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Ivermectin for Head Lice

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

Professor of Pediatrics, Tufts University School of Medicine, and Chief Academic Officer, Baystate Medical Center, Springfield, MA

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

Synopsis: *For difficult-to-treat head lice infestation, oral ivermectin had superior efficacy to topical 0.5% malathion lotion, with no significant differences in adverse events.*

Source: Chosidow O, et al. Oral ivermectin versus malathion lotion for difficult-to-treat head lice. *N Engl J Med*. 2010;362:896-905.

A multicenter, cluster (household)-randomized, double-blind, double-dummy, controlled trial was conducted in 812 patients (≥ 15 kg, and ≥ 2 years of age) from 376 households at seven study centers in the United Kingdom, Ireland, France, and Israel. Patients with head lice (determined by the presence of live lice with a standardized fine-toothed combing procedure) were randomized by household to prevent contamination between treatment groups, to receive on days 1 and 8 either oral ivermectin (400 mcg per kilogram, in 3-mg tablets) or 0.5% alcoholic malathion lotion, administered by staff on site. A double-dummy technique was used (placebo tablet or placebo lotion) to ensure that treatment remained blinded. Lotion was applied until all hair and scalp were thoroughly moistened, and allowed to dry naturally with instructions to leave the lotion in place for 10-12 hours and then to wash the hair with mild shampoo, which was provided. No other pediculicidal treatments were permitted. The primary endpoint was absence of live head lice on day 15, determined by repeat combing procedure. Patients with persistent head lice infestation on day 15 were switched to the other treatment at the same dose.

The ivermectin group consisted of 398 patients in 185 households, and the malathion group consisted of 414 patients in 191 households. The two groups were comparable with regard to household characteristics. The study population was predominantly female (86.9%), with a median age of 10 years (interquartile range, 7 to 14 years) and median weight (± SD) of 40 ± 22 kg. Ap-

VOLUME 29 • NUMBER 8 • MAY 2010 • PAGES 85-96

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proximately 15% of households had more than three family members with head lice infestation. On day 15, 35 patients (4.3%) were lost to follow-up, and 53 patients (6.5%) did not complete the study.

In the intention-to-treat population, 95.2% of patients receiving ivermectin were free of lice on day 15, compared to 85.0% of patients receiving malathion (absolute difference of 10.2%; 95% CI, 4.6-15.7%; $p < 0.001$). In the per-protocol population, 97.1% of patients in the ivermectin group were free of lice on day 15, compared to 89.8% of patients receiving malathion (absolute difference of 7.3%; 95% CI, 2.8-11.8%; $p = 0.002$). There were no significant differences in the frequency of adverse events between the two treatment groups.

■ COMMENTARY

Head lice infest more than 100 million individuals worldwide each year, with children 3 to 10 years of age most likely to be affected. Emerging pyrethroid resistance has led to the reintroduction of malathion as an effective alternative treatment. This trial showed the noninferiority and superiority of oral ivermectin (400 mcg per kilogram) to 0.5% malathion lotion, each given on days 1 and 8, for eradicating head lice infestation. Important principles of head-lice treatments include a second dose no earlier than 7 days and no more than 11 days after the first dose in order to kill head lice that hatch from eggs surviving the first treatment, and concomitant treatment of all infested family members.

In this study, more households were free of lice after oral ivermectin than after malathion lotion, suggesting that ivermectin might be more effective in controlling infestations among close contacts, such as in the classroom setting. Ivermectin has been used to treat onchocerciasis since 1987, with recent evidence of genetic selection for ivermectin-resistant *Onchocerca volvulus*. Concern about development of resistant head lice suggests that ivermectin should be considered only for patients with persistent head-lice infestation after failure of topical treatment. Ivermectin is not recommended for children < 15 kg, pregnant women, or mothers who are breast-feeding. ■

Infectious Disease Alert, ISSN 0739-7348, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305. The statement of ownership will appear in the November issue.

