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INSIDE

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Fusobacterium and Tonsillar Infections

ABSTRACT & COMMENTARY

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 serves as a consultant for Siemens Diagnostics and is on the speaker's bureau for GSK and Cubist.

Synopsis: *Eight hundred and forty-seven patients with peritonsillar abscess (PTA) admitted to Aarhus University hospitals from 2001-2006 were included in this retrospective study.* Fusobacterium necrophorum *(FN) was the most frequently detected bacterium (23%), followed by group A streptococci (GAS) (17%) and groups C and G streptococci (GCS/GGS) (5% combined).*

Source: Ehlers T, et al. *Fusobacterium necrophorum:* Most prevalent pathogen in peritonsillar abscess in Denmark. *Clin Infect Dis*. 2009;49:1467-1472.

Eight hundred and forty-seven patients with peritonsillar abscess admitted to the ENT service at Aarhus University hospitals from 2001-2006 were included in this retrospective study. Most patients underwent tonsillectomy and/or incision and drainage. Pus aspirates and pus swab samples were cultured for routine and anaerobic cultures using standard microbiological methods.

The median age of patients studied was 21 years. FN alone was isolated from 167 patients, GAS alone from 133, GCS/GGS alone from 23, FN plus beta hemolytic strep from 24, other bacteria 58, mixed oral flora from 355, no culture was obtained in 87 patients, and a diagnosis of infectious mononucleosis was made in 26 patients.

Of the 760 patients who had cultures taken, FN was recovered from 44% of those patients with PTA who received antibiotics prior to admission and from 36% of those patients who had not received antibiotics.

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■ **COMMENTARY**

The information in this paper is quite interesting. The increased isolation of FN from patients with PTA in this study vs. the relatively low prevalence of this organism in historical literature may reflect the use of better anaerobic bacteriology in the clinical setting at this institution. Brook et al, in an earlier study, found other anaerobes, including Prevotella, Porphyromonas, and Peptostreptococcus, as well as Fusobacterium in PTA and parapharyngeal abscesses.[1]

The big concern about FN is its association with Lemierre's syndrome (septic thrombophlebitis of the internal jugular vein following sore throat). Interestingly, the authors of this study do not comment on whether or not they saw Lemierre's in any of their patients. Late last year, there was a somewhat alarming "Perspective" article published in *Annals of Internal Medicine* recommending that we should stop focusing solely on GAS and "expand the pharyngitis paradigm for adolescents and young adults."[2] This recommendation was made by the author based on several case reports of FN causing (or at least being isolated from patients with) pharyngitis. His recommendation to use penicillin derivatives, and to avoid macrolides, in the treatment of GAS-negative pharyngotonsillitis seemed somewhat illogical since the concern about using macrolides would seem to be related to the increased prevalence of macrolide resistance in GAS. Also, if the recommendation to always use β-lactam agents empirically for the treatment of adolescents with pharyngotonsillitis is to prevent complications of FN infection, the results of the Danish study do not support that, since penicillins were administered to 94% of the 293 antibiotic-treated patients with PTA, if anything appeared to increase the risk for isolation of FN.

Despite the frequent isolation of FN from patients undergoing tonsillectomy or incision and drainage for PTA, Lemierre's syndrome fortunately seems to be a rare complication (I have cared for only three patients with Lemierre's in my 37-year career). While FN is clearly an important pathogen capable of causing both PTA and Lemierre's syndrome, its overall importance as a cause of all cases of pharyngotonsillitis remains uncertain. In another recently published study, throat swabs were taken from 411 mostly asymptomatic university students and from 103 patients who presented with sore throat.[3] The throat swabs were tested for β-hemolytic streptococci by routine culture and for EBV and *F. necrophorum* DNA by PCR. FN was found in 43 of 411 (10.5%) students, and this represented asymptomatic carriage in 29 of 43 (67.4%).

It is difficult to integrate all of these findings into a coherent story. Clearly, FN is a pathogen capable of causing both peritonsillar abscess (commonly) and Lemierre's syndrome (rarely). However, FN is also commonly isolated from the throats of asymptomatic adolescents and young adults. I generally prescribe antimicrobials for patients with clinically significant tonsillitis whether or not GAS is present on rapid screen or culture. Due to the common presence of FN in asymptomatic and minimally symptomatic younger patients, I am not convinced that it makes sense to routinely test patients with just pharyngitis/mild tonsillitis for the presence of FN, nor should empiric therapy be given for this organism in all cases. ■

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Human Metapneumovirus Infection in HIV Patients

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *In a prospective surveillance study, 50 HIV-positive patients who presented with febrile respiratory symptoms were evaluated for the presence of respiratory viruses by multiplex RT-PCR and a microarray assay and for atypical bacterial pathogens by PCR, in addition to sputum cultures and serologic testing. Viruses accounted for 64% of the infections. Influenza virus was identified in 22 cases, and human metapneumovirus (hMPV) was next most common, with six cases.*

Source: Klein MB, et al. Viral pathogens including human metapneumovirus are the primary cause of febrile respiratory illness in HIV-infected adults receiving antiretroviral therapy. *J Infect Dis*. 2010;201:297-301.

