg/day.

Other adverse effects of niacin products include gastrointestinal upset and increases in uric acid levels. Relative contraindications for use of niacin include gastroesophageal reflux disorder, gout, and diabetes. Absolute contraindications for niacin use include active peptic ulcer disease and hepatic dysfunction.[41-44] The manufacturer of extended-release niacin (Niaspan) recommends that liver function tests should be performed prior to and every 6-12 weeks following treatment initiation during the first year of therapy.[43] For any elevation in transaminase in excess of 3 times the upper limit of normal, the manufacturer recommends discontinuing the drug.

Ezetimibe, currently the only drug in its class, acts to decrease cholesterol absorption by acting on the brush border enzymes along the enterocyte lining the intestinal lumen. This results in less LDL-C particles formed due to a decrease in VLDL particles secreted into the blood stream. The decrease in LDL-C particles triggers an increased uptake of LDL-C particles from the systemic circulation.[47-48]

The potential for drug interactions appears to be minimal, as ezetimibe does not undergo biotransformation by CYP450. Unfortunately, when used as monotherapy, this agent induces modest reductions in LDL-C (18%) and triglycerides (8%). However, when used in combination with a statin, reductions of an additional 11-15% in LDL-C and 7-13% in triglycerides have been reported.[47-48]

Ezetimibe is available as a 10 mg tablet, taken once daily. It is generally well tolerated with the most common side effects being headache, upper respiratory tract infections, abdominal pain, and diarrhea.[47,48]

Fish oil supplements (Docosahexaenoic Acid (DHA)/Eicosapentaenoic Acid (EHA)) like Lovaza® induce reductions in triglyceride levels to a degree comparable to the changes observed with fibric acid derivatives.[49,50] Although the mechanism of action has not been fully elucidated, some investigators have proposed that DHA/EHA are poor substrates for the enzymes responsible for triglyceride synthesis. In patients with triglycerides > 500mg/dL, triglyceride and non-HDL-C levels have been shown to decrease 44.2% and 13.2% from baseline respectively.[49] HDL-C and LDL-C levels increased 9.1% and 44.5% from baseline respectively. Recommended dosing of DHA/EHA (Lovaza) is four grams (4 capsules) daily or split dosing of two grams twice daily.[49]

The most common adverse effects associated with DHA/EHA include dyspepsia and eructation. Patients concomitantly taking warfarin should exercise caution as the patient has an increased risk of bleeding.[49,50]

Patients should be encouraged to adhere to TLC along with their lipid-lowering regimens, but if they fail to achieve LDL-C goals or are at risk of myopathy with maximal doses of statins, combination therapy should be considered. *Table 9* summarizes the effects of numerous combination lipid-lowering regimens on LDL-C, HDL-C, and on triglyceride levels. ■

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CME Questions

10. In Hong Kong, as compared to nurses with less experience, recall, with SARS patients nurses who had more experience were more likely to

a. Not look for another job
b. Become afraid of falling ill with avian influenza
c. Believe there would an avian influenza outbreak in Hong Kong
d. Accept the risk of getting influenza
e. A, B, and C

11. Which of the following is correct?

a. HIV infected patients receiving HAART are at increased risk of developing hyperlipidemia.
b. HIV infection protects patients from the cardiovascular risks associated with hyperlipidemia.
c. Hyperlipidemia in HIV infected patients is most prominent in patients not receiving antiretroviral therapy.

12. Which of the following is correct with regard to potential interaction with some antiretrovirals as a consequence of an interaction with cytochrome P450 enzymes?

a. Simvastation has no interaction.
b. Lovastatin has no interaction.
c. Pravastatin has no interaction.
d. The interaction is irrelevant to the safety of statin therapy.
e. A, B, and C

Answers: 10. (e); 11. (a); 12. (c)

In Future Issues:

Schistosomiasis and Strongyloidiasis in African Refugees

UPDATES

By Carol A. Kemper, MD, FACP

More on Benchmarking...

Source: *Klompas M, Platt R. Ventilator-associated pneumonia — the wrong quality measure for benchmarking.* Ann Intern Med. *2007;147:803-805.*

INCREASINGLY, HOSPITALS ARE BEING required to make public their surveillance data on hospital-related infections as quality indicators. In addition, the Bush administration and CMS have stated that Medicare reimbursement and accreditation will be increasingly linked to these quality indicators, and that Medicare payment will not be provided for certain hospital-related infections and complications.