MANAGING EDITOR: Leslie Hamlin

ASSOCIATE PUBLISHER: Russ Underwood

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DIRECTOR of MARKETING:
Schandale Kornegay
GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Infectious Disease Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $21.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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Etiology of Sepsis in Patients Admitted from the ED

ABSTRACT AND COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA
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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: *In a prospective, observational study, > 50% of patients identified and treated for severe sepsis in the emergency department (ED) had negative cultures; 18% of patients had a noninfectious diagnosis that mimicked sepsis.*

Source: Heffner AC, et al. Etiology of illness in patients with severe sepsis admitted to the hospital from the emergency department. *Clin Infect Dis*. 2010;50:814-820.

A prospective, observational study of patients 18 years of age and older treated with goal-directed therapy of sepsis in the ED was conducted at a large county hospital in North Carolina. Inclusion criteria included two or more criteria for systemic inflammation and evidence of hypoperfusion. Clinical data were prospectively collected for two years. Blinded observers used standardized criteria to determine the final cause of hospitalization.

A total of 211 patients were enrolled in the study. Of those, 95 (45%) had positive culture results and 116 (55%) had negative cultures. Overall mortality was 19%. Patients with positive cultures were more likely to have active malignancy, have a vascular line, be a resident of a nursing home, have UTI as a primary source, and were less likely to have a pulmonary source.

Of the patients negative by culture, 51 (44%) had clinical evidence of infections, with pneumonia being the most common in 38 patients. Nine patients had atypical infections, including *C. difficile* disease (5), cryptococcosis (2), TB (1), and viral encephalitis (1). Thirty-seven patients (32%) had noninfectious mimics. The most common diagnoses included inflammatory colitis, hypovolemia, medication effect, adrenal insufficiency, acute MI, pulmonary edema, pancreatitis, diabetic ketoacidosis, and small bowel obstruction. In 19 cases (16%), the cause of the sepsis picture on presentation was indeterminate.

■ **COMMENTARY**

While this was a relatively small single-center study, I felt it was an interesting and important paper. I frequently lead the morning report with the medicine house staff at our own county hospital in San Jose, CA, and enjoy being challenged by the diagnostic possibilities present in patients who present to our ED acutely ill and require admission to the hospital. The finding of noninfectious causes of a surprisingly large number of cases of patients admitted to the hospital for "sepsis" is an important reminder to keep a broad differential diagnosis in mind in caring for such critically ill patients. This further reinforces the importance of infectious diseases clinicians remaining skilled as internists (or pediatricians) as they approach the management of these complicated patients.

As a side note, the second author on this paper, Dr. Jim Horton, is Chief of the ID Division at Carolinas Medical Center. Jim and I trained together in New Orleans many years ago. He is a great clinician and one of the finest individuals I've ever known. He invited me to give medicine grand rounds at his hospital in 2008, where I had an opportunity to meet his colleagues and tour the wards. It was apparent that CMC is a wonderful hospital that provides outstanding care to the people of Charlotte. ■

Chlorhexidine-Alcohol Is Superior to Povidone-Iodine for Pre-op Prep

ABSTRACT & COMMENTARY

By Robert Muder, MD

Hospital Epidemiologist, Pittsburgh VA Medical Center

Dr. Muder does research for Aventis and Pharmacia.

Synopsis: *In a randomized, multicenter trial involving patients undergoing clean-contaminated surgery, use of chlorhexidine for pre-operative skin preparation was associated with a 40% decrease in surgical-site infection, compared with use of povidone iodine.*

Source: Darouiche RO, et al. Chlorhexidine-alcohol versus povidone-ioding for surgical-site antisepsis. *N Engl J Med*. 2010; 362:18-26.

The superiority of a particular surgical-site preparation regimen in preventing surgical-site infection (SSI) has not been determined. Darouiche et al conducted a randomized, multicenter trial of pre-operative chlorhexidine-alcohol vs. povidone-iodine in patients undergoing clean-contaminated surgery. The study was conducted at six university-affiliated hospitals in the United States; patients were stratified by institution. All patients received pre-operative antibiotics within one hour of the start of surgery. A total of 849 patients, 409 randomized to chlorhexidine-alcohol and 440 randomized to povidone-iodine, qualified for the intention-to-treat analysis. The patient groups were well matched by age, type of procedure, duration of surgery, and underlying illness.

