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INSIDE

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New DHHS Guidelines for Antiretroviral Therapy

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

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

Dr. Winslow serves as a consultant for Siemens Diagnostics, and is on the speaker's bureau for GSK and Cubist.

Synopsis: *The revised DHHS guidelines for antiretroviral therapy (ARV) of adults and adolescents were released in December 2009. Significant changes to earlier versions of the guidelines include: recommending possible initiation of ARV at CD4+ lymphocyte counts between 350-500 cells/uL, including raltegravir and darunavir/ritonavir in ARV regimens for treatment-naïve patients, treatment of HIV-2 infection, and guidelines for management of HCV/HIV co-infected patients.*

Source: Panel on antiretroviral guidelines for adults and adolescents. Guidelines on the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services. 2009;1-161. http://www.aidsinfo.nih.gov/ContentFiles/AdultsandAdolescentGL

THE LATEST ITERATION OF THE DHHS GUIDELINES WAS RELEASED December 1, 2009. The major changes to previous versions of the guidelines include a number of changes listed below:

1. Recommending HIV-1 genotyping as the preferred resistance test for first- or second-regimen failures and consideration of phenotyping for evaluation of known or suspected complex drug resistance patterns, particularly with HIV-1 protease inhibitors.

2. In addition to the previous recommendation to initiate antiretroviral therapy in all patients with AIDS-defining illness or CD4 < 350, the guidelines clarify the recommendation to initiate ARV in the setting of pregnancy, HIV-associated nephropathy (HIVAN), and hepatitis B virus infection (or when treatment of HBV is otherwise indicated). The Panel also recommended considering institution of ARV

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when the CD4 count was between 350 and 500 but disagreed on thestrength of the evidence supporting the recommendation. The panel was divided on recommending ARV therapy in patients with CD4 > 500.

3. In addition to the recommendation of tenofovir (TDF) + emtricitabine (FTC) in combination with either efavirenz (EFV) or ritonavir-boosted atazanavir (ATV/r), the panel (following recent FDA approval) also included TDF/FTC + raltegravir and TDF/FTC + ritonavir-boosted darunavir (DRV/r) as preferred initial regimens. Kaletra (LPV/r) is now considered an alternative regimen for treatment-naïve patients.

4. The warning for clinicians to avoid interrupting ARV is reiterated, and the guidelines make it clear that IL-2 is devoid of clinical utility.

5. A section on treatment of HIV-2 infection is added, reminding clinicians that non-nucleoside RT inhibitors (nnRTIs) and enfuvirtide are not active against HIV-2.

6. A section on considerations for management of antiretroviral therapy in HCV coinfected patients is added.

■ COMMENTARY

The latest version of the DHHS guidelines for antiretroviral therapy represent a large volume of work and immediately become the standard of care for management of HIV-infected patients. The document has grown to 161 pages and contains numerous useful tables, as well as carefully worded explanations for the new recommendations made.

While the document represents an important summary of current knowledge, I have some minor concerns about some of the recommendations made in this iteration. For the record, I have known almost all of the panel members personally (for many years) and they are uniformly excellent clinicians and knowledgeable in the field of HIV medicine. Having participated in similar panel meetings in years past, I am aware of the tendency of many of us in the field to be less than critical in our embracing of new ideas and susceptibility to "group-think." Over the years, I've seen dozens of ideas, accepted as true by the opinion leaders, become "standard of care" only then to finally have the ideas disproved a few years later (i.e., aerosolized pentamidine for PCP, adefovir/ddI/hydroxyurea as an ARV regimen, the notion that PI's are superior to nnRTIs in patients with high viral loads, the utility of in vitro "replication capacity," etc.). At the meetings we all attend, it sometimes seems like unsupported ideas become accepted/true by virtue of us repeating them to each other (with serious expressions on our faces) often enough at different meetings. (Yes, I, too, nod my own head wisely in agreement with my colleagues most of the time!) Fortunately, the DHHS guidelines generally reflect the uncertainty of the quality of evidence if one reads the fine print.

One minor concern in this document includes the recommendation for phenotypic resistance testing in patients who have failed multiple regimens. While intuitively this recommendation makes sense (and most HIV doctors, including me, occasionally order phenotypic testing in this situation), no data from controlled trials have ever shown that phenotypic testing is useful in this group of patients. In fact, phenotypic testing is probably least useful in patients who have failed multiple regimens. While both the European VIRADAPT study[1] and the U.S. CPCRA-sponsored GART study[2] demonstrated that one sees a 0.5 log incremental benefit of genotypic testing (vs. standard of care — educated guessing) in selecting a new regimen in patients failing therapy, no virologic benefit of phenotyping has ever been demonstrated except in the Virco-sponsored VIRA 3001 study (which was limited to patients failing their first ARV regimen). The European NARVAL study did demonstrate a benefit of genotyping but no benefit of phenotyping in patients failing therapy.[3] Even the Monogram Biosciences-supported CCTG 575 study (chaired by a member of the Monogram Advisory

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Questions & Comments

Leslie Hamlin,
Managing Editor, at (404) 262-5416, or e-mail to leslie.hamlin@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Board) failed to demonstrate that phenotyping was any better than educated guessing in selecting a new regimen in patients failing ARV therapy.[4] (When I order a phenotype in a highly treatment-experienced group, I always think of the joke about the man frantically searching for his lost car keys under the streetlight — because that's where the light is best — rather than in the dark part of the parking lot where he probably lost them!) It should be noted that the Europeans don't order phenotypes at all — which I believe reflects their willingness to critically look at the data and to be better stewards of limited healthcare resources than we are in the United States. Despite this lack of data, American HIV-treating physicians continue to order these incredibly expensive assays ($1,200 or more per test) and, now, the DHHS panel has enshrined this practice based on paltry evidence. A much more useful (and inexpensive) alternative to phenotyping in treatment-experienced patients is the Virco "Virtual Phenotype," which gives information complementary to the genotype at a fraction of the cost of a true phenotype and with greater reliability since it is derived from the genotype sequence.

