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Infectious Disease [ALERT]

A monthly update of developments in infectious disease, hospital epidemiology, microbiology, infection control, emporiatrics, and HIV treatment

SPECIAL FEATURE

Shiga Toxin-producing E. coli, Diarrhea, Hemolytic Uremic Syndrome, and Sprouts

By Stan Deresinski, MD, FACP, FIDSA
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In May of this year, German public health authorities reported a significant increase in the number of patients with diarrhea caused by a Shiga toxin-producing *Escherichia coli* (STEC), as well as of cases of hemolytic uremic syndrome (HUS).[1] Between May 2, and June 14, 2011, 818 cases of HUS and 3,332 STEC cases were reported from European Union/European Economic Area Member States; 36 patients died. The proportion of those with STEC infection who developed HUS is much larger than reported in previous outbreaks. Also unusual is that the majority of cases occurred in adults, a finding quite different from the usual target of young children by STEC, and two-thirds of cases were in females. More than 95% of cases were reported from Germany and most of the remainder had recently traveled to northern Germany. Additional cases have been identified in Switzerland, the United States, and Canada, and also after travel, in most cases to Germany.

The culprit has been identified as STEC serogroup O104:H4, rather than the much more common serogroup 0157:H7, a factor which may have led to a delay in the recognition of the outbreak. While investigations continue, classical epidemiology has identified the likely contaminated food product as bean sprouts, including fenugreek mung beans, lentils, adzuki beans, and alfalfa. Thus, a "recipe-based restaurant cohort study" found that customers who had eaten sprouts had an 8.6-fold increased risk of diarrhea and/or HUS compared to those who had not eaten sprouts.[2] Furthermore, 100% of those who became ill had eaten sprouts.

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The implicated sprouts have been traced to a farm in Lower Saxony near Hamburg.

STRAIN

The outbreak serotype 0104:H4 strain has been extensively characterized and been found to have some unusual characteristics, including being a hybrid with enteroaggregative E. coli (EAggEC). In fact, among *E. coli* sequences to which it has been compared, the genome of the outbreak strain is most closely related to an EAggEC isolated in 2002, mostly differing by the addition of *stx*, the gene encoding Shiga toxin (also known as Vero toxin), and antibiotic resistance genes. Its hybrid nature means that it can most accurately be designated as enteroaggregative, Shiga toxin/verotoxin-producing *E. coli* (EAggEC STEC/VTEC).

EAggEC is a type of *E. coli* that causes diarrhea, but it does not secrete either the heat-stable or heat-labile toxins that characterize enteroxigenic *E. coli* and that adhere to the surface of cells in culture in characteristic aggregations that resemble stacked bricks. The adherent bacteria produce various diarrheogenic toxins. This typical aggregative growth is the result of the presence of aggregative adherence fimbriae (AAF), whose expression is regulated by a plasmid-borne gene, *aggR*. EAggEC infection most often is associated with persistent watery diarrhea, particularly in infants in developing countries, as well as in HIV individuals.[3]

The outbreak strain is multidrug resistant, carrying not only the common TEM-1 β-lactamase, but also CTX-M-15. It is resistant to cephalosporins, penicillins, and β-lactam/β-lactamase inhibitor combinations, as well as to streptomycin, nalidixic acid, tetracycline, and trimethoprim/sulfamethoxazole.

The organism is, by definition, characterized as an STEC by virtue of its possession of genes encoding Shiga toxin, in this case Shiga toxin 1 subtype 2a — the gene encoding Shiga toxin 2 is absent. Shiga toxin 1 differs from "true" Shiga toxin (of *Shigella*) by 1-7 amino acid differences, while Shiga toxin 2 shares approximately 60% homology to Shiga toxin 1.

LABORATORY DIAGNOSIS

In contrast to E. coli 0157:H7, the outbreak 0104:H4 strain does not ferment sorbitol. Since lack of sorbitol fermentation is the most commonly used characteristic in screening for STEC, this may have led to a failure of identification of the organism in some clinical laboratories. This is the reason why the Centers for Disease Control and Prevention (CDC) in 2009 recommended the following: "All stools submitted for testing from patients with acute community-acquired diarrhea (i.e., for detection of the enteric pathogens *Salmonella*, *Shigella*, and *Campylobacter*) should be cultured for O157 STEC on selective and differential agar. These stools should be simultaneously assayed for non-O157 STEC with a test that detects the Shiga toxins or the genes encoding these toxins. All O157 STEC isolates should be forwarded as soon as possible to a state or local public health laboratory for confirmation and additional molecular characterization (i.e., PFGE analysis and virulence gene characterization). Detection of STEC or Shiga toxin should be reported promptly to the treating physician, to the public health laboratory for confirmation, isolation, and subsequent testing of the organism, and to the appropriate public health authorities for case investigation. Specimens or enrichment broths in which Shiga toxin or STEC are detected, but from which O157 STEC are not recovered, should be forwarded as soon as possible to a state or local public health laboratory."[4] It is clear, however, that not many clinical microbiology laboratories in the United States follow this recommendation and thus the danger of delayed recognition of an outbreak remains a risk. Of note is that screening for serotype 0104:H4 can be performed by agglutination with K9 capsular antigen antiserum since the antigens of both are identical.[1]

TREATMENT

It has been suggested that the multidrug resistance of the outbreak strain is irrelevant since antibiotic therapy (as well as administration of antimotility agents) is believed by many to be contraindicated in these infections, because of some evidence indicating an associated increased risk of HUS. This is thought to be the result of mobilization of phage and resultant increased production of Shiga toxin caused by antibiotic activation of the bacterial SOS system. Treatment of HUS has been only supportive, including hemodialysis and plasma exchange, but other possibilities are being explored. Shiga toxin activates the complement system and this is believed to play a key role in the development of HUS. The monoclonal C5 antibody, eculizumab, which inhibits terminal complement complex formation has met primary endpoints in a Phase 2 study in children with atypical HUS, which is associated with genetically determined chronic uncontrolled complement activation. Recently, eculizumab has been administered to several patients with STEC-associated HUS with perceived benefit.[5] Separately, urtoxazumab, a humanized monoclonal antibody directed against the Shiga-like toxin 2 was safe when administered to healthy adults and children with STEC infection in a Phase 1 trial.[6]