Fifty consecutive patients from a large HIV clinic in Montreal, who presented with febrile respiratory symptoms (temperature > 38° C and one or more respiratory symptom) from November 2003-April 2006, were recruited for this prospective study. An in-house multiplex real-time PCR assay was originally used to test NP samples for influenza A and B, RSV, and hMPV. Frozen aliquots of the original samples were later tested for adenovirus groups A, B, C, and E; rhinovirus A and B; influenza A and B, hMPV A and B; RSV A and B; parainfluenza types 1-3; coronaviruses HKU1, 229E, NL63, and OC43; and enteroviruses A-D using a commercial microarray assay. Paired acute and convalescent sera were analyzed by complement fixation. NP samples were tested for rRNA genes of *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*. From all individuals with productive cough, a sputum sample was sent for bacterial culture and sensitivity.

Twenty-two patients were found to be infected with influenza virus, 12 with noninfluenza viral pathogens, six had bacterial infections, and 16 were not diagnosed. Patients with influenza had a median CD4+ lymphocyte count of 280, and those with noninfluenza viral infections had a median CD4+ count of 484. In addition to fever and myalgias, the patients with hMPV infection had predominant lower respiratory tract symptoms, with cough, dyspnea, and wheezing in most cases. Only one of the hMPV cases was complicated by documented bacterial infection (bacteremic pneumococcal disease). While the hMPV patients were less immunosuppressed than the influenza patients, almost all had underlying asthma.

■ COMMENTARY

This study, while small, highlights the potential importance of hMPV as a cause of febrile respiratory symptoms in adult patients with HIV. While some obvious caveats to the generalizability of the findings in this study apply (e.g., hMPV may or may not cause this high proportion of febrile respiratory infections in all years and in all areas of North America), the association of hMPV with prominent lower respiratory signs and symptoms, and association with underlying asthma, is notable. The authors note that despite the fact that only one hMPV-infected patient had documented bacterial superinfection, > 80% received antibiotics despite normal chest X-rays. The promise of rapid, sensitive, molecular diagnostic assays for viral pathogens in clinical use would seem to have the potential to reduce unnecessary prescription of antibiotics. However, the costs of these assays and the turn-around times need to be markedly reduced in order for this to become a reality. ■

Warfarin Interactions with Antimicrobial Agents: Part I

SPECIAL FEATURE

By Gregory Aung, PharmD Candidate: Crystal Leung, PharmD Candidate; Laura Kawamoto, PharmD Candidate; and Jessica C. Song, MA, PharmD

Gregory Aung, Crystal Leung, and Laura Kawamoto are PharmD Candidates for the University of the Pacific, and Jessica C. Song is PharmD at the University of the Pacific.

They all report no financial relationships relevant to this field of study.

Warfarin, the most common vitamin K antagonist in clinical use, consists of two optically active isomers, the R and S enantiomers.1 The S enantiomer primarily undergoes metabolism by the cytochrome P450 (CYP) enzyme 2C9 pathway, and is 3- to 4-fold more potent than the R enantiomer. The CYP1A2 and CYP3A4 pathways are involved in the metabolism of the less potent R enantiomer.[1] Warfarin dosing requirements vary greatly among individuals and can be impacted by genetic and environmental factors. Environmental factors include medications, diet, and a variety of disease states, such as liver disease and hypermetabolic conditions.[1]

Antimicrobials represent a short-term change in patient therapy that can have devastating consequences if certain drug interactions are disregarded or overlooked. The objective of this article is to compile and analyze case reports and other studies showing the interaction between various antimicrobial agents and warfarin. Moreover, this article is intended to heighten clinicians' awareness of the potential interactions between antimicrobial agents and warfarin, such that supratherapeutic or subtherapeutic INRs (international normalized ratios) are prevented and managed.

OVERVIEW OF INTERACTIONS

Table 1 provides a summary of the most commonly implicated antibiotics, with a focus on the probability of the reaction, the proposed mechanism responsible for the interaction, the time of onset/offset (if available) of the interaction, and recommendations for preventing supratherapeutic or subtherapeutic INRs. The probabilities of the interactions were derived from the findings cited in the eighth edition of the American College of Chest Physicians' *Clinical Practice Guidelines*.

Fifteen antibiotic agents have been shown to interact with warfarin in published case reports over the past four decades. Of note, linezolid, vancomycin, telavancin, daptomycin, quinupristin/dalfopristin, amikacin, gentamicin, neomycin, streptomycin, tobramycin, colistimethate, nitrofurantoin, ethambutol, and pyrazinamide have not been shown to interact with warfarin.

Metronidazole potentiates the effect of warfarin through inhibition of CYP2C9, whereas rifampin induces the metabolism of warfarin through CYP1A2, CYP2C9, and CYP3A4. Ciprofloxacin, erythromycin, clarithromycin, and telithromycin most likely inhibit the metabolism of the R enantiomer of warfarin. Other antibiotics may enhance the anticoagulant effects of warfarin through displacement of warfarin from albumin, or through disruption of intestinal flora responsible for vitamin K synthesis.

