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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

Influenza, 2014-2015 — Something Old, Something New

By Stan Deresinski, MD

Dr. Deresinski is Clinical Professor of Medicine, Stanford University.

Dr. Deresinski has served as a one-time consultant for Cubist and Bayer.

As of early January, influenza activity had reached epidemic proportions in large parts of the United States, with many of those being affected despite prior vaccination.[1] The occurrence of infection in vaccinated individuals is not unexpected since influenza vaccine efficacy is usually only approximately 60%. There is, however, an additional problem during this influenza season because of an unanticipated mismatch between the components of the 2014-2015 vaccine, which are identical to the 2013-2014 vaccine composition, and the dominating circulating virus type. Thus, current trivalent influenza vaccines contain hemagglutinin (HA) derived from an A/California/7/2009 (H1N1)-like virus, an A/Texas/50/2012 (H3N2)-like virus, and a B/Massachusetts/2/2012-like (Yamagata lineage) virus. Quadrivalent influenza vaccines contain these antigens as well as a B/Brisbane/60/2008-like (Victoria lineage) virus.

H3N2 has accounted for greater than 95% of all influenza reported to CDC from U.S. WHO and National Respiratory and Enteric Virus Surveillance System collaborating laboratories during the current influenza season. Unfortunately, most of the circulating H3N2 viruses are antigenically dissimilar to the H3N2 vaccine strain, probably as the result of significant antigenic drift. A similar circumstance occurred during the H3N3-predominant 2007-2008 season in which the virus had also significantly drifted antigenically from the vaccine strain; the vaccine efficacy that year was only 43%. Early estimates for the current season indicate that the age-adjusted overall vaccine efficacy (VE) is only approximately 23%.[2] Nonetheless, CDC modeling suggests that a VE of only 10% in older adults could prevent approximately 13,000 influenza-associated hospitalizations in those aged ≥ 65 years in the United States during a moderately severe influenza season such as in 2012–13.

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Furthermore, past seasons in which H3N2 was the predominantly identified strain were often characterized by greater severity of disease among children younger than 5 years old and adults older than 65 years old when compared to H1N1- or influenza B-predominant seasons. Thus, CDC has estimated that an average of 28,909 people died from flu during H3N2 seasons from 1976 to 2007, while only 10,648 people died during years in which H3N2 was not predominant. While estimates of influenza-related deaths are incomplete, CDC indicates that the hospitalization rates are higher than in recent years and are similar to those observed during some past seasons in which H3N2 predominated.

Antiviral treatment remains effective, particularly when administered within 48 hours of symptom onset. In situations in which influenza has reached epidemic proportions, treatment can be initiated in outpatients on the basis of a compatible symptom complex and without confirmatory testing. In other circumstances, testing should be performed, but, as the CDC states, "Decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza." The recent first-ever CLIA waiver by the FDA of a point-of-care nucleic acid-based influenza diagnostic test (Alere™ i Influenza A&B) may lead to reconsideration of this recommendation.[3] While variable specificity of the test has been reported, all studies appeared to have found a sensitivity in excess of 90% for both influenza A and influenza B virus detection.[4-7]

The current circulating viruses, including the current H3N2 strain, are, with infrequent exception, susceptible to neuraminidase inhibitors, and either oseltamivir or zanamivir can be used to treat most patients in accord with CDC recommendations. Another neuraminidase inhibitor, peramivir, which is administered intravenously in a single (quite expensive) dose was approved by the FDA in December 2014. Its niche would appear to be limited to high-risk inpatients for whom enteral administration of medications is contraindicated because of, e.g., severe ileus or intestinal obstruction. ■

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Peramivir: A Newly Approved Antiviral for Treatment of Influenza

By Samaneh Pourali, PharmD, BCPS

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

Peramivir (Rapivab™) was recently approved by the FDA in December 2014 for treatment of acute uncomplicated influenza within two days of symptom onset. This newly approved antiviral is a neuraminidase inhibitor (NI) similar to oseltamivir and zanamivir but the first to be approved in an injectable formulation.[1] Peramivir has been licensed in Japan (as Rapiacta) and South Korea (as PeramiFlu) since 2010. In addition, it has been used in the United States on an emergency basis during the 2009 H1N1 flu pandemic.

The antiviral activity of peramivir was tested in laboratory strains and clinical isolates of influenza virus A and B. Cross-resistance within the NI class has been observed in biochemical assays and cell cultures, likely conferred by amino acid substitution in the viral neuraminidase or hemagglutinin proteins; however, clinical impact of reduced susceptibility is unclear.[1] However, no single amino acid substitution has been identified that could confer cross-resistance among the NI class and the M2 ion channel inhibitor class (amantadine and rimantadine).

