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INSIDE

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Treatment of Severe 2009 Pandemic Novel H1N1 Infection. Many Questions, Few Answers.

SPECIAL FEATURE

By Stan Deresinski, MD, FACP

During the week ending October 31, 2009, 7.4% of all deaths in the United States reported to the CDC were due to pneumonia and influenza and > 99% of all subtyped influenza A viruses were 2009 influenza A H1N1 viruses.[1] While the treatment of mild influenza virus infection is relatively settled, many questions remain with regard to the management of patients with severe infection.

Antiviral Therapy

All isolates of the 2009 pandemic H1N1 influenza virus to date are resistant to the adamantanes, amantadine and rimantadine, but remain susceptible to zanamivir and are only rarely resistant to oseltamivir. Zanamivir is only commercially available for administration by inhalation with the device provided and may not be administered by nebulization, while oseltamivir is only available for enteral administration. Thus, zanamivir cannot be administered to very young children or to patients undergoing mechanical ventilations and is not recommended for individuals with underlying airways disease, while oseltamivir cannot be administered to patients unable to take oral medications, except via a nasoenteric tube.[2] Two antiviral preparations suitable for parenteral administration, an intravenous form of zanamivir and peramivir, are under investigation and may be accessed for use under treatment IND. Zanamivir has the potential advantage over peramivir of retaining activity against oseltamivir-resistant virus but the investigational IV formulation has been difficult to access, while the latter is more readily available. Additional agents, such as DAS181, a novel sialidase fusion protein that enzymatically removes sialic acids on the surface of respiratory epithelium, T-705 (an inhibitor of RNA polymerase), and antibody-based therapies are in earlier stages of investigation.

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Oseltamivir

The usually recommended (and U.S. FDA-approved) adult dose of oseltamivir for adults is 75 mg twic daily by mouth, but total daily doses approaching 1,000 mg have been reported to be tolerated in healthy volunteers. The IC50 of five isolates of novel H1N1 (A/California/04/2009) ranged from 0.28 nM to 1.41 nM, while those of zanamivir were 0.31 nM to 1.34 nM (0.09 ng/mL-0.37 ng/mL) and those of peramivir were 0.11nM to 1.98 nM (0.03 ng/ml-0.55 ng/mL).[3] The mean steady state trough concentration of oseltamivir with a dose of 75 mg twice daily is approximately 200 ng/mL, while it is approximately 300 ng/mL after 150 mg twice daily dosing in healthy volunteers and patients with mild influenza.[2] The bioavailability of oseltamivir administered by nasogastric tube has been addressed in three mechanically ventilated Vietnamese patients with H5N1 infection in whom administration of 150 mg twice-daily was associated with drug exposure in excess of that reported in normal volunteers who received the drug orally.[2] All three were receiving continuous venovenous hemofiltration; the associated ultrafiltration rate of the drug approximates the glomerular filtration rate. Of note is that one of the three was pregnant and likely had, as a result, a large volume of distribution. Published studies of oseltamivir pharmacokinetics in pregnancy, however, appear to be otherwise totally lacking.

Thus, the available data indicate that the serum concentrations of oseltamivir after oral administration are well in excess of the IC50 for pandemic H1N1. Nonetheless, although the kinetics would suggest it may be unnecessary, limited experimental evidence in mice and ferrets suggests that more intense drug administration may be beneficial, and it has been suggested that severely ill patients receive 150 mg oseltamivir twice daily, rather than the usual lower dose, and that it be administered for 10 instead of five days.[3] Studies in Thai volunteers found a 205% increase in oseltamivir area under the curve with a doubling of the administered dose without reduction in rapid conversion from the prodrug to the active carboxylate.[4] Administration of probenecid significantly reduces clearance of oseltamivir.[4] Although the available data is minimal, it is possible that higher doses may be associated with improved penetration at sites of infection. While there appear to be no published studies examining the penetration of oseltamivir into pulmonary tissue or epithelial lung fluid, the median concentration in saliva in healthy volunteers was only 4.7%.[4] It should be noted, however, that there are no studies demonstrating improved outcome with "high-dose" oseltamivir. In fact, in one study, 150 mg twice-daily regimens were associated with only a statistically nonsignificant reduction in the duration of symptoms of approximately two hours.[5] Whether this is true for more severely ill patients has not been determined.

Oseltamivir is administered as the phosphate, which is rapidly converted to the active form by hepatic carboxylesterases. Despite this, no dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score ≤ 9); there is no published data in patients with severe hepatic impairment.

Since almost all of the active metabolite is renally excreted, dose adjustments are recommended in the presence of renal insufficiency, a subject that has recently been reviewed here.[6] Assuming that the appropriate dose in an adult with normal renal function is 75 mg twice daily, the dose should be reduced to 75 mg once daily if the glomerular filtration rate (GFR) is 10-30 mL/min. No data are available at lower GFRs, and the product insert contains no recommendations in that circumstance. Others, however, have recommended 30 mg every 10 days in the absence of dialysis. Administration of oseltamivir 30 mg after alternating hemodialysis sessions or 30 mg once a week after a peritoneal dialysis session appear to represent safe and potentially effective regimens for ESRD patients.[6] In patients undergoing continuous arteriovenous or venovenous hemofiltration, 75 mg once daily may be considered.

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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.

Table

2009-2010 Influenza Season Triage Algorithm for Adults (> 18 years old) with Influenza-like Illness

Are all of the following present:

1. Age greater than 18 years
2. Fever or feverishness•
3. Cough or sore throat

• If antipyretics are taken, this may inhibit a patient's ability to mount a fever.

