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Infectious Disease [ALERT]

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

ABSTRACT & COMMENTARY

Candida Chorioretinitis and Endophthalmitis

By Stan Deresinski, MD, FACP, FIDSA

SYNOPSIS: While 16% of patients with candidemia had possible or probable ocular involvement, only 6 of 370 (1.6%) developed endophthalmitis.

SOURCES: Oude Lashof AM, et al. Ocular manifestations of candidemia. *Clin Infect Dis* 2011;53:262-268.

Oude Lashof and colleagues examined the incidence and outcomes of patients with ocular involvement in a randomized, clinical trial comparing treatment of non-neutropenic patients with candidemia with either voriconazole or amphotericin B followed by fluconazole.[1] In that study, no significant differences in overall outcome between treatment arms were detected in the 370 patients who constituted the modified intent-to-treat population and who are the subjects of this substudy. All patients underwent dilated retinal examination at baseline, 7 days, 2 weeks, and 6 weeks after the end of treatment. Abnormalities thought to be consistent with ocular candidiasis were detected in 60 patients (16%). The ocular lesions were detected at baseline in 49 of the 60 patients (81.7%), while the remaining abnormalities were first seen at follow-up examinations. Twenty had possible, and 40 had probable ocular candidiasis. Among those with probable disease, only 6 had endophthalmitis, with vitritis or "fluffy" lesions extending into the vitreous. One of these patients, with negative retinoscopy at days 1 and 8, and whose central venous catheter was not removed until day 10 of therapy, was first detected after 18 days of

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Infectious Disease [ALERT]

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treatment. The remaining 36 with probable ocular candidiasis had chorioretinitis defined as deep focal white infiltrates in the retina or hemorrhages, Roth spots, or cotton wool spots with absence of other explanation, such as diabetes mellitus or hypertension, present. If these chorioretinal findings were seen in patients with diabetes, hypertension, or bacteremia, as was true in 20 patients (33.3%), they were classified as possible ocular candidiasis. Designation as proven ocular candidiasis required vitreous sampling, which was not performed in any patient.

Ocular involvement was associated with a somewhat more prolonged duration of candidemia. The median interval from the day of randomization to a first negative blood culture was 4 days (range, 1-18 days) in those with and 3 days (range, 1-26 days) in those without ocular involvement, a difference that was statistically significant ($P = 0.026$). When compared to infection with other species, patients with bloodstream infection with *Candida albicans* were more likely to have ocular involvement, while those infected with *Candida parapsilosis* were less likely to develop this complication.

Of the 6 patients with endophthalmitis, 2 died before repeat retinal examination was performed, 3 had resolution, and 1 (the patient in whom extension of the infection into the vitreous was detected at day 18 of therapy after failure to remove his central venous catheter until day 10) was classified as a therapeutic failure when treatment was discontinued for unknown reasons.

Treatment of probable *Candida* chorioretinitis was successful in 24 of 34 patients (71%), unevaluable in 9, and classified as a failure in 1 patient whose candidemia relapsed with a new retinal lesion after apparently successful initial therapy. No patient with chorioretinitis progressed to endophthalmitis during systemic treatment.

None of the patients received intravitreous therapy, so all responses were presumably the result of systemic therapy with the study drugs, whose administration was not apparently prolonged in response to the detection of ocular lesions. The antifungals were administered for a median of 14 days after the first negative blood culture in both those with and without eye involvement.

■ COMMENTARY

The phrase "*Candida* endophthalmitis" often is inappropriately used to describe all forms of endogenous infection of the eye with this fungus. This study illustrates the importance of maintaining the distinction between infection restricted to chorioretinal layers and involvement of the vitreous, for which the term endophthalmitis in this context should be reserved.

The frequency of detection of ocular lesions in patients with candidemia has been reported to be 0%-78%,[2] an absurdly broad range. Nonspecific retinal lesions, such as cotton wool spots and superficial retinal hemorrhages, have been reported to be present in 11%-20% in most recent studies. The picture is further clouded by the fact that such lesions have been reported in 12%-26% of patients with bacteremia in the absence of candidemia. In these reports, however, many patients had confounding illnesses, such as diabetes mellitus.

In this study, as in most others, ocular candidiasis was most often asymptomatic. Thus, at baseline, only 1 patient reported decreased visual acuity, while only the 1 patient in whom endophthalmitis developed during treatment complained of visual loss. This observation is, of course, complicated by the inclusion of critically ill patients in whom visual changes may be underreported.

Ocular lesions were first detected after initial negative examinations in one-fifth of affected patients. Patients whose fungemia persists longer than 3 days after the initiation of therapy may be at increased risk of ocular involvement, as may patients whose infection is caused by *C. albicans*.

Infection with *C. parapsilosis* appears to be associated with a lesser risk of eye involvement. The authors recommend that performance of dilated fundoscopy in all patients with candidemia be performed at least 1 week after the initiation of systemic antifungal therapy and that all patients with ocular involvement have follow-up examinations.

It can, however, be asked whether careful and repeated retinal examinations affect outcome. In this study, all patients with chorioretinitis had favorable ocular outcomes. In addition, only 1.6% of patients had endophthalmitis and there was no evidence that its presence necessitated alteration of the planned therapy, with no need for intravitreal therapy or prolongation of systemic administration of antifungals. Similarly, in a study comparing caspofungin to amphotericin B in patients with invasive candidiasis (approximately 80% were candidemic), ocular lesions consistent with *Candida* endophthalmitis (not clearly defined) were detected in 7 of 217 (3.7%) and all resolved after the end of therapy, without added intervention.[3] ■

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ABSTRACT & COMMENTARY

Frequent Detection of Cytomegalovirus in Stillbirths

By Hal B. Jenson, MD, FAAP

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

SYNOPSIS: Cytomegalovirus (CMV) was identified in 15% of stillbirths as the most common infectious agent — by far — associated with stillbirth. CMV infection was significantly associated with fetal thrombotic vasculopathy, suggesting the mechanism of fetal demise and compelling evidence that CMV is a cause of many stillbirths.

