Vaccination with seasonal influenza vaccine does not provide cross-reactive antibodies to the novel 2009 A/H1N1 influenza virus.

**Background:** A novel influenza A (H1N1) virus of swine origin has spread around the world to cause a pandemic. The virus is antigenically distinct from recently circulating human influenza A/H1N1 virus strains and is more closely related to the A/New Jersey swine flu virus that caused an outbreak in Fort Dix, New Jersey, in 1976. Few data were available about pre-existing immunity to the novel strain or whether vaccination with seasonal influenza vaccine or the 1976 swine flu vaccine would lead to increases in serum antibody levels to the novel H1N1 strain.

**Design:** Convenience samples from vaccine studies or blood donors.

**Methods:** Sera were obtained from the following: (1) persons participating in seasonal vaccine studies conducted between 2005 and 2008, including children 6 months to 9 years of age, adults aged 18 to 64 years, and adults ≥60 years of age; (2) blood donors born between 1880 and 2000; and (3) adults who participated in a study of the 1976 influenza A/New Jersey swine flu vaccine. All sera were tested in hemagglutination inhibition (HAI) and microneutralization assays using the 2009 A/H1N1 virus as antigen.

**Results:** There was good correlation between microneutralization and HAI antibodies, but the former assay was more sensitive and was the one for which data were presented. Only 1 of 124 children had a microneutralization antibody level of ≥40, and none of 55 had a ≥4-fold increase to the 2009 H1N1 strain after receipt of seasonal trivalent inactivated influenza vaccine (TIV). The addition of an oil-in-water adjuvant to TIV did not increase the frequency of response to 2009 H1N1. Less than 10% of younger adults had pre-existing antibody levels ≥160, while up to one third of persons aged ≥60 years had antibody levels of this titer. Twelve percent to 22% of adults 18 to 64 years of age seroconverted to seasonal TIV, and ≤5% of adults aged ≥60 years seroconverted. Seroprevalence studies from blood donors showed a peak titer in persons born in the 1920 decade, with a steady decline thereafter, and only 4% of persons born after 1980 had a titer of ≥40. More than 50% of adults who received the A/New Jersey swine flu vaccine also seroconverted to the 2009 H1N1 strain.

**Conclusions:** Younger persons (<30 years of age) lack cross-reactive antibodies to 2009 H1N1, reflecting the age distribution in which these infections have been prevalent in the U.S. population. Vaccination with seasonal influenza also does not induce cross-reactive antibodies.

**Reviewer's Comments:** This study shows that seasonal influenza vaccine would not be expected to provide protection against the novel H1N1 virus and highlights the need to develop a vaccine for this virus. The results also explain the observed predominance of infection in younger persons. (Reviewer-Robert L. Atmar, MD).

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Keywords: Influenza, Seroprevalence, Vaccine

Print Tag: Refer to original journal article
Background: A new influenza virus, designated novel H1N1, has emerged to cause an influenza pandemic. Since June, worldwide transmission has continued in both Northern and Southern hemispheres. Disease is similar to that of seasonal influenza, but the distribution of severe disease, hospitalization, and mortality has differed from that of seasonal influenza. Only 5% of hospitalizations and 8% of deaths have been reported in persons ≥65 years of age, compared to 60% and 90%, respectively, for seasonal influenza. Hospitalization has been highest in children <4 years of age. Transmission in health care settings has been reported, and health care workers have also acquired infection in community settings.

Methods: The American Committee on Immunization Practices (ACIP) met and considered burden of illness, risk groups, anticipated vaccine supply, and vaccination strategies in making recommendations for use of a monovalent vaccine against the novel H1N1 virus.

Results: Vaccine supply for the novel H1N1 virus is anticipated to be limited in the early fall when seasonal influenza vaccine usually first becomes available, and seasonal influenza vaccine is unlikely to provide protection. Vaccination should initially target several priority groups: pregnant women; persons who care for infants <6 months of age; health care and emergency medical service personnel; persons 6 months to 24 years of age; and persons 25 to 64 years of age with medical conditions placing them at high risk of complications. In the face of more limited supplies, the first 3 groups should be prioritized along with children 6 months to 4 years of age and children and adolescents 5 to 18 years of age with medical conditions placing them at high risk of influenza-related complications. Expanding vaccination to other groups, such as persons ≥65 years of age, should occur only after demands for younger persons have been met. Additional recommendations include the following: (1) administration of seasonal influenza vaccine to all recommended groups, including persons ≥65 years of age; (2) avoiding simultaneous administration of live seasonal and novel H1N1 virus vaccines, although simultaneous administration of inactivated vaccines at separate sites is permissible; and (3) not holding in reserve extra doses of vaccine since vaccine availability is expected to increase over time, and it is not clear for whom >1 dose will be needed.