The incidence of SSI in the 30 days following surgery was 9.5% in the chlorhexidine-alcohol group, compared with 16.1% in the povidone-iodine group ($p = .004$, relative risk 0.59). Superficial incisional infections were significantly less frequent in the chlorhexidine-alcohol group (4.2%) than in the povidone-iodine group (8.6%), as were deep incisional infections (1% vs. 3%). There was no difference in the number of organ-space infections. The organisms causing SSI were similar in both study arms. The rate of adverse events was similar in both groups, and the rate of adverse drug-related events, primarily mild-to-moderate skin irritation, was 0.7% in each group. The authors estimate that 17 patients would need to be treated with chlorhexidine-alcohol to prevent one SSI.

■ **COMMENTARY**

Povidone-iodine has been a standard pre-operative skin preparation for decades. To my knowledge, there are no controlled trials comparing any two agents for comparative efficacy in preventing SSIs. In this meticulously conducted randomized trial, Darouiche et al demonstrate conclusively that chlorhexidine-alcohol is superior to povidone-iodine for pre-operative skin preparation. In contrast to povidone-iodine, chlorhexidine-alcohol has both a rapid onset of bactericidal action and has prolonged antibacterial action on the skin's surface. Since the skin is a significant source of the organisms causing SSI, these properties may explain the superiority of chlorhexidine alcohol. It's notable that the incidence of organ-space infection was similar in both study arms. Since nearly 70% of procedures were abdominal operations in both groups, it's likely that most organ-space infections were due to contamination of the field by enteric

flora, which would not be affected by skin antisepsis. Although use of alcohol in the operating room is a potential fire hazard, no fires occurred in the trial.

The CDC estimates that 300,000 SSIs occur in the United States each year. Adoption of chlorhexidine-alcohol as the standard of practice for surgical-site antisepsis is an easy way to implement action that has the potential for enormous benefit. ■

Pneumococcal Conjugate Vaccine Is Effective in HIV-infected Patients

ABSTRACT AND COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *In this study, 496 adults and adolescents (88% of whom were HIV-infected) who had recovered from invasive pneumococcal disease were administered a seven-valent pneumococcal conjugate vaccine (PCV7) in a double-blind, randomized, placebo-controlled trial. All subsequent episodes of pneumococcal disease occurred in HIV-infected patients. Twenty-four episodes of pneumococcal disease were observed with vaccine serotypes or serotype 6A. Of these, five occurred in the vaccine group and 19 in the placebo group, yielding a vaccine efficacy rate of 74%.*

Source: French N, et al. A trial of a 7-valent pneumococcal conjugate vaccine in HIV-infected adults. *N Engl J Med*. 2010;362: 812-822.

In this study, 496 adults and adolescents in Malawi, with history of recent documented invasive pneumococcal disease, were administered PCV7 or placebo in a randomized, double-blind, controlled trial, and were followed for 798 person-years. Eighty-eight percent of patients were HIV-infected. During follow-up, 67 new episodes of pneumococcal disease were seen in 52 patients, all of whom were HIV-infected. In 24 patients, 19 episodes of disease due to vaccine serotypes and five episodes due to serotype 6A were observed, yielding a vaccine efficacy of 74%. Overall mortality included 73 deaths due to all causes in the placebo group vs. 63 deaths in the vaccine group. PCV7 was well tolerated, with only minor vaccine-associated adverse events seen.

■ **COMMENTARY**

The risk of invasive pneumococcal disease is greatly elevated in HIV-infected patients, and may be as high as 30-100 times as high as in age-matched controls. The 23-valent pneumococcal polysaccharide vaccine has limited efficacy in HIV-infected patients, particularly in those with lower CD4+ lymphocyte counts, and its use is not recommended in Africa. PCV7 has been widely used in children in the developed world since 2000, and has markedly reduced the incidence of invasive pneumococcal disease in children and in adults (the latter presumably related to herd immunity). Since recurrent invasive pneumococcal disease is common in HIV-infected patients, a smaller sample size to demonstrate efficacy was needed when evaluating vaccine efficacy in patients who had already had one episode of invasive pneumococcal disease.

The demonstrated efficacy of PCV7 in HIV-infected patients in this trial is good news. The patients evaluated in this trial had fairly advanced disease, with a median CD4+ count of 212-214/uL. While PCV7 had good efficacy vs. vaccine serotypes (and serotype 6A, since PCV7 was shown in earlier studies to provide cross-protection against this serotype), it had no effect vs. non-vaccine serotypes. Recognition of invasive disease in immunocompetent children due to nonvaccine serotypes has increased over the last few years. A new 13-valent PCV is expected to receive FDA approval shortly, and will provide protection against many of these serotypes, including serotype 19A, which often displays antibiotic resistance.