SOURCE: Iwasenko JM, et al. Human cytomegalovirus infection is detected frequently in stillbirths and is associated with fetal thrombotic vasculopathy. *J Infect Dis* 2011;203:1526-1533.

A total of 130 singleton stillbirths from a single institution in Australia, from January 2005 through December 2006, of > 20 weeks gestation with no cause of death and with available formalin-fixed, paraffin-embedded tissues were examined by multiplex PCR for 19 infectious agents, and by immunohistochemistry for human cytomegalovirus (CMV). There were no statistically significant differences found in CMV-infected vs. CMV-uninfected cases for birth weight, birth weight percentile, gestational age, or maternal parity. There was a trend among CMV-infected fetuses for either early stillbirth (< 26 weeks) or term stillbirth (> 37 weeks) ($P = 0.06$), and also for female sex ($P = 0.06$).

CMV DNA was detected in 20 of 130 (15%) fetuses. All other infectious agents were detected in 21 (16%) fetuses with the most common being *Escherichia coli* (4), *Fusobacterium nucleatum* (3), and group B Streptococcus (3). CMV was consistently seen with nuclear and cytoplasmic distribution. In the placenta, CMV was commonly localized to the chorionic villi. Immunohistochemistry was less sensitive than PCR and detected CMV in 15 of the 20 PCR-positive cases (75%), including: kidney only (4); liver only (3); placenta only (4); kidney and liver (2); and kidney, liver, and placenta (2). Approximately half (52%) of mothers with a CMV-positive (45%) or CMV-uninfected (54%) stillborn infant were primiparous.

Postmortem examinations showed fetal thrombotic vasculopathy (presence of thrombi in the fetal circulation resulting in the clustering of fibrotic villi with the absence or degeneration of fetal capillaries in contiguous villi) among CMV-infected fetuses ($P = 0.010$), with an odds ratio of 3.6 (95% confidence interval, 1.3-9.9). No other

postmortem finding was associated with CMV infection.

■ COMMENTARY

Stillbirths remain the most common adverse pregnancy outcome with rates of 3-5 stillbirths per 1,000 births in developed countries and 20-40 per 1,000 births in developing countries. The etiology of stillbirths is unknown in half of cases. In this series, CMV greatly overshadowed any other infectious pathogen and was significantly associated with fetal thrombotic vasculopathy, suggesting the mechanism of stillbirth being CMV-associated vascular fibrosis. CMV infection of fetal endothelial and vascular cells leading to thrombosis is a plausible mechanism that would lead to fetal demise.

CMV is the most frequent cause of congenital infection (1%-2% of all newborns) and resulting birth defects, the most notable being congenital hearing loss. This study indicates that CMV is also the most frequently identified infectious cause of stillbirths, which was associated with 15% of stillbirths in this series. Taken together, these findings indicate the importance of developing an approach to control CMV infection, especially among women of childbearing age, and to reduce the risk of congenital disease and the incidence of stillbirths. Ultimately, the best mechanism for control is development and universal implementation of an effective CMV vaccine. ■

ABSTRACT & COMMENTARY

Azithromycin Restores Chloride Efflux in Cells of Cystic Fibrosis Patients

By Dean L. Winslow, MD, FACP, FIDSA

Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center;
Clinical Professor, Stanford University School of Medicine

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

SYNOPSIS: Azithromycin (AZM) was shown to restore chloride (Cl^-) efflux at physiologic concentrations in human bronchial epithelial cells in tissue culture, but did not have anti-inflammatory effects in this system.

SOURCES: Saint-Criq V, et al. Restoration of chloride efflux by azithromycin in airway epithelial cells of cystic fibrosis patients. *Antimicrob Agents Chemother* 2011;55:1792-1793.

Two human cystic fibrosis (CF) bronchial epithelial cell lines and one CF human primary epithelial cell line in culture were treated with AZM at 10 µg/mL. Chloride efflux was inhibited significantly in this system as assessed by two different analytical methods. In non-CF cells, AZM significantly inhibited IL-8 secretion and NF-kB activity. However, in CF cells, reduction of IL-8 secretion and NF-kB activity was not seen.

■ COMMENTARY

Many protein synthesis-inhibiting antibiotics (most notably tetracyclines and macrolides) have been shown to possess anti-inflammatory activity independent of antimicrobial activity. This anti-inflammatory effect may be in part responsible for the rapid beneficial effect observed in respiratory infections, including acute exacerbations of bronchitis and community-acquired pneumonia. The usefulness of macrolides (particularly AZM) as adjunctive therapy in CF patients has been appreciated for a number of years and their beneficial effect in these diseases was assumed to be due to this anti-inflammatory activity.

CF is a common genetic disorder caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, which encodes a Cl^- channel. In cystic fibrosis, airway epithelium inflammation is felt to be largely due to an increase in NF-kB activity, which leads to increased IL-8 production. The unexpected results from this in vitro study suggest that the beneficial effects of AZM in CF patients may be due to the drug's effects at one or more steps "upstream" from the inflammatory cascade by restoring CFTR channel activity. Additional research to further elucidate the molecular mechanisms of this observed enhancement of CFTR channel activity will be of great interest. ■

Fidaxomicin for CDI in Patients Who Continue Concomitant Antibiotics: Arrival of a Superior Treatment Option?

By Brian G. Blackburn, MD
Clinical Assistant Professor of Medicine, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine

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

SYNOPSIS: Among patients with *C. difficile* infection (CDI) who continued to take concomitant antibiotics (CA), patients treated with fidaxomicin were cured more often and had fewer relapses than patients treated with oral vancomycin.

SOURCE: Subbarayan Mullane KM, et al. Efficacy of fidaxomicin versus vancomycin as therapy for *Clostridium difficile* infection in individuals taking concomitant antibiotics for other concurrent infections. *Clin Infect Dis* 2011;53:440-447.

