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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Using Procalcitonin to Differentiate Bacterial from Viral Meningitis

By Richard R. Watkins, MD, MS, FACP

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Dr. Watkins reports that he has received research support from Forest Laboratories.

SYNOPSIS: A meta-analysis based on nine studies found an elevated serum procalcitonin to be an accurate test for differentiating bacterial from viral meningitis in adults.

SOURCE: Vikse J, et al. The role of serum procalcitonin in the diagnosis of bacterial meningitis in adults: A systematic review and meta-analysis. *Intern J Infect Dis* 2015;38:68-76.

Differentiating bacterial from viral meningitis is a frequent clinical conundrum. Usually, broad-spectrum antibiotics are administered when meningitis is suspected until cerebrospinal fluid (CSF) cultures are negative for at least 48 hours. This common practice exposes patients with viral meningitis to antibiotics unnecessarily, which raises costs, increases risk for adverse drug events, and propagates antibiotic resistance. Therefore, rapid non-culture based testing would be a great benefit in the diagnosis of meningitis.

Vikse and colleagues sought to determine if procalcitonin (PCT), a serum biomarker that is increased in serious bacterial infections, could accurately differentiate bacterial from viral meningitis. Several studies have been published on the topic, but they produced mixed results. Thus, there is no current consensus on the diagnostic utility of PCT in meningitis. PCT is an attractive test in this setting because it is rapid (i.e., results back in less than 24 hours) and has become widely available. Moreover, studies on bacterial meningitis

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have shown PCT to be elevated even if the blood was drawn following initiation of antibiotic therapy.

A total of nine studies were included in the meta-analysis (n = 725 patients). Of these, two were retrospective and seven were prospective. Different assays were used, and the cut-off for PCT ranged between 0.25 ng/mL to 2.13 ng/mL. Seven of the studies also measured C-reactive protein (CRP) as a biomarker. The sensitivity for PCT for detecting bacterial meningitis was 0.90 (95% confidence interval [CI], 0.84-0.94), specificity was 0.98 (95% CI, 0.97-0.99), and the diagnostic odds ratio was 287.0 (95% CI, 58.5-1409.0). CRP was far less accurate; the sensitivity for bacterial meningitis was 0.82 (95% CI, 0.75-0.88), specificity was 0.81 (95% CI, 0.77-0.84), and diagnostic odds ratio was 22.1 (95% CI, 12.7-38.3). However, significant heterogeneity was found for the diagnostic odds ratio for PCT (I^2 = 66.2%), which the investigators attributed to variation in the types of serum PCT assays used in the studies. Finally, a funnel plot was constructed to detect publication bias, which was asymmetrical, indicating that this type of bias may have been present in the studies included in the meta-analysis.

■ COMMENTARY

The meta-analysis conducted by Vikse and colleagues showed that PCT has a high specificity (i.e., 98%) for bacterial meningitis, making it a highly accurate biomarker for ruling in this serious infection, as well as a high sensitivity (90%). This result is similar to a previous study, which found that PCT had a sensitivity of 95%, a specificity of 100%, a negative predictive value of 100%, and a positive predictive value of 97% at a diagnostic cut-off level of 0.28 ng/mL (AUC, 0.99; 95% CI, 0.99 to 1) in distinguishing bacterial from viral meningitis in adults.[1] Moreover, using PCT with cut-off value > 2 ng/mL showed sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 66%, 68%, and 100%, respectively, for the diagnosis of bacterial meningitis in children.[2] The use of PCT to rapidly rule out bacterial meningitis has the potential to reduce the costs of unnecessary hospitalization and adverse effects from antibiotics. Another potential benefit is that PCT may provide information about prognosis. In a recent study, children with higher serum levels of PCT were found to have prolonged clinical courses and increased mortality.[3]

One of the limitations to the meta-analysis by Vikse et al. is that the overall number of studies included is small. Thus, the risk of publication bias is increased, especially since the funnel plot was asymmetrical. Another limitation is that the investigators excluded studies conducted on children, a group for whom meningitis is a frequent and serious infection. Clearly the ability to differentiate bacterial from viral meningitis in these patients is highly important.

Should serum PCT be ordered routinely in cases of meningitis? There is good quality evidence that PCT can accurately distinguish bacterial from viral meningitis. In my opinion, when the clinical suspicion for bacterial meningitis is low and the PCT is normal, I would likely stop antibiotics, especially if there is a lymphocyte predominance in the CSF and the Gram stain is negative. However, if the PCT is elevated, I would wait for CSF culture results for at least 48 hours before stopping antibiotic therapy. Whether PCT testing will be included in the next Infectious Diseases Society of America clinical guidelines on meningitis is an open question. ■

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ABSTRACT & COMMENTARY

Chagas — Multifaceted Approach Needed

By Philip R. Fischer, MD, DTM&H, and Diane H. Brown

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Dr. Fischer and Ms. Brown report no financial relationships relevant to this field of study.