Another concern regarding this latest version of the DHHS guidelines is the firm recommendation to initiate ARV therapy in all patients with CD4 between 350 and 500, and a recommendation to even consider this in patients with CD4 > 500. This recommendation is largely based on the recently published NA-ACCORD trial, which purported to show reduced mortality in patients who initiated ARVs with higher CD4 counts.[5] This case-control study was seriously flawed by the self-selection of patients who chose to initiate earlier ARV therapy also generally having other "healthier" lifestyle features; hence, fewer deaths from cardiovascular disease, homicide, suicide, and drug overdose rather than AIDS-defining events. Despite this concern that the panel's recommendation was made based on misleading evidence, the favorable toxicity profile of newer ARVs probably makes earlier initiation of therapy appropriate in the developed world, especially in those co-infected with hepatitis B, hepatitis C, and those patients with risk factors for cardiovascular disease where more evidence is accumulating that the heightened inflammatory state associated with untreated HIV infection causes more rapid progression of these non-AIDS-defining diseases. ■

Editor's Note: Dr. Winslow wrote this article while at McMurdo Station in Antartica.

References

1. Durant J, et al. Drug-resistance genotyping in HIV-1 therapy: The VIRADAPT randomised controlled trial. *Lancet* 1999;353:2195-2199.
2. Baxter JD, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral testing in patients failing therapy. *AIDS*. 2000;14:83-93.
3. Meynard JL, et al. Phenotypic or genotypic resistance testing for choosing antiretroviral therapy after treatment failure: A randomized trial. *AIDS*. 2002;16:727-736.
4. Haubrich RH, et al. A randomized prospective study of phenotype susceptibility testing versus standard of care to manage antiretroviral therapy: CCTG 575. *AIDS*. 2005;19:295-302.
5. Kitahata MM, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. 2009;360:1815-1826.

Alternative Therapeutic Options for Pandemic Influenza A H1N1

ABSTRACT & COMMENTARY

By Pamela Tien, PharmD Candidate, Jonathan Nieh, PharmD Candidate, Jessica C. Song, MA, PharmD

Pamela Tien and Jonathan Nieh are PharmD Candidates at the University of the Pacific, and Jessica C. Song is PharmD at the University of the Pacific.

They report no financial relationships relevant to this field of study.

SINCE APRIL 2009, PANDEMIC INFLUENZA A (H1N1) VIRUS isolates have been tested for resistance to adamantanes (amantadine, rimantadine) and have demonstrated 100% resistance to this class of antiviral agents. In contrast, susceptibility rates of 2009 influenza A (H1N1) viruses to the neuraminidase inhibitor oseltamivir have exceeded 99%, with a total of 14 cases of oseltamivir-resistant isolates identified in the United States since April 2009.[1] In addition, a recently published case report[2] has highlighted the use of intravenous zanamivir (available for compassionate use) in a patient failing to respond to oseltamivir therapy.

On October 23, 2009, due to the severity of the 2009-2010 influenza A (H1N1) season, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the intravenous

Table 1

Pharmacologic Properties of Neuraminidase Inhibitors: Oseltamivir,[7-9] Zanamivir,[7] and Peramivir[6]

Pharmacologic Parameter	Oseltamivir (treatment duration is five days)	Zanamivir (treatment duration is five days)	Peramivir (treatment duration is 5-10 days)
Adult Treatment Dose	CrCL > 30mL/min: 75 mg PO BID CrCL 10-30 mL/min: 75 mg PO once daily CrCl < 10 ml/min: not recommended[1]	Two 5-mg inhalations (10 mg total) twice daily. No dose adjustment required for renal dysfunction. Detailed directions on the Diskhaler and a video for proper use can be found at: www.relenza.com/inhaler-step-by-step.html.	CrCL 50-80 mL/min: 600 mg IV over 30 minutes once daily. CrCL 31-49 mL/min: 150 mg IV over 30 minutes once daily. CrCL 10-30mL/min: 100 mg IV over 30 minutes once daily. CrCL < 10ml/min or hemodialysis: 15 mg IV over 30 minutes once daily.
Off-Label Dosing	Per the CDC, some (< 10) severely ill patients from Michigan (most had BMIs in excess of 30 kg/m^2 or 40 kg/m^2) received doses of oseltamivir 150 mg PO BID	Kidd et al[2] used a dosing regimen of 600 mg IV bid in a 22-year-old neutropenic female, for a total of 10 days.	No pediatric patients have received peramivir in clinical trials. However, limited use of peramivir IV in children has been allowed under emergency IND procedures. Dosing in pediatrics is based on modeling. For more dosing information in pediatrics and children, refer to *Table 2*.
Adult Chemoprophylaxis	CrCL > 30mL/min: 75 mg PO Qday CrCL 10-30 mL/min: 75 mg PO every other day or 30 mg PO Qday. CrCL < 10 mL/min: not recommended[1]	Two 5-mg inhalations (10 mg total) once daily.	Not applicable.
Chemoprophylaxis: Children	**Children ≥ 12 Months** 15 kg or less: 30 mg PO Qday; 16-23 kg: 45 mg PO Qday; 24-40kg: 60 mg PO Qday; > 40 kg: refer to adult dose **Children < 12 Months:**[4] < 3 months: not recommended; 3-5 months: 20 mg PO Qday; 6-11 months: 25 mg PO Qday	Children ≥ 5 Years Same as adult dose (see above)	Not applicable.
Resistance	To date, at least 14 cases of H1N1 resistance have been documented in the United States. The mechanism of resistance has been shown to be due to a mutation, H275Y, of the viral neuraminidase gene.	No reports of resistance to zanamivir.	Peramivir IV should not be used for treatment of 2009 H1N1 virus infection in patients with documented or highly suspected oseltamivir resistance. Peramivir IV should be used with caution in patients with documented or highly suspected zanamivir resistance.
Off-Label Formulations	Not applicable	Available as an IV formulation through a compassionate use request to GlaxoSmithKline.[3]	
Common Adverse Effects	Nausea (10%), vomiting (9%), diarrhea (7%) in patients receiving treatment.	≥ 1.5%: sinusitis, dizziness, fever, chills, arthralgia	Diarrhea , nausea, vomiting (composite, 12% with 600-mg dose), psychiatric adverse events (11%), decrease in neutrophil count.