No →

Although influenza cannot be ruled out in this patient, this algorithm should be used to guide clinical making in this case. Advise them to contact their healthcare provider for advice about their current illness if they are concerned about their health or to call emergency care if they have any warning signs of severe illness. Many people with influenza — including 2009 H1N1 — will not have a fever. Other symptoms of influenza can include chils, body aches/muscle pain, headaches, fatigue, runny nose, and occasional diarhhea and vomiting.

Yes ↓

Are any of the following present:

- Difficulty breathing or shortness of breath
- Pain or pressure in the chest
- Dizziness
- Confusion
- Severe or persistent vomiting
- Flu-like symptoms improved but then return or worsen in a few days

These symptoms are purposely broad to minimize the possibility of misclassifying people who truly have severe disease. The person attempting to triage the patient should take into account the severity and duration of the symptoms and the patient's ability to care for him or herself or access a reliable caregiver when deciding whether or not patients should be advised to seek care immediately.

Yes →

This patient should be advised to seek emergency medical care immediately

No ↓

Is this patient:

- Age 65 years or older
- Pregnant up to two weeks postpartum (including following pregnancy loss)

Or are any of the following comorbid conditions present:

- Chronic pulmonary (including asthma), cardiovascular (except isolated hypertension), renal, hepatic, hematological (including sickle cell disease), or metabolic disorders (including diabetes mellitus)
- Disorders that can compromise respiratory function or the handling of respiratorysecretions or that can increase the risk for aspiration (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders)
- Immunosuppression, including that caused by medications or HIV

Note: Obese patients and morbidly obese patients should be carefully evaluated for the presence of underlying medical conditions that are known to increase the risk for influenza complications, and should receive empiric treatment when these conditions are present, or if signs of lower respiratory tract infections are present.

Yes →

This patient is at higher risk for influenza complications. The patient should be advised to contact their healthcare provider to discuss antiviral treatment that day. Providers may advise such patients to take antiviral medications for treatment and/or therapy. Early use of antiviral medications can reduce the risk of influenza-related complications.

No ↓

Based on the information above, this patient is at low risk for influenza complications and may not require testing or treamtnet for influenza if their symptoms are mild. Should their symptoms worsen, or if they are concerned about their health, they should be advised to seek medical care. In order to help prevent spread of influenza to others, these patients should be advised:

- to keep away from others, to the extent possible, particularly those at higher risk for complications from influenza
- to cover their coughs and sneezes
- Wash their hands frequently with soap and water or use an alcohol-based hand rub if soap and water are not available
- Stay home until 24 hours after their fever is gone.

Source: http://www.cdc.gov/H1N1flu/clinicians/pdf/adultalgorithm.pdf

Additional information available at: http://www.cdc.gov/H1N1flu/guidance_homecare.htm

Zanamivir

There appears to be very limited published information on the use of higher than recommended doses of inhaled zanamivir, < 20% of which is absorbed into the systemic circulation.[7] In a single trial, administration of 10 mg four times daily demonstrated a trend toward improved outcome relative to the standard twice-daily regime, but the differences did not achieve statistical significance.[8] The still-investigational formulation of zanamivir suitable for intravenous administation[9] is said to be available from GlaxoSmithKline, but some colleagues have had difficulty accessing it.

Peramivir

Peramivir is a neuraminidase inhibitor with a spectrum of activity similar to that of oseltamivir which is undergoing investigation as a parenteral formulation. The U.S. FDA has authorized the use of peramivir under an Emergency Use Authorization.[10] Its use is authorized for hospitalized adult patients for whom therapy with an IV agent is clinically appropriate, based upon one or more of the following reasons:

- lack of response to oseltamivir or inhaled zanamivir;
- drug delivery by inhalation or by the enteral route is not expected to be dependable or is not feasible;
- the clinician deems intravenous therapy is appropriate due to other circumstances.

The use of peramivir is appropriate in hospitalized pediatric patients for either of the first two reasons above, but not the third.

Antiviral Combinations

The use of antivirals in combination is under study. The triple combination of oseltamivir, amantadine, and ribavirin was synergistic against several influenza strains in vitro, although pandemic H1N1 was not tested.[11] This combination is being studied in comparison to oseltamivir monotherapy in randomized clinical trials in immunocompromised patients.[12]

Adjunctive Immunomodulation

The progression of pulmonary disease in some patients with severe influenza virus infection despite receipt of antiviral therapy may be due to an overexuberant inflammatory response, an observation that has led to suggestions for the use of adjunctive corticosteroid therapy, as has been recommended in the management of patients with adult respiratory distress syndrome (ARDS). A recent guideline has recommended consideration of administration of moderate-dose glucocorticosteroid (1 mg/kg/day methylprednisolone as a continuous infusion) to adults with early severe ARDS (partial pressure of arterial oxygen/fraction of inspired oxygen [PaO2/FIO2] of < 200) and before day 14 in patients with unresolving ARDS.[13] There are, however, no clinical trial data to support this approach in patients with severe influenza or other viral pneumonias. Systematic reviews of studies in patients with SARS found no evidence of benefit.[14] Dexamethasone administration to mice with acute respiratory distress due to experimental H5N1 virus infection was not beneficial.[15] Corticosteroid administration is associated with prolonged shedding of seasonal influenza.[16] A retrospective review of 67 patients with H1N1 infection, in Ho Chi Minh City, found that corticosteroid administration was associated with an increased risk of death even when controlling for neutropenia on admission, a surrogate for disease severity.[17]

Other adjunctive immunomodulatory therapies, such as macrolides and statins, have also been considered. Two retrospective cohort studies of hospitalized patients have examined the association of statin therapy with outcomes. An evaluation of 415 patients, 84 of whom were receiving statin therapy, found that statin use was independently associated with a reduced length of hospital stay.[18] In a second study, 26% of 3,921 patients with laboratory-confirmed influenza infections, administration of statins during hospitalization was independently associated with improved survival (adjusted OR = 0.34; 95% CI 0.16 to 0.70).[19]