In terms of pharmacokinetics profile, peramivir reaches peak concentrations shortly after the end of the 30-minute intravenous infusion. Protein binding is less than 30%, and the drug is not metabolized by hepatic CYP450 enzymes. Peramivir has a half-life of approximately 20 hours, and the majority of the drug (~90%) is eliminated by the kidneys via glomerular filtration as unchanged drug. In addition, hemodialysis was effective in reducing systemic exposure of peramivir by 73% to 81%. Therefore, peramivir dosing recommendations are based on a patient's renal function (CrCl) as stated in the table below.[1]

Efficacy of peramivir was established in a randomized, double blind, multicenter, placebo-controlled trial evaluating a single intravenous dose of peramivir 300 mg or 600 mg vs. placebo in 297 adult patients with uncomplicated influenza. Overall, subjects receiving peramivir 600 mg experienced alleviation of their influenza symptoms at a median of about 12 hours sooner compared to placebo.[2] In addition, two randomized, multicenter, double-blind clinical trials also compared the efficacy of peramivir with oseltamivir and demonstrated non-inferiority with peramivir for treatment of influenza.[3-4]

However, efficacy of peramivir in patients with serious influenza requiring hospitalization has not been established. A randomized, double-blind, multicenter, placebo-controlled trial was conducted in 338 subjects with serious influenza. Patients were randomized to receive peramivir 600 mg daily for 5 days plus standard of care versus standard of care plus placebo within 72 hours of symptom onset. The median time to clinical resolution was 42.5 hours (95% CI 34-57.9) for peramivir versus 49.5 hours (95% CI 40-61.9) for placebo (P = 0.97). Thus, peramivir plus standard of care did not improve median time to clinical resolution compared to standard of care alone. However, there was trend toward larger treatment effect for patients who received therapy within 48 hours of symptoms or were admitted to ICU at baseline. This study was terminated for futility after a preplanned interim analysis.[5]

Adverse effects were evaluated in five randomized, double-blind, controlled trials; 1,399 subjects with acute uncomplicated influenza received peramivir at doses up to 600 mg daily. The most common adverse effects of peramivir were diarrhea, insomnia, constipation, and hypertension. Rare but serious skin and hypersensitivity reactions including Stevens-Johnson syndrome, as well as neuropsychiatric events including delirium and abnormal behavior were also reported in post-marketing reports.[1]

A comparison of average wholesale prices for a course of therapy between NIs found that zanamivir costs approximately $70.80 for a 5-day course, oseltamivir is $144.72 for a 5-day course, and peramivir is $950 for a 1-day course for an average patient with normal renal function.

In conclusion, peramivir is a single-dose intravenous neuraminidase inhibitor approved for treatment of acute uncomplicated influenza. Data did not show any benefit in resolution of symptoms for treatment of complicated influenza in hospitalized patients. However, given availability of peramivir for intravenous administration provides an advantage in patients with difficulty with contraindications for enteral administration of oseltamivir or contraindications or inability to administer inhalation formulation of zanamivir. ■

Table. Peramivir Dosing Recommendations Based on Patient's Renal Function

Creatinine Clearance (mL/min)	≥ 50	30-49	10-29
Recommended Dose (mg)	600	200	100

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ABSTRACT & COMMENTARY

Reactive Hemophagocytic Syndrome in Adults — Results of a Large Case Series

By Dean L. Winslow, MD, FACP, FIDSA

SYNOPSIS: 162 adult patients from three centers in France were identified by consensus of three independent reviewers as having met criteria for reactive hemophagocytic syndrome. Hematologic malignancies were identified as the likely trigger in 56% of cases and these cases generally had worse outcomes than cases of reactive hemophagocytic syndrome associated with infection.

SOURCE: Riviere S, et al. Reactive hemophagocytic syndrome in adults: A retrospective analysis of 162 patients. *Am J Med* 2014;127:1118-25.

A multicenter retrospective study from three tertiary care centers in France was conducted in which charts from 312 patients with suspected hemophagocytic syndrome who underwent bone marrow aspiration were reviewed. Data were extracted in a standardized manner from the medical records. Three investigators independently reviewed the data and classified the patients into three groups: hemophagocytic syndrome (HPS) likely, HPS undetermined, and HPS unlikely. When there was disagreement with the classification, a fourth expert reviewed the data and the cases were further classified as likely or unlikely if 3 of 4 experts agreed. If there was no agreement the case was classified as undetermined.