Reviewer's Comments: The ACIP has made recommendations to target groups for vaccination that are most likely to be affected. The recommended groups are different than those normally targeted for influenza vaccination, so it will be a challenge for the health care system to comply with these recommendations. Hopefully, restriction of access will not result in decreased utilization of vaccine, as has been seen in previous years. (Reviewer—Robert L. Atmar, MD).

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Keywords: Influenza, Vaccine, H1N1

Print Tag: Refer to original journal article
A single dose of monovalent inactivated H1N1 vaccine yielded titers of ≥40 in >90% of healthy adults.

**Background:** The emergence of a novel H1N1 virus as the cause of the first influenza virus pandemic in 41 years has led to attempts to develop an effective vaccine against this virus. Vaccination against influenza is the primary method recommended for influenza prevention.

**Objective:** To evaluate immune responses after the first dose of a 2-dose regimen in healthy Australian adults aged 18 to 49 years or ≥50 years.

**Design:** Randomized, observer-blinded, parallel-group study.

**Methods:** Healthy adults 18 to 64 years of age were randomized to receive 15 or 30 μg of a monovalent inactivated influenza A/H1N1 vaccine at days 0 and 21. Persons with confirmed or suspected previous infection with novel A/H1N1 were excluded, and equal numbers of persons aged 18 to 49 years and 50 to 64 years were included. Local reactions were assessed in the 7-day period after vaccination, and immunogenicity was assessed by serum hemagglutination inhibition (HAI) and microneutralization assays. A seroresponse was considered an increase in antibody from 5 to ≥40 or a ≥4-fold increase in serum HAI antibody titer.

**Results:** 240 persons were enrolled and completed follow-up through day 21. Of these, 32% had a serum HAI antibody titer of ≥40 at baseline, with no significant differences between age or dosage groups. Interestingly, twice as many persons with titers ≥40 had received the 2009 seasonal vaccine compared to those who had not (44% vs 21%; P <0.001). Overall, 74% of persons responded to the vaccine, and >90% had serum HAI titers of ≥40 at day 21. Persons >50 years of age had lower numerical responses than younger persons on all immunologic parameters measured (response frequencies, fold-change in antibody, and postvaccination geometric mean titers). Eighty-six percent of seronegative persons seroconverted after a single vaccine dose. One of 3 persons with an influenza-like illness was infected with the novel H1N1 virus. The safety profile was similar to previous reports of inactivated influenza vaccine, with local reactions in approximately one half of the subjects.

**Conclusions:** A single dose of monovalent inactivated influenza A/H1N1 vaccine was safe and immunogenic in adults.

**Reviewer’s Comments:** This is an important study because it suggests that a single dose of monovalent vaccine can be used to immunize adults. About the time this article was published, the National Institutes of Health reported similar results in U.S. adults and in children >10 years of age. Thus, it appears that a single dose of monovalent H1N1 vaccine will be sufficient to provide levels of serum antibody associated with protection from illness. Further studies of the immunogenicity of a second dose will tell us whether >1 dose will provide additional benefit. (Reviewer-Robert L. Atmar, MD).
Nurses using N95 respirators for contact with patients with influenza-like illnesses have a frequency of influenza similar to that of nurses using surgical masks.

**Background/Objective:** Transmission of influenza can occur by droplet aerosol after coughing or sneezing. Uncertainty exists about the size of the droplet that is able to transmit influenza, and the uncertainty has led to questions about the appropriate personal protective equipment needed by health care workers to prevent acquisition of influenza in the workplace. Few data are available comparing the protective efficacy of surgical masks to N95 respirators for the prevention of influenza acquisition in the workplace.

**Design:** Randomized, comparative trial.

**Methods:** Enrolled nurses were full-time employees who worked in emergency departments, medical units, or pediatric units of 1 of 8 hospitals. All nurses were fit tested and instructed on the proper use of the N95 respirators. Nurses were randomized, with stratification by site, to use surgical masks or N95 respirators for close contact with patients having febrile respiratory illness. Nurses were then followed up twice weekly during the influenza season for symptoms and signs of influenza; if new symptoms occurred, a nasal swab was collected for diagnosis. Swabs were assessed for influenza infection using a multiplex RT-PCR assay. Participants who did not receive the 2008-2009 seasonal influenza vaccine were also evaluated for the influenza infection with serology over the course of the study.