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Table 1...continued from previous page

Pharmacologic Properties of Neuraminidase Inhibitors: Oseltamivir,[7-9] Zanamivir,[7] and Peramivir[6]

Contraindications/ Warnings	Hypersensitivity to oseltamivir. seizures, hallucinations, delirium, and abnormal behavior (especially children)	Lactose/milk protein allergy; hypersensitivity. Avoid using this agent in patients with underlying airway disease.	Hypersensitivty to other neuraminidase inhibitors (oseltamivir or zanamivir) or to any component of peramivir.
Storage Condition for Intravenous Formulation	Not applicable	Not applicable	Available as single-use 10mg/mL, 20 mL vial. Store at 15^0C-30^0C (59^0F-86^0F). Diluted product (*see below*) can be stored at 2^0C-8^0C (36^0F-46^0F) for 24h.
Dilution of Intravenous Formulation	Not applicable	Not applicable	For patients with normal renal function, transfer 600 mg (60 mL) to an empty sterile container for IV use. Add 40 mL of 0.9% NaCL or 0.45% NaCLl to reach a total volume of 100 mL (maximum concentration, 6 mg/mL). For renally impaired patients, use appropriate volumes based on recommended dosing; final total volume, 100 mL.
Administration of Intravenous Formulation	Not applicable	Not applicable	Once the product is diluted, administer immediately, or if stored in refrigerator, let it come to room temperature. For adults, usual infusion time is 30 minutes; maximum rate, 40 mg/min. Infuse over one hour in pediatric patients.

[1]One study conducted by Robson et al.[8] recommended a dose of oseltamivir 30-mg oral suspension given once weekly in CAPD patients for both treatment and chemoprophylaxis. The investigators proposed a dose of oseltamivir 30-mg oral suspension given after alternate sessions in hemodialysis sessions for both treatment and chemoprophylaxis.

[2]Gastrointestinal side effects are the most likely adverse effects seen with higher doses of oseltamivir. A recent pharmacokinetic study conducted by Wattanagoon and associates[9] used doses up to 675 mg of oseltamivir in healthy volunteers (n = 8), and no major adverse effects were reported. Weight, age, and gender had no effects on the pharmacokinetics of oseltamivir phosphate or oseltamivir carboxylate. The authors proposed that higher doses of oseltamivir may lead to more rapid attainment of therapeutic concentrations. Since obese patients have been shown to be more likely to experience complications from H1N1 infection, perhaps some clinicians may choose higher doses for this patient population.

[3]Compassionate use can be requested by calling 1-888-825-5249. A physician should be expected to provide contact information to the operator so that a GSK physician may call to discuss eligibility criteria. Inclusion criteria (all 4 must be met): 1) hospitalized with severe influenza symptoms, 2) laboratory confirmation of influenza infection, 3) unable to use any other treatment, and 4) ≥ 6 months of age. Exclusion criteria include pregnancy and hypersensitivity.

[4]Treatment of infants younger than the age of 12 months old has been recently approved for Emergency Use Authorization (EUA) by the FDA. When applicable, the FDA may allow the use of unapproved medications or the unapproved use approved agents in times of emergencies with specific products.

neuraminidase inhibitor peramivir (BioCryst Pharmaceuticals).[1]

The purpose of this article is to describe cross-resistance among neuraminidase inhibitors, to summarize therapeutic options available for oseltamivir-resistant and for oseltamivir-refractory 2009 influenza A (H1N1), and to discuss the use of combination antiviral regimens.

Table 2

Pediatric Dosing of Intravenous Peramivir (Do not exceed 600 mg/day in larger children)[6]

Age	50-80 mL/min	31-49 mL/min	10-30 mL/min	< 10 mL/min or hemodialysis (on dialysis < days, give post-dialysis)
Birth-30 days	6 mg/kg IV qday	1.5 mg/kg IV qday	1 mg/kg IV qday	0.15 mg/kg IV qday
31 days-90 days	8 mg/kg IV qday	2 mg/kg IV qday	1.3 mg/kg IV qday	0.2 mg/kg IV qday
91 days-180 days	10 mg/kg IV qday	2.5 mg/kg IV qday	1.6 mg/kg IV qday	0.25 mg/kg IV qday
181 days-5 years	12 mg/kg IV qday	3.0 mg/kg IV qday	1.9 mg/kg IV qday	0.3 mg/kg IV qday
6 years-17 years	10 mg/kg IV qday	2.5 mg/kg IV qday	1.6 mg/kg IV qday	0.25 mg/kg IV qday

Creatinine Clearance (http://www-users.med.cornell.edu/~spon/picu/calc/crclschw.htm)

Neuraminidase-Inhibitor Resistance

At present, neuraminidase-inhibitor resistance patterns of the pandemic influenza A (H1N1) virus have not been fully elucidated. However, structural comparisons between the active sites of the enzymes of seasonal and pandemic influenza A (H1N1) have shown great similarities and, hence, resistance patterns of pandemic influenza A (H1N1) may parallel those of seasonal influenza A (H1N1). A single nucleotide mutation (cytosine to thymine) at position 823 of the pandemic neuraminidase gene can lead to a histidine to tyrosine substitution at position 275 (H275Y mutation).[3] Of note, the Centers for Disease Control and Prevention (CDC) reported the emergence of a second type of mutation (I223V) in two young females infected with oseltamivir-resistant 2009 influenza A (H1N1) virus following chemoprophylaxis. The functional significance of the mutation could not be determined since neuraminidase-inhibitory assays were not performed.[4]