CDI can be a difficult-to-manage complication of antibiotic therapy. Although it is preferable to discontinue the inciting antibiotic when CDI occurs, this is not always possible given that many patients have serious infections, which require ongoing antibiotic therapy.

While oral vancomycin is recommended as first-line therapy for severe or complicated CDI (and metronidazole for mild-to-moderate CDI), relapse rates are high even with appropriate therapy.[1] Unfortunately, the number of alternative treatments available for CDI is small.[1] A new treatment option is fidaxomicin, a macrocyclic antibiotic that is more active in vitro against *C. difficile* than vancomycin. This drug also is found in high fecal concentrations after oral dosing, is absorbed minimally, and has limited activity against the normal intestinal flora. Recently, fidaxomicin was shown in a prospective, double-blind, randomized trial to be non-inferior to oral vancomycin for the cure of uncomplicated CDI, and was associated with lower relapse rates.[2]

Few studies have addressed the outcomes of treatment for CDI in patients who continue CA. The authors therefore performed post-hoc analysis of the above trial and pooled these data with a second, similar study to examine the outcome of CDI treatment in patients who continued to receive CA (i.e., in addition to treatment for CDI).

Adult patients were enrolled into the studies if they had diarrhea and a positive stool test for *C. difficile* toxin A or B. They were randomized 1:1 to receive either a 10-day course of fidaxomicin 200 mg orally twice daily or vancomycin 125 mg orally four times daily. The study was sponsored by Optimer Pharmaceuticals, the company that manufactures fidaxomicin. Patients with life-threatening or fulminant *C. difficile* infection, or toxic megacolon, were excluded.

Overall, 28% of the 999 patients evaluable for cure took at least one CA during the CDI treatment period, and 23% of the 794 patients evaluable for relapse took at least one CA during CDI treatment or the 40-day follow-up period. Ninety-three percent of patients who did not take CA were clinically cured, compared to 84% of those who did take CA ($P < 0.001$). The median time to cure was 54 hours among those who did not take CA, and 97 hours for those who did ($P < 0.001$). Recurrence was seen in 18% of those who did not take CA and in 23% of those who did ($P = 0.08$).

Among those who took CA, 90% of fidaxomicin-treated patients were clinically cured, compared to 79% of vancomycin-treated patients ($P < 0.05$); recurrence rates were 17% and 29%, respectively ($P < 0.05$). Among those who did not take CA, fidaxomicin-treated patients were clinically cured 92% of the time compared to 93% of vancomycin-treated patients ($P = 0.80$); recurrence rates were 12% and 23%, respectively ($P < 0.001$).

■ COMMENTARY

Although it is preferable that CA be discontinued once CDI is diagnosed, this is not always possible; in this study, more than a quarter of patients continued CA during CDI therapy. This study

demonstrates (perhaps better than any other to date) that continued CA during therapy for CDI significantly decreases the chances of cure, delays the time to cure in those who are successfully treated, and tends to increase the risk of relapse. Compared to vancomycin, fidaxomicin has previously been shown to be non-inferior for the treatment of CDI and to be associated with significantly fewer relapses.[2] In the current paper, fidaxomicin was again non-inferior to vancomycin for cure of CDI among patients overall; it also was significantly better among those who took CA for both cure and relapse. Even among those who did not take CA, fidaxomicin-treated patients experienced fewer relapses than vancomycin-treated patients, although the cure rates were the same for both drugs in this cohort.

The mechanism that renders fidaxomicin superior to vancomycin in patients receiving CA is unknown. Fidaxomicin does achieve high levels in the GI tract, and spares the commensal flora, perhaps reducing the risk that residual *C. difficile* could propagate and cause recurrence. The drug also is more active against *C. difficile* than vancomycin in vitro.

Fidaxomicin is a promising new option for the treatment of CDI. Based on these preliminary data in a drug company-sponsored trial, it appears superior to vancomycin (at least in certain circumstances), and has few adverse effects. Fidaxomicin is expensive, and cost could be a factor limiting widespread use of this agent. Another limitation is that fidaxomicin has not yet been tested in patients with severe CDI, nor has it been compared to other treatment regimens aside from vancomycin monotherapy. Still, fidaxomicin seems to be a welcome addition to the armamentarium for the treatment of CDI. ■

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ABSTRACT & COMMENTARY

Activation of HIV by STI Pathogens

By Dean L. Winslow, MD, FACP, FIDSA

SYNOPSIS: HSV-1/2, *N. gonorrhoeae*, and TLR ligands directly induced HIV-LTR activation in T cells in cell culture. Additionally, supernatants obtained from genital epithelial cells (GEC) exposed to TLR ligands and sexually transmitted infection (STI) pathogens also induced LTR activation in T cells. Inhibition of nuclear factor kB (NFkB) and activator protein-1 (AP-1) signaling pathways abrogated HIV-LTR activation.

SOURCES: Ferreira VH, et al. Endometrial epithelial cell responses to coinfecting viral and bacterial pathogens in the genital tract can activate the HIV-1 LTR in an NFkB- and AP-1- dependent manner. *J Infect Dis* 2011;204:299-308.

The authors conducted a series of experiments in which HIV-1 transfected 1G5 T cells were exposed to either a series of known long terminal repeat (TLR) ligands (FimH/TLR-4, flagellin/TLR-5, and poly I:C/TLR-3) or STI pathogens (HSV-1, HSV-2, and *N. gonorrhoeae*). Direct LTR activation in 1G5 cells was measured with a luciferase assay. Indirect activation of the HIV-LTR in 1G5 cells by these substances was assessed as follows: Primary human GECs growing confluently as a monolayer in culture were treated with the same TLR ligands and STI pathogens as the T-cell line in the initial experiments, then washed five times with PBS after incubation and replaced with fresh media. After 24 hours, the supernatant from the GECs was added to the 1G5 cells. The cells were lysed after an additional 24 hours of incubation and luciferase activity was measured. LTR activation was demonstrated both directly by application of the antigens to the T-cell line and indirectly by incubation of the T-cells in supernatant from the GECs. Both direct and indirect activation of HIV-LTR was shown to be abrogated by pretreatment of the T-cell line with PDTC (an inhibitor of NFkB activation) and with both a MAP kinase inhibitor and a JNK inhibitor (the latter two pathways activate AP-1).