CONCLUSION

This STEC outbreak is one of the largest ever described anywhere in the world and is associated with an unusually high incidence of HUS. It has resulted from the capture of a bacteriophage encoding Shiga toxin by a typical strain of EAggEC, resulting in an organism that is hypervirulent and may also have the ability to persist in the gastrointestinal tract. The lack of sorbitol fermentation by the outbreak strain means it is not detected by many clinical microbiology laboratories that do not test directly for the toxin or its gene. The lesson is that clinicians and clinical laboratories in the United States need to be alert to the detection of STEC and STEC-EAggEAC hybrids of all stripes. ■

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ABSTRACT & COMMENTARY

Going Green in the CSF

By Joseph F. John, MD

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Dr. John reports no financial relationship to this field of study.

SYNOPSIS: Pigment production by P. aeruginosa made the cerebral spinal fluid green.

SOURCES: Escota G, Como J, Kessler H. The green cerebrospinal fluid. Am J Med 2011;124:411-413.

A 52-year-old woman had systemic symptoms including nausea and vomiting. Seven months prior to admission she had a subarachnoid hemorrhage and needed multiple ventriculo-pleural shunts. The newest shunt was 2 months old at the time of the patient's admission. She was alert on admission, but had a left pleural effusion. The shunt was externalized and the external ventricular drain provided. Cerebral spinal fluid (CSF) then was sampled and sent daily for chemistries and culture. The initial CSF formula included 10,000 RBCs and 40 WBCs,

of which 58% were monos. CSF glucose and protein were normal. The daily CSF sample was a light green color, had Gram-negative rods on microscopic examination, and consistently grew *Pseudomonas aeruginosa*.

The patient was treated with cefipime 2 g Q 8 hours, but the organism was only intermediately susceptible. The spinal fluid persisted to be green. Cefepime was stopped and meropenem 2 g Q 12 hours was begun. The CSF remained green. Intrathecal amikacin 20 mg/day was initiated. After 1 day, the CSF cleared and the patient eventually had a complete recovery.

■ COMMENTARY

The group from Rush Medical School's Infectious Disease Section headed by Dr. Harold Kessler brought this case to light. The article brings up many experiences by us older ID clinicians that in the treatment of Gram-negative CNS infections still pertain to modern care. About 20 years ago in the midst of a rash of CNS infections with Gram-negative bacilli, a study commenced to determine the efficacy of intrathecal amikacin. I remember the massive consent form, itself a challenge to enrolling these unusual patients.[1]

Yet the clinical trial provided experience with intrathecal dosing and use of aminoglycoside, which impacts still today as evidenced by this patient's eventual happy outcome. The authors discuss the process of choosing antibiotics for Gram-negative meningitis, a process that may end in use of intrathecal antibiotics. New studies suggest the cure rate for Gram-negative meningitis may only be slightly more than 50% and *P. aeruginosa* still causes 35% of the cases.[2]

The novelty of this report was the green color (due to the pyoverdin and pyocyanin pigments produced by *P. aeruginosa*) of what should otherwise be a crystal clear CSF. The CSF remains one of the few areas of modern life where we would choose not to "go green." ■

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ABSTRACT & COMMENTARY

Three Months, 27 Supervised Doses for Latent TB

By Stan Deresinski, MD, FACP, FIDSA
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SYNOPSIS: A 3-month weekly supervised regimen of rifapentine plus INH was non-inferior to a 9-month daily self-administered dose of isoniazid (INH) alone in the treatment of latent tuberculosis in an as-yet unpublished study.

SOURCES: Centers for Disease Control and Prevention. Press Release: Session B9, oral presentation: Sterling, PREVENT TB: Results of a 12-dose,once-weeklytreatmentofLatentTuberculosisInfection(LTBI).Availableat:http://www.cdc.gov/nchhstp/newsroom/PREVENTTBPressRelease.html; Smith M. ATS: Rapid treatment effective for latent TB. Source reference: Sterling TR, et al. "The PREVENT TB STUDY" ATS 2011. Available at: http://www.medpagetoday.com/MeetingCoverage/ATS/26508.

The number of individuals with active tuberculosis in the United States reached an all-time low of 11,181 cases in 2010. At the same time, it is estimated that approximately 11 million people, or 4% of the population, is latently infected and at risk of developing active disease due to *Mycobacterium tuberculosis*. A major strategy for control of tuberculosis in the United States, where BCG vaccination is not routinely recommended, includes the identification and treatment of latently infected individuals, as recognized by the presence of a positive PPD skin test and/or interferon gamma release assay (IGRA) in the absence of clinical or radiographic evidence of active tuberculosis. The standard therapeutic approach has been the daily self-administration of INH for 9 months, a regimen that, because of its duration, is often not completed in actual practice. A 3-month regimen of rifampin and pyrazinamide is associated with a

generally unacceptably high risk of hepatotoxicity and a 4-month regimen of daily rifampin is of uncertain efficacy and raises concerns regarding the selection of microbial resistance.