Conclusion

In summary, concomitant use of warfarin with metronidazole, trimethoprim/sulfamethoxazole, ciprofloxacin, and erythromycin necessitates dose reduction of warfarin in order to prevent supratherapeutic INRs and/or major bleeding events. In contrast, patients taking warfarin and rifampin concurrently will require more frequent INR monitoring, along with gradual changes in warfarin dosing during the time of dual therapy and up to several months after discontinuation of rifampin therapy. The propensity of other antibiotics to interact with warfarin has not been validated by published case reports, but warrants closer INR monitoring during each treatment course. ■

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Table 1
Overview of the most commonly implicated antibiotics and their interactions

Drug/Probability of Interaction[1]	Effect on Warfarin/Mechanism	Timing of Interaction/Recommendations
Metronidazole: highly probable First case report published in 1976; four other case reports/series published after initial case report	Potentiates effect of warfarin Mechanism: inhibition of cytochrome P450 (CYP) enzyme 2C9 and possibly displaces warfarin from albumin[2,3]	Thompson et al[2] reported an onset of five days (INR not measured earlier) in a patient taking warfarin concomitantly with metronidazole and levofloxacin. Tonna at al[3] reported an onset ranging between 2-4 days in patients who stopped taking warfarin and received metronidazole. Recommendation: Santa Clara Valley Medical Center (SCVMC) the weekly dose of warfarin by 20%-30%.
Trimethoprim/Sulfamethoxazole: highly probable	Potentiates effect of warfarin Mechanism: not well established; sulfonamide may impair hepatic metabolism of warfarin or it may displace warfarin from protein-binding sites[4,5]	Cook et al[4] cited seven other published case reports of this interaction and reported an onset ranging from 1 to 13 days; onset of three days cited in more recent literature.[5] Cook et al[4] reported an offset of the interaction of three days. Recommendation: Ahmed et al[5] recommended warfarin dose by 10%-20%; SCVMC, warfarin dose by 20%-30%.
Quinolones Ciprofloxacin: highly probable Levofloxacin: probable Moxifloxacin: probable	Potentiates effect of warfarin Mechanism: ciprofloxacin most likely inhibits metabolism of R-enantiomer of warfarin;[6] other quinolones may disrupt intestinal flora responsible for vitamin K synthesis or displace warfarin from protein-binding sites.[7]	Carroll et al[7] summarized 21 publications of warfarin interactions with ciprofloxacin, levofloxavin, and moxifloxacin. Average time of onset for ciprofloxacin (earliest, three days) and for levofloxacin (earliest, 5.5 days) was 5 to 6 days; moxifloxacin interaction occurred earlier (2-4 days). Recommendation: SCVMC, warfarin dose by 10% if taking ciprofloxacin; no recommendation for other quinolones.
Rifampin: highly probable	Decreases effect of warfarin Mechanism: induction of warfarin metabolism through CYP1A2, CYP2C9, and CYP3A48	Kim et al[9] stated that a total of 7 case reports (including her own) and 3 pharmacokinetic-pharmacodynamic studies described the interaction between rifampin and warfarin. Krajewski et al[10] published a detailed report on this interaction in 2010, stating an onset of the induction effect of days and an initial offset of the inducing effect of 6 days. The inducing effects of rifampin (after 6-week course) took 4 months to completely subside. Recommendation: Krajewski et al.[10] the weekly dose of warfarin by ~ 30% after five days; warfarin dose by an additional 30% on days 7-16; warfarin dose by additional 25% on days 17-30; warfarin dose by additional 20% on days 31-37; warfarin dose by additional 30% on days 38-40; warfarin dose by additional 25% on days 41-45. Despite five-fold in warfarin dose over 45 days, INRs remained subtherapeutic. After rifampin dc'd: warfarin dose by 30% on day 6; dose by 30% on days 7-10; dose by 20% on day 11; checked INRs ~ every 2-4 weeks

Drug/Probability of Interaction[1]	Effect on Warfarin/Mechanism	Timing of Interaction/Recommendations
Macrolides Erythromycin: highly probable Clarithromycin: probable Azithromycin: probable	Potentiates effect of warfarin Mechanism: disruption of warfarin metabolism by CYP1A2 and CYP3A4 inhibition while receiving concomitant erythromycin or clarithromycin.[11-14] The proposed mechanism for the interaction with azithromycin not well-established, given the presence of confounding factors in various case reports. Possible mechanism might involve impairment of vitamin K production by gastrointestinal flora.[15-16]	Erythromycin: time of onset ranges from 0-18 days (median, 5 days).[12] One recent report showed that after 3 weeks of concomitant treatment with warfarin and ophthalmic erythromycin, a patient presented with elevated INR; offset of four days. Clarithromycin: time of onset has ranged from five days[14] to 14 days.[11] Azithromycin: six case reports with oral azithromycin[15] showed a range in onset of 3 days to 5 days after completion of azithromycin (five-day course). One case report of intravenous azithromycin[16] showed an onset of one day. Both reports showed multiple confounding factors such as use of prednisone, fever, decreased appetite, use of ampicillin, heart failure, decreased cigarette smoking, worsening liver function, and decreased albumin. Recommendation: SCVMC, warfarin dose by 15%-30% if taking erythromycin; no changes for other macrolides
Telithromycin: one case report	Potentiates effect of warfarin Mechanism: possibly through inhibition of the metabolism of R-enantiomer of warfarin, but is not established.[17]	Kolilekas et al1 seven showed an onset of five days in a patient who took warfarin and telithromycin. Possible confounding factor was the patient's illness, since infection can affect the activity of the CYP enzyme system. Also, fever catabolism of clotting factors. Recommendation: enhanced monitoring of INR within five days
Penicillins Dicloxacillin: probable Amoxicillin: possible Nafcillin: highly improbable	Dicloxacillin[18-20] and Nafcillin:[21] decreases effect of warfarin. Amoxicillin:[22] potentiates warfarin effect Mechanism: not established for dicloxacillin or nafcillin; possible induction of hepatic enzymes,[18,21] but not confirmed. Amoxicillin therapy may result in vitamin-K producing gut flora.[22]	Dicloxacillin: case reports[18-20] have shown an onset as early as 4-5 days and an offset of three weeks. Nafcillin: Kim et al[21] summarized the interaction between warfarin and nafcillin in her case report; a total of seven published cases of this interaction exist at present. The time of onset is ~ 1 week, and the offset is ~ 4 weeks. Amoxicillin: Davydov et al[22] summarized data from four case reports of warfarin interacting with amoxicillin ± clavulanic acid and found an onset between 7 days to 2.5 weeks after stopping amoxicillin therapy. Recommendations: SCVMC, if taking nafcillin, may need to increase warfarin dose as much as four-fold. Gradually decrease dose of warfarin 1-4 weeks after stopping nafcillin.