Tangible improvements in the quality of care is a laudable goal, but data clearly linking several so-called quality indicators to improved patient outcome is lacking. It's the worst possible medicine (Gee, this seems like it should be a good idea, so lets do it). If physicians actually practiced in such a non-evidence-based manner, patient care would be in serious trouble. Witness the ongoing debacle with community-acquired pneumonia "bundles," where every person hitting the emergency room door with cough and fever is given antibiotics, even before they are given a diagnosis. And this manipulation of good clinical practice is occurring against a backdrop of sky-rocketing *C. difficile* cases in many hospitals. (So, the very organizations that demand universal administration of antibiotics for every possible CAP are now refusing to pay for the consequences of antibiotic overuse?).

In addition, the measurement of some quality indicators may be fraught with variability and subjectivity (Yes, the CVP line was needed for one more day). For these reasons, these authors argue that ventilator-associated pneumonia (VAP) surveillance should not be used as a quality indicator for hospital care. The diagnosis of VAP requires a combination of several objective measures (eg, white blood count > 12 x 109 cells/L), multiple subjective measures (eg, change in character of sputum, increased respiratory secretions, worsening cough), and radiographic findings of persistent pulmonary infiltrates. In the ICU setting, pulmonary infiltrates can often be due to non-infectious causes; increased respiratory secretions could be for multiple reasons, including simply failure to adequately clear secretions; and bacterial cultures in intubated patients can easily represent colonization. For all these reasons, the clinical diagnosis of VAP is "notoriously inaccurate," and can lead to very different rates of VAP for different hospitals.

The original surveillance definition for VAP proposed by the CDC acknowledged the ambiguity of these clinical signs and symptoms, and the error rate inherent in that assessment. At least one-third of those patients diagnosed with VAP have no evidence of pneumonia at autopsy. Conversely, one-fourth of ventilated patients without a clinical diagnosis of PNA who come to autopsy are found to have pneumonia. In prospective assessments, only 30%-40% of intubated patients with fever, purulent secretions, and abnormal chest radiographs actually have VAP.

The intent of the CDC was to provide a mechanism for hospitals and their infection control staff to internally monitor their critical care over time, so that appropriate measures could be taken as needed. To make this a mandatory reportable to the public, and a basis for financial reimbursement, risks undermining that original objective turn this instructional epidemiologic tool into a numbers game.

Zinc Beneficial in PPD Testing

Source: *Rao VB, et al. Zinc cream and reliability of tuberculosis skin testing. Emerg Infect Dis. 2007;13:1101-1104.*

ZINC IS KNOWN TO HAVE IMPORtant affects on white blood cell function, antimycobacterial immunity, and cutaneous responses to intradermal PPD. Zinc deficiency is not uncommon in poorer communities, especially in those with malnutrition or active tuberculosis.

In order to improve the utility of PPD testing in poorer populations, Rao and colleagues examined skin test responses to PPD in 50 shanty town residents in Lima, Peru. PPD was injected intradermally into the volar surface of each forearm, one of which was covered with a placebo cream and the other was covered with a cream containing zinc sulfate (dissolved in an aqueous

cream to a concentration of 1% elemental zinc). These areas were promptly covered with an occlusive dressing. Assessments of induration were made at 24, 48, and 72 hours. The skin test results were compared with plasma concentrations of zinc.

Ten percent of study subjects were underweight, and plasma zinc concentrations were deficient in 31%. Skin test responses were significantly less in patients with lower plasma concentrations of zinc. For those who were zinc deficient, the average skin test response in the control arm was 14 mm, compared with 27 mm in subjects with normal zinc levels (P = .03). Applications of zinc cream resulted in larger areas of induration by an average of 32% compared with the other forearm, and skin tests were more likely to be positive in zinc-treated arms. The affect on the skin test response was greatest in those with the lowest plasma zinc levels.

Zinc cream applied to PPD skin testing sites can augment the skin test response, yielding higher rates of positive results and enhancing the utility of skin testing. Topical zinc creams are an easy and inexpensive way to improve skin test responses, especially in populations at risk for zinc deficiency.