Three hundred twelve patients fulfilled the initial inclusion criteria. After resolution of discordances, a diagnosis of likely HPS was found for 162 patients (52%), unlikely HPS in 104 patients (33%), and undetermined in 46 (15%). Of the 162 patients classified as HPS likely, hematologic malignancies (mainly non-Hodgkin lymphoma) were present in 92 (57%), infections were thought to be the trigger in 40 patients (24%), and hematologic malignancy plus active infection in 6 patients (4%).

Compared to patients without HPS, patients with HPS were more likely to be immunosuppressed, had higher temperature, ferritin, triglycerides, transaminases, bilirubin, LDH, CRP, and lower hemoglobin, leukocytes, platelets and sodium levels. Only 70% of patients with likely HPS actually had definite hemophagocytosis demonstrated on bone marrow examination.

Of the 162 patients with likely HPS, 61 (38%) received treatment for the underlying disease rather than treatment specifically directed to treat the HPS. Of the 101 patients specifically treated for HPS, 58 (58%) received only glucocorticoids or etoposide, 42 (42%) received both glucocorticoids plus etoposide, and 1 patient with infection-associated HPS received only IVIG. Sixty-eight patients (42%) with likely HPS died during follow up with 33 (20%) dying within 1 month of bone marrow aspiration. One-month survival analysis demonstrated that patients with hematologic malignancy-associated HPS had a poorer outcomes than did patients with infection-associated HPS.

■ COMMENTARY

Infectious disease specialists are often the clinicians who end up seeing in consultation and suspecting the diagnosis of reactive hemophagocytic in hospitalized patients presenting with fever and varying degrees of pancytopenia. Typically the patient has already received multiple courses of empiric antibiotics and continues to experience clinical deterioration. Hemophagocytic syndrome is a relatively rare disease characterized by an uncontrolled immune response resulting in inflammation, prolonged high fever, hepatosplenomegaly, and cytopenias associated with histiocytic infiltration of bone marrow, lymph nodes and other tissues. More recently it has been called histiocytic lymphohistiocytosis (HLH). Rare familial cases associated with several known genetic polymorphisms generally present in early childhood whereas most cases in adults are associated temporally with the presence of underlying hematologic malignancy, various infections or autoimmune disease.

At Stanford Hospital, we have seen about 6 cases of HLH in adults in the past 18 months. It is not clear whether we are actually seeing this rare disease more frequently or it is due to greater awareness and resulting diagnosis. I find HLH to be a challenging diagnosis to make since its major manifestations (fever, varying degrees of cytopenias, and elevated levels of inflammatory biomarkers) are nonspecific and can be seen with sepsis, viral infections, and cancer. Despite various scoring systems for diagnosis of HLH that have been described over the years, none of them have particularly good positive and negative predictive value. Also, in a large number of cases of HLH/HPS in which the diagnosis is confirmed, no clear trigger is identified due to the limitations of serologic testing for viral and other pathogens.

The most recent case of HLH seen by my team was a middle-aged man who had been admitted to the trauma service following a motor vehicle/pedestrian accident who developed fever in the ICU in the setting of catheter-associated bacteriuria, who remained febrile despite antibiotics, and was later noted to have progressive pancytopenia for which he underwent bone marrow aspiration (which demonstrated hemophagocytosis). An extensive workup for infections was negative except for slightly elevated IgM titers for *Mycoplasma pneumoniae*, but the final diagnosis (made by biopsy of his spleen) was B-cell lymphoma. One of our excellent Medicine interns deserves the lion's share of credit for his persistence in making the diagnosis in this case. ■

ABSTRACT & COMMENTARY

Antiviral Therapy Improves Outcomes in Immunocompromised but Not Immunocompetent HSV Meningitis Patients

By Richard R. Watkins, MD, MS, FACP

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

SYNOPSIS: A retrospective, observational, single-center study found immunocompromised patients are at increased risk for neurologic sequelae from HSV meningitis and likely benefit from antiviral therapy. There is no benefit to antiviral therapy in immunocompetent individuals.

SOURCE: Noska A, et al. The role of antiviral therapy in immunocompromised patients with herpes simplex virus meningitis. *Clin Infect Dis.* 2015;60:237-242.