Drug/Probability of Interaction[1]	Effect on Warfarin/Mechanism	Timing of Interaction/Recommendations
Cephalosporins Cefazolin: highly improbable	Potentiates effect of warfarin Mechanism: alteration of bacterial bowel flora; not well established.	Angaran et al[23] conducted a study that showed that after two days of treatment, the percentage change in PT for 20 cefazolin-treated patients was 51.1 ± 18.0% (nonsignificant).
Tetracyclines Doxycycline: probable Minocycline: theoretical Tigecycline: no case reports	Potentiates effect of warfarin Mechanism: not well-established for tetracyclines. Doxycycline:[24] competition for protein-binding displaces albumin-bound warfarin.	Doxycycline: Baciewicz et al[24] indicated a time of onset of 7-10 days and an offset of 3-7 days, based on a summary of three earlier case reports. Recommendation: Monitor INRs more closely after seven days of doxycycline therapy.

Myocarditis with Pandemic H1N1 Influenza A in Children

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *During a 30-day period in October 2009, 80 children were admitted to Rady Children's Hospital with confirmed H1N1 infection. Of those, four children were diagnosed with fulminant myocarditis, including one child who died.*

Source: Bratinecsak A, et al. Fulminant myocarditis associated with pandemic H1N1 influenza A virus in children. *J Am Coll Cardiol*. 2010; 55: epub Feb 10.

Eighty children with PCR-documented pandemic H1N1 influenza A virus infection were admitted to Rady Children's Hospital in San Diego during a 30-day period in October 2009. Serum troponin I and creatine-kinase MB band levels were obtained in 11 children; eight underwent echocardiography. Four of these H1N1-infected children were diagnosed with myocarditis based on elevated cardiac enzymes (n = 2), significant decrease in left ventricular systolic function on echocardiogram (n = 3), or histologic evidence of severe myocarditis (n = 1). The children ranged in age from three months to nine years old. The five-year-old child who died had evidence of extensive myocardial damage at autopsy, including myocyte necrosis and lymphocytic infiltration of the interventricular septum and the AV node. This child experienced third-degree AV block antemortum. The three-month-old and nine-month-old patients required ECMO support and sustained intracranial hemorrhage and ischemic encephalopathy, although they recovered LV systolic function over 5-7 days.

■ COMMENTARY

While thankfully the numbers of new cases of pandemic H1N1 influenza A appear to be decreasing over the peak seen in the fall of 2009 in the United States and Canada, we are still seeing sporadic cases of critically ill adults and children with pandemic H1N1 requiring admission to our intensive care units at our county hospital. These case reports highlight the severity of clinical manifestations associated with infection in many cases of pandemic H1N1 influenza A seen over the last year. Influenza A virus-associated myocarditis has been exceedingly rare in the past, with only a handful of cases reported previously in the literature.[1-3] Clinicians need to maintain a high index of suspicion for myocarditis in influenza A patients admitted to the intensive care unit with respiratory distress, since supportive treatment of acute congestive heart failure (possibly associated with conduction system abnormalities) will require other modalities in addition to ventilatory support. ■

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Kissing Bugs, Ticks, and Fleas: Disease Vectors in the Southwestern U.S.

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Sources: Reisenman CE, et al. Infection of kissing bugs with *Trypanosoma cruzi*, Tucson, Arizona, USA. *Emerg Infect Dis.* 2010;16:400-405; Williamson PC, et al. Borrelia, Ehrlichia, and Rickettsia spp. in ticks removed from persons, Texas, USA. *Emerg Infect Dis*. 2010;16:441-446; Adjemian J, et al. Murine typhus in Austin, Texas, USA, 2008. *Emerg Infect Dis.* 2010;16:412-417.

Synopsis: *Epidemiologists and clinicians must be alert to tick-borne, flea-borne, and triatomine-borne infections in the United States.*

Vector-borne diseases remain a danger in the United States, a problem highlighted by recent studies in Arizona and Texas. Reisenman et al detected DNA of *Trypanosoma cruzi* in 68 of 164 (41.5%) triatomine insects (kissing bugs) collected in Tucson, AZ.

Separately, 144 (15.9%) of 903 ticks representing 11 individual species were removed from persons in Texas from 2004-2008, submitted for examination, and were found to contain DNA of at least one of the following pathogenic genera: Borrelia, Ehrlichia, or Rickettsia. *Amblyomma americanum* and *Dermacentor variabilis* were the most frequently identified ticks, and spotted fever group Rickettsia were the most frequently detected bacteria. Borrelia spp. was detected in a Dermacentor tick, while one Ixodes scapularis yielded a DNA sequence with 99% identity with that of *B. burgodorferi*. Ehrlichia chafeensis DNA was detected in four Amblyomma ticks.