The administration of erythromycin to mice experimentally infected with influenza A/Kumamoto/Y5/67 (H2N2) was associated with reduced local inflammation and improved survival,[20] and administration of clarithromycin to patients with influenza was similarly associated with reduced inflammatory markers.[21]

Treatment of Bacterial Superinfection

Patients with influenza are at increased risk of bacterial pulmonary superinfection, most often due to *Streptococcus pneumoniae* or *Staphylococcus aureus*.[22] Early recognition and institution of appropriate antibiotic therapy is critical to outcome. Experiments utilizing a murine model of influenza with *S. pneumoniae* superinfection found that administration of clindamycin or azithromycin was associated with improved survival when compared to β-lactam therapy.[23] Evidence suggested that this was related to a reduced inflammatory response as evidenced by lower concentrations of inflammatory cells and proinflammatory cytokines, as well as less severe histopathologic changes in the lungs.

Extracorporeal Membrane Oxygenation (ECMO)

In addition to these pharmacological considerations, some evidence suggests the possibility that the use of extracorporeal membrane oxygenation in patients with influenza and respiratory failure may be associated with improved survival.[24] The strength of the evidence is, however, severely limited by the non-randomized nature of the study.

Many Questions, Few Answers

The treatment of severe pandemic H1N1infection presents many choices, but little in the way of firm data with regard to many important therapeutic issues. The challenges presented to the clinician provide strong evidence of the need for federal support of a national clinical trials organization capable of moving quickly to implement appropriate investigations of therapeutic approaches to this and other infectious diseases. The following is a list of only some of the questions that urgently require answers:

• What is the appropriate dose of oseltamivir, including in special populations such as late pregnancy and massive obesity, as well as in patients with severe immunocompromise?

• What is the role of combination antiviral therapy, such as a regimen of oseltamivir, zanamivir, and ribavirin?

• What is the role of adjunctive corticosteroid therapy in patients with severe infection? What is the role of other immunomodulators, such as statins and macrolide antibiotics?

• Does ECMO have benefit in patients with severe influenza requiring mechanical ventilation?

The answers to these questions can only be addressed in multicenter clinical trials.

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Influenza H1N1 Can Hurt Muscles Bad

ABSTRACT & COMMENTARY

By Joseph F. John, MD

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Dr. John is a consultant for Cubist, Genzyme, and bioMerieux, and is on the speaker's bureau for Cubist, GSK, Merck, Bayer, and Wyeth.

Source: Ayala E et al. Rhabdomyolysis associated with 2009 influenza H1N1. *JAMA*. 2009;302:1863-1864.

IT HAS BEEN KNOWN FOR DECADES THAT INFLUENZA VIRUSes have a propensity to affect muscle. Muscle aches from mild to severe occur regularly with the acute attack of the virus. I can remember as a young resident being so sore that I had to be rolled over and back during the first few days of influenza illness.

In the most recent issue of *JAMA*, filled with reports of H1N1 from North America, a short letter to the editor from Stanford University Medical Center highlighted the versatility of 2009 H1N1.

The patient in question is a 28-year-old influenza survivor who had one week of shortness of breath, muscle aches, and fever. Her pulse oximetry on presentation was 80% on room air. Her WBC was only 2800/uL, the LDH was 1875 U/L, and the creatine kinase (CPK) was a massive 27,820 U/L (normal 13-156). There was hemoglobin in the urine and infiltrates on the chest radiograph.

The patient had to be intubated but was able to be treated with oseltamivir and broad-spectrum antibacterials. A bronchoscopic exam revealed very friable hyperemic mucosa. The BAL fluid, when cultured at the California state lab, grew influenza A 2009 H1N1. With intensive critical care, the CPK decreased from 27,820 to 18,000 on day two to 3,000 on day four, and then normalized. She was removed from mechanical ventilation on day 15 and discharged to home at day 18.

■ COMMENTARY

It would be ideal to know how many patients with 2009 H1N1 have major muscle involvement. My clinical impression is that it occurs in < 1% of patients who have seasonal influenza. A 2005 Japanese study of patients with influenza pneumonia placed the value much higher (9.3%), though only 63 patients were studied (*Nihon Kokyuki Gakkai Zashi*. 2005;43:731-735). Yet, for a disease that affects millions of patients per year, even 1% of 1 million is 10,000! When the year of novel influenza ends, perhaps we can get a better idea of the real prevalence.

Whatever the attack rate upon muscle, rhabdomyolysis is a real phenomenon that should fix the attention of providers when they see patients with severe influenza. In the Stanford patient, the CPK returned to normal quickly, but she still needed intubated and critical care in order to survive. The ability to diagnose 2009 H1N1 by viral culture resided in the Public Department of California Health, a testimony to our public health systems that have stepped up to the plate to help document strains of this season's influenza viruses. Culture from fluid obtained by BAL is a caveat of the present case, particularly since the nasopharyngeal sample was negative by PCR.

We await further descriptions of known and unknown complications as we watch the 2009 H1N1 pandemic unravel. Influenza remains a disease that can humble clinicians. Yet to quote a recent poem by the illustrious physician poet Jack Coulehan, "The grace of humility is a precious gift." ■

Red-cell ATP depletion and Protection Against *P. falciparum* Malaria

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: *ATP levels are reduced in homozygous PKLR-/- and heterozygous PKLR+/- erythrocytes. Sodium fluoride (NaF) produces ATP depletion in normal erythrocytes. A dose-dependent effect of ATP depletion on inhibition of parasite invasion and enhancement of phagocytosis of erythrocytes infected with ring-stage parasites was observed. A parallel increase in intraerythrocytic ATP levels by means of parasite-derived ATP was also seen.*

Source: Ayi K, et al. Adenosine triphosphate depletion of erythrocytes simulates the phenotype associated with pyruvate kinase deficiency and confers protection against *Plasmodium falciparum* in vitro. *J Infect Dis*. 2009;200: 1289-1299.