SYNOPSIS: Prolonged recurrent exposure to *Trypanosoma cruzi* leads to an increased risk of inflammatory cardiomyopathy, but to decreased congenital transmission of *T. cruzi*. As housing and vector control improve, concurrent attention to early treatment is needed in order to reduce both cardiomyopathy and congenital infection.

SOURCE: Kaplinski M, Jois M, Galdos-Cardenas G, et al. Sustained domestic vector exposure is associated with increased Chagas cardiomyopathy risk but decreased parasitemia and congenital transmission risk among young women in Bolivia. *Clin Infect Dis* 2015;61:918-926.

Kaplinski and colleagues evaluated *T. cruzi* vertical transmission rates and risks of cardiomyopathy in urban and rural women in Bolivia. Of 1696 study participants, 1213 were from an urban area of Bolivia where housing changes and vector control have essentially removed residential exposure to the triatomine bug that serves as the vector of Chagas disease. The other 483 participants were in a rural part of Bolivia where mud- or dirt-walled homes are commonly infested with *T. cruzi*-infected vectors.

Pregnant women presenting for delivery were eligible for study entry. Infection with *T. cruzi* was confirmed when two or more conventional tests were positive. *T. cruzi*-infected study subjects underwent electrocardiography (ECG) and had cord blood tested at delivery. Infants of infected mothers were further evaluated for *T. cruzi* antigenemia and/or serology at 1, 6, and 9 months of age.

Overall, 456 (26.9%) of the women were infected with *T. cruzi*. Women from rural areas were much more likely to be infected with *T. cruzi* at the time of delivery than women from urban areas (47.4% vs 18.7%, respectively; $P < 0.0001$). Also, there was an inverse relationship between vertical transmission to the infant and duration of living in rural areas. The women who reported never having lived in a vector-infested house had a higher rate of vertical transmission than the women who had resided in a house known to contain triatomines (9.7% vs 4.6%, respectively; $P = 0.04$).

Of 302 infected women who underwent electrocardiography, 28 (9.3%) had ECG changes that were consistent with Chagas cardiomyopathy. The most common types of ECG change were bradycardia and bundle branch block. Women with abnormal ECGs had been residents of infected houses longer than women with normal ECGs (17.5 vs 1.0 years; $P = 0.001$). Women with abnormal ECGs were similarly likely to transmit *T. cruzi* to their infants as were women with normal ECGs (3.6% vs 8.0%, respectively; $P = 0.40$).

Thus, Kaplinski and colleagues showed that women who have longer exposure to *T. cruzi* are more at risk for Chagas cardiomyopathy as they get older. But they are less likely to transmit *T. cruzi* to their infants than are women who have less vector exposure.

[... Kaplinski and colleagues showed that women who have longer exposure to *T. cruzi* are more at risk for Chagas cardiomyopathy as they get older.]

■ COMMENTARY

In the Americas, *T. cruzi* causes more disease than any other parasite; it is estimated that 6 million people are infected. Approximately one-fourth of the infected individuals will develop life-altering cardiomyopathy.[1] There could be as many as 1 million infected individuals in the United States,[2] where transmission occurs congenitally, via blood transfusion, and even via insect vectors.[3]

Infection triggers immunity that alters parasite loads, but this immunity neither eradicates the infection nor protects from future infection. And, the immune

response is implicated in the pathogenesis of the inflammatory cardiomyopathy.

When treatment is not given and household insect vectors repeatedly induce recurrent infection, the body struggles to keep a tenuous balance between suppressed infection (with, as shown by this study, lower parasite loads and less congenital transmission) and immunity-triggered pathology (such as cardiomyopathy). With urbanization and improved housing, previously infected women develop less cardiomyopathy but are at greater risk of congenital transmission of infection.

So, what can be done? Clearly, we need a multifaceted approach.

Improvements in housing with resultant decreases in housing-related triatomine bugs will reduce the overall incidence of infection. Development efforts must continue to promote improved housing in areas of Latin America where Chagas disease is endemic. Similarly, improved access to medical care would allow for more timely diagnosis and effective treatment of infected individuals in rural areas.

