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Chronically Infected Patients with *Trypanosoma cruzi* Parasitemia: Further Support for Screening

ABSTRACT & COMMENTARY

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This article originally appeared in the October 2008 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, Clinical Professor of Medicine, Stanford, Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center. It was peer reviewed by Connie Price, MD, Assistant Professor, University of Colorado School of Medicine.*

Dr. Blackburn reports no financial relationships relevant to this field of study. Dr. Deresinski serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck. Dr. Price reports no financial relationships relevant to this field of study.

Synopsis: *A cohort of patients seropositive for Chagas disease were tested by PCR and hemoculture for patent* Trypanosoma cruzi *infection. Sixty-three percent had parasitemia, confirming the transmission potential in such persons.*

Source: Leiby DA, et al. *Trypanosoma cruzi* parasitemia in US blood donors with serologic evidence of infection. *J Infect Dis.* 2008;198:609-613.

CHAGAS DISEASE (AMERICAN TRYPANOSOMIASIS) IS CAUSED BY INFECTION with the protozoan parasite *Trypanosoma cruzi*, and is spread primarily by triatomine insect vectors ("kissing bugs"). Although vector-borne transmission is primarily confined to rural Latin America, other routes of transmission (eg, blood transfusion) are also possible. Untreated infection seems to persist indefinitely, and the estimated lifetime risk of developing cardiac or other sequelae is about 20%-30%.[1] When combined with increasing migration from Latin America, this long-term infection persistence means there is an increasing risk of blood transfusion-associated *T. cruzi* transmission in non-endemic areas such as the United States; estimates of the number of infected US immigrants range from tens of thousands to more than 100,000.[2] Furthermore, some data indicate that the estimated *T. cruzi*-seropositivity rate among blood donors in Los Angeles rose between 1996 and 1998.[3]

In the United States, the largest contributor to the blood supply (the American Red Cross) began screening blood products for *T. cruzi* in 2007 with

an ELISA-based test that had been FDA approved just months earlier.[4] Recent data suggest one in 4,655 donations to be positive by both ELISA and a confirmatory, second immunologic assay (data were derived from donors in California and Arizona) for *T. cruzi*.[4] Although hundreds of potentially infective blood products are transfused annually, only five US transfusion-associated cases have been documented to date.[5] This discordance raises the question of whether seropositive persons have patent infection and, thus, the potential to transmit *T. cruzi* to others through blood transfusion, or simply evidence of prior infection.

Leiby et al undertook a study that attempted to confirm that *T. cruzi*-seropositive donors do have persistent, patent infection by identifying 147 persons who had previously been identified as seropositive for *T. cruzi*. Fifty-two (35%) of these 147 persons consented to enrollment, and they were asked to provide both epidemiologic data and blood for analysis by *T. cruzi*-polymerase chain reaction (PCR) and hemoculture testing. Although three samples (drawn six months apart) were requested from all participants, only 17 (33%) of the 52 patients in the study submitted more than a single sample for analysis.

Overall, 33 (63%) of the 52 participants had *T. cruzi* detectable in their blood by PCR; three of the PCR-positive samples were also positive by hemoculture. Of the 11 PCR-positive persons who provided more than one blood sample for testing, eight (73%) were positive on multiple occasions, although most only intermittently (ie, not on every sample tested). Epidemiologic data indicated that 80% were from either Mexico or El Salvador, and the median time since immigration to the United States was 18 years. Eighty-six percent of the cohort reported living in substandard housing during their time in Latin America, and 64% reported seeing triatomine insects at some point in their lives.

COMMENTARY

This study supports the notion that untreated patients who are infected with *T. cruzi* probably remain so indefinitely (the patients in the study had immigrated to the United States approximately two decades, on average, before testing), and are at least intermittently parasitemic.

Primarily through the use of PCR technology, Leiby et al confirmed that seropositive patients likely do pose some risk of *T. cruzi* transmission through blood transfusion.