BLOOD WAS DRAWN FROM HEALTHY INDIVIDUALS LIVing in Toronto with normal hemoglobins and from donors who were known to have protein kinase deficiency (PKD), G6PD deficiency, and Beta thalassemia. Decreased ATP levels were observed in PKD and in NaF-treated normal erythrocytes in vitro. NaF had no direct antiparasitic activity. NaF treatment of normal erythrocytes simulated the phenotype associated with PKD, and these treated red blood cells demonstrated relative refractoriness to invasion by *P. falciparum*. NaF-treated erythrocytes infected by ring-stage parasites were more avidly phagocytosed by macrophages than normal untreated parasitized erythrocytes. Increased parasite-generated ATP was observed after *P. falciparum* invasion, and may compensate for low levels of ATP in PKD and in NaF-treated cells, thereby facilitating intracellular maturation of the trophozoite. This increase in parasite-generated ATP after invasion was not seen in G6PD deficient and thalassemic erythrocytes. PfPyrK (a *P. falciparum* pyruvate kinase) gene expression was shown to correlate with ATP levels in parasitized erythrocytes.

■ COMMENTARY

This study is the first to show that ATP depletion (and secondarily increased production of 2,3-DPG with a variety of downstream effects resulting in red cell membrane destabilization) is the mechanism underlying PKD-associated protection against *P. falciparum* malaria. These membrane effects impair parasite invasion and, by increased IgG and C3c binding to the damaged red cell membrane, also enhance monocyte-mediated phagocytosis of ring-stage parasitized erythrocytes.

The high prevalence of hemoglobinopathies and red-cell enzyme deficiencies (which presumably resulted from selective evolutionary pressure) in human populations who live in malaria-endemic areas has long fascinated clinicians. This study sheds some light on the mechanism likely responsible for the protective effect of PKD against infection with *P. falciparum*. ■

Respiratory Symptoms among Military Personnel Deployed to Iraq/Afghanistan

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *Data from the large prospective Millenium Cohort Study were examined with respect to respiratory symptoms, chronic bronchitis/emphysema, and asthma. Personnel deploying to Iraq or Afghanistan had higher rates of newly reported respiratory symptoms than non-deployers. This was seen only in Army and Marine Corps members who participated in land-based deployments.*

Source: Smith B, et al. Newly reported respiratory symptoms and conditions among military personnel deployed to Iraq and Afghanistan: A prospective population-based study. *Am J Epidemiology*. 2009;(epub 22 Oct): 1-9.

IN THIS STUDY, 77,047 PARTICIPANTS FROM THE U.S. Department of Defense prospective Millenium Cohort Study were enrolled in 2001; 55,021 underwent follow-up screening in 2004-2006. New-onset respiratory symptoms were defined as persistent or recurring cough or dyspnea reported at follow-up, with no previous report at baseline. Chronic bronchitis, emphysema, and asthma were defined as member-reported physician diagnoses. Multivariate analyses were conducted on the cohort. For deployed vs. non-deployed U.S. Army personnel, an unadjusted odds ratio (OR) of 1.79 for development of new-onset respiratory symptoms was observed. After adjustment for deployment status, sex, birth year, marital status, race/ethnicity, education,

smoking status, service branch, service component, military rank, and occupation, the adjusted odds ratio (AOR) remained 1.73. For Marine Corps personnel, the OR and AOR were 1.51 and 1.49, respectively. For Air Force and Navy/Coast Guard personnel, no significant association between deployment and respiratory symptoms was seen. No significant relationship between deployment and the diagnosis of chronic bronchitis/emphysema or asthma was seen in Army, Air Force, Navy/Coast Guard, or Marine Corps personnel.

■ COMMENTARY

Concern has been raised about possible increased rates of respiratory illnesses in military members during and following deployments to Iraq and Afghanistan. This large, prospective cohort study seems to confirm a signal supporting these previously anecdotal reports. Further analysis of the data show that specific exposure, rather than deployment, in general, is associated with new-onset respiratory symptoms. This is supported by the fact that elevated odds of developing respiratory symptoms were associated with land-based, rather than sea-based, deployment. A trend toward a dose-response effect was seen with longer deployments, typically performed by Army troops (often 12-15 months "boots on the ground"), being more commonly associated with new-onset respiratory symptoms.

My own anecdotal experience with four deployments to Iraq and one to Afghanistan since 2003 suggests that environmental exposure is likely multifactorial, with frequent exposure to dust (which is like fine talcum powder in Iraq) being the largest contributing factor. During sand storms, the daylight turns to a weird, dark orange glow, with visibility reduced to just a few meters, and these conditions can persist for days at a time. Concern has also recently been raised by the *Air Force Times* about the environmental effects of burn pits, particularly at the large Joint Base at Balad (about 80 km north of Baghdad), but the preliminary information I've read elsewhere in the lay press suggests that this is likely not a significant exposure contributing to respiratory illness. Speaking with Iraqi doctors and parents of children since 2006, I've also come away with the impression that they are seeing more frequent and prolonged respiratory symptoms in civilians in Iraq (especially children) as well. This may be related to the prolonged drought Iraq has experienced over the last several years due to decreased rainfall and to desertification from the diversion of water by Turkey from the Tigris and Euphrates Rivers and by Saddam Hussein's draining of the marshes in southern Iraq during the 1990s.