Medication can also help, especially when given early after infection (whether the infection was acquired congenitally or from insects). Benznidazole and nifurtimox can eradicate some infection, and benznidazole is associated with relatively fewer side effects. In adult infection, benznidazole can eradicate detectable parasites in 94% of patients.[4] However, benznidazole, even while decreasing parasite load, does not seem to reverse or even prevent progression of established Chagas cardiomyopathy.[5] Priority should be placed on the treatment of congenitally infected children (since children experience both better cure rates and fewer side effects than adults) and young adults, especially women who risk transmitting the infection to their offspring.[6] ■

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ABSTRACT & COMMENTARY

Intestinal Fibrosis and Immune Reconstitution in Patients with HIV Infection

By Dean L. Winslow, MD, FACP, FIDSA

Dr. Winslow is Clinical Professor of Medicine, Division of General Medical Disciplines, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, CA.

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

SYNOPSIS: Duodenal biopsies in patients naïve to combination antiretroviral therapy (cART) underwent tissue staining and were examined. Intestinal myofibroblast activation was correlated with intestinal fibrotic changes and poor immune reconstitution following cART.

SOURCE: Asmuth DM, et al. Role of intestinal myofibroblasts in HIV-associated intestinal collagen deposition and immune reconstitution following combination antiretroviral therapy. *AIDS* 2015;29:877-888.

Five normal controls and 20 combination antiretroviral therapy (cART)-naïve HIV patients underwent duodenal biopsy. Normal subjects had virtually no fibrosis evident on both trichrome-stained biopsies and specimens examined by confocal microscopy. In contrast, HIV patients had variable amounts of fibrosis evident in the lamina propria. Immunostaining demonstrated that myofibroblasts were immediately adjacent to areas of collagen deposition, and these intestinal myofibroblasts (IMFs) expressed fibroblast activation protein (FAP). Confocal microscopy also revealed that in HIV patients, TLR4 was abundantly expressed in intestinal lamina propria. Primary cultures of

HIV patient-derived IMFs were stimulated with lipopolysaccharide (LPS) and showed significantly increased mRNA expression of both TGF-B and IL-6 by real-time RT-PCR.

Using real-time RT-PCR to assess mRNA expression in intestinal tissue, HIV patients demonstrated significantly greater TGF-B expression than did normal controls, and that the level of TGF-B expression was positively correlated with pro-collagen type 1 expression and was negatively correlated with both baseline duodenal CD4+ T-cell count and change in peripheral CD4+ T-cell count measured 9 months after initiation of cART.

■ COMMENTARY

I remember attending a lecture back in the 1980s at one of the first International AIDS conferences and hearing Hans Wigzell (now president of the Karolinska Institute) presciently say, "The final battle of HIV is fought in the lymph nodes." He was (and is) right. Later, many researchers correctly focused on the largest lymphoid organ in our bodies, gut-associated lymphoid tissue (GALT). A large body of evidence has emerged from both the study of humans and primate models of HIV that demonstrate profound and early (often within days of infection) depletion of CD4+ T-cells from GALT and an inflammatory response within the intestine. This inflammation is correlated with microbial translocation (elevated serum levels of bacterial 16 rDNA and endotoxin) as well as pro-inflammatory cytokines (TNF alpha, IL-6, sCD14, etc.) and markers of activation of the coagulation system (D-dimer).

The elegant work reported in this paper adds further understanding of these complex interactions between HIV and both inflammation and fibrosis within the intestine. The relationship between GALT IMF activation, inflammation, fibrosis, intestinal CD4+ T-cell depletion, and the effect on peripheral CD4+ lymphocyte recovery with cART is an important observation. Sadly, these patients who have poor immunological recovery despite effective viral suppression with cART have not responded to experimental treatment with hyper-intense cART regimens or immune enhancement therapy. The observations reported in this paper potentially open the door to other modes of treatment, including intestine-specific modulation of inflammation/fibrosis or microbiome manipulation. If effective interventions are eventually identified, beneficial effects on both immune reconstitution and amelioration of many of the adverse effects of HIV-associated inflammation (including accelerated vascular disease) can be anticipated. ■

[The elegant work reported in this paper adds further understanding of these complex interactions between HIV and both inflammation and fibrosis within the intestine.]

ABSTRACT & COMMENTARY

Clostridium difficile Infection — Back to the Future

By Stan Deresinski, MD, FACP, FIDSA

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

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

SYNOPSIS: This study provides strong evidence that the diagnosis of *Clostridium difficile* infection (as opposed to colonization) should be made on the basis of evidence of toxin production, not the mere presence of the organism as detected by glutamate dehydrogenase testing or the presence of toxin genes.

SOURCE: Polage CR, Gyorke CE, Kennedy MA, et al. Overdiagnosis of *Clostridium difficile* infection in the molecular test era. *JAMA Intern Med* 2015 Sep 8:1-10.[Epub ahead of print.]