Parenthetically, Malawi is an interesting place. It is very poor in natural resources. It is not part of the PEPFAR program. However, some NGOs are doing excellent work there treating both TB and HIV. One of the best of these is an organization known as GAIA (Global AIDS Interfaith Alliance, www.thegaia.org), headquartered here in San Francisco, and founded by the Rt. Rev. Bill Rankin, retired Dean of the Episcopal Church Divinity School of the Pacific seminary in Berkeley. In addition to providing antiretroviral therapy and TB treatment, a big part of their work is empowering women in villages in Malawi, including providing microloans so they can start small businesses. ■

Antiretroviral Initiation During or Following Treatment of TB

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *In this study, 642 patients coinfected with HIV and TB were studied in an open-label, randomized, controlled trial in which patients were assigned to initiating antiretroviral therapy (HAART) early, later during the course of TB treatment, or after the completion of TB*

treatment. Initiation of antiretroviral therapy during TB treatment improved survival.

Source: Abdool Karim SS, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. 2010; 362:697-706.

An open-label, randomized, controlled trial of early vs. delayed initiation of HAART was conducted in 642 patients with active TB and HIV infection in Durban, South Africa. Patients were randomized 1:1:1 to one of three study groups. In the "early integrated therapy" group, ARV therapy (consisting of ddI, 3TC, and efavirenz) was initiated within four weeks after starting TB treatment. In the "late integrated therapy" group, HAART was initiated within four weeks after the completion of the intensive phase of TB treatment (initial two months of INH, rifampin, PZA, and EMB in patients with first episode TB and three months of RIPE plus SM for two months in patients with recurrent TB). In the "sequential therapy" group, HAART was initiated within four weeks after completion of the 6-8 month entire course of TB treatment.

The primary endpoint of the study was death. There were 25 deaths in the integrated therapy group (rate 5.4 per 100 person-years) vs. 27 deaths in the sequential therapy group (rate 12.1 per 100 person-years).

Although not quite reaching statistical significance, the combined integrated therapy groups were more likely to be cured, or to successfully complete TB therapy, and were less likely to require interruption of TB treatment. Integrated therapy patients were significantly more likely to achieve HIV RNA < 400 copies/mL at 12 months following randomization than were sequential therapy patients (90% vs. 78%), and to have a better CD4+ lymphocyte count incremental increase (207 vs. 84 cells/uL).

■ **COMMENTARY**

This is an important study which is likely to alter clinical practice in both the developed and developing worlds. Current practice of many TB clinics is to defer antiretroviral therapy in patients with HIV/TB coinfection unless CD4+ count is < 200 cells/uL.

This study provides strong clinical support for not delaying HAART while treating TB. However, one of the limitations of this study is that the somewhat unusual HAART regimen studied (ddI, 3TC, and EFV) does not result in significant drug interactions with the TB medications used. From a practical standpoint, it is most problematic to use ritonavir-boosted protease inhibitor (PI) regimens in patients receiving rifampin. Rifampin is a potent inducer of the cytochrome P450 CyP 3A/4 isoforms, and results in marked reduction of PI serum levels, even in the presence of ritonavir boosting. Rifabutin in significantly reduced doses can be substituted for rifampin but, in combination with ritonavir, it may cause ocular toxicity. Also, concern has recently been raised about frequent subtherapeutic levels of rifabutin seen when used in combination with ARVs.