From March to October 2008, 33 human cases of confirmed murine typhus were identified in Austin, TX, clustered in the central portion of the city. Hospitalization was required for 23 (70%) of the patients, whose mean age was 39 years (range 7 to 64 years); nine received intensive care, but none died. One-half received antibiotics, but only 13 received doxycycline; the mean interval from symptom onset to receipt of antibiotics was eight days (range 1 to 19 days). Only 46% had a rash. Nineteen of 56 (33.9%) animals, including dogs, cats, opossums, raccoons, and rats were seropositive for *Rickettsia typhi*, but none of the fleas examined contained DNA of this organism.

■ COMMENTARY

T. cruzi has previously been identified in triatomines in south Texas as well as Arizona. Despite this, only seven authocthonous cases of Chagas disease have been reported in the United States, most recently a case from New Orleans reported in 2006. None have been identified in Arizona, despite the findings reported by Reisenman et al. While this may be, at least in part, the result of lack of diagnostic acumen, other reasons may also account for this. The authors note that the triatomines in southern Arizona live in association with sylvatic animal reservoirs and appear to have a low capacity for adaptation to human habitats. These and other factors, together with generally better housing conditions than in regions with recognized Chagas disease, do not provide the crevices in walls and ceilings preferred by the insects.

The Texas Department of Health Services (TDHS) web site lists four tick-borne diseases in the state: Lyme disease, ehrlichiosis, relapsing fever, and Rocky Mountain spotted fever.[1] They state that fewer than 10 cases of ehrlichiosis are reported annually.[1] There were 105 confirmed cases of Lyme disease reported in 2008, yielding an incidence of 0.4 per 100,000 population.[2] TDHS reports that the incidence of Rocky Mountain spotted fever is < 1 per million population per year,[1] while CDC indicates that in 2001-2002 it was < 2 per million.[3] Another tick-borne disease which may be acquired in Texas is relapsing fever. Between 6 and 10 cases of relapsing fever, which in Texas is due to *B. turicatae* and is often associated with spelunking, were reported in that state between 1977 and 2000.[4]

Although the investigators were unable to detect DNA of *R. typhi*, the etiologic agent of murine typhus, in fleas captured from animals in proximity to human cases, fleas are the vector of this rickettsial infection. Other pathogens transmitted by fleas in the United States include *R. felis*, Bartonella, and *Yersinia pestis*.[5] *Murine typhus* occurs in Hawaii and California, in addition to Texas, and is likely underdiagnosed everywhere. One serological study in Texas found a seroprevalence of approximately 13% in asymptomatic children tested.[6] *Murine typhus* is a readily treatable disease, and lack of early diagnosis and treatment may be associated with severe complications.

These seemingly exotic diseases should be on the radar of physicians in the southwestern U.S. Alertness to the potential for emergence of Chagas disease in the United States must also be maintained. ■

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Beware Sandflies While in Europe!

SPECIAL FEATURE

By Stan Deresinski, MD, FACP

Source: Depaquit J, et al. Arthropod-borne viruses transmitted by Phlebotomine sandflies in Europe: a review. *Euro Surv.* 2010; 15(10):pii=19507. http://www.eurosurveillance.org/ViewArticle.aspx?Articled=19507

Synopsis: *Sandfly bites may transmit several viral infections in Europe, including some that result in the development of meningoencephalitis.*

Leishmaniasis, transmitted by sandflies of the genus Phlebotomus, is well-established in the Mediterranean region of Europe, and visceral leishmaniasis has become a particular danger to AIDS patients in that area.[1] Depaquit et al have now examined the current status of viral infections that are transmitted by sandflies in Europe and assessed the prospects for their further spread, as well as the potential for introduction of new viral pathogens into the region.

Sicilian and Naples viruses are bunyaviruses transmitted by *Phelobotomus pattasi*. Sandfly fever, due to these two related viruses, caused outbreaks of febrile illness in troops during the invasion of Italy in 1943 and 1944, and Major Albert Sabin et al identified the etiologic agent.[2] They each cause a self-limited febrile illness, with frequent retro-orbital pain and myalgia. Within Europe, these viruses have been directly, or indirectly, identified in Cyprus and the former Yugoslavia, as well as in Italy. The virus is also present in north Africa, the horn of Africa, the Middle East, and some central Asian republics.

Toscana is a bunyavirus transmitted by *Phlebotomus perniciousus*. It is highly prevalent in central Italy, as its name implies, where the seroprevalence is 22%, but it has also been recognized to be of importance in Portugal, southern France, and Spain. Seroprevalence studies have also detected evidence of infection with this virus in Turkey. The Toscana virus is neurotropic and is a major cause of meningitis and meningoencephalitis from May to October in Italy. Toscana was also identified as the cause of bacterial culture-negative meningitis in six patients (three adults and three children among 308; 5.6%) studied in a metropolitan area of northern Portugal.[3] Toscana virus also produces a non-specific febrile illness, as well as asymptomatic infections.