Hospitals that introduced polymerase chain reaction (PCR) testing for *Clostridium difficile* toxin genes in stool were suddenly confronted with an apparent 40% to 50% increase in detection of the organism — not a good thing in a world of public reporting and value-based purchasing. This did not

represent an increased infection rate, but, rather, the detection of colonization by the organism, something that is found in as many as 8% of patients without diarrhea admitted to the hospital. This is not just a bad thing for the reputation and finances of the hospital, it is a bad thing for the patients who receive unnecessary treatment.

In 2013, Planche and colleagues reported the results of a large study evaluating the ability of various diagnostic methods to predict outcomes in those with positive results.[1] They found that the detection of *C. difficile* by PCR for toxin gene or by a glutamate dehydrogenase assay was not predictive of increased mortality in the absence of a positive test by either enzyme immunoassay (EIA) or cytotoxigenic culture positivity, with the latter being the most highly correlated with fatality. In contrast, Rao et al, using a two-step system that detects *C. difficile* glutaraldehyde dehydrogenase and toxin, recently concluded that toxin detection was not predictive of severe disease or mortality,[2] although their results have been questioned by Planche and colleagues.[3]

Thus, we have a problem and a controversy, one that now has been addressed by another group. Polage and colleagues set out "to determine the natural history and need for treatment of patients who are toxin immunoassay negative and polymerase chain reaction (PCR) positive (Toxin–/PCR+) for CDI." They performed a series of tests on unformed PCR of stool samples submitted to their laboratory for *C. difficile* testing that began with PCR for toxin gene (the result of which was not reported to the clinician) and toxin immunoassay.

Of the 1416 hospitalized adults whose stools were tested, 131 (9.3%) were Toxin+/PCR+, 162 (11.4%) Toxin–/PCR+, and 1123 (79.3%) were Toxin–/PCR–. Patients who were Toxin+/PCR+ had had greater prior antibiotic exposure, more frequently had leukocytosis, had more diarrhea on day 1, and were more likely to have elevated fecal lactoferrin than those in the other groups — who largely did not differ from each other clinically. They also had a longer duration of diarrhea than Toxin–/PCR+ patients and Toxin–/PCR– patients ($P < 0.001$), and had a greater risk of diarrhea during the follow-up. In multivariate analysis, Toxin+/PCR+ status had the strongest effect on the duration of diarrhea. Toxin–/PCR+ status and pretest exposure to metronidazole or oral vancomycin were not significant predictors in the multivariable model. One hundred percent of Toxin+/PCR+ patients were treated for a median duration of 14 days with vancomycin or metronidazole. Among the Toxin–/PCR+ patients, 40.7% were treated, but only for a median duration of 6 days; 32.1% of those Toxin–/PCR– received one of these antibiotics for a median of 5 days.

Complications, such as megacolon, need for colectomy or intensive care unit care, and death, occurred in 10 (7.6%) of 131 Toxin+/PCR+ patients, compared to 0 of 162 who were Toxin–/PCR+ and 3 (0.3%) of 1123 ($P < 0.001$) Toxin–/PCR– patients. There was no significant difference between the latter two groups. In addition, 11 (8.4%) Toxin+/PCR+ patients died compared to 1 (0.6%) and none ($P < 0.001$) who were Toxin–/PCR+ and Toxin–/PCR–, respectively. The single death in the Toxin–/PCR+ group occurred in a patient with severe comorbidities who had uncomplicated recurrent diarrhea that had resolved prior to withdrawal of care.

[These data provide a strong argument that the diagnosis of disease caused by *Clostridium difficile* should be made on the basis of the detection of toxin, not toxin gene ...]

These data provide a strong argument that the diagnosis of disease caused by *Clostridium difficile* should be made on the basis of the detection of toxin, not toxin gene (or glutamate dehydrogenase). This would appear to reduce unnecessary treatment, as well as heartburn, for Infection Prevention Programs and hospital administrators.

The data also provide an argument for antimicrobial stewardship — and not just regarding apparent unnecessary anti-*C. difficile* treatment in Toxin–/PCR+ patients. Why was a median duration of 6 days of such treatment administered to approximately one-third of patients who were Toxin–/PCR–? ■

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ABSTRACT & COMMENTARY

Treatment of Vertebral Osteomyelitis: A Brief Narrative Summary of the New IDSA Recommendations

By Stan Deresinski, MD, FACP, FIDSA

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

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

SYNOPSIS: A new IDSA guideline has recommendations providing best expert advice on management of native vertebral osteomyelitis.

SOURCE: Berbari EF, Kanj SS, Kowalski TJ, et al. Executive Summary: 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults. *Clin Infect Dis* 2015;61:859-863.