While this study strongly suggests that a "signal" is present that links deployment to Southwest Asia and new-onset respiratory symptoms, more work needs to be done. This would include more detailed evaluations and characterization of the illnesses in individual service members, additional teasing out of the survey data, and environmental assessment studies conducted in Iraq and Afghanistan. ■

Antibiotic Prophylaxis for Recurrent Urinary Tract Infections in Children

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

Professor of Pediatrics, Tufts University School of Medicine, and Chief Academic Officer, Baystate Medical Center, Springfield, MA

Dr. Jenson reports no financial relationships relevant to this field of study.

Synopsis: *The benefits of long-term, low-dose antibiotic prophylaxis to prevent recurrent urinary tract infection among predisposed children are modest (six percentage points); 14 children would require treatment for 12 months to prevent one urinary tract infection.*

Source: Craig JC, et al. Antibiotic prophylaxis and recurrent urinary tract infection in children. *N Engl J Med*. 2009; 363:1748-1759.

A PROSPECTIVE, MULTI-CENTER, DOUBLE-BLIND, PLACEBO-controlled, randomized trial of daily trimethoprim-sulfamethoxazole (TMP-SMZ; 2 mg TMP and 10 mg SMZ per kg) vs. placebo was conducted in four centers in Australia during 1998-2007 among children birth to 18 years of age with a history of at least one symptomatic, culture-proven urinary tract infection. All children received TMP-SMZ for two weeks during a single-blind run-in period, followed by randomization to TMP-SMZ or placebo (matched for color, taste, and texture) for 12 months. Clinical and demographical characteristics were comparable between the two groups. The median age at enrollment was 14 months, 64% were girls, and 71% were enrolled after the first documented urinary tract infection. Urinary tract imaging was not mandated; vesicoureteral reflux was documented in 42% of patients, with 53% of these having Grade III reflux.

Recurrent urinary tract infection developed in 36 of

288 patients (13%) in the TMP-SMZ group compared to 55 of 288 (19%) in the placebo group (hazard ratio in the TMP-SMZ group of 061; 95% CI, 0.40 to 0.93; p = 0.02). The reduction in the absolute risk of urinary tract infection (six percentage points) appeared consistent across all subgroups of patients — age, sex, reflux status, history of more than one urinary tract infection, or susceptibility of the index organism to TMP-SMZ. Thus, at 12 months, 14 patients (95% CI, 9 to 86) would have to be treated to prevent one urinary tract infection.

One-half of the repeat infections in the placebo group occurred in the first three months, and one-quarter occurred in the second three months. *Escherichia coli* was the most common organism in the TMP-SMZ group (30 of 36 patients) and in the placebo group (46 of 55 patients).

Very few patients had worsening of renal scanning results, with no significant differences between the two groups. Fewer hospitalizations and adverse drug events occurred in the TMP-SMZ group compared to the placebo group, but the differences were not significant. A test for trend, although not significant, showed that children in the placebo group were more likely to receive multiple courses of antibiotics than were children in the TMP-SMZ group.

■ COMMENTARY

Urinary tract infection is common among children and affects 8% of girls and 2% of boys by seven years of age. Daily, secondary prophylaxis with low-dose oral antibiotics has been advocated traditionally to reduce the risk of renal damage associated with recurrent urinary tract infections, especially in the presence of vesicoureteral reflux. There has been a dearth of controlled trials to justify this widespread practice. Recent studies published in 2006 (one study) and 2008 (three studies) found no benefit from antibiotic prophylaxis on reducing the incidence of urinary tract infection. Those studies had 218, 225, 100, and 338 subjects, compared to 576 in this new study, which appears to have contributed to limited statistical power of the previous studies to detect such a modest effect.

This study showed that the benefit of prophylaxis was greatest during the first six months. These results of modest reduction in the absolute risk of urinary tract infection in predisposed children (six percentage points), coupled with the low risk of new renal damage occurring with a single urinary tract infection (approximately 5%), suggest that the benefits of long-term, low-dose prophylaxis are small when applied across all patient groups. Additional randomized, controlled studies are underway to define which patient subgroups might have greater benefit from secondary prophylaxis. ■

Vertical Transmission of Hepatitis B from HBsAg-Negative Mothers

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

Synopsis: *Hepatitis B can be vertically transmitted even in the absence of maternal hepatitis B surface antigen (HBsAg), underscoring the importance and benefit of routine hepatitis B immunization of all newborns at birth.*

Source: Walz A, et al. Vertical transmission of hepatitis B virus (HBV) from mothers negative for HBV surface antigen and positive for antibody to HBV core antigen. *J Infect Dis*. 2009;200:1227-1231.

A STUDY OF VERTICAL TRANSMISSION OF HEPATITIS B virus (HBV) was conducted among 2,365 pregnant women in Germany who were negative for HBV surface antigen (HBsAg). The mothers were screened for antibody to HBV core antigen (anti-HBc) one day before or after delivery. Infants of mothers who were positive for anti-HBc were tested 3-4 months after birth for evidence of hepatitis B infection, as evidenced by HBsAg or HBV DNA using a highly sensitive polymerase chain reaction assay (Taq PCR).

Of the 2,365 mothers, 147 (6.2%) were anti-HBc positive at 3-4 months of age. Follow-up tests were available from 105 infants; seven infants had evidence of hepatitis B infection, five who were positive by HBV DNA and two who were positive for HBsAg. Follow-up assays were performed for five of these children at 5-15 months of age; none of these children developed chronic hepatitis B infection. Children in Germany typically begin HBV vaccination series at 2-3 months of age.