**Results:** 446 nurses were randomized; 225 were assigned to a surgical mask, and 221 to an N95 respirator. The 2 groups had similar characteristics (age, sex, work assignment, vaccination status, and underlying illness). Of the 446 nurses, 422 completed the study. The incidence of laboratory-confirmed influenza (23.6% vs 22.9%), infection with other respiratory viruses (9.4% vs 10.5%), and physician visits for respiratory illness (6.1% vs 6.2%) were the same in the surgical mask and N95 respirator groups, respectively. Exposure at home to persons with febrile respiratory illnesses was similar, and audits of mask use showed high compliance. A significantly higher number of nurses in the surgical mask group reported fever (5.7% vs 0.9%), although there were no other differences in symptom occurrence between the 2 groups.

**Conclusions:** The frequency of laboratory-confirmed influenza among nurses was similar in the 2 study groups, suggesting noninferiority of surgical masks compared to N95 respirators in preventing influenza.

**Reviewer's Comments:** This study addresses a controversy in the infection control literature—the need for N95 respirators in managing patients with influenza. There are conflicting recommendations from the Centers for Disease Control and Prevention (CDC; use N95 masks for novel H1N1 infection) and the Society for Hospital Epidemiology of America (surgical masks are sufficient protection unless aerosols are expected to be generated). This study provides support for the latter recommendation, although it evaluated predominantly seasonal influenza. However, the CDC continues to recommend N95 respirators as a minimal level of protection for contact with novel H1N1-infected patients. (Reviewer-Robert L. Atmar, MD).

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Keywords: Influenza, Infection Control, Transmission

Print Tag: Refer to original journal article
**Background:** The second most common gram-negative bloodstream isolate has been reported to be *Klebsiella pneumoniae*. Both community- and hospital-acquired bloodstream infections have been reported to be increasing in incidence, but no population-based studies have been published on this bacterial pathogen.

**Objective:** To conduct a population-based surveillance study of *K. pneumoniae* bloodstream infections and to define the incidence, risk factors, and outcomes with this infection.

**Design:** This was a retrospective, population-based surveillance cohort design in a large health region of Alberta, Canada, between 2000 and 2007.

**Methods:** A regional laboratory system received the majority of all submitted blood samples. Clinical and outcome information was available on most patients from a regional corporate data warehouse. Bacteremias were defined as being nosocomial (>48 hours after admission), community acquired (<48 hours after admission), or health care associated (contact with clinic, hospital, nursing home, or dialysis center in the previous 5 to 30 days).

**Results:** 640 bacteremic *K. pneumoniae* infections occurred among 633 residents over the 8-year study period; 27% were nosocomial, 30% were community acquired, and 43% were health care associated. The incidence was calculated to be 7.1 bacteremias per 100,000 population. The median age was 68.9 years, and 58% were in men. The overall median length of hospital stay was 11 days. The median time to development of nosocomial bacteremia was 11.4 days. Antibiotic susceptibility revealed significant resistance to ampicillin, but low levels of extended spectrum beta-lactamase (ESBL) producing isolates (<1%). The fatality rate was 20%, which did not change significantly over the 8-year study. Risk factors for increased mortality rates included older age, nosocomial infections, underlying malignancy, heart disease, COPD, rheumatoid arthritis, and alcoholism. Diabetes mellitus was not a risk factor for increased mortality rates. A biliary tract or genitourinary tract source had lower mortality rates compared to other sources, such as an intra-abdominal source or pneumonia. Fourteen cases of primary liver abscess were reported with a 7% mortality rate.

**Conclusions:** *K. pneumoniae* bloodstream infections are second to *Escherichia coli* bacteremias in incidence. This population-based study defined the mortality rate and risk factors for this serious gram-negative infection.

**Reviewer’s Comments:** There are several limitations outlined by the authors of this well-done analysis. First, only patients with blood cultures were studied; therefore, the true extent of *K. pneumoniae* infections may be underestimated. Second, patients were not assessed prospectively for the source of infection. Therefore, the number of patients reported with no identified source may be overestimated. Third, the severity of disease, ICU care, and line placement were not known, limiting our understanding of potential risk factors for acquisition. Last, the authors have no explanation for the low (<1%) percentage of ESBL isolates identified in their population. Nevertheless, this study underscores the increasing impact of this serious gram-negative pathogen. (Reviewer-Stephen B. Greenberg, MD).

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Keywords: Bacteremia, *Klebsiella pneumoniae*, Nosocomial Infection

Print Tag: Refer to original journal article
Liposomal amphotericin B is 4 times more likely to produce a successful outcome than other antifungal agents or combination of agents for the treatment of invasive zygomycosis in solid-organ transplant recipients.