■ COMMENTARY

While this study is very much a "basic science" paper, it nicely sheds light on the inter-relationship between co-infection with STI pathogens and activation of HIV replication in the presence of

these pathogens. The LTR is a promoter region present at both the 5' and 3' end of the 9.4 kB HIV-1 genome. As with most regions of retrovirus genomes, these promoter regions picked up genes from their hosts over centuries of time. The HIV-LTR is particularly interesting since it contains numerous mammalian promoter/enhancer genes including AP-1, SP-1, NFAT, and NFkB. The experiments nicely demonstrate that TLR ligands, HSV-1, HSV-2, and *N. gonorrhoeae* can both directly activate HIV-LTR and indirectly activate HIV-LTR by their effect on GECs via pro-inflammatory signaling pathways. This increased HIV-1 replication, resulting from increased viral transcription, may enhance sexual and vertical HIV transmission. ■

ABSTRACT & COMMENTARY

Imported Pediatric Malaria

By Philip R. Fischer, MD, DTM&H

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Dr. Fischer reports no financial relationship to this field of study. This article originally appeared in the October 2011 issue of *Travel Medicine Advisor*. It was peer reviewed by Mary-Louise Scully, MD, Director, Travel and Tropical Medicine Center, Sansum Clinic, Santa Barbara, CA. Dr. Scully reports no financial relationship to this field of study.

SYNOPSIS: A retrospective survey shows that imported pediatric malaria continues to occur. Children most at risk are those traveling to visit friends and relatives, especially in West Africa, without effective chemoprophylaxis.

SOURCES: Hickey PW, et al. A local, regional, and national assessment of pediatric malaria in the United States. *J Travel Med* 2011;18:153-160.

A retrospective review of pediatric malaria at a Washington, DC, children's hospital identified 98 cases over 8 years (1999-2006). Their mean age was 9.6 years. Approximately half of the children were long-term U.S. residents who had visited friends or relatives in their country of origin; most of the others were recent immigrants. Eighty-five percent of these children had been exposed to malaria in West Africa. Only 6% reported having been properly adherent to an effective malaria chemoprophylaxis regimen. Seventeen were initially diagnosed with something other than malaria, but 82% of patients were accurately diagnosed as having malaria on the day they presented for care. The mean duration of symptoms prior to diagnosis was 5 days (range, 1-30). One child recovered following cardiac arrest, 19% required intensive care, and all survived.

The authors then reviewed the Pediatric Health Information System database and identified 306 children with malaria at 40 large American children's hospitals from January 2003 to June 2008. *P. falciparum* accounted for the majority of infections. The hospitals' charges for the care of these 306 children totaled $5.3 million ($17,519/patient).

■ COMMENTARY

Imported malaria continues to be diagnosed among children in the United States, as well as in Europe.[1,2] In the United States during 2009, there were 1,484 reported cases of malaria, and 16% of these cases were among those younger than 18 years of age.[3] Of these pediatric cases, 89% occurred after travel in Africa, and 73% were in children who had traveled to visit friends and relatives; only 4% reported adherence to an accepted anti-malarial chemoprophylaxis regimen.[3]

While important, malaria is not the most common problem occurring in returned travelers. Of 1,591 children presenting for health care in 19 countries following travel to 218 destinations, 28% had diarrhea, 25% had skin conditions, 23% had fever (8% of the total with malaria), and 11% had respiratory illnesses.[4] When compared to adults presenting for post-travel care, children presented sooner, required more hospitalizations, more often lacked pre-travel care, and more often had traveled to visit friends and relatives.[4]

So, what are the practical implications of these new data? First, realizing that the majority of sick returned pediatric travelers and the majority of patients with imported malaria had traveled to visit friends and relatives, we should expand our pre-travel efforts specifically directed toward these travelers.[5] Second, realizing that most of these travelers did not take appropriate

chemoprophylaxis, we should identify ways of both bringing these travelers into contact with pre-travel care and ensuring that they apply appropriate preventive efforts.

Strategies should be developed to engage travelers who are not currently presenting for pre-travel care. Current practices could be supplemented with new efforts focused on immigrant populations (those most likely to take children to other countries to visit friends and relatives). A goal would be to reach into communities with good pre-travel interventions. This could be facilitated by including questionnaires about future travel plans in community clinic and primary care practice health maintenance visits.[6] To this end, a new Pediatric Interest Group of the International Society of Travel Medicine is seeking to work in and beyond the travel medicine community to improve pre-travel care of children.[7] ■

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ABSTRACT & COMMENTARY

Strongyloidiasis in a Patient with HTLV-1 Infection

By Maria D. Mileno, MD, and Peter Ackerman, MD

Dr. Mileno is Director, Travel Medicine, The Miriam Hospital, and Associate Professor of Medicine, Brown University, Providence, RI; Dr. Ackerman is an Infectious Disease Fellow, The Miriam Hospital, Brown University.

Drs. Mileno and Ackerman report no financial relationship to this field of study. This article originally appeared in the August 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. Dr. Chen has received research grants from the Centers for Disease Control and Prevention and Xcellerex.

SYNOPSIS: The risk of travelers acquiring acute strongyloidiasis while walking barefoot in tropical and subtropical areas is highlighted in a case published in the *Journal of Travel Medicine*, and presented at the annual meeting of the Infectious Disease Society of America.