Depaquit et al suggest that other viruses transmitted by sandflies that have the potential to emerge in Europe include Chandipura vurus, a vesiculovirus and, thus, related to vesicular stomatitis virus. Chandipura virus is a cause of epidemic illness, including encephalitis, in India.[4]

While these infections are of obvious importance to Europeans, they also must be considered as possible causes of febrile illness, including meningoencephalitis in travelers to this region. While undoubtedly vastly underdiagnosed, infections caused by sandfly-associated viral pathogens have been reported in tourists and others. Between 1986 and 1989, 36 Swedish tourists acquired infection with Sicilian virus and one acquired Naples virus infection while visiting Cyprus. Many cases of travel-acquired Toscana virus infection, including meningoencephalitis, have been reported in the literature. ■

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CME Questions

28. Which of the following is the usual cause of Lemierre's syndrome?

a. *Streptococcus pyogenes*

b. *Arcanobacterium hemolyticum*

c. Epstein Barr virus

d. *Fusobacterium necrophorum*

29. Which of the following has been reported to have a pharmacokinetic drug-drug interaction with warfarin?

a. Metronidazole

b. Gentamicin

c. Vancomycin

d. Daptomycin

30. Which of the following diseases results from transmission of the etiologic pathogen by fleas?

a. Rocky Mountain spotted fever

b. Murine typhus

c. Chagas disease

d. Relapsing fever

Answers: 28. (d); 29. (a); 30. (b)

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:

Selective Decontamination and Antibiotic Resistance

UPDATES

By Carol Kemper, MD, FACP

Neonatal Yellow Fever — Vaccine Strain

Source: MMWR. Transmission of Yellow Fever Vaccine Virus through Breast-Feeding — Brazil, 2009. *MMWR*. 2010;59:130-132.

Yellow fever vaccine (YFV) is a live, attenuated viral vaccine that is manufactured using a variety of strains of YF virus. Milder side effects of YFV occur in 2%-10% of people (headache, muscle aches, and fever) within 3 to 9 days of vaccination. More severe and life-threatening YFV-related side effects are rare; the incidence of vaccine-related encephalitis in adults is 0.4 in 100,000 cases, although it is more frequent in infants (0.5-4.0/1,000 cases). It is for this reason that YFV is contraindicated in infants < 6 months of age. In addition, based on a theoretical risk of transmission from mother to infant, YFV is contraindicated in nursing women. Limited data suggest that flaviviruses, such as West Nile Virus, may be transmitted in breast milk during periods of viremia, although the data for YF virus in breast milk is even more limited.

This unusual case report describes a 23-day-old infant who presented with one day of fever and irritability and progressive seizures requiring hospitalization. An initial lumbar puncture was unremarkable, with 1 WBC/mm^3 and a slightly elevated protein level and diminished glucose; all cultures and serologic studies were negative. Despite empiric treatment for meningoencephalitis, the baby continued to do poorly, with progressive seizures (every 10 minutes), requiring intensive care. A repeat CSF examination on the third day of hospitalization showed lymphocytosis, with 128 WBC/mm^3 and a protein level of 106 mg/dL.

Mom reported receiving 17DD YFV 15 days post-partum when she presented for postpartum care. About five days after vaccination, she developed headache and low grade fever for two days. An epidemic of yellow fever was occurring near her home.

Remarkably, YF vaccine virus RNA was detected by PCR in the baby's CSF — which was identical to 17DD vaccine strain received by mom. Serological studies demonstrated YF virus IgM in both sera and CSF, consistent with intrathecal antibody production. The onset of the infant's symptoms coincided within a day or two of the period of mom's presumed vaccine-related viremia. Fortunately, the baby gradually improved and was eventually discharged from hospital with no evident sequelae. Further data on the duration of excretion of vaccine-strain virus in breast milk would be useful.

TB in Haiti

Source: ProMED-mail post, February 5, 2010; www.promedmail.org

Haiti is one of the poorer countries in the world, with the highest per-capita rate of tuberculosis in Latin America and the Caribbean. According to the WHO 2009 Global TB Control Report, 29,333 new cases of tuberculosis were diagnosed in Haiti in 2007 (approximate incidence, 300 cases per 100,000 population). Of these, 53% were sputum smear positive, and 1.8% were multi-drug resistant. An estimated 6,814 people died from TB in Haiti in 2007 alone.

Since 1998, the Ministry of Health stepped up TB control efforts in the country, increasing detection efforts and initiating a DOT program. Attempts at DOT therapy have varied from region to region, but it was used for as many as 91% of cases in 2006, although that number declined somewhat to 70% in 2007. The situation is compounded by the high rate of HIV and TB co-infection, which is as much as 30% of TB cases in some areas.

The recent earthquake not only demolished buildings and infrastructure in Haiti, but also has devastated TB control efforts. The only TB hospital/sanitorium in the country, which housed several hundred of the sickest patients, was critically damaged, and *The New York Times* reports that patients have fled and are now living in tent cities, where TB transmission seems likely. "Hundreds" still report daily to pick up their medications, but the efforts of trained personnel have been diverted, or they have died in the quake. The obvious concern is the potential for increasing drug resistance and widespread infection.

If Only Mr. Oster Knew

Source: Silverman MS, et al. Success of self-administered home fecal transplantation for chronic *Clostridium difficile* infection. *Clin Gastroentero Hepatol*. 2010;

Increasingly, my partner and I are seeing patients with recurrent *Clostridium difficile* enterocolitis (CDI) who are "vancomycin-dependent." Whenever they attempt to taper or stop their orally administered vancomycin, their symptoms recur. We've tried prolonged vancomycin tapers for 6-12 weeks, "terminal" treatment with rifaximine,

intermittent courses of nitazoxanide, and IVIg infusions without success (the latter seemed to work in one person). These patients are incredibly frustrated by their infection and hamstrung by the financial burden, which can cost anywhere from $1,200-$3,000 per month (depending on the dosage and formulation of oral vancomycin).

Fecal transplants have been proposed for such patients, with preliminary reports from Europe and Canada of success in small numbers of patients, but the procedure has not gained acceptance in the United States. A family member as donor is considered best, perhaps because they may share fecal flora.