■ COMMENTARY

Hepatitis B can be transmitted by blood donors and organ donors who are positive for anti-HBc and negative for all other HBV serologic markers. This appears to reflect low-level viremia, even below the limits of detection of HBV DNA by PCR. This study similarly found that HBV can be vertically transmitted even in the absence of maternal HBsAg.

It is reassuring that, at least among this small number, all of these children apparently cleared the vertically acquired infection and none developed chronic HBV

infection. A high rate of clearance among these infants would be anticipated, especially with initiation of HBV vaccination at birth. In the United States, it is recommended that all newborns receive their first dose of HBV vaccine (not using a combination vaccine) at birth, prior to discharge from the newborn nursery. ■

CME Questions

16. Which of the following is correct with regard to oseltamivir?
a. The U.S. FDA-approved dose is 150 mg three times daily.
b. It is converted to the active form by hepatic enzymes.
c. The active form is almost entirely renally excreted.
d. It is metabolized by hepatic CYP450 enzymes.

17. Which of the following is correct
a. Peramivir is active against most influenza viruses resistant to oseltamivir.
b. Commercially available zanamivir may be administered through a nebulizer in mechanically ventilated patients.
c. Zanamivir is active against most influenza viruses resistant to oseltamivir.
d. Adjunctive systemically administered corticosteroids have been demonstrated in clinical trials to be beneficial to patients with severe influenza virus infection.

18. What is the major way to document major muscle involvement (rhabdomyolosis) in novel H1N1 infection?
a. Muscle biopsy
b. Urinary hemoglobin
c. Creatine phosphokinase (CPK)
d. Muscle MRI

Answers: 16. (b); 17. (c); 18. (c)

CME Objectives

The objectives of *Infectious Disease Alert* are to:

• discuss the diagnosis and treatment of infectious diseases;

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

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

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

In Future Issues:

Alternative Therapy Options for Influenza A H1N1

UPDATES

By Carol A. Kemper, MD, FACP

I've Got the Feline Flu

Source: ProMED-mail post November 5, 2009; www.promedmail.org; www.avma.org/public_health/influenza/new_virus.

VARIOUS STRAINS OF HUMAN INFLUENza virus can infect other mammalian species. Strains of H1N1 have been shown to cause respiratory illness in pigs, birds, and a group of family ferrets in Oregon. The American Veterinary Med-ical Association (AVMA) reports the first case of H1N1 influenza illness in a family cat. Two of three human members of the household were ill with flu-like symptoms before the 13-year-old cat developed respiratory symptoms and was taken to the Iowa State University's College of Veterinary Medicine for care. Nasal swab specimens were positive for 2009 influenza A (H1N1) virus. The WHO emphasizes that H1N1 infection in pets are "isolated events and pose no risk to human health." The Iowa DPH stated this event should not be too surprising, as other human influenza viruses have infected domestic cats.

The AVMA has posted and a FAQ sheet on their website for pet owners, warning that family pets can get the flu, and suggest that pets be protected from ill family members.

Bacterial Co-infection in H1N1 Influenza

Source: Bacterial Coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1) - US, May-August 2009. *MMWR*. 2009;58.

DATA EARLY ON IN THE PANDEMIC influenza outbreak suggested that most severely ill patients with Influenza A were not suffering from bacterial co-infection. An initial *MMWR* report found no evidence of bacterial superinfection in 30 patients hospitalized in April-May 2009 with confirmed H1N1 in California,[1] although 15 of 25 (60%) with chest radiographs had pulmonary infiltrates. Two-thirds had multilobar infiltrates and four patients required mechanical ventilation. A second report in the *MMWR* this summer described an additional 10 patients with H1N1 influenza requiring critical care in Michigan lacking evidence of bacterial pneumonia.[2]

These reports may have been misleading, insomuch as causative agents of pneumonia are difficult to identify, even under optimal circumstances. Newer data, based on autopsy specimens, suggest that nearly one-third of patients with fatal H1N1 illness have evidence of super-infecting bacterial pneumonia. Respiratory specimens (lung, trachea, and large-airway specimens) collected at autopsy from 77 patients with laboratory-confirmed fatal H1N1 infection were evaluated for evidence of bacterial infection. This included tissues stains, immunohistochemical antibody testing for various bacterial pathogens (including antibodies to *S. pneumoniae*, *S. pyogenes*, *S. aureus*, *H. influenza* but not legionella spp.), and PCR-based assays to further characterize streptococcal and pneumococcal infection. H1N1 infection was confirmed in 41 of the patients before death and identified in 36 patients post-mortem.

Of the 77 fatal cases of H1N1 infection submitted for analysis, 22 (29%) had histopathological, immunohistochemical, and molecular evidence of bacterial pneumonia.

Streptococcus pneumoniae was the most frequently identified pathogen, occurring in 10 persons (13%), followed by *S. aureus* (9.1%), *S. pyogenes* (7.8%), *S. mitis* (2.6%), and *H. influenza* (1.3%). Multiple bacterial pathogens were found in four patients (5%). The mean age at death was 31 (range, two months to 56 years), and half were male. The median duration of illness, available for 17 of the patients, was six days (range, 1 to 25 days). Fourteen had received some kind of medical care, at least seven had received antibiotics, and eight had been hospitalized. In 21 patients for whom this kind of information was available, 16 had significant underlying medical conditions known to increase the risk for severe influenza infection (five were described as obese, two each with diabetes, asthma, and Down Syndrome, and one with HIV infection).