Herpes simplex virus (HSV) is a very common cause of viral meningitis in adults. It occurs in approximately 30% of women and 10% of men at the time of primary genital acquisition, although many patients report no history of genital lesions. The vast majority of HSV meningitis in adults is due to HSV-2 and most cases of encephalitis are caused by HSV-1. While clinical practice guidelines recommend IV acyclovir for HSV encephalitis, similar data and recommendations for antiviral therapy in HSV meningitis are limited. Therefore, Noska and colleagues sought to determine if antiviral therapy has an impact on the clinical course of HSV meningitis and if there are differences between immunocompetent and immunocompromised patients.

The study was a retrospective observational one from a single institution that evaluated all patients with a positive cerebral spinal fluid (CSF) sample for HSV-1 or HSV-2 between July 2000 and November 2012. Patients were classified as immunocompromised if they had any of the following: HIV with a CD4 count < 500 cells/μL; diabetes mellitus; alcohol dependence; malignancy; severe malnutrition; or receiving steroids. Neurologic outcomes were determined by chart review. All cases had outpatient follow up with a primary care physician, an infectious diseases physician and/or a neurologist.

A total of 63 episodes of HSV CNS infection in 53 patients were identified. Of these, 42 were meningitis including 15 in immunocompromised patients. The median age was 35 years and 65% were women.

Among the 15 immunocompromised patients, 3 were treated with supportive care only and all developed neurologic sequelae (2 with chronic headaches and 1 had paresthesias of the hands and discoordination); 3 received oral antiviral therapy (median duration, 7 days) and all recovered completely; and 9 received a combination of intravenous (IV) and oral antiviral therapy, with 2 developing neurologic sequelae (1 with paresthesias of the hands and 1 with left arm pain). Two immunocompromised patients had recurrences and both developed neurologic sequelae (paresthesias in one and headaches and discoordination and paresthesias in the other). No CNS sequelae occurred in the immunocompetent group. The association between treatment and outcome was significant in the immunocompromised group ($P < 0.05$) but not in the immunocompetent group ($P = 1.0$). In other words, treating immunocompromised patients with antiviral therapy was associated with significantly fewer neurologic sequelae. Interesting, patients with HSV meningitis had higher CSF white blood cell (WBC) counts compared to those with encephalitis (median, 328 cells/μL vs. 50 cells/μL, respectively) and in one episode of HSV meningitis and 3 of HSV encephalitis the CSF WBC count was normal (< 5 cells/μL).

■ COMMENTARY

HSV meningitis is frequently encountered in clinical practice, yet there is a lack of strong evidence for its management. Therefore, the study by Noska and colleagues is welcomed because it adds to this body of evidence and helps inform medical decision making. Their main finding was that short course antiviral therapy seems to help immunocompromised patients by reducing neurologic sequelae but had no benefits for immunocompetent patients. In their short discussion they do not offer any possible explanation for this result and recommend treating immunocompromised patients with HSV meningitis with a 7 to 10 day course of antiviral therapy. Although this approach seems reasonable, the limitations of the study reduce its impact. These include a retrospective design that could have been influenced by confounding factors, a small sample, and that it was conducted at a single center which lessens its applicability to other settings. Moreover, differences in the routes of antiviral therapy could have influenced the results i.e. it is unclear if IV therapy led to better outcomes compared to oral therapy. Finally, the lack of benefit from antiviral therapy seen in immunocompetent patients is not surprising since these patients have a very low risk of neurologic sequelae at baseline.

Despite the informative study by Noska and colleagues, it will likely take a prospective randomized clinical trial with a large sample size to determine the optimal management of HSV meningitis. In the interim, I suggest treating immunocompromised patients with oral antiviral therapy (e.g., valacyclovir) for 7 days and using clinical judgment to decide about treating immunocompetent patients. For instance, antiviral therapy may be considered for immunocompetent patients who are severely ill or not improving after several days of supportive/conservative treatment. ■

ABSTRACT & COMMENTARY

Controlling the Spread of Chikungunya Virus: A New Possibility

By Leonard A. Haas and Philip R. Fischer, MD

Dr. Fischer is professor of pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN. Leonard A. Haas is a student at Mayo Medical School.

Dr. Fischer and Mr. Haas have no financial relationships relevant to this field of study.

SYNOPSIS: A phase-1 clinical trial of a virus-like particle (VLP)-based vaccine demonstrates safety, tolerability, and immunogenicity against rapidly spreading Chikungunya virus.

SOURCE: Chang L-J, Dowd K, Mendoza F, Saunders J, Sitar S, Plummer S, et al. Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: A phase 1 dose escalation trial. *Lancet* 2014;384(9959):2046-2052.