**Objective:** To identify epidemiologic characteristics, risk factors, and outcome of solid organ transplant recipients who developed zygomycosis.

**Participants:** 50 case patients with invasive zygomycosis and 50 matched-control patients from multiple international sites, all of whom underwent solid-organ transplantation.

**Design/Methods:** Prospective, matched case-control study that enrolled all consecutive patients who developed invasive zygomycosis after transplantation. These patients were matched to 50 transplanted patients who were within close temporal proximity to the case patients but who did not develop zygomycosis. The primary outcome evaluated was success at 90 days' posttransplantation.

**Results:** 50 consecutive patients from multiple international sites with invasive zygomycosis were identified. Twenty-four of the 50 patients had pulmonary infection; in 18 of these patients, the lung was the only organ involved. Thirteen patients had rhinocerebral disease, and 2 of these patients had CNS involvement. Thirteen patients had disseminated disease. The most frequently identified fungal species were *Rhizopus* species, *Mucor* species, and *Mycocladus corymbifer* (formerly *Absidia corymbifera*), but there was no difference in outcome among these different species. Significant factors associated with a higher risk of developing zygomycosis were renal failure, diabetes mellitus, and prior voriconazole and/or caspofungin use. The use of the calcineurin inhibitor tacrolimus was associated with a lower risk of zygomycosis. When the different types of solid organ transplantation were compared, liver transplant recipients were more likely to develop disseminated disease and developed zygomycosis much sooner after transplantation (0.8 months) than other solid-organ transplant recipients (5.7 months; *P* <0.001). Sixty percent of patients had successful treatment of their infection; independent factors that predicted treatment failure included renal failure and disseminated disease, while surgical resection improved treatment success. A variety of treatment regimens were evaluated. Patients treated with combinations of agents had a less favorable outcome, likely because most had disseminated disease. The use of liposomal amphotericin B was 4 times more likely to produce a successful outcome.

**Conclusions:** Some previously identified risk factors (eg, renal failure, diabetes mellitus) for invasive zygomycosis continue to be important in solid-organ transplant recipients. Previous exposure to antifungal agents has now emerged as an important risk factor. Tacrolimus appears to be protective. Surgical intervention is still important for successful outcome, and liposomal amphotericin B appears to be the drug of choice for medical therapy.

**Reviewer's Comments:** This paper reinforces our previous knowledge about risk factors for invasive zygomycosis in solid-organ transplant recipients. Similar to the situation seen in cryptococcal disease, the use of calcineurin inhibitors seem to be protective; this is supported by some in vitro data suggesting synergism between these drugs and antifungal agents. Further evaluation of these interactions is necessary. (Reviewer-Richard J. Hamill, MD).

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**Keywords:** Zygomycosis, Solid Organ Transplant Recipients

**Print Tag:** Refer to original journal article
**background:** Typhoid fever is a common infection in the United States for patients with recent international travel, and there have been reports of increasing drug resistance among Salmonella ser Typhi.

**Objective:** To determine the current epidemiology of S. Typhi infection in the United States and to assess trends of drug resistance among S. Typhi.

**Methods:** This laboratory-based surveillance study collected S. Typhi isolates causing invasive infection in the United States that were reported to the Centers for Disease Control and Prevention (CDC) from 1999 to 2006. Antimicrobial susceptibility patterns of the S. Typhi isolates were examined. When available, epidemiologic information from patients was reviewed.

**Results:** A total of 1902 cases were identified during the study period. More than half the cases came from California, New York, and New Jersey. Seventy-three percent of patients were hospitalized for a median of 6 days, and 0.2% of patients died. Seventy-nine percent of cases were travel associated, with most patients having visited friends and family. Travel to India, Pakistan, and Bangladesh accounted for two thirds of the cases. The majority of domestically acquired cases were traced to a typhoid carrier, with the remainder of cases being linked to typhoid outbreaks. About half of S. Typhi isolates were fully susceptible to all tested antimicrobials. Nalidixic acid-resistant S. Typhi (NARST) accounted for 38% of isolates, whereas 13% of isolates were multi-drug resistant strains of S. Typhi (MDRST; defined as resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole). Only 5 isolates were frankly resistant to ciprofloxacin (minimum inhibitory concentration [MIC] ≥4 µg/mL), but 36% of isolates had decreased susceptibility to ciprofloxacin (MIC ≥0.12 µg/mL). Over time, the proportion of MDRST decreased (from 19% in 2001 to 6% in 2006), whereas the proportion of NARST increased (from 19% in 1999 to 54% in 2006). There were no differences in the clinical outcomes of patients with susceptible S. Typhi, NARST, or MDRST. Travel to the Indian subcontinent was associated with MDRST and NARST infection.