On May 16, 2011, the results of an international, multicenter randomized clinical trial comparing supervised once-weekly rifapentine plus INH to daily self-administered INH were presented to the annual meeting of the American Thoracic Society by the principal investigator, Timothy Sterling. The trial, which was sponsored by the Centers for Disease Control and Prevention (CDC) in collaboration with the Department of Veterans Affairs and was initiated in 2002,[1] was performed in countries with low or medium incidences of tuberculosis, with the majority of subjects enrolled in the United States and Canada, and others in Brazil and Spain. Enrollees were > 2 years of age; HIV-infected patients receiving antiretroviral therapy were excluded because of the interaction between rifapentine and many antiretrovirals. Pregnancy and breastfeeding were among additional reasons for exclusion.

The experimental group received 900 mg rifapentine and 900 mg INH, each given under supervision once weekly, while the control group self-administered 5-15 mg/kg INH (300 mg for most adults) daily for 9 months. A total of 8,053 participants were enrolled, 71% of which had a close contact who had active TB, while 22% had evidence of skin test conversion. None, of course, had evidence of active tuberculosis and none had previously received antituberculous therapy. This was designed as a non-inferiority trial. Non-inferiority was considered to be achieved if the upper limit of the 95% confidence interval of the difference between the outcomes in the two arms was < 0.75 percentage points.

Patients were observed for 33 months after completion of therapy. The regimen was successfully completed by 82% of those assigned the weekly regimen and by only 69% of those assigned daily INH ($P = 0.0001$). Among the modified intent-to-treat population of 7,731 subjects, 7 in the weekly rifapentine/INH and 15 in the daily INH arms developed active tuberculosis. Among the 5,858 subjects who successfully completed the protocol, active tuberculosis developed in 4 and 8, respectively. Non-inferiority was demonstrated in both of the analyzed populations.

Both regimens were well tolerated, but discontinuation because of an adverse event was more frequent in the weekly (4.7%) than the daily (3.6%) administration groups ($P = 0.004$). Hepatoxicity, both study drug-related and -unrelated, occurred significantly more commonly in the daily INH recipients ($P < 0.0001$).

■ COMMENTARY

Rifapentine is a cyclopentyl derivative of rifampicin whose major metabolite, 25-desacetyl rifapentine, retains microbiological activity. The parent compound has a mean plasma $T_{1/2}$ of 13-14 hours, while that of the metabolite is 13-24 hours.[2] The bioavailability of rifapentine is significantly enhanced by its administration with a high-fat meal.[3] Rifapentine is more active in vitro than rifampin or rifabutin against *M. tuberculosis*, although its high degree of protein binding (97%) would be expected to significantly diminish its activity in the presence of albumin.

The weekly regimen of supervised administration of INH and rifapentine reduced the number of doses required for treatment of latent tuberculosis from 270 daily doses to 12 once-weekly doses. As expected, this was associated with a significantly greater proportion of participants successfully completing the regimen and it did so without compromising efficacy. The majority of patients in this study were enrolled in the United States and Canada. Whether this weekly regimen would be applicable to countries with significantly higher incidences of tuberculosis is uncertain. Among the concerns in such settings is the risk of re-infection.

Another issue is that of cost, one element of which is the cost of the drugs themselves. One internet site sells a 150 mg rifapentine tablet for $3.63 (U.S.) and a 300 mg INH tablet for $0.10 (U.S.). Thus, the 6 weekly rifapentine tablets given 12 times would cost $392.04 while the 2 weekly INH tablets cost $3.60 for a total of $395.64 for the entire regimen. In contrast, the drug acquisition cost of the 9-month daily INH regimen would be only $27.00. However, there would likely be less laboratory monitoring costs associated with the 3-month regimen. Perhaps most importantly, the cost of weekly supervision of drug administration adds significant cost.

Also to be considered are the many drug interactions associated with administration of rifampicins, including rifapentine. These are largely the result of induction of CYP450 enzymes and affect a large number of drugs, including, as indicated above, many antiretroviral agents.

While the available results are important, it must be recognized that they have not yet gone through peer review and are subject to alteration. I look

forward to their publication. ■

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ABSTRACT & COMMENTARY

Resistance to HIV Integrase Inhibitors

By Dean L. Winslow, MD, FACP, FIDSA

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Dr. Winslow is a speaker for Cubist Pharmaceuticals and GSK, and is a consultant for Siemens Diagnostics.

SYNOPSIS: Integrase inhibitors (INI) have a low genetic barrier to resistance. Raltegravir (RAL) and elvitegravir (EVG) share extensive cross-resistance, whereas S/GSK 1349572 appears to have less cross-resistance. Three common genetic pathways to integrase inhibitor resistance have been identified.

SOURCES: Blanco JL, Varghese V, Rhee SY, et al. HIV-1 integrase inhibitor resistance and its clinical implications. J Infect Dis 2011;203:1204-1214.

Raltegravir (RAL) received FDA approval in 2007 and is now used in treatment of both treatment-experienced and treatment-naïve patients. Two other integrase inhibitors, elvitegravir (EVG) and S/GSK 1349572, are in late-stage clinical development. In patients receiving RAL, three common pathways associated with INI resistance have been observed: 1) Q148HRK+/-G140SA, 2) N155H+/-E92Q, and 3) Y143CR+/-T97A. It has been observed that INI resistance can be rapidly selected in vitro and virological failure on INI-containing regimens often occurs within the first several months of therapy. Significant cross-resistance between the INIs exists. Q148HRK-substituted viruses generally display a > 150 times increase in IC_{50} to both RAL and EVG with a 3-8 times increase in IC_{50} to S/GSK 1349572. 155H-substituted viruses generally display a 10-150 times increase in IC_{50} to RAL and EVG with a 1-3 times increase in IC_{50} to S/GSK 1349572. 143CR-substituted viruses show from a 3 to > 150 times increase in IC_{50} to RAL, but only a 1.5-2 times increased IC_{50} to EVG and no effect on in vitro susceptibility to S/GSK 1349572.