In this phase-1, dose-escalation trial conducted by Chang and colleagues, 25 healthy adult participants were divided into three dosage groups in order to test the safety, tolerability, and immunogenicity of a new candidate vaccine for Chikungunya virus. The vaccine is based on a virus-like particle (VLP), which

is highly immunogenic, safe, and capable of eliciting high titer neutralizing antibodies in non-human primates. VLP vaccines are also relatively easy to manage since live virus production is not needed. These virus-like particles included the E1, E2, and capsid proteins from the West African virus strain. The vaccine was given to participants in three sets of injections at weeks 0, 4, and 20, with three different dosages: 10 µg (n = 5), 20 µg (n = 10), and 40 µg (n = 10).
Immunogenicity was measured by determining the Chikungunya virus-specified humoral immune responses by ELISA and by neutralization antibody assays, measured at several time points. Additionally, green fluorescent protein (GFP)-expressing chimeric Chikungunya virus and a flow-based cytometry assay were used to measure neutralization titers.

The vaccine was well tolerated by the participants, with no major problems reported. Nine out of 25 participants (36%) reported mild localized symptoms after injection (pain/tenderness) and 10 of 25 participants (40%) reported mild systemic symptoms (malaise, myalgia, headache, and nausea). There were no reports of arthralgia after vaccination. Seven mild to moderate adverse reactions (transient alanine aminotransferase increases and transient neutropenia) were thought to be related to the vaccine because they occurred within 2-4 weeks after vaccination and resolved without problem. Further, antibodies to Chikungunya antigens were detected by ELISA in 100% of participants in the 10 µg and 40 µg groups and in 80% of the 20 µg group after the first injection and were substantially boosted by 4 weeks after the second and third injections, respectively. The geometric mean titers were not significantly different between the three dose groups and there was no significant difference between the group geometric mean titers 4 weeks after the second and third vaccinations. Neutralizing antibodies were also found against the east, central, and south African outbreak strain (OPY1) in all participants 4 weeks after the second vaccination and remained detectable six months after the third vaccination.

■ COMMENTARY

Since its initial recognition in the 1950s, Chikungunya has been rapidly spreading to new places across the world. Originally found in Tanzania during a large epidemic of polyarthralgia and myalgia, it later spread from Africa to Thailand.[1] Since these initial outbreaks, there have been a myriad of epidemics in Africa and Asia. Chikungunya has many clinical similarities to dengue virus, and Chikungunya is often misdiagnosed. In April 2005, a severe epidemic of Chikungunya occurred on the Comoros Islands and spread across the southwestern Indian Ocean region with attack rates as high as 35% to 75%.[2] Once Chikungunya began to spread to non-endemic areas like Italy and France by viremic travelers, the CDC and PAHO got involved to prepare for potential epidemics in Americas.[2] In July 2014, Chikungunya was found locally in the Caribbean. A few months later in December 2014, locally transmitted cases of Chikungunya were found in Mexico and the United States, which represents a further move northward.[3] Specifically, Florida has seen a significant number of Chikungunya cases, with a total of 272 imported cases, compared with a total of 1,110 cases in all of the other 47 contiguous states combined. As of December 29, 2014, 11 locally acquired Chikungunya cases have been identified, signifying that Chikungunya virus has not only been imported into the United States, but also competent Aedes mosquitoes exist within the United States locally spreading the disease.[4] Overall, PAHO reports that over one million suspected autochthonous transmission cases of Chikungunya have occurred in the Americas as of December 29, 2014.[5]

Previous attempts at creating a vaccine began in the 1960s with formalin-killed virus-based vaccines and live-attenuated viruses had adverse effects.[1] In a phase 2 trial of a live-attenuated virus, immunogenicity was lower than that achieved in the VLP vaccine phase 1 trial and 8% of participants displayed arthralgia as a side-effect. Many groups are currently working on creating vaccines through different approaches, such as single recombinant antigens, VLPs, chimeric alphaviruses, and codon re-encoding. For those already infected, several antiviral therapies, including interferon, ribavirin, chloroquine, arbidol, furin inhibitors, and other inhibitors of viral replication have been shown effective in vitro, yet none are currently a recognized treatment.[1]

This VLP vaccine trial is an important step in determining the viability of this vaccine in order to combat this rapidly spreading virus. The vaccine needs further clinical trials to determine its safety and immunogenicity in larger populations, including diverse and at-risk populations. The VLP vaccine was created based on the West African strain of Chikungunya, and this strain has the greatest genotypic differences from the east, central, and south African (OPY1) strain. The VLP vaccine effectively produced neutralizing antibodies against the OPY1 strain, which suggests that cross-reactive neutralizing activity against the other Chikungunya strains could be achieved as well. Until an effective vaccine can be created, it is critical for travelers to Chikungunya-endemic locations to use preventive measures against mosquitoes. ■

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A New Expanded Human Papillomavirus Vaccine

By Stan Deresinski, MD

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Dr. Deresinski has served as a one time consultant for Cubist and Bayer.