Female physicians at greater risk for suicide

Source: *Peterson MR, Burnett CA. The suicide mortality of working physicians and dentists. Occupational Medicine Advance Access published October 27, 2007*

Female physicians have more than twice the rate of suicide as other professional women and are proportionally at greater risk compared with their male physician counterparts. That was the unhappy conclusion of these authors who examined the National Occupational Mortality Surveillance Data for 26 states in the United States from 1984-1992. Age-standardized suicide rates were calculated for male and female physicians and male dentists (there were too few female dentists to assess); data for white vs non-white workers were also examined.

White male physicians > 45 years of age had two times the rate of suicide as their white female physician counterparts. But when proportional risk assessments to other working groups were made, women were at far greater risk relative to their working professional female colleagues. In contrast, because the overall rate of suicide for men in the general population is 5 times higher than that for woman, the proportional rate for male physicians relative to their male counterparts was significantly less than the proportional rate for female physicians relative to their female counterparts. (White male dentists had similar suicide rates to white male physicians). Suicide rates for male physicians was similar to that for other male professionals, but lower than non-professionals. In addition, suicide rates for man < 45 years of age were lower than then their older colleagues, and clearly increased with age. Suicide rates in women were not age-related.

Similar results were observed by the AMA in the 1960s-1970s. That earlier data also found a higher risk of suicide in female physicians, but also found that location may be an important factor, as may the physician speciality, neither of which was examined in the current study.

Raw milk Campy Outbreak

Source: *ProMED-mail Post, December 4, 2007; www.promedmail.org*

It is always fun to pimp medical students on infections possibly transmitted by raw milk, most of whom are too young to have seen or drunk unpasteurized milk. A partial list includes listeria, brucella, campylobacter, salmonella, *Mycobacterium bovis*, and *E. coli* 0157:H7. But raw milk is making a comeback in many states. At least 27 states in the United States now permit the sale of raw milk, including California, where it can now be purchased just down the road from Stanford Medical Center at the local family market. Previously, most of the cases of raw milk-related infections seen in this area were the result of soft cheeses ingested or illegally brought in from Mexico.

An outbreak of campylobacteriosis occurred this fall in Kansas, involving at least 87 people, which has been attributed to ingestion of raw milk from two different dairies in the state. One dairy supplied the milk for a soft cheese for a large community event, resulting in 68 cases, including at least 2 patients who were hospitalized. While most cases of campylobacter enteritis are self-limited, some patients may develop bacteremia, hemolytic uremic syndrome, or later complications, such as reactive arthritis and Guillain-Barré. ID physicians should be alert to the possible connection of this pathogen to ingestion of locally produced raw milk. ■

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.

FDA Warnings Dominate Pharmaceutical News

In this issue: *FDA warnings for existing drugs dominate pharmaceutical news this month. The FDA and its advisory committees have issued warnings on erythropoiesis-stimulating agents, oseltamivir (Tamiflu) and zanamivir (Relenza) for the treatment of influenza, rosiglitazone (Avandia) for the treatment of type 2 diabetes, varenicline (Chantix) to help stop smoking, the beta agonist salmeterol (Serevent), and modafinil (Provigil) for use in children. The FDA has also asked for marketing suspension of Bayer's aprotinin (Trasylol). These warnings represent a new push by the FDA to regulate existing drugs for safety after they have been approved for marketing. It also comes at a time when the FDA is cleaning up its advisory committee processes, especially with regard to limiting potential conflict of interest by advisory committee members. A summary of the new committee processes can be found at www.FDA.gov.*

Erythropoiesis-stimulating agents (ESAs) are the subject of new warnings from the FDA. The drugs, Aranesp, Epogen, and Procrit are used to treat anemia associated with cancer chemotherapy and chronic kidney failure. For cancer patients, several studies have shown that the drugs promote tumor growth and decrease survival rates in patients with advanced breast, head neck, lymphoid, and non-small cell lung cancer when given in doses that achieve a hemoglobin level of 12 g/dl or greater—the target in clinical practice. There is currently no evidence to know whether the ESA's promote tumor growth or shorten survival in patients who achieve hemoglobin levels less than 12 g/dl. The warning also specifically states that ESA's should only be used in cancer patients to treat chemotherapy-related anemia, not other causes of anemia associated with cancer and stress, and that the drug should be discontinued once chemotherapy is discontinued. For patients with chronic kidney failure, the new warnings states that ESA's should be used to maintain hemoglobin levels between 10 to 12g/dl. Higher hemoglobin levels increase risk for death and serious cardiovascular events such as stroke, heart attack, or heart failure. Finally, the new labeling emphasizes that there is no data that demonstrates that ESA's improve symptoms associated with anemia such as quality of life, fatigue, or patient well-being for patients with cancer or for patients with HIV undergoing AZT therapy.