■ COMMENTARY

HIV integrase represents the most 3' gene product of the HIV *pol* gene. It performs two basic functions: 1) following reverse transcription, integrase (IN) cleaves the conserved GT nucleotides from the 3' ends of the double-stranded HIV-1 cDNA leaving CA overhangs (3' processing reaction), and 2) IN remains bound to the 3' ends of the cDNA, circularizing it, complexes with a host protein, lens epithelial-derived growth factor (LEDGF), translocates to the nucleus where it catalyzes the insertion of the viral 3'-hydroxy ends of the cDNA on to the phosphodiester bonds of the host genomic DNA (strand transfer reaction).

HIV-1 IN integrase inhibitors are structurally diverse molecules that interfere with the strand transfer reaction by binding a divalent metal cation (Mg^{++} or Mn^{++}) and a hydrophobic region for binding within the catalytic domain, displacing viral DNA in the active site. Crystal structures of IN bound to various inhibitors exist and have aided in drug discovery. Historically, Merck scientists originally identified INI as an attractive potential target for an antiretroviral in the late 1980s. Despite a number of compounds falling out of development for various reasons, Merck persisted and their diketo compound, RAL, eventually received FDA approval in 2007, initially for use in treatment-experienced patients and later for treatment-naïve patients.

RAL has proven to be a very valuable drug over the last 4 years. When combined with other potentially active agents, it often allows patients with multidrug-resistant HIV to fully suppress their HIV RNA levels. It is also a very safe drug

and has fewer drug-drug interactions than do HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

One of the minor downsides of RAL is the requirement for twice daily dosing; unfortunately, once-daily dosing of RAL in clinical trials resulted in lower efficacy than twice-daily dosing. Also, when RAL is used in patients in combination with fewer than two other active antiretroviral agents, relatively rapid virological failure ensues and is associated with INI resistance-associated substitutions as described above.

EVG can be dosed once daily, but requires pharmacologic boosting with either ritonavir or Gilead's proprietary boosting agent, cobicistat. These EVG combinations do have the downside of more drug-drug interactions, and although cobicistat causes elevation of serum creatinine, it appears this is a specific tubular effect and does not represent true nephrotoxicity. Unfortunately, this creatinine elevation results in loss of the utility of serum creatinine to be reliably used to assess renal function changes.

The extensive and high-level cross resistance between RAL and EVG suggest that one would not be able to sequence these two agents. While S/GSK 1349572 does not appear to share high-level cross-resistance with RAL and EVG in vitro, there is little clinical experience using the GSK integrase inhibitor following virological failure on RAL or EVG-containing regimens. ■

ABSTRACT & COMMENTARY

Human Jamestown Canyon Virus

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Dr. Winslow is a speaker for Cubist Pharmaceuticals and GSK, and is a consultant for Siemens Diagnostics.

SYNOPSIS: Human infection with the mosquito-borne bunyavirus Jamestown Canyon Virus (JCV) is rare. A case of encephalitis in a 51-year-old man from Montana is reported. Diagnosis was made by detection of JCV-specific IgM ELISA results and a four-fold rise in JCV plaque reduction neutralization test (PRNT) titers.

SOURCES: Centers for Disease Control and Prevention. Human jamestown canyon virus infection — Montana, 2009. MMWR Morb Mortal Wkly Rep 2011;60:652-655.

A previously healthy 51-year-old man with no history of travel outside of Montana presented to a local emergency department in May 2009 with fever, frontal headache, dizziness, numbness, and tingling. Initial evaluation, including CT scan of the brain, was negative and he was given symptomatic treatment. One week later he presented to his primary care physician (PCP) with continued fever, headache, and new onset of myalgias and weakness. A lumbar puncture yielded normal CSF. He was later referred to a neurologist who treated him for migraine. An acute phase serum drawn at the time of his visit to his PCP tested positive for West Nile Virus (WNV)-specific IgM and IgG by ELISA at the Montana Public Health Laboratory. The sample was sent to the CDC's arbovirus diagnostic laboratory at Fort Collins, CO, and convalescent samples were obtained 16 days and 189 days after symptom onset. Analysis of these three samples demonstrated stable WNV titers suggestive of remote infection with this virus and equivocal results for La Crosse Virus (LACV), but an increase in JCV titers.

■ COMMENTARY

JCV is a mosquito-borne zoonotic pathogen belonging to the California serogroup of bunyaviruses. The natural vertebrate host for JCV is the white-tailed deer. While JCV is widely distributed throughout North America, human infection is rare, with only 15 cases reported in the United States since 2004. This is the first case reported from Montana. The patient experienced a relatively mild, but prolonged encephalitis illness and seemingly recovered completely with supportive treatment. JCV should be considered by clinicians in the differential diagnosis of suspected arboviral infections. The *MMWR* report of this case emphasizes the extensive antibody cross-reactivity between JCV, WNV, and other arboviruses associated with neurologic disease in humans. The two-year interval between initial presentation of this case, submission of serologic

specimens, and final report of this case in *MMWR* also suggests that clinicians should not expect prompt confirmation of the diagnosis of this infection. ■

ABSTRACT & COMMENTARY

Timing of Initiation of ART in Patients with TB Meningitis

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Dr. Winslow is a speaker for Cubist Pharmaceuticals and GSK, and is a consultant for Siemens Diagnostics.

SYNOPSIS: Two hundred fifty-three patients with HIV-associated tuberculous meningitis (TBM) were randomized to immediate vs. deferred ART. Immediate ART initiation did not improve outcome and was associated with more grade 4 adverse events.

SOURCES: Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis. Clin Infect Dis 2011;52:1374-1383.