Almost two-thirds of the patients in the study were parasitemic, and it is also possible that the observed parasitemia prevalence was an underestimate, as suboptimal sensitivity could have occurred (depending on true vs. false-negative PCR, and given the difficulties in properly performing hemoculture). Furthermore, most participants provided only one blood specimen (instead of the three requested). Given the intermittent parasitemia that was observed in the PCR-positive patients, the prevalence may have been higher if all patients had provided three samples; during the chronic phase of *T. cruz*i infection, fluctuating, low-level parasitemia is characteristic.

The data in this paper serve to strengthen the scientific basis for the development of screening programs to prevent transmission of Chagas disease in countries like the United States. With the FDA approval of the ELISA screening test in 2006, and subsequent initiation of the

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American Red Cross screening program in 2007, such programs are now beginning to appear. While the majority of the blood supply is now tested for *T. cruzi*, universal screening in the United States is not yet a reality. Donor testing also has the potential to lead to prevention of morbidity and mortality in persons who remain undiagnosed and untreated for *T. cruzi*. These findings are also applicable to the solid organ and bone marrow transplant communities, as transmission risk from *T. cruzi*-seropositive donors exists with these procedures as well. ■

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When Is the Best Time to Obtain Blood Cultures from My Potentially Septic Patient?

ABSTRACT & COMMENTARY

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This article originally appeared in the November 2008 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, Clinical Professor of Medicine, Stanford, Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center. It was peer reviewed by Connie Price, MD, Assistant Professor, University of Colorado School of Medicine.*

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Many physicians have followed the historical practice of ordering blood cultures to be drawn as close as possible to the time of the peak of the febrile episode (fever spike). In the absence of prescient knowledge of this moment, physicians order blood cultures to be drawn at intervals ranging from 30 minutes to 2 hours. A paper by Jaimes et al suggested that many factors, other than fever, such as shaking chills, WBC counts, hypotension, and more were needed to better predict whether a patient was experiencing bacteremia.[3]

For many years, the only data comparing the yield of blood cultures in relationship to the patient's fever was from a study that was presented as an abstract but never officially published. Dr. Richard Thomson performed the study when he was a new microbiology laboratory director in Akron, Ohio, soon after leaving his post-doctoral fellowship at the Mayo Clinic.[6] The results were presented in the abstracts of the 1989 American Society for Microbiology Annual Meeting and included in an American Society for Clinical Pathology Check Sample exercise distributed in 1991.[6] Only a few contemporary microbiologists ever even had a copy of the report. Thomson et al looked at numbers of clinically relevant positive blood cultures obtained during four different time periods relative to a patient's fever spike.

Although there was a trend toward more true positive blood cultures being obtained in the period directly before the fever spike, there were no statistically significant differences among the four time periods.

These data served as the basis for most microbiologists' recommendation to obtain all of the blood cultures as soon as a patient becomes febrile, without any time period between draws. A 1994 publication by Li et al basically corroborated the Thomson results.[4] The 1994 study showed that the yield of clinically significant blood cultures performed during a 24-hour period did not vary whether the blood was obtained all at once or over a period of several time intervals. Without stronger data, physicians have continued to pursue their idiosyncratic blood culture ordering practices. By asking phlebotomists to obtain blood cultures at intervals spanning several hours, unnecessary additional time is spent in the process and the overall cost and inefficiency of procuring blood cultures is increased. And if antibiotic therapy is withheld while blood cultures are being obtained, patient care also suffers.

Dr. Gary Doern set out to perform the definitive study

to answer the question without nuance. He enlisted the aid of six additional medical centers in addition to his own, University of Iowa. Workers collaborating from Geisinger Medical Center (Danville, PA), VA Boston Healthcare System, Johns Hopkins University School of Medicine, Barnes-Jewish Hospital Washington University School of Medicine (St. Louis), University of Texas Health Science Center in San Antonio, TX, and the VA Medical Center (Portland) enrolled 1,436 adult patients with clinically significant episodes of bacteremia and fungemia during 2006.[5] For each patient enrolled, the workers noted the time at which the highest temperatures were recorded in both the 24 hours preceding and those following the time that the first positive blood culture was obtained, as well as the temperature of the patient recorded closest to the time of that blood culture. Clinical relevance was determined by criteria in place at each medical center. The patients were two-thirds male, average age 59 years, and their blood cultures grew a variety of microorganisms, including 54% gram-positive bacteria such as staphylococci (38%, 42% of which were coagulase negative) and *Enterococcus* (10%); 38% gram-negative bacteria such as *Enterobacteriaceae* (> 23%) and *Pseudomonas aeruginosa* (4%); 3% anaerobic bacteria; and 5% yeast.