SOURCES: Caumes E, Keystone J. Acute strongyloidiasis: A rarity. Chronic strongyloidiasis: A time bomb! *J Travel Med* 2011;18:71-72; Wang S, Ackerman P. Disseminated cryptococcosis in Liberian Female with new Diagnosis of HTLV-1 and Adult T-cell Leukemia. Submitted for presentation at the Annual meetings of the Infectious Disease Society of America. Boston, MA; October, 2011.

A 58-year-old Liberian-born woman was in excellent general health, living and working in a large academic medical center in Rhode Island for more than 20 years, when she developed nonspecific gastrointestinal symptoms and underwent endoscopy, which revealed *Strongyloides stercoralis* larvae on a duodenal biopsy in March 2010. Symptoms resolved with ivermectin therapy. No immunologic work-up was performed.

In February 2011 the patient began to experience fevers, night sweats, non-productive cough, and shortness of breath. Her symptoms were refractory to outpatient management and she was briefly admitted to the hospital on two separate occasions in early March. Chest radiographs showed a persistent left upper lobe consolidation. She had mild neurologic complaints during those admissions, including headache and dizziness. She was discharged each time with a diagnosis of community-acquired pneumonia and treated with oral antibiotics.

Two days after her second hospital discharge she returned to the emergency room with

meningismus. At that time a lumbar puncture showed an opening pressure of 30 cm H_2O and a WBC count of 23 with 56% neutrophils, 20% monocytes, and 14% lymphocytes. The cerebrospinal fluid (CSF) protein and glucose were within normal limits (42 mg/dL and 54 mg/dL, respectively). Routine gram stain demonstrated many yeast forms and special staining showed encapsulated fungal elements consistent with *Cryptococcus* infection. Serum cryptococcal antigen was positive with a titer > 1:256. Ultimately, CSF, blood, and urine cultures grew *Cryptococcus neoformans*. The patient clinically improved during her 2-week course of induction therapy with liposomal amphotericin B (5 mg/kg IV daily) and flucytosine (25 mg/kg every 6 hours) followed by consolidation therapy with fluconazole 800 mg, daily, prior to her discharge. Epidemiologic investigation did not reveal any obvious cryptococcal exposure risk in this compromised host.

Rapid HIV and HIV-ELISA tests were negative. Analysis of the patient's peripheral blood smear showed a very small subset of small to medium sized lymphoid cells with irregularly lobulated nuclei resembling "flower-like cells." Flow cytometry immunophenotype was most consistent with adult T-cell leukemia-lymphoma. Serologic and nucleic acid testing confirmed a new diagnosis of human T-cell lymphotropic virus-type 1 (HTLV-I).

Multiple sputum and urine samples were negative on staining for acid-fast organisms, and mycobacterial cultures showed no growth to date. Strongyloides serological testing and direct microscopy of stool for ova and parasites were negative. The patient's CD4+ cell count was 203 cells/µL (11.3%) and she received prophylactic doses of trimethoprim-sulfamethoxazole. Given the grave prognosis for adult T-cell leukemia, the patient underwent a staging CT of the abdomen and pelvis, which showed extensive retroperitoneal lymphadenopathy. The hematology oncology and infectious disease consultants have been justifiably concerned about potential *Strongyloides stercoralis* hyperinfection, if and when chemotherapy must be initiated for this immunocompromised patient.

■ COMMENTARY

Caumes and Keystone discuss the presentation of chronic strongyloidiasis as one that is usually asymptomatic or as seen in our patient with mild gastrointestinal symptoms and occasionally peptic ulcer-like symptoms. Disseminated infection resulting from decreased cell-mediated immunity is a clear possibility in our patient with HTLV- 1 infection and profound depression of CD4+ cell counts. The authors cite additional references that describe mortality rates ranging from 50% to 87% even with treatment. Our patient has presumably carried this infection for at least 20 years — since she moved to the United States from Liberia. This is made possible by the fascinating property of the nematode to persist via autoinfection of the host. Although this disease has classically been associated with immigration, recent Canadian data showed numerous cases of strongyloidiasis in tourists.[1] Of 43 travelers with strongyloidiasis in Canada, the infection was associated with visiting friends and relatives in 37% of cases, tourism in 30%, and immigration in only 21%.

The patient was treated with the recommended course of ivermectin 200 µg/kg for 2 days in 2010. Although we cannot presently demonstrate larvae or serologic evidence of disease, we chose to presumptively repeat the regimen again in anticipation of potential life-threatening disseminated strongyloidiasis and hyperinfection syndrome.

Acute T-cell leukemia (ATL) is characterized by clonal proliferation of CD4+ T cells that may be identified on peripheral blood smear by their hyperlobulated nuclei (referred to as "flower cells"). There are actually four distinct clinical forms of ATL. The smoldering subtype, seen in this patient, is the least common and generally has a more favorable prognosis with median survival of more than 5 years. While there are no standard treatment recommendations for the management of HTLV-I disease, progressive adult T-cell leukemia-lymphoma is generally treated with conventional chemotherapeutic regimens such as cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP). Combination therapy with nucleoside reverse transcriptase inhibitors (NRTIs), such as zidovudine (AZT), plus interferon-alpha may also be effective. The clonal CD4+ T cells proliferating during this process are numerous, yet they are clearly ineffective against opportunistic pathogens. For example, infections associated with *Cryptococcus neoformans* are typically seen in patients with compromised cell-mediated immunity such as those with advanced HIV infection or, much less commonly, HTLV-1 infections. The most common clinical manifestation of cryptococcal disease is meningitis, which can present with little or no meningeal signs.

HTLV-1 is a human retrovirus that infects an estimated 10-20 million people worldwide. Transfer of bodily fluids

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Updates

By Carol A. Kemper, MD, FACP

New *Ehrlichia* species discovered

Source: Pritt BS, et al. Emergence of a new pathogenic *Ehrlichia* species, Wisconsin and Minnesota, 2009. *N Engl J Med* 2011;365:422-429.