A randomized, double-blind, placebo-controlled trial of immediate vs. deferred ART in 253 patients with HIV-associated TB meningitis was conducted to determine whether immediate ART reduced the risk of death. ARV drugs (AZT, 3TC, and efavirenz) were started either at study entry (n = 127) or 2 months after randomization (n = 126). All patients received standard antituberculosis treatment, adjunctive dexamethasone, and prophylactic trimethoprim-sulfamethoxazole, and were followed for 12 months. Seventy-six patients in the immediate arm and 70 patients in the deferred arm died within 9 months. There was no relationship between timing of ART and the time to a new AIDS event or death. Percentage of patients with serious adverse events (grade 3 or 4) was high in both arms (90% in the immediate and 89% in the deferred arm), but there were significantly more grade 4 adverse events in the immediate vs. deferred arm (102 vs. 87; $P = 0.04$) grade 4 adverse reactions, although an increase in neurologic events in the immediate ART group was not observed, possibly related to the use of adjunctive corticosteroids. The most common laboratory adverse event was hepatitis (grade 4, defined as serum transaminase > 5× upper limit of normal). HBV and HCV infection were both common in this population, but were equally prevalent in the immediate and deferred groups.

■ COMMENTARY

This study was conducted in Vietnam in collaboration with research teams from the United Kingdom and the Netherlands. The patients were young (median age, 28-29 years), were quite ill (many with focal neurologic findings), had low baseline CD4+ counts (median 39-44), and 35-37% had positive CSF AFB smears. The study conclusively demonstrated no association between immediate ART and improved survival of patients with HIV-associated TBM. However immediate ART was associated with a higher frequency of

This study is important in that two studies presented recently as abstracts suggested a benefit of early ARV initiation in patients with pulmonary TB (not TBM) and CD4+ < 50.[1,2] A study of patients with HIV-associated cryptococcal meningitis showed that early ART initiation was detrimental,[3] but this latter study was conducted in Africa and there was little attempt to manage increased intracranial pressure. Bottom line from my perspective is that briefly deferring ART (for 2 months) in patients with HIV-associated TBM seems to be prudent and simplifies management of these very ill and complicated patients. ■

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Pets in the Bedroom — Move Over Rover!

By Mary-Louise Scully, MD
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This article originally appeared in the June 2011 issue of *Travel Medicine Advisor*. At that time it was peer reviewed by Lin Chen, MD, Assistant Clinical Professor, Harvard Medical School; Director, Travel Medicine Center, Mt. Auburn Hospital, Cambridge, MA. Drs. Scully and Chen report no financial relationship to this field of study.

SYNOPSIS: The increasingly close and almost intimate relationships with our pets can lead to increased numbers of cases and the emergence of zoonotic diseases, including human plague (Yersinia pestis).

SOURCES: Chomel BB, Sun B. Zoonoses in the bedroom. Emer Infect Dis 2011;17:167-172.

The numbers of households with pets are increasing in many countries across the world. In addition, data obtained from media sources note a trend in the percentage of these pets sleeping in, or on, the owner's bed. To address whether this behavior is associated with the acquisition of zoonotic disease(s), the authors searched PubMed for peer-reviewed publications that demonstrated disease likely to have been acquired by sleeping with, sharing a bed with, kissing, or being licked by pets.

The results encompassed bacterial, parasitic, and viral associated zoonoses. The bacterial zoonoses included those with known animal associations such as *Yersinia pestis* (plague), *Bartonella* species (cat-scratch disease), *Pasturella* species, and *Capnocytophaga camimorsus*. In the case of a plague outbreak, 1 patient had the onset of his illness the morning after noting bites from his flea-infested cat who had shared his bed.[1] Another case-control study of plague survivors found 44% of survivors vs. 10% of controls reported sleeping in the same bed with a pet dog.[2] Although *Bartonella* infections are often associated with a scratch of a cat that harbors *Bartonella henselae*-infected fleas, a 9-year-old girl from Taiwan with multi-organ (hepatic, splenic, and renal) disease from *Bartonella*, became ill after sleeping with her cat at night.[3] In a study of *Pasturella multicida* meningitis, 27 (87%) of 31 infants exposed to animals had been exposed in various ways to oropharyngeal animal secretions through either licking or sniffing.[4] In addition, *Pasturella* wound infections have been reported when the animals had been observed licking the wounds prior to onset of illness.[5]

*C. camimorsu*s is a gram-negative bacillus that is known for its presentation of a purpura fulminans-like sepsis, especially in asplenic, alcoholic, or steroid-dependant patients. Several cases in the literature exist for which the portal of entry was felt to be a direct result of a pet licking an ulcer or abraded skin of the patient. For example, a patient with chronic ulcerous eczema of the legs whose dog used to lick his legs, died of septic shock and renal failure caused by *C. camimorsus*.[6]

■ COMMENTARY

These are just some of the highlighted cases discussed in this article. I recently saw a patient with a post-surgical septic olecranon bursitis caused by *Staphylococcus intermedius*. The patient admitted his dog may have licked the wound or provided saliva exposure during their playful nightly wrestling on the floor. The most recent reference I found to include data on this evolving topic is from the Center for Food Security & Public Health from Iowa State University from January 2011 — an MRSA article with more than 180 references![7] We are very likely seeing the tip of the iceberg on this emerging issue.

In May of 2011, shortly after the Chomel article was published, the CDC published two cases of human plague in *MMWR* from Oregon in 2010. These were the first cases reported from Oregon since 1995 and they were the only plague cases reported in the United States in 2010. The patients, ages 17 and 42, lived in the same household with a dog that was later found to be seropositive for *Y. pestis* by passive hemagglutination-inhibition assay. Although both patients had clinical illness compatible with human plague, including bilateral inguinal buboes, fever, and hypotension, plague was not suspected initially. One patient's blood culture specimen was later identified as positive, and the other patient had a positive serology. One of the patients admitted sleeping in the same bed with the dog during the 2 weeks prior to the onset of illness. Fortunately, both patients recovered after empiric therapy with doxycycline.