An FDA panel is recommending new warnings on the flu drugs oseltamivir (Tamiflu-Roche) and zanamivir (Relenza-Glaxo) regarding abnormal psychiatric behavior associated with the drugs. This issue came up last year with a number of reports from Japan of erratic behavior including jumping from buildings resulting in deaths in patients taking the

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drugs. Many of the cases involved children. Japan has already taken the step of warning prescribers not to use the drugs in those aged 10 to 19. The panel reports 700 cases of psychiatric adverse events associated with both drugs, and 25 potential deaths in patients taking Tamiflu. No fatalities have been reported with Relenza. Both companies insist their drugs are safe and suggest that it is difficult to know if symptoms are caused by influenza or by medications. In the meantime Roche has agreed to stronger warnings for Tamiflu. Both medications reduce the symptoms of influenza and reduce the duration by approximately one-and-a-half days.

The manufacturers of rosiglitazone (Avandia-GlaxoSmithKline) have agreed to add new information to the existing black box warning regarding the potential increased risk of heart attacks associated with drug. The FDA's press release states that "People with type 2 diabetes who have underlying heart disease or who are at high risk of heart attack should talk with their health-care provider about the revised warning as they evaluate treatment options. FDA advises health-care providers to closely monitor patients who take Avandia for cardiovascular risks." Rosiglitazone is approved for treatment of type 2 diabetes as single therapy or in combination therapy with metformin, sulfonylureas or other oral anti-diabetes treatments. GSK has been asked by the FDA to conduct a long-term study to evaluate the potential cardiovascular risks of rosiglitazone.

The FDA has issued an "Early Communication" regarding varenicline (Chantix), Pfizer's prescription medication to help adults stop smoking. Pfizer has received reports describing suicidal ideation and erratic behavior in some patients taking the drug which have been submitted to the FDA. The Agency is soliciting any additional similar cases from Pfizer and will complete analysis when more data is available and then communicate conclusions and recommendations. In the meantime the FDA recommends health-care providers monitor patients taking Chantix for behavior and mood changes.

An expert panel of the FDA is also recommending a new warning for the long acting beta agonist salmeterol (Serevent-GlaxoSmithKline) regarding use in children. Nine new adverse event reports including five deaths in children using the drug had been reported in the last year as well as reports of increased hospitalizations and asthma-related deaths in children. Before a final recommendation is made by the FDA, review of other long-acting beta agonists will also be included, including formoterol (Foradil), Novartis' long-acting beta agonist and GlaxoSmithKline's Advair which is a combination inhaler of salmeterol and fluticasone. There is some evidence that steroid inhalers mitigate the risk of asthma-related deaths in patients taking long-acting beta agonists.

An FDA panel is recommending stronger warnings for use of modafinil (Provigil) in children. The drug is approved to treat certain sleep disorders in adults, and is not approved for use in children, but is occasionally used off label for the treatment of attention deficit hyperactivity disorder. The drug's labeling was recently updated to warn of serious skin reactions and psychological problems such as hallucinations and suicidal ideation.

Bayer Pharmaceuticals is complying with the FDA's request for a marketing suspension of aprotinin (Trasylol). The drug, which is used to control bleeding during heart surgery, is the subject of a large Canadian study, the preliminary results of which have shown an increased risk of death associate with the drug.

FDA Actions

The FDA has approved over-the-counter sales of cetirizine 5 mg plus pseudoephedrine HCL 120 mg (Zyrtec-D) for adults and children aged 12 years and older. The product has been available as a prescription drug since 2001 for the treatment of upper respiratory allergies.

The FDA has approved several new generics for marketing. Oxcarbazepine (Trileptal) will soon be available as a generic in 150, 300, and 600 mg strengths the treatment of partial seizures in adults and children. Hydrocodone/ibuprofen (Vicoprofen) is also approved as a new generic. The drug is approved for short-term treatment of acute pain. Rivastigmine (Exelon) will be available in generic 1.5, 3, 4 .5, and 6 mg strengths for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia assisted with Parkinson's disease. ■