Leung et al reported the resistance patterns of neuraminidase inhibitors over a two-month period (May-June 2009) in Hong Kong, and found that of 200 influenza A (H1N1) isolates, one strain (A/Hong Kong/2369/2009 [H1N1]) was resistant to oseltamivir. The 50% inhibition concentration (IC50) of zanamivir was approximately 200-fold lower compared with oseltamivir, demonstrating a lack of cross-resistance between the two neuraminidase inhibitors.[5] In the United States, of the 14 tested oseltamivir-resistant 2009 influenza A (H1N1) viruses, all isolates retained sensitivity to zanamivir.[1]

To date, no clinical data are available on resistance rates of 2009 influenza A (H1N1) to the neuraminidase inhibitor peramivir. Cross-resistance between peramivir and oseltamivir have been observed in other influenza viruses. Neuraminidase assay analysis of the oseltamivir resistance-associated substitutions E119V (A/H3N2), D198N (B), H275Y (A/H1N1), and R292(K) revealed 1-, 4.8-, 100-, and 80-fold reductions in susceptibility to peramivir, respectively. In addition, zanamivir resistance-associated mutations E119A (H4N2), E119D (H4N2), E119G (H4N2), and R152K (B) resulted in 1-, 33-, 2-, and 400-fold reductions in susceptibility to peramivir, respectively. Consequently, patients with documented oseltamivir-resistant 2009 influenza A (H1N1) virus should not receive peramivir as an alternative antiviral treatment option.[6]

Alternative Therapies

The CDC currently recommends the use of oral oseltamivir or inhaled zanamivir for the treatment of hospitalized patients with 2009 influenza A (H1N1) infection.[7] Peramivir, the only intravenous neuraminidase inhibitor available for use in the United States, serves as another option for patients who cannot take oral (including enteral oseltamivir) or inhaled medications.[7] Recently, it has become available through EUA, provided that the patient fulfills at least one of the following conditions: 1) insufficient clinical response to oral or inhaled antiviral therapy, 2) intravenous route is the only feasible treatment approach, and/or 3) physician's professional judgment deems its use necessary (in the adult population only). Based on the EUA, peramivir should not be used for the treatment of patients infected with seasonal influenza A or B virus, and this agent should not be used for chemoprophylaxis.[6] *Table 1* summarizes

key pharmacologic properties of the three neuraminidase inhibitors.[6-9]

The Shionogi development program has enrolled a total of 1,891 patients who received peramivir (any dose, any formulation) in phase I, II, and III trials.[6] Of the 1,891 patients, a total of 137 patients were enrolled in a Phase II efficacy and safety study of hospitalized adults infected with seasonal influenza virus. This double-dummy, randomized trial included patients who received intravenous peramivir 200 mg or 400 mg once daily for five days or oseltamivir (oral suspension) administered twice daily. Unfortunately, the results of this trial are difficult to interpret, given that the treatment effect of oseltamivir for the primary outcome of time to clinical efficacy has not been established in patients hospitalized for acute influenza infection. Furthermore, this trial did not show a dose-response effect for peramivir, and did not show superiority of peramivir (for both doses) over oseltamivir for the primary outcome.[6] Other unresolved issues include the dosing of this agent in morbidly obese patients (body mass index ≥ 40 kg/m^2) and the use of this drug in combination with other antiviral agents. A total of 847 patients have received ≥ 600 mg (intravenous or intramuscular route) peramivir and 33 patients have received 600 mg intravenous peramivir for at least five days.[6]

Intravenous zanamivir may be an option for patients who do not respond to oseltamivir treatment and who are unable to utilize the inhaled neuraminidase inhibitor, zanamivir. The intravenous formulation is currently offered under its manufacturer's (GlaxoSmithKline) compassionate use policy. Kidd et al reported the case of a neutropenic (post-chemotherapy for Hodgkin's disease) 22-year old female admitted to the intensive care unit (ICU) for laboratory-confirmed pandemic 2009 influenza A (H1N1) infection.[2] The patient initially received six days of oseltamivir 75 mg, administered twice daily through her nasogastric tube, followed by nebulized zanamivir over the next eight days. Oseltamivir 150 mg, dosed twice daily, was added to nebulized zanamivir on days 13-16, with no clinical or virological response. On day 16, the combination regimen of nebulized zanamivir and high-dose oseltamivir was replaced by intravenous zanamivir, given as a twice-daily dose of 600 mg. The patient's condition improved within two days, and she received a total of 10 days of treatment with intravenous zanamivir.

Intravenous zanamivir has been combined with aerosolized ribavirin or oral ribavirin in oseltamivir-resistant pandemic 2009 influenza A (H1N1) infection.[10] The CDC reported the case of a female hematopoietic stem cell transplant patient (age ~ 40 years old) from Seattle, Washington, who failed to respond to combination treatment with high-dose oseltamivir (150 mg twice daily) and oral ribavirin 100 mg, given twice daily.[10] During her 4-5 week course of combination therapy, the 2009 influenza A (H1N1) virus became resistant to oseltamivir, thereby prompting the attempted use of inhaled zanamivir, which was not tolerated by the patient. After the second failed attempt of administering inhaled zanamivir, the patient's therapeutic regimen was switched to a combination regimen of intravenous zanamivir (dose not specified) and aerosolized ribavirin. After nearly a week of receiving this combination regimen, aerosolized ribavirin was replaced by oral ribavirin, since the patient could not tolerate the aerosolized formulation. The CDC did not report whether this patient recovered from her infection.

Conclusion

Oseltamivir and inhaled zanamivir represent the two FDA-approved antivirals that can treat patients infected with pandemic 2009 influenza A (H1N1) virus. With the emergence of 2009 influenza A (H1N1) viruses that have become resistant to oseltamivir therapy, clinicians need to be aware of alternative treatment options for this potentially devastating infection. Moreover, since many patients may not respond to oseltamivir therapy and/or are unable to receive oral or inhaled therapy, healthcare providers must be informed of usage conditions applicable to intravenous peramivir. Future studies will hopefully address unresolved issues such as dosing of peramivir in morbidly obese patients, and the use of combination regimens consisting of two or more antiviral agents. ■

References

1. Centers for Disease Control and Prevention. Fluview: a weekly surveillance report prepared by the influenza division. Atlanta, GA: US Department of Health and Human Services, CDC; 2009. Available at www.cdc.gov/flu/weekly/
2. Kidd IM, et al. H1N1 pneumonitis treated with intravenous zanamivir. *Lancet*. 2009;374:1036.
3. Van der Vries E, et al. Evaluation of a rapid molecular algorithm for deletion of pandemic influenza A (H1N1) 2009 virus and screening for a key oseltamivir resistance (H275Y) substitution in neuraminidase.