The presence of bacterial pneumonia in nearly one-third of patients with fatal H1N1 infection should be viewed as a minimum estimate of the risk of bacterial superinfection in such patients. Even with the best techniques, super-infecting bacterial pneumonia in patients with viral pneumonia or ARDS may be difficult to confirm. Based on this data, empiric antibacterial therapy should be considered for critically ill patients with influenza, at least until their respiratory status has stabilized or improved. An agent with activity against MRSA should be considered, especially in persons at risk.

References

1. CDC. Hospitalized patients with novel influenza A (H1N1) virus

infection — California, April-May, 2009. *MMWR*. 2009;58:749-752.
2. CDC. Intensive-care patients with severe novel influenza A (H1N1) virus infection — Michigan, June 2009. *MMWR*. 2009;58:749-752.

Just Say "No" to N95s?

The debate over the use of N95s respirator masks when caring for persons with influenza has become contentious in our area, although it was obvious to most ID specialists and infection-control personnel that the unusually hyped-up requirements for PPE with this flu season were not evidence-based and added to the anxiety of health care workers caring for ill patients. Clinical and hospital staff have filed reports with Cal-OSHA reporting inadequate workplace precautions and a lack of access to respirators (these are some of the same nursing staff who refuse influenza vaccination every year). Despite CDC and Cal-OSHA recommendations for use of respirators in caring for patients with the flu, inadequate supplies of masks have been made available, and we've run out of the smaller masks at our hospital (which created problems when an infectious TB patient was recently admitted).

The initial CDC recommendations for the use of respirators with this flu season appear to have been based on early reports of higher than expected mortality (which were erroneous), the unknown potential for mutation to a more virulent strain, and the results of a single study, initially presented at ICAAC in September 2009,[1] suggesting that N95 masks provided superior protection against transmission of flu virus relative to regular surgical masks (although later data, presented at IDSA in October, found no statistically significant benefit[2]). These initially confusing results stemmed from an investigation of 1,936 health care workers from 24 hospitals in Beijing who were randomly assigned to N95 masks (fit tested), N95 masks (not fit tested), and regular surgical masks for four weeks, and then followed for five weeks. Preliminary data suggest that N95s were 56% protective against confirmed clinical respiratory illness and 70% protective against confirmed influenza. Regular surgical masks did not appear to offer protection. Subsequent analysis and adjustment for clustering and multiple comparisons failed to confirm a benefit for the use of N95s vs. regular masks.

These data were further supported by Loeb at al., published in *JAMA* in October 2009.[3] This non-inferiority trial compared N95s vs. regular surgical masks in 446 nurses in medical, surgical, and emergency units in eight Toronto hospitals during the 2008-2009 influenza season. Staff were randomly assigned to either mask. The primary outcome was confirmation of influenza by PCR or by a four-fold increase in hemagglutinin titers. Confirmed influenza occurred in 50 nurses (23.6%) wearing surgical masks and 48 nurses (22.9%) in the N95 group (absolute risk difference, — 0.73%, with the lower confidence limit not meeting criteria for non-inferiority).

Interesting data demonstrating a lack of airborne transmission for H1N1 influenza virus was observed during an outbreak of Influenza A (H1N1) among an American tour group traveling to China in June 2009.[4] A 40-year-old woman developed influenza-like illness, confirmed as H1N1, shortly before landing in China; her travel itinerary required three separate airflights and a tour bus (the kind where you cannot open the windows and 70% of the air is conditioned and recirculated). Several members of the tour group were quarantined, and everyone on the tour and on the airplanes was queried regarding the presence of ILI for the next two weeks. Ten additional cases of H1N1 were confirmed, including nine members of the tour group. The attack rate was higher for women than men (50% vs. 13%). Amazingly, of the 16 persons on the tour who had talked with the index case for at least two minutes, 56% developed influenza; if they had chatted for more than 10 minutes, the risk of infection was 5x greater. None of 14 members of the tour group who had not conversed with the index case became ill. Only one of 87 passengers on one of the flights, who was not on the tour group, but who had sat within two rows of the index case, developed influenza.

Just the act of chatting with the index case (as woman were obviously more wont to do) resulted in transmission of influenza virus through droplets. These data provide no evidence of airborne transmission of virus on the bus or on the airplanes. SHEA/IDSA/APIC have appealed to the Obama administration urging the White House to modify 2009 H1N1 guidelines for health care workers and to issue a moratorium on OSHA enforcement. Let's hope for a sensible response. ■

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1. MacIntyre C, et al. 49th ICAAC, September 15, 2009 (abstract K-1918b).
2. The IDSA abstract, 47th IDSA, October 2009 (abstract 1247)
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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*.

Insulin Regimens in Type 2 Diabetes

In this issue: Efficacy of once-daily insulin, aldosterone use in heart failure, erectile dysfunction Clinical Practice Guidelines, and FDA Actions.

Efficacy of once-daily insulin

Most type 2 diabetics, even those on oral medications, will eventually require insulin for glycemic control. A new study suggests that simple once-a-day insulin may be as effective as more complex regimens. Researchers from England evaluated 708 patients who had suboptimal hemoglobin A1c (HbA1c) levels while taking metformin and a sulfonylurea.

Patients were randomly assigned to receive biphasic insulin aspart twice daily, prandial insulin aspart three times daily, or basal insulin detemir once daily with an increase to twice daily if needed. Sulfonylurea therapy was replaced by a second type of insulin if hyperglycemia became unacceptable during the first year of this study or if HbA1c levels were > 6.5%. Outcomes measures were HbA1c levels, the proportion of patients with HbA1c ≤ 6.5%, the rate of hypoglycemia, and weight gain. After 3 years, median HbA1c levels were similar in all 3 groups. More patients had HbA1c levels < 6.5% in the prandial and basal groups, although more than 80% of patients in the basal group required a second type of insulin. The median number of hypoglycemic events per patient per year during the trial was lowest in the basal group (1.7) compared to the the biphasic (3.0) and prandial (5.7) groups ($P < 0.001$). Weight gain was highest in the prandial group. The authors conclude that the basal or prandial insulin-based regimens added to oral therapy resulted in better HbA1c levels compared to a biphasic insulin regimen. In addition, the basal group also had fewer hypoglycemic episodes and less weight gain. The authors state that the "results support the initial addition of a basal insulin to oral therapy, with subsequent intensification to a basal-prandial regimen..." (published at www.nejm.org Oct. 22, 2009).