In this pilot study, donors were excluded if they had a history of hospitalization within the previous three months, a history of malignancy, or a history of bowel disorders, such as irritable or inflammatory bowel disease. Seven patients with recalcitrant CDI agreed to participate; all of them had had repeated episodes of CDI whenever they attempted to taper or stop their vancomycin. Stool cultures for CD were positive in one of the seven (during treatment with oral vanco); studies demonstrated this isolate was consistent with the epidemic hypervirulent NAP1 strain.

The procedure is somewhat more complicated than you would imagine, and begins with formal laboratory screening of the donor, much the same as in transplantation of body parts (including cell counts, chemistries, serologies for HIV, HTLV I/II, RPR, Hepatitis A IgM, Hepatitis Bs antigen, HCV antibody, *H. pylori* Ab, and stool for culture, O&P x 3, and *C. difficile* assay). Stools were prepared in a kitchen blender at home, mixed with 200 mL of saline, and administered at home using a standard enema kit. (An earlier procedure recommended straining the stool, presumably to remove any of the residual peas and carrots, but this adds to the complexity and mess.) The recipient lay down for as long as possible, but if he or she passed the transplant within an hour, the procedure was repeated.

All seven patients recovered without recurrence of their CDI and remained disease-free for 4-14 months. Three patients received antibiotics in the post-transplantation period (two for UTI and one for perioperative prophylaxis for hip replacement), and none developed recurrent symptoms. One patient developed symptoms of intermittent constipation and diarrhea, but colonoscopy and studies for CD were negative. These data lend added support for the idea of home-stool transplants for patients with recalcitrant CDI. One hopes that Mr. Oster would approve.

C. difficile Ubiquitous Following Treatment

Source: Sethi AK, et al. Persistence of skin contamination and environmental shedding of *Clostridium difficile* during and after treatment of *C. difficile* infection. *Infect Control Hosp Epidemiol*. 2010;31:21-26.

CD is fast becoming one of the most significant and stubborn infections in the hospital setting. Questions remain whether asymptomatic patients with positive CD PCR tests require isolation in the hospital, what patient hygiene and environmental measures are necessary and effective, and how long patients require contact isolation following resolution of symptoms. To assess the frequency of persistent skin and environmental colonization, these authors from the Cleveland Clinic prospectively collected stool, skin, and environmental samples from 52 patients with active CDI every 2-3 days during treatment, and weekly following resolution of symptoms, as long as they remained hospitalized or resided at a long-term care facility. Of these, 34 received oral metronidazole and 18 received oral vancomycin; ten (29%) were switched to oral vancomycin for persistent symptoms.

Samples were cultured for CD, and cytotoxic assays and molecular ribotyping using PCR were performed on a subset of isolates. Environmental samples were taken using premoistened cotton gauze pads, applied to the call button, bedrails, telephone, and bedside table, immediately following which, the areas would be cleansed with a bleach solution. At baseline, before initiation of therapy, 100% of stool specimens and approximately 88% of skin specimens were culture-positive for CD. Nearly two-thirds of the isolates were the epidemic NAP 1 strain, and produced binary toxin.

By the time diarrheal symptoms resolved (an average of 4.2 days), stool cultures were negative (on therapy) in 82% of patients, and only two (7%) patients had positive stool cultures at the end of therapy. However, more than half (56%) of patients who had successfully completed treatment and remained asymptomatic had one or more positive stool cultures 1-6 weeks following discontinuation of treatment; six patients (12%) eventually relapsed.

Furthermore, despite the inability to demonstrate CD in stool specimens at the end of therapy, skin contamination remained common at the end of treatment. During the first 1-4 weeks following completion of treatment, 58% of patients had positive skin cultures. And, despite ongoing environmental measures, shedding of CD organisms during this period was common, resulting in positive cultures in 50% of environmental specimens. Persistent skin and environmental colonization was more common in patients who received antibiotics for other indications compared with those who did not (80% vs. 36%, $p = .04$). The investigators also donned gloves, and examined the frequency of glove contamination with CD organisms following skin contact with 18 of the patients (groin, chest and abdomen, and arms and hands). Three to 22 days following resolution of diarrhea, 50% of the gloves were positive.

These data support aggressive environmental measures to combat environmental colonization with CD, for at least 4-6 weeks after resolution of CDI symptoms. Further study should also focus on measures to improve patient hygiene in reducing environmental colonization. Based on these data, contact isolation should be extended for at least six weeks post-CD treatment, either during hospitalization or if the patient requires readmission. ■

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*.

Thiazolidinediones and Risk of Heart Failure

In this issue: FDA is reviewing safety of TZDs; SSRI use with tamoxifen; Metformin smells like fish; FDA Actions.

FDA reviews TZD safety

Thiazolidinediones (TZDs) have been under intense scrutiny in recent years after rosiglitazone (Avandia®) was linked to increased cardiovascular morbidity and mortality in several studies. In recent weeks, *The New York Times* has reported that some FDA staffers are recommending that rosiglitazone be removed from the market. According to the story in the *Times*, a "confidential government report" states that about 500 heart attacks and 300 cases of heart failure per month could be averted if patients were switched from rosiglitazone to pioglitazone (Actos®). Congress has even gotten involved, specifically the Senate's Committee on Finance, which in January issued a 350-page report on rosiglitazone, focusing on GlaxoSmithKline's handling of evidence of possible cardiac risks associated with use of the drug. Now the American Heart Association and the American College of Cardiology have weighed in on the issue suggesting there is insufficient evidence to support the use of pioglitazone over rosiglitazone and that both drugs increase the risk for heart failure and should not be initiated in patients with class III/IV heart failure. They further state that the drugs should not be used with an expectation of benefit with respect to ischemic heart disease events (*Circulation*, published on-line Feb. 23, 2010). Meanwhile, the FDA web site reports that the Agency is reviewing data on rosiglitazone and is planning a public meeting in July 2010 to present all known heart-related safety data on the drug and provide an updated assessment of the risks and benefits of rosiglitazone and the treatment of type 2 diabetes. ■