The Infectious Diseases Society of America (IDSA) has published a new guideline dealing with the diagnosis and treatment of native vertebral osteomyelitis (NVO) in adults. The guideline contains a total of 38 recommendations that were rated using the GRADE system, and while the strength of the recommendations was variable, many were based on low-level evidence — a result of the fact that there are so few comparative clinical trials in this field. In the GRADE system, low-level evidence is defined as "Evidence for at least one critical outcome from observational studies, RCTs with serious flaws, or indirect evidence" — not exactly a booming endorsement. For assessment of the strength and quality of evidence for the recommendations contained in this narrative summary, please examine the original document.

The diagnosis of NVO, which often results from unrecognized episodes of bacteremia, is often delayed with resultant severe adverse consequences. The first set of recommendations revolve around the critical need for early consideration of the diagnosis in patients with new or worsening neck or back pain, especially in the presence of fever (which, unfortunately, frequently may be absent). Examination of such patients should include a directed motor and sensory neurologic examination and laboratory studies to include blood cultures, erythrocyte sedimentation rate, and C-reative protein. If clinical or epidemiological evidence points to the need, blood cultures and serological tests for Brucella or fungi may be indicated. For those with a subacute presentation or appropriate epidemiological history, a purified protein derivative (PPD) or interferon gamma release assay (IGRA) should be performed.

Magnetic resonance imaging (MRI) is the recommended diagnostic imaging procedure, with combined spinal gallium/Tc99 bone scan or PET scan in those in whom MRI cannot be performed. Unless blood cultures or serological tests for an undisputed pathogen are positive, patients should undergo an

[The first set of recommendations revolve around the critical need for early consideration of the diagnosis in patients with new or worsening neck or back pain, especially in the presence of fever ...]

imaging-guided aspiration biopsy for microbiological studies (including fungal and/or mycobacterial, when indicated) and, if sufficient material is recovered, for histopathological examination. In the absence of neurological compromise, sepsis, or hemodynamic instability, antibiotic therapy may be temporarily withheld prior to the procedure. In the presence of such findings, however, empiric antibiotic therapy should be initiated immediately (blood cultures should be obtained first) and, in the case of neurological compromise, immediate surgical intervention is indicated, regardless of the presence or absence of sepsis or hemodynamic instability.

If no etiology is determined from blood or aspiration specimens, a second aspiration biopsy should be performed — alternatively, a specimen may be obtained by percutaneous endoscopy discectomy and

drainage or by an open surgical procedure. If cultures of specimens from a first or second procedure remain negative, nucleic acid amplification testing for bacterial, mycobacterial, and fungal etiologies should be performed on appropriately stored specimens.

Antibiotic treatment, either parenterally or orally, should be continued for a total duration of 6 weeks, with 3 months of therapy indicated for patients with brucellosis. Inflammatory makers, along with a clinical assessment, should be performed approximately 4 weeks after initiation of therapy. There is no indication for a routine follow-up MRI in the patient with a favorable and laboratory response to antibiotic therapy. In those with a poor clinical response, repeat MRI can be performed to evaluate epidural and paraspinal soft tissue changes. If there is clinical evidence of treatment failure and imaging indicates evidence of failure of improvement in epidural or paraspinal infection, specimens for further microbiological evaluation should be obtained.

Surgical debridement, with or without a stabilization procedure, should be performed in patients receiving appropriate antibiotic therapy who have persistent or recurrently positive blood cultures for whom no alternative source of the microbemia is present. Patients who suffer from worsening neurological deficits, vertebral deformity, and instability of the spine should also undergo surgical intervention. In the absence of one of these indications, patients who have clinical improvement and a decrease in the levels of inflammatory markers, but who have worsened bony changes on imaging at 4-6 weeks do not have an indication for surgical intervention. ■

ABSTRACT & COMMENTARY

Arboviral Infections in the United States — Not Just West Nile

By Stan Deresinski, MD, FACP, FIDSA

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

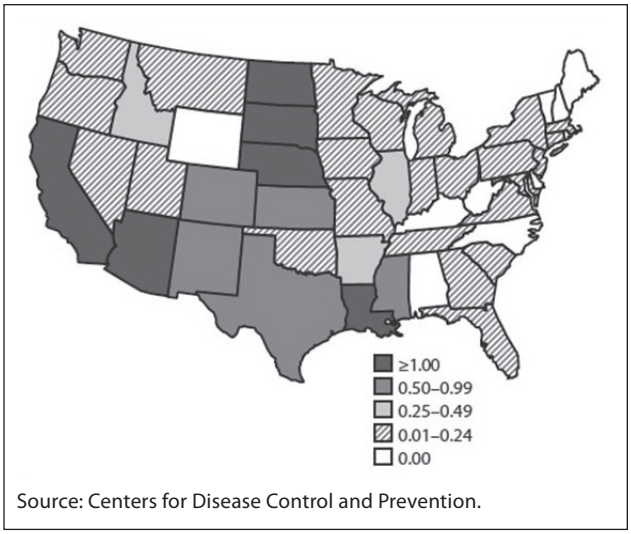
SYNOPSIS: West Nile virus accounted for 95% of arbovirus infections in 2013 reported to CDC, with the majority causing neuroinvasive disease.