The increasing sophistication of molecular tools is allowing for the discovery of all kinds of novel strains of bacteria; witness the multiple new strains of *Rickettsia* discovered around the world. *Ehrlichia* and *Anaplasma* are obligate intracellular parasites, which infect various white blood cells, and are transmitted by tick species. While strains of some *Ehrlichia* (*E. muris* and *E. canis*) have been implicated in human infection in other parts of the world, *Ehrlichia chaffeensis* and *Ehrlichia ewingii* are believed to cause human disease limited to the United States.

These authors describe a novel species of *Ehrlichia* closely related to *E. muris*, which resulted in symptomatic infection in 4 people from Minnesota and Wisconsin. In the process of conducting a large epidemiological study for these organisms in the United States, whole blood specimens from 4247 patients suspected of having *Ehrlichia* or *Anaplasma* infection were collected from 45 states from June through December 2009. Real-time PCR targeting a conserved region of GroEL heat-shock protein operon was used. Specimens with an atypical result (not consistent with recognized species of *Ehrlichia*) were tested using broad range 16S ribosomal primers and Anaplasmataceae *rrs* assay.

Of 1,518 specimens submitted from Minnesota and Wisconsin residents, 163 (10.7%) were positive for *A. phagocytophilum* and none were positive for *E. chaffeensis* or *E. ewingii*. However, 4 of the specimens had an atypical GroEL PCR reaction; all 4 also tested positive by the Anaplasmataceae PCR assay. Nucleotide sequencing suggested that all 4 specimens were identical and shared 98% homology with *E. muris*. Cultures of whole blood did yield an organism when inoculated on live cell culture, and produced morulae visible by light microscopy at 5 weeks.

All 4 patients were suspected of having some kind of ehrlichial-like infection but their initial tests were negative or inconclusive. All 4 presented with fever, headache, and lymphocytopenia, three had thrombocytopenia, and 2 had abnormal liver function tests. One patient had a lung transplant and another had a kidney transplant; both were receiving immunosuppressive therapy. One required hospitalization. All 4 recovered with administration of doxycycline. The authors indicate that all 4 had "peri-domestic" activities that put them at risk for tick exposure (such as mowing the lawn or hiking).

Peripheral blood specimens from the 4 patients failed to demonstrate parasites or morulae. Serum from one patient was positive for *E. chaffeensis* IgG antibodies at days 5 and 54 of illness by immunofluorescence, but another patient had negative studies at days 2 and 15 of illness. At least one serum and plasma specimen from each patient submitted to the CDC tested positive for IgM or IgG by IFA for *E. chaffeensis* but not *A. phagocytophilum*.

DNA consistent with this new species was identified in 16 of 534 *Ixodes scapularis* ticks and 1 of 15 nymph groups submitted from Minnesota, but was not found in 9 *I. scapularis* or 88 dermocentor ticks from Wisconsin.

Commercial assays currently available may not detect this new species of *Ehrlichia*, although specific PCR and IFA studies are available through the CDC, if needed. The molecular similarity to *E. muris* raises an interesting point — *E. muris* is an Old World parasite, present in Eastern Europe, Russia, and Japan, where it infects mice and deer, and their ticks. Serological studies have found that 1.1% of residents in Tokyo test positive for *E. muris*. Perhaps these organisms are distantly related. ■

Chinese herbal remedy for H1N1

Source: Wang C, et al. Oseltamivir compared with the Chinese Traditional Therapy Maxingshigan-Yinqiaosan in the treatment of H1N1 Influenza. *Ann Intern Med* 2011;15:217-225.

Thousands of Chinese used a compound called maxingshigan-yinqiaosan (MY) for treatment of flu symptoms during the 2009 H1N1 epidemic. MY is a concoction of 12 different herbs, including toasted *Herba ephedra*, as well as qinghao, gypsum fibrosum, and rhizoma.

To test the efficacy of this herbal remedy for influenza, the authors conducted an unblinded, randomized study of 410 adults (ages 15-59; average age, 19 years) with laboratory-confirmed influenza H1N1. Patients were randomly assigned in a 1:1 fashion to receive 5 days of either os-

eltamivir (OS), OS plus MY, MY alone, or nothing. Patients were excluded from study if they had pneumonia or abnormal chest radiographs, other significant underlying illness or HIV infection, or had received influenza vaccination in the past year. All of the participants were hospitalized for quarantine and close monitoring. Serial real-time PCR for viral RNA titers were conducted daily in a subset of 148 randomly selected patients.

The MY compound met Chinese safety standards and was tested for heavy metals, bacterial contamination, and pesticides, and was centrally distributed to the study sites. Antibiotics could be used at the discretion of the treating physician.

The median time from onset of illness to randomization was 35 hours (range, 18-48 hours), and was similar between the three active treatment groups and controls. The use of concomitant antibacterials was similar in the 4 groups prior to randomization. Following randomization, the control group received significantly more antibiotics than the three active treatment groups (34% vs. 15.7% for OS, 9.7% for MY, and 7.8% for OS + MY; $P < 0.001$). Time to resolution of fever was significantly less for all three treatment groups compared with the control group (median time, 15 hours for OS + MY, 16 hours for MY, 20 hours for OS, and 26 hours for the control group; $P < 0.001$). A borderline statistically significant difference in favor of the combined treatment group compared with the OS group was observed for time to resolution of fever. No difference in the reduction of other symptoms (cough, headache, fatigue) between the groups was observed. Only two patients developed nausea and vomiting to MY, and none reported side effects to OS.

Throat swabs demonstrated a rapid reduction in H1N1 viral shedding between baseline and day 5, although no significant difference between the treatment groups and controls was detected. By day 5 of illness, viral shedding was still detectable by PCR in 40% of the control group, 30% of the MY group, and 16-18% of the groups receiving OS. Further analysis revealed that this subgroup of patients had a lower symptom score compared with the other study patients.