**Conclusions:** Nalidixic acid resistance has been increasing among S. Typhi-causing disease in the United States, with travel to the Indian subcontinent being a major risk factor for acquisition of drug-resistant S. Typhi.

**Reviewer's Comments:** This is a useful report from the CDC examining >1000 cases of typhoid fever occurring in the United States over the past several years. The data herein provide excellent epidemiologic information regarding patients at highest risk for typhoid fever as well as offering insights into which patients are most likely to have drug-resistant S. Typhi. Given that fluoroquinolones are considered the drug of choice for typhoid fever, the increasing rates of nalidixic acid resistance are cause for some concern and indicate that continued monitoring of drug-resistant trends among S. Typhi isolates is indicated. (Reviewer-Samuel Shelburne, MD).

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Keywords: Typhoid Fever, Drug Resistance, Travel

Print Tag: Refer to original journal article
Infectious diseases consultation is associated with lower mortality for patients with *Staphylococcus aureus* bacteremia.

**Background:** *Staphylococcus aureus* bacteremia (SAB) is a common indication for consultation with an infectious diseases (ID) physician, but whether infectious diseases consultation (IDC) for SAB is associated with decreased patient morbidity and mortality is unknown.

**Objective:** To determine whether consultation with an infectious diseases practitioner is associated with altered clinical management and lower morbidity and mortality for patients with SAB.

**Design/Methods:** A prospective study of the medical records was performed for all patients with blood cultures that were positive for *S. aureus* at the Dartmouth-Hitchcock Medical Center between 2002 and 2006. Medical records were reviewed for clinical characteristics, antibiotic administration, invasive procedures, and outcomes. Appropriate antibiotic selection was defined as receipt of an intravenous β-lactam, vancomycin, daptomycin, or linezolid for a staphylococcal isolate that was sensitive to the chosen agent.

**Results:** Of the 240 patients with SAB, 51% received an IDC. Patients who received an IDC were older and more likely to have health care-associated SAB. Patients with IDC were more likely to have complicated SAB such as endocarditis, central nervous system involvement, or osteomyelitis. Patients with IDC were more likely to have additional blood cultures drawn, to receive appropriate antibiotics, and to have a longer course of antimicrobials. Interventions to drain abscesses or remove prosthetic devices were more likely in patients who received IDC. The mean duration of bacteremia was similar between patients who did and did not receive IDC. All-cause hospital mortality was lower in patients who received IDC (13.9% vs 23.7%; *P* = 0.05). In a Cox regression model, mortality was lower in patients who received IDC after controlling for multiple variables. SAB-related mortality was lower in patients who received IDC, but non–SAB-related mortality was not significantly different between those who did and did not receive IDC.

**Conclusions:** IDC was associated with lower mortality rates in patients with SAB.

**Reviewer's Comments:** The usefulness of an IDC on patient outcomes is difficult to quantify. The data herein suggest that consultation by an ID specialist resulted in improved outcomes for patients with SAB. The reason for clinical improvement could not be determined but was likely due to the combination of improved antibiotic selection and a more aggressive approach to device removal and abscess drainage. Of note, a study published in the *Journal of Infection* in October 2009 came to a similar conclusion regarding the usefulness of IDC in patients with staphylococcal bacteremia. The presence of confounding variables in these types of studies cannot be fully accounted for, so this study does not definitively show the utility of IDC. More information regarding the clinical impact of IDC may be forthcoming in this era of optimizing the cost-benefit ratio of medical practice. (Reviewer-Samuel Shelburne, MD).

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Keywords: Bacteremia Referral, Consultation, Hospital Mortality

Print Tag: Refer to original journal article
Mupirocin Use May Increase Resistance Among Staphylococci

Mupirocin Resistance.
Patel JB, Gorwitz RJ, Jernigan JA:

Clin Infect Dis 2009; 49 (September 15): 935-941

The widespread use of mupirocin is associated with increased rates of mupirocin resistance among staphylococci.

**Background:** Eradication of methicillin-resistant *Staphylococcus aureus* (MRSA) is being performed in an increasingly systematic manner in an attempt to reduce nosocomial MRSA infections. Mupirocin is a mainstay of MRSA eradication strategies, but the increasing use of mupirocin may result in increasing mupirocin resistance, thereby limiting its effectiveness.