SSRI use with tamoxifen

The SSRI paroxetine (Paxil®) reduces the effect of tamoxifen in women with breast cancer leading to higher breast cancer mortality according to a new study in the *British Medical Journal*. Concern about SSRIs interfering with the metabolism of tamoxifen was raised last June at the American Society of Clinical Oncology meeting. Tamoxifen is converted from its prodrug to the active metabolite via the cytochrome P450 pathway, specifically CYP2D6. Paroxetine is an exceptionally strong inhibitor of CYP2D6, the strongest inhibitor of all the SSRIs. In the study, Canadian researchers looked at more than 2400 women from Ontario treated with tamoxifen for breast cancer along with a single SSRI. After adjustment for confounders, absolute increases of 25%, 50%, and 75% in the proportion of time on tamoxifen with overlapping use of paroxetine were associated with 24%, 54%, and 91% increases in the risk

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of death from breast cancer, respectively ($P < 0.05$, for each comparison). No such risk was seen with any other antidepressant. The authors conclude that paroxetine use during tamoxifen treatments is associated with an increased risk of death from breast cancer, supporting the hypothesis that paroxetine can reduce or abolish the benefit of tamoxifen in women with breast cancer (*BMJ* 2010;340:c693). The study is important because up to one-quarter of women diagnosed with breast cancer experience a depressive disorder, and antidepressants are commonly used during tamoxifen treatment for not only depression, but also for treatment of hot flashes and other symptoms. It is evident that paroxetine should never be prescribed to women taking tamoxifen for treatment of breast cancer and that preference should be given to antidepressants that show little or no inhibition of CYP2D6. Among the SSRIs, the strongest inhibitors of CYP2D6 besides paroxetine are fluoxetine (Prozac®), duloxetine (Cymbalta®), and to a lesser extent sertraline (Zoloft®). Among non-SSRI antidepressants, bupropion (Wellbutrin®) also is a strong CYP2D6 inhibitor. Drugs that are not inhibitors of the enzyme include citalopram (Celexa®) and venlafaxine (Effexor®). ■

Generic metformin smells fishy?

If your patients tell you their pills smell like fish, they may be taking generic metformin. A letter to the *Annals of Internal Medicine* describes two patients who stopped taking generic metformin because of a fishy taste that caused nausea. The fishy smell is a property of metformin and is well known to pharmacists. Apparently the film-coated extended-release formulations have less smell and may be better tolerated (*Ann Intern Med* 2010;152:267-268). ■

FDA actions

A new FDA warning states that **long-acting beta agonists** (LABAs) should never be used alone in the treatment of asthma in children or adults. The LABAs salmeterol (Serevent®) and formoterol (Foradil®) have been associated with severe worsening of symptoms when used without a controller medication such as an inhaled corticosteroid. Both products will be required to include warnings on the product label that states:

- Use of LABAs is contraindicated without the use of an asthma controller medication;
- LABAs should only be used long term in patients whose asthma cannot be adequately controlled on asthma controller medications;
- LABAs should be used for the shortest duration of time required to achieve control, and should be discontinued once asthma control is achieved;
- Pediatric and adolescent patients who require an LABA in addition to an inhaled corticosteroid should use a combination product containing both an inhaled steroid and a LABA to ensure compliance with both medications.

The FDA has approved **rosuvastatin (Crestor®)** for primary prevention in patients without elevated LDL-cholesterol but who have an elevated C-reactive protein (2 mg/L or higher) and at least one additional cardiovascular risk factors such as low HDL, hypertension, or family history of premature heart disease. The approval was based on the JUPITER trial, which showed a 44% reduced relative risk of cardiovascular events in patients with normal LDL cholesterol but elevated CRP.

The FDA has approved a new **pneumococcal vaccine** for infants and children. Wyeth Pharmaceuticals' **Prevnar 13™** is a 13-valent conjugate vaccine that will replace the currently available 7-valent Prevnar®. It is approved for the prevention of invasive disease caused by 13 different serotypes of *S. pneumoniae*.

The FDA has approved the **monoclonal antibody rituximab (Rituxan®)** to treat certain patients with chronic lymphocytic leukemia (CLL). Rituximab is approved for CLL patients who are starting chemotherapy for the first time and also for those who have not responded to other CLL therapies. It is administered with fludarabine and cyclophosphamide for the treatment of CLL. Rituximab is manufactured by Genentech.

The FDA is initiating a risk-management program for **erythropoiesis-stimulating agents** (ESAs) for the treatment of chemotherapy-related anemia. The drugs, which include epoetin alfa (Procrit®, Epogen®) and darbepoetin alfa (Aranesp®), have been associated with accelerated tumor growth and higher mortality rates in some cancer patients. The Risk Evaluation and Medication Strategy (REMS) requires that patients receive a medication guide on safety issues associated with the drugs and requires training and certification of health care professionals who administer chemotherapy to patients with cancer and counseling of patient regarding the risks of the drugs. The REMS does not currently apply to patients being treated with an ESA for anemia due to other conditions, specifically renal failure. ■