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Are You "Coated" with Bacteria?

Source: Burden M, et al. Newly cleaned physician uniforms and infrequently washed white coats have similar rates of bacterial contamination after an 8-hour workday. J Hosp Med 2011;6:177-182.

The National Health Service in Britain in 2007 elected to ban traditional white coats and other long-sleeved garments for physicians in the workplace (including long-sleeved blouses and shirts). Subsequently, Scotland adopted similar policies. This decision was based on limited data suggesting that the cuffs and lower pockets of long-sleeved garments are more heavily colonized with bacteria than shorter garments.

These authors have succeeded in debunking this notion. One hundred residents and hospitalists working on the internal medicine service in hospital (in Colorado) were randomly assigned either to start the day fresh with a newly laundered standard short-sleeved uniform or to wear their own (presumably not recently laundered) white coats. The latter group was not informed of their randomization assignment till the day they showed up for work, giving them no chance to switch to an unused coat. Cultures were obtained throughout the workday, beginning before the coat was put on to 2.5, 5, and 8 hours later. Cultures were obtained from the breast pocket, sleeve cuff (of either the short uniform sleeve or the long sleeve), and the skin of the volar surface of the wrist area. Cultures were incubated for 18-22 hours, and colony counts (up to 200) were determined. In addition, colonies of *Staphylococcus* were tested for coagulase production and methicillin resistance.

At the end of the day, no differences were found between the colony counts cultured from the clean uniforms and that of the white coats (respectively, mean colony counts, 142 [range 83-213] vs. 104 [range 80-127]; $P = 0.61$). No significant differences were found between the colony counts cultured from the sleeve cuffs of the short-sleeved uniforms vs. the longer sleeve cuffs of the white coats (mean colony counts, 37 vs. 58), or between the pockets of either garment (mean colony counts, 75 vs. 46). Colony counts were generally greater for the sleeve cuffs compared with the breast pocket of the long-sleeved coat (although the difference was small), whereas no difference in colony counts was observed between the short sleeve cuffs and breast pockets of the uniforms. No differences were found between the degree of bacterial colonization of the wrists for either those wearing a white coat or a short-sleeved uniform.

In addition, colonization with MRSA was similar for those wearing their own long white coats compared with the group assigned to wear clean uniforms (16% vs. 20%).

Serial cultures obtained throughout the workday demonstrated that a freshly laundered uniform starts out nearly sterile. But within 2.5-3 hours, the uniform is colonized with 50% of the bacterial colonies found at 8 hours of wear.

These data demonstrate that, when worn by a resident or hospitalist on the hospital wards, bacterial colonization of a freshly laundered garment is remarkably fast, and within 1 workday is similar to that of an unwashed days-old long-sleeved white coat. There is no evidence that long sleeves vs. short sleeves is less likely to result in bacterial colonization of either the garment or the wearer's wrists. ■

Bacteria Wired on Caffeine

Source: Harmon K. Newly discovered bacteria lives on caffeine. Scientific American. Available at: http://www.scientificamerican.com/blog/post.cfm?id=new-bacteria-lives-on-caffeine-2011-05-24.

A novel strain of bacteria, *Pseudomonas putida* CBB5, has been found to enzymatically "digest" caffeine. Researchers at the 111th General Meeting of the ASM in New Orleans recently reported the discovery of this bacterium in the flowerbeds at the University of Iowa. Using N-demethylase enzymes called NdmA and NdmB, the organism is capable of breaking down the components of caffeine (which is nothing more than a complex blend of roasted carbon, hydrogen, nitrogen, and oxygen) into carbon dioxide and ammonia. These are then used as substrates for bacterial growth and reproduction.

Following isolation of the genes responsible for these enzymes, they were inserted into *E. coli*, which then was capable of similar enzymatic caffeine "consumption." It is uncertain whether these bacteria are naturally capable of breaking down caffeine, or whether this capa-

bility has evolved because of the ubiquitous presence of caffeine in the environment. Finding this organism on a college campus, where the organism was clearly pulling an all-nighter, might be a clue. ■

Leishmaniasis and Human Trafficking

Source: Cannella AP, et al. A cluster of cutaneous Leishmaniasis associated with human smuggling. Am J Trop Med Hyg 2011;84: 847-850.

Physicians at the University of California-San Diego (UCSD) report a cluster of 5 cases of cutaneous Leishmaniasis in illegal immigrants from East Africa, which surprisingly turned out to be consistent with New World Leishmaniasis, although all 5 had come from an area endemic for Old World Leishmaniasis. How did this occur?

Four Somali and 1 Ethiopian were brought to the Emergency Room at UCSD by Immigration and Custom Enforcement Agents. They had all been found being smuggled across the U.S.-Mexico border about 20 miles south of the city, and had been held in custody for up to 60 days. They each presented with one small cutaneous ulcer, either nodular or pustular, in different locations on the body (thumb, ear, foot, etc.) and in different stages of development. Initially thought to be MRSA folliculitis, prison officials had attempted administration of trimethoprim-sulfamethoxazole and doxycycline without response. The patients were then referred to UCSD for further care.

Skin biopsies were obtained, and the histology was consistent with leishmaniasis, although the presence of a number of features, such as large vacuoles, was more consistent with New World Leishmaniasis. Cultures yielded a *Leishmania* spp. and isoenzyme analysis confirmed *L. panamensis*, which is a member of the *Viannia* group of *Leishmania*. Confirmatory PCR was performed at the Centers for Disease Control and Prevention. All of the patients responded to liposomal amphotericin, although one patient relapsed, requiring a second course of therapy.