**Objective:** To review the mechanisms of mupirocin resistance, provide protocols for testing for mupirocin resistance, and to summarize available data regarding the impact of mupirocin use on resistance.

**Results:** Mupirocin is thought to work by inhibiting isoleucine t-RNA synthetase. Although there are no FDA-approved breakpoints for staphylococcal susceptibility to mupirocin, isolates are considered susceptible with minimum inhibitory concentrations (MICs) of ≤4 µg/mL, low-level resistance with MICs of 8 to 64 µg/mL, and high-level resistance with MICs >512 µg/mL. High-level mupirocin resistance is due to acquisition of a plasmid with *mupA*, which encodes a novel isoleucine RNA synthetase. Low-level resistance is due to base pair changes in the native isoleucyl RNA synthetase gene *ileS*. High-level mupirocin resistance has been observed in strain USA300 due to the presence of *mupA* on a conjugative plasmid encoding other antimicrobial resistant determinants. Commercial testing of mupirocin in the United States has been limited by the lack of FDA-approved interpretive breakpoints, but testing can be done using a double-disk agar diffusion method that can detect low-level and high-level resistance. There are several studies in which the presence of high-level mupirocin resistance was associated with a decreased ability to eradicate MRSA and a failure to sustain negative MRSA cultures over several weeks to months. The relationship between low-level mupirocin resistance and clinical failures is less clear. The widespread use of mupirocin, such as occurred in New Zealand, is associated with increased resistance rates. However, the use of mupirocin in a targeted fashion, such as to decolonize patients to prevent surgical site infections, has not been found to result in a significant emergence of resistance.

**Conclusions:** Increasing use of mupirocin as part of MRSA eradication strategies has the potential for increasing mupirocin resistance, but most clinical laboratories are not currently equipped to monitor mupirocin resistance rates.

**Reviewer's Comments:** I found this to be a very useful summary of the existing data on the efficacy, mechanisms of resistance, and epidemiology of resistance to mupirocin among staphylococci. It is concerning that MRSA eradication strategies rely heavily on a drug that clearly is not effective when resistance emerges, for which resistance has been documented to emerge following widespread use, and for which systematic resistance testing is not being done. Persons involved in infection control decisions may find this review particularly helpful. (Reviewer-Samuel Shelburne, MD).

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Keywords: Mupirocin Resistance, Staphylococcal Carriage, Infection Control

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Gastroenteritis in HSCT Patients--Consider Norovirus

Allogeneic Hematopoietic Stem Cell Transplantation and Norovirus Gastroenteritis: A Previously Unrecognized Cause of Morbidity.

Roddie C, Paul JPV, et al:

Clin Infect Dis 2009; 49 (October 1): 1061-1068

Prolonged diarrhea in the immunocompromised host should include norovirus as a possible etiology.

**Background:** Diarrhea is a frequent complication in patients who have undergone hematopoietic stem cell transplantation (HSCT). Non-infectious causes include graft-versus-host-disease (GVHD). Infectious causes include viruses such as adenovirus, rotavirus, and cytomegalovirus. Although norovirus is the most common cause of non-bacterial diarrhea worldwide, it has not been reported as a significant cause of diarrhea in these patients.

**Design/Methods:** This retrospective study describes the clinical, epidemiological, and virologic characteristics of norovirus gastroenteritis in 12 adult patients who had had HSCT.

**Results:** The median time from transplant to the onset of diarrhea was 10.5 months (range, 0.25 to 96 months). Ten of 12 patients had transient nausea and vomiting at the onset of their diarrhea. Eleven patients were on immunosuppression at the onset of diarrhea, and 9 patients had GVHD at some site. The diarrhea was prolonged in the majority of patients, with a median duration of 3 months. Two patients died while still symptomatic, and 1 death was attributable to malnutrition secondary to diarrhea. Electron microscopy was insensitive in diagnosing norovirus, with only 2 of 9 samples positive.

**Conclusions:** Norovirus should be considered as a possible etiology in HSCT patients who develop diarrhea.

**Reviewer's Comments:** Although this was a small retrospective study, it is important because it demonstrates that our differential diagnosis of diarrhea in immunocompromised patients in general and in HSCT patients specifically should be broadened to include norovirus. Koo and DuPont write a nice editorial in the same issue that makes some useful points about this study. It is clear that prolonged shedding of the virus can occur even when the patient is clinically asymptomatic. This makes interpreting positive PCR tests in these patients difficult. In addition, direct tissue examination can show changes that are not specific for norovirus and that can be seen in other causes of diarrhea such as GVHD. Electron microscopy is clearly insensitive in making the diagnosis and should not be considered the gold standard diagnostic test. It was interesting that the majority of patients had nausea and vomiting early in the course of their gastroenteritis. This is unusual for the other causes of diarrhea (such as GVHD) and may provide a clue to the clinician that norovirus may be the cause of the diarrhea. (Reviewer-David E. Greenberg, MD).