SOURCE: Lindsey NP, Lehman JA, Staples JE, et al. West Nile virus and other nationally notifiable arboviral diseases — United States, 2014. *MMWR Morb Mortal Wkly Rep* 2015;64:929-934.

In 2014, 2327 cases of arbovirus infection were reported to the CDC, mostly via ArboNET, by the District of Columbia and all the states with the exception of Alaska, Delaware, Rhode Island, and Vermont. The vast majority — 2205 (95%) — were due to West Nile virus (WNV), and 1347 (61%) of these caused neuroinvasive infections (*see Figure*) such as meningitis (42% of those with neuroinvasive disease), encephalitis (46%), and acute flaccid paralysis (10%) — accounting for a national incidence of 0.42 per 100,000 population. The incidence in the six states with the highest rates (Nebraska, North Dakota, California, South Dakota, Louisiana, and Arizona) ranged from 2.2 to 1.2 per 100,000. The incidence in California was significantly increased from previous years, and two California counties, Los Angeles and Orange, accounted for 70%. Of the total cases, 90% had onset during July to September, with a peak in late August. Almost two-thirds occurred in males. Hospitalization was thought to be necessary for 72%. Overall, 4% of the patients died — the median age of those who died was 75 years, while it was only 57 years for the total cohort. The incidence of neuroinvasive disease increased with increasing age, and all but 4% of patients with neuroinvasive disease were hospitalized; 6% died. An important feature of WNV is its potential transmission by blood transfusion and organ transplantation from infected asymptomatic donors.

The other 5% of reported arboviral infections included La Crosse virus (80 cases), Jamestown Canyon virus (11), St. Louis encephalitis virus (10), Powassan virus (8), Eastern equine encephalitis virus (8), and unspecified California serogroup virus (5). The 80 cases of La Crosse virus disease, 95% of which were neuroinvasive, were reported from nine states. While 28 of the 90 were reported by South

Figure. Rate (Cases per 100,000 Population) of Reported Cases of West Nile Virus Neuroinvasive Disease — United States, 2014.



Source: Centers for Disease Control and Prevention.

Atlantic states, Ohio had the highest incidence (0.26 per 100,000 population), just beating out North Carolina (0.23 per 100,000). The demographics were almost the opposite of those of WNV disease: The median age was only 8 years, and 53% were female. All but one were hospitalized, and three (4%) died.

Four states (Massachusetts, Minnesota, Tennessee, and Wisconsin) reported a total of 11 cases of Jamestown Canyon virus disease; none were fatal. Jamestown Canyon virus, like La Crosse virus, belongs to the California serogroup virus. There were an additional five cases of California serogroup disease for which the specific virus was undetermined. No fatalities were reported among the 10 cases of St. Louis encephalitis or the eight cases of Powassan virus disease, while three of the eight patients with Eastern equine encephalitis died.

■ COMMENTARY

As pointed out by CDC, this report is not the whole story, and the true number of cases is likely much greater. Since the majority of infections are asymptomatic and many of the rest are associated with only a nonspecific febrile illness, a diagnosis is only likely to be made with more severe disease, especially those causing neurological manifestations. They estimate that there are actually 40,000 to 94,000 infections annually, with only a few percent identified. In addition, other arboviral infections, including chikungunya, dengue, and Colorado tick fever, are not notifiable on a national level. Finally, novel viruses, such as Heartland[1] and Bourbon[2] viruses, continue to be discovered.

Heartland virus is a phlebovirus that has been identified in a small number of patients in Missouri and Tennesse and is believed to be transmitted by the bite of the Lone Star tick, and has been fatal in at least one instance.[1] The Bourbon virus, a thogotovirus, was first recovered in a patient from Bourbon County, KS, with a history of tick bites.[2] The patient presented with fever, thrombocytopenia, and leukopenia, went on to develop multi-organ system failure, and died.

In the United States, annual federal funding for arbovirus surveillance decreased by 39% between 2006 and 2012, when it reached a low of only $9.3 million.[3] In that same year, the United States experienced the highest incidence of confirmed WNV neuroinvasive disease since 2003, as well as the highest number of confirmed deaths ever. With reports of arbovirus vectors appearing in new areas and the identification of novel arboviruses, we likely will have more such infections due to a variety of viruses in the future. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Coccidioidomycosis: Is the "Zone" Growing?