The combination of this Chinese herbal remedy plus oseltamivir for influenza H1N1 appeared more effective than OS alone in the reduction of fever, and was well-tolerated. ■

UTIs increased after PAP testing

Source: Tiemstra JD, et al. Genitourinary infections after a routine pelvic exam. *J Am Board Fam Med* 2011;24:296-303.

Anecdotal data suggest that women may be at increased risk for UTI following routine PAP and pelvic examination. To examine the risk of UTI following PAP smear, these authors conducted a historical cohort study to assess the frequency of UTI in women attending a family medicine clinic who had undergone a PAP in the previous 52 weeks. The frequency of UTI was compared in women who had undergone PAP smear within the previous 1-7 weeks vs. the remaining women, who served as a control group, who had had PAP smears 8-52 weeks earlier.

A total of 1,582 women were included in the analysis, 30% of whom had student health insurance. Variables such as vaginitis, sexually transmitted disease, and the frequency of visits for UTI before and after the PAP smear were examined. The women were examined by 22 different clinicians, one-fourth of whom were students or residents. Although the frequency of bimanual pelvic examination was not specifically assessed, the authors commented that a bimanual exam was generally performed with the PAP smear. Specific information on sexual activity was not available.

UTIs were significantly more frequent in women who had undergone PAP smear in the previous 7 weeks compared with controls (12.7% vs. 6.51% per 100 person-years; $P < 0.01$). An increased frequency of *Candida* and bacterial vaginitis in the 7 weeks following PAP compared to weeks 8-52 also was observed. The frequency of STDs remained uniform throughout the 52-week follow-up period. There was no significant difference in the frequency of UTI within 2 weeks of PAP compared with weeks 3-7, suggesting that occult infection at the time of the PAP was not responsible for the increased incidence of UTI observed (0.3% risk of asymptomatic colonization).

Based on these data, the risk of UTI per individual following a PAP smear was approximately 0.83%. Although seemingly small, this figure translates into 415,000 extra UTIs in the United States when factoring in the number of women who have an annual PAP smear. This figure represents approximately 11% of all observed UTIs in the United States. The authors suggest that the increased risk of UTI following routine PAP smear lends further weight to the argument that routine annual PAP smears may not be necessary in all women, especially those with no risk factors or a history of abnormal PAPs. In addition, no good data exist to support the use of the bimanual pelvic examination as a screening tool in asymptomatic women. Since the bimanual exam may further add to the risk of UTI beyond just the simple speculum exam, perhaps it should not be routine in otherwise healthy, asymptomatic young women. ■

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such as breast milk, blood, or genital secretions is the primary means of transmission. Endemic in parts of the South American, Asian, and African continents, it rarely causes clinical disease in infected individuals (~5% lifetime risk). Primary disease manifestations include HTLV-I-associated myelopathy (HAM) or adult T-cell leukemia-lymphoma (ATL). Its association with strongyloidiasis is well described and our case is presented both here and at the annual meetings of the Infectious Disease Society of America to illustrate the complexities involved in diagnosing and treating immunocompromised hosts, as well as the insidious nature of infection with *Strongyloides stercoralis*. ■

Reference

1. Angheben A, et al. Acute strongyloidiasis in Italian tourists returning from Southeast Asia. *J Travel Med* 2011;18:138-140.

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 *true* of fidaxomicin?

a. Fidaxomicin is inexpensive.
b. Low fecal concentrations occur after oral dosing of fidaxomicin.
c. Fidaxomicin is less active in vitro against *C. difficile* than vancomycin.
d. Fidaxomicin is well-absorbed systemically.
e. Fidaxomicin has little activity against normal intestinal flora.

2. Imported pediatric malaria:

a. usually occurs after travel to the Indian sub-continent.
b. frequently is identified in children who were compliant with chemoprophylaxis.
c. is more frequent among tourists to game parks.
d. especially occurs in children visiting friends and relatives in Africa.

3. Which of the following statements is *true*?

a. Chronic HTLV-1 infection suppresses the expression of asymptomatic strongyloidiasis.
b. Strongyloidiasis occurring during HTLV-1 infections causes severe myelopathy if left untreated.
c. Treatment for strongyloidiasis is generally indicated if HTLV-1 infection is diagnosed, even if the patient is asymptomatic.
d. Ivermectin is no longer effective in the treatment of strongyloidiasis when HTLV-1 infection becomes clinically apparent.

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]

HIV-1 protein, NEF, contributes to insulin resistance

Effect of oxazolidinone and clindamycin on production of *Staph aureaus* virulence factors

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.*

Apixaban is Heating Up the Anticoagulation Market

In this issue: Apixaban could soon join the anticoagulation market; Chinese herbs for flu; chronic medication and discontinuation after hospitalization; and FDA actions.