In an accompanying editorial, Michael Roden, MD, points out that regardless of group, most subjects were accelerated to multiple doses of insulin per day. The study was sponsored by a manufacturer of insulin analogues, and only their analogue products were used in the study, whereas current consensus statements recommend regular human insulin. The editorial also points out that blood sugar control is only part of the equation with diabetics. Aggressive blood pressure control and use of statins and aspirin are equally important. Still, more studies are suggesting an early intensification of treatment with insulin may effectively reduce complications in type 2 diabetes (published at www.nejm.org Oct. 22, 2009).

For updated guidelines on the treatment of type 2 diabetes, see the recently released one-page algorithm from the American Association of Clinical Endocrinologists: www.aace.com/pub/pdf/GlycemicControlAlgorithm.pdf. ■

Aldosterone use in heart failure

Aldosterone antagonists are underused in

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. Dr. Elliott reports no financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

patients with moderate-to-severe heart failure (HF) and systolic dysfunction according to a new study in the *Journal of the American Medical Association*. Aldosterone antagonists (spironolactone and eplerenone) have been shown to be very effective in the treatment of HF such that they were designated class I (useful and recommended) in the recent American College of Cardiology/American Heart Association Chronic HF Guidelines. Despite this, the drugs are underused in eligible patients.

The current study was an observational analysis of more than 43,000 patients admitted to the hospital with HF and discharged home from 241 hospitals participating in the Get With The Guidelines — HF quality improvement registry between 2005 and 2007. Among 12,565 patients eligible for aldosterone antagonist therapy, only 4087 (32.5%) received one of the drugs at discharge. There was wide variation in aldosterone antagonist usage among hospitals (0%-90.6%) and was more likely to be used in younger patients, African Americans, those with lower blood pressure, history of implantable cardioverter-defibrillator, depression, alcohol use, pacemaker implantation, and those having no history of renal insufficiency. Inappropriate use of aldosterone antagonist therapy was low. The authors conclude that use of aldosterone antagonist therapy is underutilized in HF patients, occurring in only one-third of eligible patients, although the rate of use increased gradually throughout the course of the study. They also state that use of evidence-based guidelines in hospitals may be warranted to improve treatment of HF patients (*JAMA* 2009;302:1658-1665).

Many clinicians shy away from use of aldosterone antagonists because of concerns regarding hyperkalemia, especially since many of these patients are also on ACE inhibitors or ARBs. Aldosterone inhibitor use in HF is not part of the Joint Commission/Centers for Medicare and Medicaid Services core performance measures. Regardless, aldosterone antagonists have been shown to benefit patients with HF and they are clearly underutilized. ■

Erectile dysfunction guidelines

The American College of Physicians has published a Clinical Practice Guidelines regarding hormonal testing and pharmacologic treatment of erectile dysfunction (ED) in men. The guideline recommends that clinicians initiate therapy with a PDE-5 inhibitor (sildenafil, vardenafil, or tadalafil) in men who seek treatment for ED and do not have a contraindication such as concomitant nitrate use. They rate this a strong recommendation with high-quality evidence. The choice of a PDE-5 should be based on preference, including ease of use, cost, and adverse effects profile. The guideline does not recommend for or against routine use of hormonal blood tests or hormonal treatment in the management of patients with erectile dysfunction due to insufficient evidence to determine benefits and harm. The guideline reviewed more than 100 randomized controlled trials that showed that PDE-5 inhibitors improved successful sexual intercourse and improved erections in men with ED (*Ann Intern Med* 2009 Oct 19;). ■

FDA Actions

The FDA has authorized emergency use of IV antiviral peramivir for treatment of 2009 H1N1 influenza in hospitalized patients. The drug is not yet approved for use in this country, but was authorized in response to a request from the CDC. IV peramivir is approved only for hospitalized adult and pediatric patients for whom an IV drug is clinically appropriate because the patient is not responding to either oral or inhaled antiviral therapy, because enteral or respiratory therapy is not feasible, or in adults when a clinician judges that IV therapy is appropriate due to other circumstances. This is the first available IV antiviral available for 2009 H1N1 infections. For more information see www.cdc.gov/h1n1flu/eua/.

The FDA has approved the quadrivalent human papilloma virus (HPV) vaccine (Gardasil®) for use in boys and young men. The vaccine is approved for males ages 9-26 as 3 injections given over a 3-month period. HPV is the most common sexually transmitted disease in the United States with 1 of 500 men infected every year. Previously, the vaccine had only been approved for use in females ages 9-26 years. In related news, a recent study from the National Cancer Institute, CDC, and American Cancer Society has suggested that the vaccine is not cost-effective for women older than age 30 who undergo annual or biennial screening for cervical cancer (*Ann Intern Med* 2009;151:538-545). Similarly, a study from Harvard found that HPV vaccination for 12-year-old girls was cost-effective, but the same vaccination for 12-year-old boys was not (*BMJ* 2009 Oct. 8).

The FDA has also approved a bivalent HPV vaccine for use in females, which protects against HPV types 16 and 18. The vaccine is being marketed as a "cervical cancer vaccine" by GlaxoSmithKline under the trade name Cevarix®. ■