The U.S. FDA approved a new human papillomavirus (HPV) vaccine in December of 2014.[1] Two HPV vaccines have been available for several years — a bivalent vaccine (HP2) containing L1 protein of the oncogenic types 16 and 18 as well as a quadrivalent vaccine (HP4)containing type 16 and 18 together with types 6 and 11 (which cause genital warts). The Advisory Committee on Immunization Practices (ACIP) has recently updated their recommendations for the use of these vaccines:

"ACIP recommends routine vaccination with HPV4 or HPV2 for females aged 11 or 12 years and with HPV4 for males aged 11 or 12 years. Vaccination also is recommended for females aged 13 through 26 years and for males aged 13 through 21 years who were not vaccinated previously. Males aged 22 through 26 years may be vaccinated. ACIP recommends vaccination of men who have sex with men and immunocompromised persons (including those with HIV infection) through age 26 years if not previously vaccinated."

The new vaccine, in contrast to these two, contains capsid proteins of 9 HPV types. It has been approved for use in girls and young women 9 to 26 years of age for the prevention of cervical, vulvar, vaginal, and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58; pre-cancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV types 6 and 11. GARDASIL 9 is also approved for use in boys 9 to 15 years of age for the prevention of anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58; precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV types 6 and 11. GARDASIL 9 is contraindicated in individuals with hypersensitivity, including severe allergic reactions to yeast, or after a previous dose of GARDASIL 9 or GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]. Three doses are administered intramuscularly at 0, 6, and 12 months. Local reactions at the injection site commonly occur.

The efficacy of HP9 in 16- through 26-year-old girls and women was assessed in an active comparator-controlled, double-blind, randomized clinical trial (Study 1) that included a total of 14,204 women who were enrolled and vaccinated without pre-screening for the presence of HPV infection. Participants were followed up with a median duration of 40 months (range 0 to 64 months) after the last vaccination. Multiple evaluations each demonstrated efficacy rates in excess of 90%.

This vaccine represents a significant public health advance that has the potential to reduce the worldwide incidence of invasive cervical cancer by 90% or more.[3] ■

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Updates

By Carol A. Kemper, MD, FACP

Treatment of *C. Diff.* — follow the guidelines

Brown AT, et al. Effect of treatment variation on outcomes in patients with *Clostridium difficile*. *Am J Med* 2014;127(9):865-870.

Formal recommendations for the treatment of *C. difficile* infection (CDI), based on expert opinion and available literature, were published by the IDSA in 2010.[1] These authors performed a retrospective study for 6 months in 2011, evaluating the effectiveness of the IDSA Guideline-directed CDI treatment compared with alternate treatment at their tertiary care county teaching hospital. IDSA recommendations for CDI treatment are included in Table 1. Patients with CDI were identified based on ICD-9 coding at discharge and treatment for CDI infection. Demographic information was collected, and patients were classified as mild-to-moderate, severe, or severe-complicated based on the IDSA guidelines. The primary outcome of study was the occurrence of complications, including relapse within 4 weeks, surgery, toxic megacolon, and 30-day mortality. Secondary outcomes included length of stay and clinical cure.

A total of 180 adults with CDI met criteria for inclusion in the study, 93 of whom (52%) were treated in accordance with the IDSA guidelines. The two groups (guideline-directed care and alternate care) were similar with respect to race and classification of disease severity, although those who received alternate care tended to be older and were more likely male. Only 116 of the participants (64%) had received antibiotics within the previous 8 weeks. In these subjects, antibacterials were used for an average of 8 days +/- 10 days. Quinolones were received more often (32%) than other agents. In addition, proton pump therapy was administered within the previous 8 weeks to 100 patients (55%).

The NAP-1 strain was identified in 37% of the group receiving guideline-directed care, compared with 41.4% of the group receiving alternate care (p = NS), although was more frequently identified in patients with severe/complicated infection. Patients with the NAP-1 strain had a higher rate of ICU admission and significantly higher risk of mortality.