The highest recorded fevers, determined as the one of the three temperatures that was 0.5°C higher than the other two, occurred during the time of the blood culture draw in 44% of episodes. It was noted that 10%-31% of maximum fevers occurred before or after the blood draw in the remaining patients. In general, none of the results were statistically significantly different from each other.

In addition, no significant associations were found between temperatures of patients and their genders, white blood counts, or even when organism types were evaluated. Unfortunately, not enough cultures yielded fungi to allow reliable statistical analysis. One caveat was that for patients 18-30 years old, the maximum temperature was significantly more likely to occur one to < 24 hours after the first positive blood culture. For other age groups (majority of patients enrolled), there were no differences.

Riedel et al concluded that the best practices for collecting blood cultures are to obtain enough blood volume (recent studies summarized in the ASM Cumitech and the CLSI guideline on blood cultures have suggested from 40-60 mL), to obtain suitable numbers of separate blood cultures (at least two), and to use stringent aseptic technique to avoid contamination. ■

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PHARMACOLOGY WATCH

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JUPITER: C-reactive Protein a Marker for CV Events?

In this issue: The JUPITER trial causes a stir; ACP practice guideline for antidepressant use; testosterone for low libido; continued shortage of Hib vaccine; FDA Actions.

The JUPITER trial causes a stir

Elevated high-sensitivity C-reactive protein (CRP) may help identify otherwise healthy patients with normal cholesterol levels who will benefit from statin therapy, according to the JUPITER trial published in November. Researchers randomized nearly 18,000 healthy men and women with normal cholesterol levels (LDL < 130 mg/dL) with CRP levels of 2.0 mg/L or greater to rosuvastatin (Crestor) 20 mg daily or placebo. The combined primary endpoint was myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular cause. The trial was stopped early at 1.9 years when the rate of the primary endpoint was found to be 0.77 per 100 person-years in the treatment group vs 1.36 per 100 person-years in the placebo (HR 0.56; 95% CI, 0.46-0.69; $P < 0.00001$). Overall, the rate of events was low in both groups: 142 of 8901 in the treatment group vs 251 of 8901 in the placebo group. The individual endpoints of myocardial infarction, stroke, and revascularization or unstable angina were all reduced by approximately 50% in the rosuvastatin group, LDL cholesterol levels were decreased by 50%, and CRP levels were decreased 37%. There was not a significant increase in myopathy or cancer in the treatment group, but there was a higher incidence of physician-reported diabetes. The authors conclude that in apparently healthy persons without hyperlipidemia but with elevated CRPs, rosuvastatin significantly reduced the incidence of major cardiovascular events (*N Engl J Med* 2008;359:2195-2207).

In an accompanying editorial, Mark Hlatky, MD, Stanford University School of Medicine, points out that although the relative risk reductions in the JUPITER trial were clearly significant, the absolute difference in risk was less impressive with 120 participants treated for 1.9 years to prevent one event. It is also difficult to know the role of CRP in risk stratification since patients with normal CRP levels were not treated and it is possible that lowering cholesterol with statins may benefit even those with low CRP levels. CRP may have a role in deciding whether to treat patients with intermediate risk, but it may be too early to use it to recommend treatment for those at low risk. Hlatky writes that "guidelines for primary prevention will surely be reassessed on the basis of the JUPITER results, but the appropriate size of the orbit of statin therapy depends on the balance between the benefits of treatment and long-term safety and cost" (*N Engl J Med* 2008;359:2280-2282). It is safe to say that JUPITER has been the subject of many lively discussions in hospital lunchrooms

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

across the country. Whether the benefit of rosuvastatin can be generalized to all statins, whether CRP should be a standard part of yearly blood panels for adults patients, and whether everyone with an elevated CRP should be offered treatment with a statin are all questions that are being hotly debated and will need further evaluation.