The story of how they had arrived at the Mexican border from East Africa was not readily forthcoming, but eventually it was learned that all 5 individuals had been smuggled at different times along an identical route from Djibouti to Dubai to Moscow to Havana, Cuba, and then to Quito, Ecuador, through Colombia, and then by ground via Panama to the U.S.-Mexico border. The trip through Panama required foot travel, and the individuals slept outdoors on the ground at night in sleeping bags. They described many insect bites.

New World Leishmaniasis occurs throughout Central and South America and is caused by the bite of a sand fly. Only a small number of the 76 sand fly species in Ecuador, Colombia, and Panama can transmit Leishmaniasis, and recent data suggest that up to 1% of female *Lutzomyia* sand flies are infected. Within 2-8 weeks of a sand fly bite, a small pustule develops, which progresses to a painless ulcer. Fourteen different species of *Leishmania* exist in the New World, a number of which can cause mucocutaneous involvement, including *L. panamensis*. More aggressive therapy with amphotericin is therefore warranted.

Subsequent to this event, 3 individuals from East Africa presented to the physicians in Tacoma, WA, with a similar story. They had been smuggled along the identical route, and skin biopsies yielded the same organism. The discovery of two clusters of Leishmaniasis, in San Diego and in Tacoma, suggest that human trafficking from East Africa through this route must be fairly common with important public health implications for U.S. residents. ■

Space Suits in the OR?

Source: Hooper GJ, et al. Does the use of laminar flow and space suits reduce early deep infection after total hip and knee replacement? The ten-year results of the New Zealand Joint Registry. J Bone Joint Surg (Br) 2011;93-B:85-89.

Ten years of data from the New Zealand Registry of Surgical Cases were examined to assess the risk of early postoperative infection in total hip replacement (THR) and total knee replacement (TKR), with regard to the use of a laminar flow room or wearing a space suit during the procedure. Surprising, the results were quite the opposite of what one might imagine.

A total of 51,485 primary THR and 36,826 TKR procedures were examined. Laminar flow operating suites were used in 35.5% of these procedures, and space suits were worn by the orthopedic surgeon during 23.5% of cases. The risk of infection was actually greater for those procedures performed with a space suit compared to those without. For example, 46 (0.089%) of THR procedures required revision for early infection within 6 months of the original procedure. The risk of early infection for cases involving the use of a space suit was 0.186% compared to without 0.064% ($P < 0.0001$). Similarly, the risk of infection was significantly greater for procedures performed in a laminar flow operating suite (0.148%) compared to the usual OR (0.061%), as well as for those procedures where both a space suit and laminar flow room were used compared with the usual OR without a suit. These results were independent of the age of the patient or underlying diagnosis. ■

continued from page 105 Pets are known to provide company and assuage the loneliness of countless human beings worldwide and as such, they are often considered "part of the family." Although transmission of zoonotic infections from pets is rare, it would seem prudent to ensure our pets are properly de-wormed and free of fleas, and defer from sharing the same bed with them to prevent serious and potentially fatal infections. ■

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CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; 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.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. Which of the following is *correct* with regard to the outbreak strain of Shiga toxin-producing *E. coli* arising in Germany?

a. It is a hybrid, also containing genes encoding the enteroaggregative phenotype.
b. It is associated with an unusually low proportion of cases complicated by hemolytic uremic syndrome.
c. Most cases have occurred in children.
d. The majority of cases have occurred in males.

2. Which of the following is correct with regard to the outbreak strain of Shiga toxin-producing *E. coli* arising in Germany?

a. It has been associated with *E. coli* 0157:H7.
b. It exhibits little antibiotic resistance.
c. It does not ferment sorbitol.
d. It contains two different Shiga toxins.

3. Which of the following is correct?

a. Rifapentine has a serum half-life of approximately 2 hours.
b. Weekly rifapentine plus INH given for 3 months was non-inferior to daily INH for 9 months in the treatment of latent TB.
c. Patients were more likely to successfully complete a 9-month course of daily INH than a 3-month course of weekly rifapentine and INH.
d. In contrast to other rifampicin derivatives, rifapentine has no pharmacokinetic drug-drug interactions.

CME OBJECTIVES

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

- discuss the diagnosis and treatment of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.

[IN FUTURE ISSUES]

Getting tired of XMRV

Staphylococcus aureus from skin and soft-tissue infections in ED patients

PHARMACOLOGY WATCH

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

Two New Drugs Approved for Treatment of Hepatitis C

In this issue: Two new drugs for treatment of hepatitis C; NSAIDs and myocardial infarction risk; AIM-HIGH clinical trial stopped; and FDA actions.

Two new drugs for hepatitis C

The FDA has approved two new drugs for the treatment of hepatitis C — the first new drugs to be approved in years. The approvals came within days of each other, pitting the two drugs (and their companies' marketing departments) against each other in this multibillion dollar market. Both drugs are protease inhibitors and both have similar indications. First to be approved was Merck's boceprevir (Victrelis), which is indicated for adults with hepatitis C who still have some liver function and who either have not been treated previously with drug therapy or who have failed drug therapy. Boceprevir is approved for use in combination with peginterferon alpha and ribavirin. The approval was based on two phase 3 clinical trials of 1500 adults in which two-thirds of patients in the boceprevir, interferon, and ribavirin treatment group experienced a significantly increased sustained virologic response at 24 weeks compared to 38% with interferon and ribavirin alone. Boceprevir is taken orally three times a day with food. The second drug approved was Vertex Pharmaceutical's telaprevir (Incivek), which also was approved for patients with hepatitis C who either have not received interferon-based drug therapy or who have not responded adequately to prior therapies. Telaprevir is also approved for use with peginterferon alpha and ribavirin. Approval was based on three phase 3 clinical trials of over 2000 adults. In previously untreated patients, 79% of patients in the telaprevir group experienced a sustained viral response compared to 46% for standard treatment. Most patients experienced virologic response at 24 weeks suggesting that treatment times may be reduced from 48 weeks to 24 weeks. Telaprevir is also taken orally three times a day with food. Both drugs are approved to treat genotype-1, the most common form of hepatitis C and the most difficult to treat. The drugs have similar side effects, which include anemia and serious rashes. Several other drug manufacturers have similar drugs in the pipeline with approval expected within the next year or two. It is estimated that about 170 million people worldwide and 3.2 million Americans are infected with chronic hepatitis C, which is the most common cause of progressive liver disease leading to liver transplant. Telaprevir is expected to cost nearly $50,000 per treatment course, while bocepavir is expected to cost between $26,000 to $48,000 per treatment course depending on the duration. ■