Table. IDSA *Clostridium Difficile* Treatment Recommendations

Clinical Definition	Supportive Clinical Data	Recommended Treatment	Strength of Recommendation
Initial episode, mild or moderate	Leukocytosis with a white blood cell count of 15,000 cells/μL or lower and a serum creatinine level < 1.5 times the premorbid level	Metronidazole, 500 mg 3 times per day by mouth for 10-14 days	A-I
Initial episode, severe	Leukocytosis with a white blood cell count of 15,000 cells/μL or higher or a serum creatinine level ≥ 1.5 times the premorbid level	Vancomycin, 125 mg 4 times per day by mouth for 10-14 days	B-I
Initial episode, severe, complicated	Hypotension or shock, ileus, megacolon	Vancomycin, 500 mg 4 times per day by mouth or by nasogastric tube, plus metronidazole, 500 mg every 8 hours intravenously. If complete ileus, consider adding rectal instillation of vancomycin.	C-III
First recurrence	—	Same as for initial episode	A-II
Second recurrence	—	Vancomycin in a tapered or pulsed regimen	B-III

Reprinted with permission from: Cohen SH, et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol* 2010;31:431-455.

Guideline-directed care was associated with significantly fewer complications than alternate care (17.2% vs 56.3%; p < .0001). This was due in large part to a lower rate of mortality in persons receiving guideline-directed care compared with those in the alternate therapy group (5% vs 21.8%, p = 0.0012), as well as a lower rate of recurrence (14% vs 35.6%, p = 0.0007). Clinical cures were more frequent in patients receiving guideline-directed care compared with alternate care (93.5% vs 71.3%). Multiple logistical regression analysis demonstrated that relapses were 72% less likely in patients receiving guideline-directed care compared with alternate care.

Guideline-directed care was more often used in patients with mild-to-moderate disease (81%) compared with those with severe disease (35%) or those with severe-complicated disease (19.7%). The main reasons for patients with severe disease not meeting criteria for guideline-directed care included the use of flagyl as a single agent (55%) and failure to receive a taper or pulse therapy in those with multiple recurrences (23%). The main reasons for patients with severe-complicated disease not meeting criteria for guideline-directed care were the use of flagyl as single agent (57%) and the use of oral vancomycin without parenterally administered flagyl (35%).

In conclusion, many of the patients with CDI in this study were initially treated with flagyl — regardless of their disease classification — which meant those with mild-to-moderate disease met the Guidelines (and did well), while many of those with more severe disease received inadequate therapy with flagyl or vancomycin alone, with a resulting increased risk of complications and mortality. Treatment based on the IDSA guidelines appears to improve outcomes, with a lower risk of relapse, surgery, and death, and should be broadly implemented. Teaching hospitals, in particular, have a responsibility to train and educate their house staff about the use of currently recommended therapies.

REFERENCE

1. Cohen SH, et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol* 2010;31(5): 431-455.

Semi roll-over causes Cryptosporidiosis

Outbreak of Cryptosporidiosis among responders to a rollover of a truck carrying calves — Kansas, April 2013. *MMWR Morbid Mortal Wkly Rep* December 10, 2014;63(5):1185-1188.

A disastrous roll-over accident of a semi-tractor-trailer carrying baby Holsteins in a late winter snowstorm near Colby, Kansas, occurred in March 2013. There were 350 pre-weaned, less than 10-day-old Holsteins on board — many of which died in the accident, the bodies spread over the pavement. Calves that survived the accident were collected and loaded onto another truck by police, emergency personnel, and volunteers at the site. Once the wrecked truck was righted with the help of a towing company and local volunteers on horseback, the dead calves were loaded onto the wrecked truck and hauled away by a towing company to a local sale barn. The next day, the towing company employees had to remove the dead calves from the truck, loading them onto another truck that took them to a rendering plant.

Holsteins are the most common dairy cow in the United States (the black and white ones, like the California Clover Stornetta Farms ads with "Clo"), and a newborn calf weighs about 85 lbs. The emergency personnel later commented that many of the calves seemed ill with diarrhea — or what is commonly called "scours." Baby calves are especially vulnerable to diarrheal illness, especially when transported under stressful or crowded conditions. Pre-weaned calves are the most likely to develop diarrheal illness, especially from *Cryptosporidium parvum* because they may not have received their full dose of colostrum from the mother. Like human babies, a newborn calf does not have a fully developed immune system and relies on passive antibodies in its mother's milk to provide protection. A calf typically receives up to 5% of its body weight in colostrum with each feeding twice daily — a good portion of which is antibodies —

much more so than in standard whole milk. Colostrum is only produced by prepartum cows — which ends at birth — so farmers save it, and administer it to calves when they are young. Not until they are at least 1-2 months old does their immune system start to provide better protection.