J Clin Virol. 2009 [Epub ahead of print].
4. Centers for Disease Control and Prevention (CDC). Oseltamivir-resistant 2009 pandemic influenza A (H1N1) virus infection in two summer campers receiving prophylaxis - North Carolina, 2009. *MMWR Morb Mortal Wkly Rep*. 2009;58:969-72.
5. Leung TW, et al. Detection of an oseltamivir-resistant pandemic influenza A H1N1 virus in Hong Kong. *J Clin Virol*. 2009;46:298-9.
6. FDA. Emergency use authorization of peramivir IV fact sheet for healthcare professionals. Food and Drug Administration. Silver Spring, MD: U.S. Department of Health and Human Services, FDA; 2009. Available at http://www.cdc.gov/h1n1flu/eua/Final%20HCP%20Fact%20sheet%20Peramivir%20IV_CDC.pdf
7. Centers for Disease Control and Prevention (CDC). Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza in the 2009-2010 season. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2009. Available at www.cdc.gov/h1n1flu/recommendations.htm
8. Robson R, et al. The pharmacokinetics and tolerability of oseltamivir suspension in patients on haemodialysis and continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant*. 2006;21:2556-2562.
9. Wattanagoon Y, et al. Pharmacokinetics of high-dose oseltamivir in healthy volunteers. *Antimicrob Agents Chemother*. 2009;53:945-952.
10. Centers for Disease Control and Prevention (CDC). Oseltamivir-resistant novel influenza A (H1N1) virus infection in two immunocompromised patients - Seattle, Washington, 2009. *MMWR Morb Mortal Wkly Rep*. 2009;58:890-896.

Should Patients with Prosthetic Joints Routinely Receive Antibiotic Prophylaxis When Undergoing Dental Pocedures?

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Synopsis: *A case-control study found no evidence supporting the use of routine antibiotic prophylaxis in patients with prosthetic knee or hip joints when undergoing dental procedures.*

Source: Berbari EF, et al. Dental prodecures as risk factors for prosthetic hip or knee infection: A hospital-based prospective case-control study. *Clin Infect Dis*. 2009 Dec 1. [Epub ahead of print].

In 2003, the American Academy of Orthopedic Surgeons (AAOS) and the American Dental Association jointly published recommendations regarding antibiotic prophylaxis for dental patients who had had total joint replacements.[1] They concluded that "antibiotic prophylaxis is not indicated for dental patients with pins, plates, or screws, nor is it routinely indicated for most dental patients with total joint replacements. However, it is advisable to consider premedication in a small number of patients who may be at potential increased risk of experiencing hematogenous total joint infection." In 2009, however, the AAOS electronically published an "Information Statement" with a radically different recommendation: "the AAOS recommends that clinicians consider antibiotic prophylaxis for most patients with total joint replacements."[2] The following disclaimer accompanied the recommendation: "This Information Statement was developed as an educational tool based on the opinion of the authors. Readers are encouraged to consider the information presented and reach their own conclusions." This change in position by the AAOS was made in the apparent absence of new data in its support. Berbari et al at the Mayo Clinic in Rochester, Minnesota, have now published a case-control study that instead supports the previous position and provides a more solid basis for clinicians to come to a rational conclusion.

Case patients were individuals hospitalized with hip or knee prosthetic infections from 2001-2006, while controls were patients who had undergone hip or knee replacements who were hospitalized during the same time period on the same orthopedic floor. Dental records were examined directly or indirectly for each subject. Among patients who received no dental prophylaxis, there was no evidence of an increased risk of prosthetic joint infection (PJI). This was true whether they had undergone a low-risk or high-risk dental procedure.

Only 35 of the 339 infections (10.3%) were caused by organisms that were potentially of oral or dental origin. Analysis of this group along with 35 controls also failed to demonstrate an increased risk of infec-

tion in association with a lack of antibiotic prophylaxis. This was also true in subset analyses of patients who were immunocompromised, had diabetes mellitus, prior arthroplasty, or who had undergone joint replacement in the previous 12 months. The investigators concluded that "Dental procedures were not risk factors for subsequent total hip or knee infection. The use of antibiotic prophylaxis prior to dental procedures did not decrease the risk of subsequent total hip or knee infection."

Most PJI occurring in the months following joint implantation are the result of inoculation of the surgical site at the time of the procedure. Hematogenous infection is much more likely to occur later — generally more than 1 or 2 years after the procedure and the majority of these are due to staphylococci. As in this study, only approximately 10% of PJI are caused by organisms that could potentially be considered of oral or dental origin. This is true despite the fact that bacteria, including those of dental origin, enter the bloodstream with amazing frequency as the result of activities of daily living, such as toothbrushing and even the chewing of food. Thus, it has been estimated that such activities result in approximately 5,370 minutes (89.5 hours) of bacteremia each month.[3] If correct, this means that 12.4% of our lives are spent with bacteria in our bloodstream. Bacteremia resulting from a dental extraction generally lasts for only 6 to 30 minutes. Thus, for an individual who has a single dental extraction in a year, the resulting bacteremia accounts for only 0.01%-0.05% of the total duration of bacteremia in those 12 months.