NSAID use in patients with prior MI

A new study points out the risk of nonsteroidal anti-inflammatory drug (NSAID) use in patients who have had a myocardial infarction (MI) — suggesting that even brief use increases the risk for death and recurrent MI. Researchers from Denmark reviewed the records of nearly 84,000 patients who were admitted with first time MI and their subsequent NSAID use. The risk of death and recurrent MI was correlated to the duration of NSAID treatment. From 1997-2006, 42.3% of patients received NSAIDs. There

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were more than 35,000 deaths or recurrent MIs in the cohort of whom 43% had filled a prescription for an NSAID. Use of an NSAID was significantly associated with an increased risk of death or recurrent MI at the beginning of treatment (hazard ratio [HR] 1.45; 95% confidence interval [CI], 1.29 to 1.62) and persisted throughout the NSAID treatment course (HR 1.55; 95% CI, 1.46 to 1.64 after 90 days), returning to baseline soon after stopping the drug. The risk of death or recurrent MI varied with different drugs and was somewhat higher with increased COX-2 selectivity. Diclofenac was associated with the highest risk (HR 3.26; 95% CI, 2.57 to 3.86). Duration of therapy was also reviewed with diclofenac causing an increased risk from the beginning of treatment and persisting throughout the treatment course. Ibuprofen showed an increased risk when used for more than one week, whereas celecoxib showed an increased risk after 14-30 days of treatment. Naproxen was not associated with a statistically significant increased risk of death or MI for the entire treatment duration. The authors conclude that short-term treatment with most NSAIDs is associated with increased cardiovascular risk. This suggests that there is no apparent safe therapeutic window for NSAIDs in patients with prior MI and "challenge the current recommendations of low-dose and short-term use of NSAIDs as being safe" (*Circulation* 2011;123:2226-2235). One interesting aspect of this study was the use of rofecoxib (Vioxx) prior to its withdrawal in 2004. While rofecoxib was found to increase cardiovascular risk (the reason for its withdrawal from the market), it appeared to be no more dangerous than other commonly used NSAIDs and was apparently safer than diclofenac. ■

NHLBI stops AIM-HIGH trial

Niacin may not be effective in preventing cardiovascular disease. The National Heart Lung and Blood Institute (NHLBI) has prematurely stopped the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health (AIM-HIGH) clinical trial 18 months earlier than planned. Analysis of the data found that adding high-dose, extended-release niacin to statin treatment in people with heart and vascular disease did not reduce the risk of cardiovascular events. AIM-HIGH participants had well-controlled low-density lipoprotein levels on a statin, however they were at risk of cardiovascular disease due to previous history of cardiovascular disease and a combination of low high-density lipoprotein (HDL) cholesterol and high triglycerides. During the nearly 3 years of the study, patients who took high-dose, extended-release niacin with a statin had increased HDL cholesterol and lower triglyceride levels compared to those who took a statin alone; however, the combination was not effective at reducing fatal or nonfatal heart attacks, strokes, hospitalizations for acute coronary syndrome, or revascularization procedures. There also was a "small and unexplained increase in ischemic stroke rates in the high-dose, extended-release niacin group" that contributed to the decision to halt the trial. Termination of the AIM-HIGH trial was announced by press release from the NHLBI on May 26. ■

FDA actions

The FDA has approved linagliptin for the treatment of type 2 diabetes in adults. The drug is an inhibitor of DPP-4, an enzyme that degrades incretin hormones (GLP-1 and GIP). It is approved for use as a stand-alone therapy or in combination with other drugs for type 2 diabetes including metformin. The approval was based on eight double-blind, placebo-controlled trials of nearly 4000 patients that showed improved blood glucose control compared to placebo. Linagliptin is marketed by Boehringer Ingelheim Pharmaceuticals as Tradjenta.

The FDA has approved rilpivirine, a new non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of adults with HIV-1 infections who are treatment naïve. Rilpivirine is to be used as part of a highly active antiretroviral therapy (HAART). The approval was based on two phase 3 trials of nearly 1400 adults with HIV who were observed for 48 weeks, and an additional 96-week trial in which the drug was compared to efavirenz as part of multidrug combinations. Rilpivirine was found to be comparable to efavirenz with regard to percentage of patients with undetectable HIV viral load. Patients who failed rilpivirine are more likely to develop drug resistance than patients who failed efavirenz. Rilpivirine is marketed by Tibotec Therapeutics as Edurant.

Rosiglitazone (Avandia) remains on the U.S. market, but its days may be numbered. In a new step to restrict use of the drug, the FDA has updated the Risk Evaluation and Mitigation Strategy to include a restricted access in distribution plan. Physicians and patients must enroll in the distribution program in order to receive the drug. Rosiglitazone will no longer be available in commercial pharmacies after mid-November and will only be available by mail order through certified pharmacies. Use of the drug is limited to patients who are currently on rosiglitazone and whose diabetes is not controlled by other treatments and who are unwilling to change to pioglitazone (Actos). ■