SOURCE: Coccidioidomycosis — USA (Nevada), Pro-MED-mail post, August 12, 2015; www.promedmail.org.

Reports of valley fever (coccidioidomycosis) appear to be steadily on the rise in California and the Southwest during the past few years. Increasing numbers of cases are being documented throughout California and the Southwest. For example, from 1998 to 2011, cases in humans in

California increased from 719 to 5366 — with a big jump in 2010-2011.[1] While we generally see a case or two of cocci per year in our clinic, I had three cases back to back within a three-week period in July — two of whom drove down Highway 5 through the Central Valley a few weeks earlier.

This new report describes a cluster of five cases of valley fever in Washoe County, NV; two of these individuals never left the area. Washoe County is just east of the Sierra Nevada mountain range, and runs northward from Reno to the Oregon border. While cocci is endemic to southern Nevada, it is unusual in this part of northern Nevada. Officials in Washoe County say that whenever a case is identified in their county, the patient has invariably traveled to an area endemic for cocci.

Little is known about the soil conditions that promote the growth of the fungi — which generally grows within the top 2 to 8 inches of soil. It is thought that heavier rains in the winter to spring nourish the growth of the organism, and then spring and summer winds kick up the topsoil, carrying the infectious arthroconidia for miles. As little as 15 arthroconidia may be infectious to humans.

The fungus is endemic to the San Joaquin Valley of California, that swath of agricultural land that runs roughly south of Stockton and Fresno to the Grapevine Mountain Range north of Los Angeles. Then its range roughly follows the lower Sonoran life zone, that arid stretch of low desert land extending from Joshua Tree to southern Nevada, and parts of Arizona, New Mexico, and northern Mexico. It was, however, recently found in soil samples from southwestern Washington — outside of its recognized range.[2] One wonders whether these newer cases in northern Nevada are a clue that global warming or the current drought are creating conditions more favorable to the fungus — and perhaps extending its range farther north and east of the Sierras and Cascades.

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Cocci as a Cause of Marine Mammal Mortality

SOURCE: Huckabone SE, et al. Coccidioidomycosis and other systemic mycoses of marine mammals stranding along the central California, USA coast: 1998-2012. *J Wildlife* 2015;51:295-308.

This interesting article reveals some of the fascinating details of a longitudinal study of > 7000 necropsies performed on stranded marine mammals along the central California coast from 1998 to 2012. Full necropsies are routinely performed on all stranded animals at three facilities. Nineteen different kinds of mycosis have been found in 24 species of marine mammals, either captive or free-living; most commonly, these pathogens include Coccioides, Blastomyces spp, and *Cryptococcus gattii*.

Of these, cocci is the most common pathogen causing mycosis in marine mammals on the California coast. Thirty-six animals had either culture or histological confirmation of cocci infection, including 15 sea lions, 20 sea otters, and one wild harbor seal. Real-time quantitative PCRs and sequencing performed at University of California Davis confirmed all infections to be due to *C. immitis*. For both sea lions and otters, there appears to be an increasing number of fatal cases of cocci — eight sea otters and one pinniped were found with cocci infection from 1998 to 2005, compared with 12 sea otters and 15 sea lions from 2006 to 2012. Similar numbers of pinnipeds have been found all along the central California coast, extending from San Luis Obispo County to Marin — but, interestingly, dead sea otters with cocci are now being found along the northern California coast for the first time in more than 45 years of monitoring.

Coccidioidomycosis appeared to be the primary cause of death for 90% of the sea otters; the remainder died from domoic acid poisoning. Dissemination of infection was the norm (92%), and pathologic findings identified pulmonary nodules (94%), pleural effusion (92%), pneumothorax (25%), peritoneal effusions (55%) and peritonitis (29%), and infected hilar, mediastinal, or other lymph nodes (100%). Many of the otters exhibited numerous tan, raised, subcutaneous plaques — which turned out to be a clue to disseminated infection — which demonstrated pyogranulomatous inflammation with rare spherules on sectioning. Interestingly, cardiac involvement was not uncommon: 55% of the animals had pericarditis, and 43% had fungal myocarditis. The brain was involved in eight of nine animals (89%), and coccidioidal ophthalmitis was found in one-third of animals with microscopic examinations of the eye.

Similar to the sea otters, cocci was the primary cause of death for 87% of the pinnipeds and the rest primarily died from domoic acid poisoning. Dissemination was also common to pinnipeds

(91%), with a wide range of organ involvement. Coccioides-peritonitis or peritoneal effusion was found with possible greater frequency (92%) in sea lions compared with otters.