Thus, there appears to be no rationale for the routine administration of antibiotic prophylaxis to patients with prosthetic hip or knee joints who are undergoing either dental procedures, including those considered high risk. The optimal approach to prevention of late PJI of dental origin is, instead, the provision of optimal dental hygiene. ■

References

1. Antibiotic prophylaxis for dental patients with total joint replacements. *J Am Dent Assoc*. 2003;134:895-899.
2. AAOS. Antibiotic Prophylaxis for Bacteremia in Patients with Joint Replacements. http://www.aaos.org/about/papers/advistmt/1033.asp
3. Guntheroth WG. How important are dental procedures as a cause of infective endocarditis? *Am J Cardiol*. 1984;54:97-801.

CME Questions

19. Which of the following is correct with regard to the recommendations in the most recent (December 2009) DHHS Guidelines for Antiretroviral Therapy?

a. Antiretroviral therapy should not be initiated until the CD4 count drops below 200 cells/mm^3.
b. Efurtivide is active against and may be used to treat HIV-2 infections.
c. Tenofovir and emtricitabine are included as part of all the recommended first-line regimens.
d. Tenofovir plus emtricitabine plus ritonavir-boosted lopinavir is recommended as a first-line regimen.

20. Which of the following is correct?

a. Peramivir is active against influenza A virus resistant to oseltamivir.
b. Zanamivir is active against influenza A virus resistant to oseltamivir.
c. Resistance to oseltamivir is associated with mutations in the viral hemagglutinin gene.
d. Resistance to oseltamivir is associated with mutations in the viral M2 protein gene.

21. Which of the following is correct regarding the case-control study of antibiotic prophylaxis for dental surgery in patients with prosthetic joints?

a. Antibiotic prophylaxis was demonstrated to be protective.
b. Antibiotic prophylaxis was demonstrated to be protective, but only in patients undergoing high-risk dental procedures.
c. Antibiotic prophylaxis was demonstrated to be protective, but only in patients with diabetes mellitus.
d. Dental procedures were not found to be a risk factor for the development of infection of hip or knee prostheses.

Answers: 19. (c); 20. (b); 21. (d)

CME Objectives

Upon completion of this educational activity, participants should be able to:

• discuss the diagnosis and treatment of infectious diseases;

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

• discuss the latest information regarding risks, benefits and cost-effectiveness of new and traditional diagnostic tests; and

• discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies. ■

CME Instructions

Physicians participate in this CME program by reading the issue, using the references for research, and studying the questions. Participants should select what they believe to the correct answers, then refer to the answer key to test their knowledge. ■

In Future Issues:

Histoplasmosis in Patients Eeceiving TNF Antagonists

UPDATES

By Carol A. Kemper, MD, FACP

Garlic Soup

Source:
www.nytimes.com/2009/11/20/world/europe

Watching my sniffling boyfriend boil six garlic cloves into tea the other day, he explained his Sicilian grandmother would do the same for them as kids when they had colds. Apparently, the Chief Medical Officer for the Moldovan Army agrees. With increasing numbers of H1N1 influenza cases occurring in Eastern Europe, the Moldovan Army will be providing every soldier two extra garlic cloves and a small onion with the usual daily rations in an effort to boost their immune systems.

Garlic has been used for centuries for its "antimicrobial" effects, along with several other foodstuffs and herbs, including allspice, pepper, oregano, thyme, lemon balm, onions, and green and black tea. Studies suggest that garlic extract may inhibit the growth of various bacteria, such as *E. coli* and pseudomonas. The garlic enzyme alliinase has been shown to have a wide range of antifungal activity, appears to act synergistically with azoles against *Candida spp*. in vitro, and has been used to target fungi using antibody-alliinase conjugates. In food preparation and storage, biofilms of oregano oil or garlic oil have been tested to help provide an aesthetically pleasing and palatable "antimicrobial barrier." Besides possible antimicrobial effects, some individuals believe that garlic functions as both an antioxidant and has potential beneficial cardiovascular effects by lowering blood pressure.

TB Screening Before Anti-TNF-alpha Therapy

Screening for latent TB infection (LTBI) seems to have only gotten that much more complicated and, increasingly, infectious disease experts are being asked to interpret the newer tests results, especially in persons with inflammatory disorders or underlying immune suppression. In addition to the different gamma-interferon-based (GIB) assays available on the market, newer versions of outdated tests have been introduced. While GIB assays are more sensitive and specific for LTBI than TST, especially in previously BCG-vaccinated persons, only a minority of healthy individuals with LTBI remain at risk for reactivation TB. What is really needed is a diagnostic test that can tell you who those people are.

On the other hand, GIB results have reportedly waned in some patients with prior TB exposure, suggesting that some patients at risk for reactivation TB may be missed with currently available screening tools. Immunosuppression, such as the use of corticosteroids, not only increases the risk of falsely-negative TST, but increases the risk of indeterminate GIB assay results.

A retrospective analysis examined 50 patients with psoriasis who were screened for LTBI using TST, T-SPOT.TB, and chest radiographs in advance of treatment with an anti-TNF-alpha agent.[1] Risk factors for LTBI, including prior TB exposure, abnormal chest radiograph suggestive of prior granulomatous disease, or residence in a country endemic for TB were compared to TST and T-SPOT.TB results. Ninety percent of the patients reported prior BCG vaccination; 20% had come from a country endemic for TB, 22% had had prior exposure to someone with TB, and 8% had abnormal chest radiographs.

The agreement between the TST and T-SPOT.TB tests, using kappa-quantified statistics, was poor (K = .3). Test results were discordant in 14 persons (28%) (both tests were negative in 28 persons and positive in 8). Twelve persons had a positiv TST (defined as > 5 mm), a negative T-SPOT.TB test, and a normal chest radiograph, while two persons had a negative TST, a positive T-SPOT.TB test, and an abnormal chest radiograph. The T-SPOT.TB test strongly correlated with risk factors for LTBI compared with the TST.

Ten of 12 patients with a positive TST/negative T-SPOT.TB and a normal chest radiograph received no treatment for LTBI. This group received anti-TNF therapy with a mean follow-up of 76 weeks, with no evidence of reactivation TB. In contrast, one of 10 patients with a +T-SPOT.TB test developed miliary TB while receiving treatment for LTBI and anti-TNF-alpha therapy. Remarkably, 68% of the patients had received prior immunosuppressive therapy, which, while not further specified, raised the possibility of selection of patients at lower risk for developing reactivation TB.