ACP treatment guideline for antidepressants

The American College of Physicians has issued a practice guideline for the use of antidepressants to treat depressive disorders. The guideline encompasses the use of newer "second-generation antidepressants," including the SSRIs: fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), escitalopram (Lexapro), and fluvoxamine (Luvox). Also included were the SNRIs venlafaxine (Effexor), and duloxetine (Cymbalta), as well as other drugs such as mirtazapine (Remeron), bupropion (Wellbutrin), nefazodone, and trazadone. After reviewing 203 clinical trials, the guideline group concluded that there were no significant differences between the drugs with regard to efficacy. The guideline group recommends that second-generation antidepressants should be selected on the basis of adverse effect profiles, cost, and patient preference. They further recommend that clinicians should assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis beginning within 1-2 weeks of initiation of therapy and that treatment should be modified if the patient does not have an adequate response to pharmacotherapy within 6-8 weeks. Finally, they recommend that clinicians continue treatment for 4-9 months after a satisfactory response in patients with a first episode of major depressive disorder. For patients with history of depression, a longer duration of therapy may be beneficial (*Ann Intern Med* 2008;149:725-733).

Testosterone for low libido: Questions remain

Low sexual desire is commonly reported by postmenopausal women. A new study suggests that testosterone replacement may be of benefit. Researchers randomized 814 postmenopausal women with hypoactive sexual desire or disorder to testosterone patches delivering 150 or 300 mg of testosterone per day or placebo. The primary endpoint was change from baseline to week 24 in the 4-week frequency of satisfying sexual episodes. Safety outcomes were followed out to one year. At 24 weeks the primary endpoint was significantly greater in the group receiving 300 mg of testosterone per day than placebo (increase in sexually satisfied episodes of 2.1 vs 0.7, $P < 0.001$) but not in the group receiving 150 mg per day. Both doses of testosterone were associated with significant increases in desire and decreases in distress. The rate of androgenic side effects including unwanted hair growth was higher in the group receiving 300 mg per day. Breast cancer was diagnosed in 4 women who received testosterone vs none in the placebo group. The authors conclude that a testosterone patch delivering 300 mg per day results in modest but meaningful improvement in sexual function although the long-term effects of testosterone including effects on the breasts remain uncertain (*N Engl J Med* 2008;359:2005-2017). This study confirms previous reports that testosterone has a positive effect on sexuality in women. The rate of breast cancer, although not reaching statistical significance in this study, raises concern.

Continued shortage for Hib vaccine

The continued shortage of the *Haemophilus influenza* type b (Hib) vaccine has not led to an increase in *Haemophilus* infections according to the *MMWR*. It has been a year since the CDC recommended deferring the fourth dose of the Hib vaccine in healthy children (at 12-15 months of age) because of a shortage due to contamination concerns in the manufacturing process. Merck & Co. now reports that mid-2009 is a realistic date for normal production. The CDC has undertaken national surveillance for Hib infections including 748 cases in children < 5 years old. Of these, only 6% were clearly identified as serotype b (the most invasive strain of *Haemophilus*), although serotyping information was missing in nearly 40% of cases. The CDC is concerned because antibody levels fall 12 months after vaccination in children. In the U.K., where the fourth booster was not initially recommended, Hib infections rebounded after 12-15 months. CDC is recommending vigilance on the part of pediatricians and also is emphasizing that state and hospital labs should perform serotyping on all *Haemophilus* infections.

FDA Actions

The FDA has approved fesoterodine fumarate for the treatment of overactive bladder. The drug relaxes smooth muscle of the bladder reducing urinary frequency, urge to urinate, and sudden urinary incontinence. Fesoterodine fumarate will be available in 4 mg and 8 mg strengths for use once daily. The drug is manufactured by Schwartz Pharma and will be marketed as Toviaz . ■