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Keywords: Diarrhea, Immunocompromise, Norovirus

Print Tag: Refer to original journal article
Patients with isoniazid-resistant tuberculosis have higher failure rates if treated with initial intermittent therapy or if given rifampin or isoniazid for a short duration.

**Background:** Every year, approximately 1 million individuals require retreatment for tuberculosis (TB) worldwide. The World Health Organization (WHO) recommends an 8-month retreatment regimen (8 month of isoniazid, rifampin, ethambutol with pyrazinamide added for the first 3 months, and streptomycin added for the first 2 months). This regimen is believed to be adequate for patients who received no more than 2 months of rifampin treatment in the past and for those with mono-drug resistance, such as isoniazid. However, poor results have been reported with this regimen.

**Objective:** The WHO commissioned a review of the rates of failure, relapse, and acquired-drug resistance with the current retreatment regimen and the risk factors associated with these outcomes.

**Design:** A meta-analysis of published, randomized trials and cohort studies that evaluated TB retreatment regimens or treatment of isoniazid-resistant TB.

**Results:** The authors identified 6 cohort studies in which the drug susceptibility patterns of the Mycobacterium tuberculosis were described and the WHO retreatment regimen was utilized; failure rates were low in drug-susceptible TB, but ranged from 9% to 45% in drug-resistant TB. They also identified 33 trials evaluating the outcome of treating isoniazid-resistant TB; worse outcomes were found if therapy was administered on an intermittent basis in the initial intensive phase or if a shorter duration of treatment with rifampin or pyrazinamide was used. Patients with isoniazid-resistant TB received numerous types of treatment regimens and none received the regimen recommended by the WHO.

**Conclusions:** The outcome of isoniazid-resistant TB is worse with the use of initial intermittent therapy or with short treatment duration with pyrazinamide or rifampin. Also, little data supports the use of the WHO retreatment regimen.

**Reviewer’s Comments:** The most important finding of this review is that there are no well-conducted, randomized clinical trials that evaluate the outcome of the WHO recommended TB retreatment regimen. This regimen was based on expert opinion. But it is important to validate the outcome of this regimen in various epidemiologic settings, especially that the preconditions for using this regimen are not always present (ie, the use of rifampin for no more than 2 months in a previous regimen, and low prevalence of TB drug resistance). In fact, TB drug resistance is on the rise in various countries. Clinical trials that evaluate the outcomes of retreatment of TB using standardized regimens are needed in order to propose evidence-based revisions to the current recommendations. (Reviewer-Hana El Sahly, MD).

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**Keywords:** Tuberculosis, Retreatment, Isoniazid, WHO

**Print Tag:** Refer to original journal article
New British Infection Society Guidelines for Tx of CNS TB

British Infection Society Guidelines for the Diagnosis and Treatment of Tuberculosis of the Central Nervous System in Adults and Children.
Thwaites G, Fisher M, et al:
J Infect 2009; 59 (September): 167-187

The British Infection Society has provided new guidelines for the treatment of tuberculosis of the central nervous system.

Background: Central nervous system (CNS) tuberculosis (TB) is relatively difficult to diagnose, and outcomes worsen with delays in treatment initiation.

Objective: To present evidence-based guidelines for the diagnosis and treatment of CNS TB.