Apixaban trial results look promising

There is soon to be a third player in the anticoagulation wars. Apixaban, an oral factor Xa inhibitor, will likely soon join dabigatran and rivaroxaban as alternatives to warfarin for preventing stroke in patients with atrial fibrillation (AF). Dabigatran, a direct thrombin inhibitor, was approved for this indication last year and rivaroxaban, also a factor Xa inhibitor, is likely to be approved in early September. (Rivaroxaban was previously approved for DVT prevention in patients undergoing orthopedic surgery.) Apixaban also looks very promising based on results of the ARISTOTLE trial, which was published online in the *New England Journal of Medicine* on August 28. ARISTOTLE enrolled 18,201 patients with AF and at least one additional risk factor for stroke. Patients were randomly assigned to apixaban 5 mg twice daily or warfarin with a target INR of 2-3. ARISTOTLE was designed as a noninferiority study with a primary outcome of ischemic or hemorrhagic stroke, or systemic embolism. After median follow-up of 1.8 years, the rate of the primary outcome was 1.27% per year in the apixaban group vs 1.60% in the warfarin group (hazard ratio [HR] 0.79; 95% confidence interval [CI] 0.66 to 0.95; $P < 0.0014$ noninferiority; $P = 0.01$ for superiority). The rate of major bleeding was 30% less with apixaban and the rate of death from any cause was 3.52% with apixaban and 3.94% with warfarin ($P = 0.047$). The rate of hemorrhagic stroke in the apixaban group was about half that in the warfarin group (0.24% per year vs 0.47% per year, $P < 0.001$) and the rate of all other strokes was 0.97% with apixaban vs 1.05% with warfarin ($P = 0.42$). The authors conclude that in patients with AF, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality (*N Engl J Med* published online August 28, 2011). An excellent accompanying editorial discusses the seminal studies that compared the three new anticoagulants to warfarin for stroke prevention in patients with AF: RE-LY — dabigatran; ROCKET AF — rivaroxaban; and ARISTOTLE — apixaban. All three showed that the new drugs were significantly better than warfarin at reducing hemorrhagic stroke and all were at least as effective as warfarin at preventing ischemic stroke. All three drugs were also associated with a significantly lower rate of serious bleeding compared to warfarin. Apixaban was the only drug that showed a significant reduction in overall mortality, although both dabigatran and rivaroxaban showed trends in that direction. ROCKET AF has been criticized because the warfarin comparator group had a time in therapeutic range of only 55% compared to 64% in the RE-LY trial and 62% in ARISTOTLE; however, patients in the ROCKET AF study were at higher risk for stroke than in the other two studies. The bottom line is that all three drugs are effective in preventing stroke in patients with nonvalvular

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AF and seem to be safer than warfarin as well. The new drugs do not require any laboratory monitoring, which is convenient for patients and also lowers the overall cost of care (although all three drugs will be priced significantly higher than generic warfarin). Rivaroxaban has the advantage of a once daily dose vs the other two drugs, which must be dosed twice daily. None of the three drugs can be quickly reversed in the event of major bleeding or need for surgery. Apixaban is not yet approved in this country but when it is, it is likely that the competition between these three agents will be fierce, and for many purchasers of health care it may come down to cost. ■

Chinese herbs for flu treatment

For the flu season this year, you might consider Chinese herbs instead of antivirals based on the results of a study from China published in the *Annals of Internal Medicine*. More than 400 adults age 15-59 years with confirmed H1N1 influenza were randomized to oseltamivir 75 mg twice daily or a combination of 12 Chinese herbal medicines called maxingshigan-yinqiaosan 200 mL four times a day, a combination of oseltamivir plus maxingshigan-yinqiaosan, or placebo for 5 days. The primary outcome was time-to-fever resolution and the secondary outcomes included symptom scores and viral shedding. Both oseltamivir and maxingshigan-yinqiaosan, as well as the combination, resulted in significant reductions in the estimated median time-to-fever resolution compared to the control group (median time-to-fever resolution — no treatment 26 hours; oseltamivir 20 hours; maxingshigan-yinqiaosan 16 hours; combination 15 hours; all statistically significant at $P < 0.001$). Side effects were similar in all groups. The authors conclude that oseltamivir and maxingshigan-yinqiaosan, alone or in combination with each other, reduce time-to-fever resolution in patients with H1N1 influenza. They go so far as to suggest that maxingshigan-yinqiaosan may be used as an alternative treatment for H1N1 infections (*Ann Int Med* published online August 26, 2011). It may be difficult to obtain maxingshigan-yinqiaosan since it contains ephedra (which is not available in this country) and the authors could not determine if the benefits of maxingshigan-yinqiaosan were due to an antiviral effect or merely an antipyretic effect. ■

Chronic medications and hospitalization

Your patients' chronic medications may be inadvertently discontinued after hospitalization according to a population-based cohort study of almost 400,000 patients published recently in the *Journal of the American Medical Association*. Researchers from Canada reviewed the records of residents age 66 or older who were on statins, antiplatelet/anticoagulant agents, levothyroxine, respiratory inhalers, or gastric acid suppressing drugs on a chronic basis. When compared to nonhospitalized patients, patients admitted to the hospital — especially the ICU — were more likely to have their chronic medications discontinued. Discontinuation rates ranged from a low for levothyroxine of 12.3% discontinuation for hospitalizations vs 11% for controls, to antiplatelet/anticoagulant agents which were discontinued at a rate of 19.4% for hospitalizations vs 11.8% for controls. The discontinuation rates were even higher for patients who were admitted to the ICU. The authors conclude that patients admitted to the hospital are at relatively high risk for potential unintentional discontinuation of chronic medications (*JAMA* 2011;306:840-847). This study points out the importance of medication reconciliation at all post-hospital visits and may validate the role of computerized medical records, especially with regard to medication lists. ■

FDA actions

The FDA has approved a new fixed-dose combination pill for HIV-infected patients. Emticitabibine/rilpirivine/tenfovir DF is approved as a once-a-day pill for treatment of HIV-1 infection in treatment-naïve patients. This is the second triple combination anti-HIV agent approved and differs from the previous agent (Atripla) in that it contains the NNRTI rilpirivine rather than efavirenz. The new combination will be marketed as Complera.

The FDA has approved brentuximab vedotin to treat Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma. The drug is approved for HL patients who have progressed after autologous stem cell transplant or after prior chemotherapy regimens and cannot receive a transplant. This represents the first the drug to treat HL since 1977. Brentuximab will be marketed as Adcetris.

The FDA has approved vemurafenib for the treatment of metastatic and unresectable melanoma, specifically in patients whose tumors have the BRAF V600E mutation. The approval was accompanied by a companion diagnostic test that will determine if a patient's melanoma cells have that mutation (about half of the patients with late stage melanomas). Only patients with the BRAF V600E mutation will respond to the drug since it targets the mutated protein that regulates cell growth. Vemurafenib is marketed by Genentech as Zelboraf. ■