In total, 5 police and county sheriffs, 8 volunteers, and 2 tow truck personnel had close contact with the animals. It was a grueling night — and the tow truck personnel who loaded and unloaded the animals at the sale barn did not have access to electricity or running water. Six of these individuals developed symptomatic cryptosporidiosis, including one law enforcement officer, both tow truck employees, the driver of the wrecked truck, and 2 volunteers. Five of the 6 sought medical care; 2 of the cases were confirmed by rapid antigen testing. The incubation period ranged from 6 to 8 days, and the duration of illness ranged from 7 to 13 days.

This was the first recognized occupational-associated "outbreak" of cryptosporidiosis in law enforcement and volunteer emergency responders. Although such close contact with ill animals is not common, emergency responders and law enforcement should be educated about the benefits of good hand washing and disinfecting clothing worn at the scene of an accident and when in contact with animals.

Antibiotics prescribed from decision-fatigue?

Linder JA, et al. Time of day and the decision to prescribe antibiotics (letter). *JAMA* 2014;174(12):2029-2031.

Psychologists describe the erosion of self-control after repeated decisions as "decision fatigue." Specifically, it is the erosion of judgment or the increased risk of poor choices after a long session requiring decisions. A good example of this is the car salesman's technique — wearing down the consumer with many decisions, and eventually "decision avoidance" or bad default decisions will occur. It has been known to occur in judges after a long session in court, in which the default is to more frequently deny parole (the "safer" option).

These authors hypothesized that decision fatigue may affect physicians as they work through their day. They examined 21,867 visits for acute respiratory infection (ARI) (in adults aged 18-64 years) to 204 clinicians in 23 practices during a 5-month period in 2012. Clinicians with fewer than 40 visits for ARI were excluded. For all ARI visits, 44% were prescribed antibiotics.

Each of the physician's clinic day was divided into hourly segments, so if they worked from 8 to noon — each hour of the day was considered ARI visit 1 through 4 to represent a visit time. Prescriptions for antibiotics for ARI were reviewed according to national guidelines and designated as "sometimes indicated" and "never indicated." In this study, 65.5% of antibiotics prescribed were "never indicated."

Clinicians were increasingly more likely to prescribe antibiotics for each of the consecutive hours of their day, both for antibiotics that were sometimes indicated and for antibiotics that were never indicated. Relative adjusted odds ratios for antibiotic prescriptions for the second, third, and fourth hours were 1.01, 1.14, and 1.26 ($p < .001$, for a linear trend).

Two-thirds of the prescriptions for acute respiratory illness in this study were not indicated — and the risk for prescribing any antibiotic, and especially an unwarranted antibiotic, increased throughout a physician's day. I was not entirely convinced this was due to physician decision fatigue or diminished judgment — I would argue that most physicians understand that antibiotics are not the "safer" option — although it might be the easier option. You simply get tired of arguing with people and run out of time to convince them otherwise. Not prescribing an antibiotic requires time for education. How many times have you spent 10 or 15 minutes trying to explain why an antibiotic was not necessary? And even then, with patient satisfaction scores dictating some physician reimbursement, who cares about a Z-Pak or two? ■

CME INSTRUCTIONS

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2. Scan the QR code to the right, or log on to **www.cmecity.com** to take a post-test. After Jan. 5, log onto the new AHCMEDIA.com and select MyAHC, then My Courses. Tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
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CME QUESTIONS

1. Infection with Chikungunya virus:

a. is limited to areas of Africa and Asia near the Indian Ocean

b. may be prevented with a widely available vaccine

c. has been seen in the United States but only in travelers

d. has been transmitted by mosquitoes within the United States

2. Which of the following is correct regarding the 2014-2015 influenza season?

a. The predominant virus is H1N1 identical to the 2009 pandemic strain.

b. The predominant virus is influenza B.

c. The predominant virus is well-covered by the 2014-2015 vaccine.

d. The predominant virus is H3N2.

3. Which of the following patients has the best indication for treatment with acyclovir?

a. a 24-year-old previously healthy woman with herpes simplex meningitis

b. a 24-year-old woman, kidney transplant recipient on immunosuppressive therapy with herpes simplex meningitis

c. a 24-year-old previously healthy woman with a third episode of herpes simplex meningitis

d. a 24-year-old previously healthy woman with herpes labialis and a headache

CME OBJECTIVES

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

- discuss the diagnosis 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

[IN FUTURE ISSUES]

Albendazole in Pregnant HIV Patients