Methods: The British Infection Society systematically reviewed the published literature and evaluated the evidence for various diagnostic and treatment methods. Summary: Subacute disease onset is common, and the cerebrospinal fluid (CSF) findings of lymphocytic pleocytosis, elevated protein, and glucose <50% of serum value are highly suggestive of disease, and therapy should be considered in this setting. The ability to detect bacilli is dependent on the CSF volume and at least 6 mL should be sent for mycobacterial evaluation or a repeat tap should be done. A tissue biopsy (neural or extraneural) has a higher diagnostic yield for tuberculoma or spinal TB. Performance of commercial nucleic amplification tests on the CSF is recommended, but a negative result does not rule out the diagnosis. For patients with meningitis, CT with contrast is recommended prior to initiation of treatment or within 48 hours. An MRI of the brain or spine is recommended for tuberculomas or TB of the spine, with a follow-up imaging study to document improvement on therapy. Patients should be treated for a minimum of 12 months, and drugs should be taken daily (usually isoniazid and rifampin for 12 months with ethambutol and pyrazinamide for the first 2 months). Patients should receive adjunctive steroid therapy tapered over 8 weeks. There is not enough evidence to recommend steroid therapy for all patients with spinal TB or tuberculomas, although steroids may be helpful for patients with spinal cord compression. Hydrocephalus, tuberculous cerebral abscess, and vertebral tuberculosis with paraparesis are indications for neurosurgical evaluation. Shunting is needed for those with noncommunicating hydrocephalus or those with communicating hydrocephalus who are not responding to medical therapy. All patients with CNS TB should be tested for coinfection with the human immunodeficiency virus (HIV). Patients co-infected with HIV should be managed by experts in the treatment of HIV and TB. All patients should be tested for drug resistance and managed according to the pattern of resistance. Multidrug resistant CNS TB should be managed with the help of experts, with a recommended initial regimen containing a quinolone, pyrazinamide, ethionamide, and an injectable agent. Worsening neurologic symptoms should prompt imaging. Hyponatremia can also be a cause of seizures and coma. Elevated liver enzymes are generally more tolerated in CNS TB than with TB of other sites. If the liver enzymes are >5 times the upper normal, pyrazinamide is discontinued first.

Reviewer's Comments: These new guidelines point to many areas of uncertainty and to many research priorities: improved diagnostics; treatment of drug resistant disease; and adjunctive measures. (Reviewer-Hana El Sahly, MD).

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Keywords: Tuberculosis, Central Nervous System, Guidelines, Diagnosis, Treatment

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Raltegravir-Based Regimen Effective for Treatment-Naïve Patients

Safety and Efficacy of Raltegravir-Based Versus Efavirenz-Based Combination Therapy in Treatment-Naïve Patients With HIV-1 Infection: A Multicentre, Double-Blind Randomised Controlled Trial.

Lennox JL, DeJesus E, et al:
Lancet 2009; 374 (September 5): 796-806

A raltegravir-based regimen is non-inferior to an efavirenz-based regimen for treatment-naïve patients.

**Background**: Raltegravir is effective and well tolerated in treatment-experienced patients when combined with an optimized background therapy regimen. Its favorable metabolic profile and potency make it an attractive medication as part of a regimen for treatment-naïve patients as well.

**Design/Objective**: This phase III, Merck-sponsored study compares the safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection.

**Methods**: Treatment-naïve HIV-1 patients with an HIV-1 viral load (VL) >5000 copies/mL, with no baseline resistance to efavirenz, tenofovir or emtricitabine, were randomized 1:1 to receive either raltegravir 400 mg twice daily or efavirenz 600 mg once daily in combination with emtricitabine and tenofovir. Patients were stratified by VL greater than or ≤50,000 and viral hepatitis status. The primary efficacy end point was achievement of a VL <50 copies/mL at week 48. The design was a noninferiority comparison with a 12% margin, using a per-protocol analysis.

**Results**: 566 patients were enrolled. Approximately 50% of the subjects had VLs >50,000 and 50% had CD4 cell counts <200; the distribution did not differ between treatment arms. Approximately 86% of the raltegravir group and 81% of the efavirenz group achieved the end point of VL <50 at 48 weeks, meeting the criteria for noninferiority. The time to viral suppression was shorter in the raltegravir arm. Fewer drug-related adverse events were noted in patients on raltegravir compared to those on efavirenz (44% vs 77%; P <0.0001), mostly due to a higher incidence of dizziness, headaches, and abnormal dreams in the efavirenz group. However, serious adverse events were rare (<2%) and not different between groups.

**Conclusions**: Raltegravir plus tenofovir and emtricitabine was well-tolerated and potent, and was non-inferior to efavirenz plus tenofovir and emtricitabine for treatment-naïve patients.

**Reviewer's Comments**: Raltegravir appears to be non-inferior in efficacy and may have some potential advantages. Consistent with other studies, raltegravir recipients achieved viral suppression quicker, although the clinical significance of this is still uncertain. The raltegravir group also experienced less change in most lipid parameters. Efavirenz, or the single-pill formulation of Atripla, is certainly more convenient than twice daily raltegravir, but these potential advantages on adherence were negated in this placebo-controlled trial. Even so, a raltegravir-based regimen is certainly an important option for treatment-naïve patients. Other studies are underway comparing raltegravir-based regimens to proton inhibitor-based regimens for treatment-naïve patients, as well as evaluating other raltegravir-containing combinations. (Reviewer-Michael T. Yin, MD).

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Keywords: Raltegravir, Treatment-Naïve Patients, Efavirenz, HIV-1 Infection

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