Similar data were observed using the first-generation Quantiferon TB Gold test compared with TST in

a group of 302 patients with inflammatory diseases (ie., rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis) who were candidates for anti-TNF-alpha therapy.[2] Sixty percent of the patients were female, with an average age of 50 years. In those with available histories, 152 of 200 reported prior BCG vaccination (76%), 9% reported prior exposure to TB, 8% were from countries endemic for TB, 4% had abnormal chest radiographs consistent with previous granulomatous infection, and 3% had received prior TB treatment. In all, 69 (29%) of the patients had one or more risk factor for LTBI. Using Danish guidelines, 45/241 (19%) patients had a positive TST (> 6 mm, or > 12 mm for those with prior BCG vaccination), while using U.S. Guidelines, 66 (28%) had a positive TST. In comparison, the Quantiferon was positive in 7%, negative in 88%, and indeterminate in 5%. Higher CD4 counts in patients correlated with a higher level of interferon-gamma production and greater likelihood of indeterminate quantiferon test results. In addition, corticosteroid therapy increased the number of indeterminate tests results, while decreasing the sensitivity of the TST.

Using kappa-quantified statistics results, the agreement between the two tests was only K = .2. The Quantiferon TB Gold was significantly associated with risk factors for TB (RR 4.7, p = .002), especially prior residence in a TB endemic area (RR 7.8, p > .0001). Interestingly, 18 of 45 had +TST negative Quantiferon TB Gold test. Of those 18 with a positive Quantiferon results, only nine (50%) had a positive TST. Thus, the authors postulate that by using the TST alone significantly more patients would have received unnecessary treatment for LTBI, especially based on U.S. guidelines, but 50% of those at risk for reactivation LTBI would have been missed. Based on the lower sensitivity of the TST in this group compared with the Quantiferon TB Gold, and despite the discordant results, the authors advocate that both tests should be taken in consideration when screening for LTBI in patients with inflammatory diseases.

References

1. Laffitte E., et al. Tuberculosis screening in patients with psoriasis before antitumor necrosis factor therapy: Comparison of an interferon-gamma release assay vs tuberculin skin test. *Brit J Dermatol*. 2009;1-4.
2. Soborg B, et al. Comparison of screening procedures for *Mycobacterium tuberculosis* infection among patients with inflammatory diseases. *J Rheumatol*. 2009;36:1-9.

Chronic HEV in HIV

Source: Dalton HR, et al. Persistent carriage of Hepatitis E Virus in Patients with HIV infection. *N Engl J Med*. 2009;361:1025-1027.

Hepatitis e virus, similar to Hepatitis A virus, is transmitted by fecal-oral contact, and is believed to cause a self-limited acute viral hepatic infection. Recently, chronic HEV infection with progression to chronic liver disease has been described in solid organ recipients with immunosuppression and in a patient with lymphoma taking rituximab.

Dalton et al describes a 48-year-old HIV-positive man with a history of heavy alcohol use and a CD4 count less than 200 cells/mm^3, despite virologic suppression. For nearly two years, he had modest elevation in transaminases. Using PCR, HEV RNA was found in serum and feces — and looking back at samples from 18 months earlier, HEV was isolated from earlier specimens. ELIZA tests were positive for IgM and IgG during the previous 18 months (but were negative using an alternate assay). Genotyping confirmed HEV as genotype 3, the most prevalent genotype in developing countries. Liver biopsy confirmed active inflammation and cirrhosis.

This report indicates that patients with more advanced HIV may develop chronic HEV infection and progressive liver disease. How frequently this occurs is not known. HEV seroprevalence data from various countries vary from 5.9% in healthy Indonesian adults, to 11.4% in healthy Iranian blood donors, to 17.7% in Brazilian women attending an STD clinic for HIV screening. In Malaysia, anti-HEV antibodies were found in 14.4% of HIV-seropositive patients, although RNA studies were not performed. However, no evidence of HEV infection was found in 50 HIV-positive individuals with CD4 counts < 200 mm^3 or in 43 HIV-positive individuals with cryptogenic cirrhosis in Spain. A single report from France described a case of acute HEV infection in an HIV-infected patient with a CD4 count of 246 cells/mm^3. Initial studies demonstrated HEV RNA in serum, but subsequent studies demonstrated resolution of infection.

HEV screening should be considered in patients with HIV infection, especially those with persistent unexplained elevations in hepatic transaminases. Serum HEV RNA may be useful in monitoring resolution of active HEV replication in HIV+ persons. ■

PHARMACOLOGY WATCH

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

Niacin Beats Ezetimibe Head to Head

In this issue: *Statin and niacin increase HDL-C, omeprazole reduces effectiveness of clopidogrel, darbepoetin increases risk of stroke, statins decrease risk of gallstone disease, FDA Actions.*

Statin plus niacin or ezetimibe?

Raising HDL-cholesterol (HDL-C) with niacin plus a statin is superior to lowering LDL-cholesterol (LDL-C) with ezetimibe plus statin in reversing atherosclerosis according to the widely reported ARBITER trial published on-line in the *New England Journal of Medicine* in November and simultaneously reported at the American Heart Association meeting in Orlando, FL. The trial enrolled more than 200 patients with coronary heart disease or a coronary heart disease equivalent who were receiving long-term statin therapy with an LDL-C < 100 mg/dL along with an HDL-C < 50 mg/dL for men or 55 mg/dL for women. The patients were randomly assigned to receive extended-release niacin (target is 2000 mg/day) or ezetimibe (10 mg/day). The primary endpoint was the difference in change from baseline in mean and maximal carotid intima-media thickness after 14 months. The trial was terminated early in July of 2009. Both drugs were effective in their roles — the mean HDL-C in the niacin group increased by 18.4% over the 14-month study period ($P < 0.001$) and the mean LDL-C level in the ezetimibe group decreased by 19.2% ($P < 0.001$). Niacin significantly reduced LDL-C and triglycerides as well, while ezetimibe lead to a reduction in HDL-C and triglycerides. Niacin was superior to ezetimibe in reducing the primary endpoint, leading to a reduction of both mean ($P = 0.001$) and maximal carotid intima-media thickness ($P \leq 0.001$ for all comparisons). Paradoxically, greater reductions in LDL-C seen with ezetimibe were significantly associated with increases in the carotid intima-media thickness. The incidence of major cardiovascular events was also lower in the niacin group than in the ezetimibe group (1% vs 5%; $P = 0.04$ by the chi square test) (published on-line at: www.nejm.org; Nov. 15, 2009).