Importantly, fresh fungal growth with the development of hyphae and arthroconidia was observed in the decomposing tissues of one animal, which could be a source of infection for others. Monitoring endemic mycosis in marine mammals is not only important for marine health surveillance, but one more clue as to what might be happening to the human population in these areas. Furthermore, the finding of large numbers of cases of coccidioidomycosis along the California coast, particularly in the area of San Luis Obispo, suggests the presence of this organism in previously unrecognized habitats.

Initial and Much Too Subtle Ebola Virus Infection

SOURCE: Liddell AM, et al. Characteristics and clinical management of a cluster of 3 patients with Ebola Virus Disease, including the first domestically acquired cases in the United States. *Ann Intern Med* 2015;163:81-90.

These authors present a blow-by-blow picture of the presentation and clinical course of three patients cared for with Ebola Virus Disease at three different hospitals in the United States, including the index case from Liberia cared for at Texas Health Presbyterian Hospital in Dallas, and the two nurses with secondary infection who provided his care.

There are many fascinating features to this article, but one of the most striking features was the all-too-subtle and nonspecific nature of the presenting signs and symptoms for all three patients. The first nurse to be hospitalized last took care of the index case on October 7, 2014. By October 9, she thought she had an exacerbation of allergic rhinitis with nasal congestion and rhinorrhea. The following night, she had an oral temperature of 100.1 F, with mild headache, mild nasal congestion, throat discomfort, and insomnia. At that point, she presented to the emergency department (ED) for care. In the ED, her temperature was 38.1, her heart rate was 117 beats/minute, and her blood pressure was normal. Her labs were unremarkable, including a WBC 4.1, normal platelets, and normal transaminases. A plasma specimen taken at the time of presentation later proved positive for moderate amounts of EBOV RNA. Even during the first 4 days of her hospitalization, she remained stable, with fever, headache, nausea, and vomiting, but no diarrhea. It was not until day 5 of hospitalization that she developed pulmonary edema, abnormal transaminases, diarrhea, and a morbilliform rash — a week into her illness.

The second nurse also last cared for the index patient on October 7, and was monitoring her symptoms and temperature. Beginning on October 10, her only complaints were fatigue and anorexia. It was not until October 14 when she developed a macular rash and two non-bloody diarrheal stools and presented to the ED, where she was found to have a temperature of 37.9 to 38.1, heart rate of 138 beats/minute, and normal blood pressure. Her WBC was 2.67 cells/mm^3, platelets 120,000, and abnormal transaminases. Her plasma specimen on the day of presentation was positive for moderate amounts of EBOV RNA.

In going back over the index patient's initial presentation to the hospital, his primary complaints were one day of headache and abdominal pain, with rhinorrhea and nasal congestion and chills. His initial temperature was only 37.8, with a heart rate of 90, and mild leukopenia (3.0 cells/mm^3). He did not provide a travel history, and it's not clear that one was requested. An abdominal CT was unremarkable. The diagnosis of Ebola was not even considered at that time.

And why would it have been, based on these signs and symptoms? I had previously thought rhinorrhea, nasal congestion, and sore throat steered the diagnosis into safer waters, and yet two of these patients had upper respiratory infection-like symptoms. The key to the diagnosis must be a detailed history of exposures and travel — not the presentation — which, for at least several days, may look like many other types of illness. Despite the subtlety of the presentation, and the fairly unremarkable laboratory findings for at least the first 1-7 days of illness, all three patients were actively viremic. ■

[The key to the diagnosis must be a detailed history of exposures and travel — not the presentation — which, for at least several days, may look like many other types of illness.]

CME INSTRUCTIONS

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CME QUESTIONS

1. Chagas disease:

A. is transmitted by anopheline mosquitoes.

B. is transmitted congenitally, especially by women exposed to chronic recurring infections.

C. is transmitted in the United States.

D. is rarely transmitted congenitally by Bolivian women after they move to urban houses.

2. Which of the following is correct with regard to the recommendations concerning the diagnosis and treatment of native vertebral osteomyelitis in the new guideline of the Infectious Diseases Society of America?

A. The diagnostic imaging method of choice is computerized tomography.

B. The recommended duration of treatment is 6 weeks.

C. Follow-up imaging after 6 weeks of therapy should routinely be performed.

D. Measurement of CRP is of no value in the evaluation and follow-up of the patient during treatment.

3. In the study by Polage and colleagues, which combination of tests was most predictive of the development of complications of *Clostridium difficile* colitis?

A. Toxin negative, PCR positive

B. Toxin negative, PCR negative

C. Toxin positive, PCR negative

D. Toxin positive, PCR positive

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.