The study has received enormous attention not only because of the primary endpoint, but also because of the significant reduction in major adverse cardiac events in the niacin group, even though the numbers were quite small. At least one editorialist laments the early termination of the study and feels that it is impossible to make recommendations regarding the "adjuvant agent of choice" based on the small numbers (The HALTS Trial — Halting Atherosclerosis or Halted Too Early; published on-line at: www.nejm.org; Nov. 15, 2009). Still, this study provides enough evidence to consider adding niacin to a statin in patients who are at risk of or have low HDL-C. It also deals another blow to ezetimibe (Zetia®) and its partner drug ezetimibe/simvastatin (Vytorin®).

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) 262-5468. E-mail: paula.cousins@ahcmedia.com.

Omeprazole's effect on clopidogrel

The FDA has issued a warning regarding the combination of clopidogrel (Plavix®) with omeprazole (Prilosec®) citing new data that suggest that the combination reduces clopidogrel's effectiveness by about half. Studies reported in 2009 suggested that omeprazole may block clopidogrel's conversion to its active metabolite via CYP2C19, an enzyme that is inhibited by omeprazole. New studies requested by the FDA from the manufacturers confirm a significant interaction between the two drugs, which can significantly hinder clopidogrel's ability to prevent platelet aggregation in patients at risk for heart disease. Omeprazole and clopidogrel are commonly prescribed together to prevent GI bleeding. At this time it is unclear whether this interaction extends to other proton pump inhibitors, although physicians are encouraged to avoid a combination of clopidogrel with esomeprazole (Nexium®, cimetidine (Tagamet®), and other drugs known to inhibit CYP2C19. The FDA is recommending that patients who need GI protection in conjunction with clopidogrel may safely use ranitidine (Zantac®), famotidine (Pepcid®), nizatidine (Axid®), or oral antacids.

Darbepoetin and risk of stroke

Darbepoetin alfa (Aranesp®) is commonly used in patients with chronic kidney disease and diabetes for the treatment of anemia. A new study suggests that the drug may be associated with increased risk of stroke in this patient population. More than 4000 patients with diabetes, chronic kidney disease, and anemia were randomly assigned to darbepoetin alfa to achieve a hemoglobin level of 13 g/dL or placebo with rescue darbepoetin alfa if hemoglobin levels dropped < 9 g/dL. The primary endpoints were the composite outcomes of death or cardiovascular event, and death or end-stage renal disease. After a follow up of 2.5 years, darbepoetin alfa was ineffective at preventing either primary outcome, and, more importantly, the rate of fatal or nonfatal stroke occurred almost twice as often in the treatment group (101 patients assigned to darbepoetin alfa vs 53 patients assigned to placebo; HR, 1.92; 95% confidence interval, 1.38-2.68; $P < 0.001$). The authors conclude that the use of darbepoetin alfa in patients with diabetes, chronic kidney disease, and moderate anemia who are not undergoing dialysis did not reduce the outcome of death, cardiovascular events, or renal events, but was associated with increased risk of stroke. For many "this risk will outweigh the potential benefits" of the drug (*N Engl J Med* 2009;361:2019-2032). Erythropoiesis-stimulating agents have come under fire in the treatment of cancer-associated anemia, and now in renal patients as well. As pointed out in an accompanying editorial, the risks and benefits of these agents must be weighed, namely an increased risk of stroke vs a perceived improvement in quality of life (*N Engl J Med* 2009; 361:2089-2090).

Statins and gallstone disease

Statins have been shown to reduce the risk of cardiovascular disease and death from all causes. Now another potential benefit is being reported: Statins may reduce gallstone disease. Utilizing a large patient database from the United Kingdom, researchers looked at the risk of developing gallstones followed by cholecystectomy in relation to exposure to lipid-lowering agents. The longer patients took statins, the lower the risk for gallstone disease, with patients who had filled 20 or more prescriptions noticing 36% reduction in risk (AOR, 0.64; 95% confidence interval, 0.59-0.70). The authors conclude that long-term use of statins is associated with a decrease risk of gallstones followed by cholecystectomy (*JAMA* 2009;302:2001-2007).

FDA Actions

The FDA has approved a new topical treatment for the treatment of post-herpetic neuralgia (PHN). The capsaicin 8% patch must be applied to the skin by a health care professional since placement may be quite painful, requiring the use of a local topical anesthetic. The patch is applied for one hour during which patients must be monitored, including observation for increases in blood pressure. The patches may be cut to conform to the area of pain and up to 4 patches may be used. The one-hour application is reported to provide up to 12 weeks of reduced pain from PHN. The capsaicin 8% patch will be manufactured by Lohmann Therapie-Systems and distributed by NeurogesX as Qutenza™.

The FDA has approved romidepsin for the treatment of cutaneous T-cell lymphoma in patients who received at least one prior systemic therapy. The drug is a histone deacetylase inhibitor, the first of a new class of antineoplastics. Romidepsin will be marketed as Istodax® by Gloucester Pharmaceuticals. ■

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Donald R. Johnston
Senior Vice President/Group Publisher
AHC Media LLC

N #4005

3525 Piedmont Road NE
Building Six, Suite 400
Atlanta, Georgia 30305-1515
Tel (404) 262-7436
Fax (404) 262-7837
www.ahcmedia.com