The bottom line from this study, from my perspective, is that EFV-containing HAART regimens can and should be started early during TB treatment in patients whose baseline HIV genotypes do not show primary NNRTI resistance. However, additional studies should be done to better define optimal dosing of TB regimens and timing of initiation of HAART, with respect to TB treatment in patients who require ritonavir-boosted PI regimens. Although I am not aware of published data to support this practice, another attractive treatment option in patients on TB treatment that require non-EFV-containing HAART regimens would be a combination of NRTIs, plus the integrase inhibitor raltegravir due to the paucity of drug interactions associated with raltegravir since it is not metabolized by the cytochrome P450 system. ■

Changing Pneumococcal Serotypes Causing Disease

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

Professor of Pediatrics, Tufts University School of Medicine, and Chief Academic Officer, Baystate Medical Center, Springfield, MA

Synopsis: *An increase in non-vaccine pneumococcal serotypes, especially serotype 19A, accompanied by decreased antibiotic susceptibility, was observed in cases of invasive pneumococcal disease in Massachusetts from 2001 to 2007. The new PCV13 vaccine provides protection against at least 44% of non-PCV7 serotypes causing invasive pneumococcal disease.*

Source: Hsu KK, et al. Changing serotypes causing childhood invasive pneumococcal disease; Massachusetts, 2001-2007. *Pediatr Infect Dis J*. 2010;29:289-293.

Clinical laboratories in Massachusetts are required to submit to the state all isolates of *Streptococcus pneumoniae* cultured from blood, cerebrospinal fluid, or other normally sterile body fluids from children < 18 years of age. Pneumococcal isolates were serotyped using the Quellung reaction, and antibiotic susceptibility to penicillin, ceftriaxone, and azithromycin were determined by E-test and minimum inhibitory concentration interpretations based on the Clinical and Laboratory Standards Institute (CLSI) 2007 guidelines.

A total of 569 cases of invasive pneumococcal disease

were identified from October 2001 through September 2007. There were no significant changes in the distribution of invasive pneumococcal disease, hospitalization rates, or mortality rates during the study period. Among 433 (74%) isolates available for serotyping, 366 (85%) were caused by non-PCV7 serotypes and 67 (15%) were caused by PCV7 serotypes, which occurred primarily from 2001 to 2005. The most common serotypes identified during the six years were 19A (20%), 7F (12%), 6A (7%), 22F (6%), 33F (6%), 15B/C (5%), and 3 (5%).

PCV7 serotypes accounted for 25% of isolates in 2001 and 2002, and none of the isolates in 2006 and 2007. During the six years of the study, there were no significant changes in the incidence of invasive pneumococcal disease, which averaged 6.5 cases/100,000 children < 18 years of age. There was a decline of PCV7 serotype disease from 1.0 cases/100,000 in 2001-2002 to 0 cases in 2006-2007. Non-PCV7 serotype disease progressively increased from 3.0 cases/100,000 in 2001-2002 to 5.3 cases/100,000 in 2005-2006.

The highest age-specific rates of invasive pneumococcal disease were among children < 1 year of age. Black and Hispanic children continued to be a higher risk for invasive pneumococcal disease than white children. This difference was not attributable to unequal vaccination coverage. During this period, an increasing proportion of invasive pneumococcal disease was reported among recipients with at least two doses of PCV7 (39% in 2001-2002 vs. 63% in 2006-2007). Statistically significant shifts were noted only for serotype 19A, with steadily increasing incidence from 0.4 cases/100,000 (95% CI, 0.1-0.7) in 2001-2002, to 1.4 cases/100,000 (95% CI, 0.8-2.0) in 2003-2004, to 1.7 cases/100,000 (95% CI, 1.0-2.3) in 2006-2007.

Using a penicillin breakpoint of > 0.06 mcg/mL to define non-susceptible isolates, penicillin nonsusceptible isolates constituted 39% of isolates in 2001-2002, 28% of isolates in 2002-2003, and approximately half of isolates in 2003-2007 ($p = 0.03$). Using a ceftriaxone breakpoint of > 0.5 mcg/mL to define non-susceptible (intermediate and resistance) isolates, ceftriaxone non-susceptible isolates constituted < 10% of isolates in 2001-2002, compared to almost 20% of isolates in 2005-2007 ($p = 0.01$).

■ COMMENTARY

The heptavalent pneumococcal vaccine (PCV7) was introduced in the United States in February 2000, and included serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F linked to the protein carrier CRM197, a nontoxic mutant of diphtheria toxin. This vaccine was recommended in a three-dose primary series for all infants beginning at two months of age, followed by a booster dose at 12-15 months of age. The study shows a decrease in the rate of invasive disease caused by PCV7 serotypes, accompanied by an increase in the rate of invasive disease caused by non-PCV7 serotypes, resulting in stable incidence of invasive pneumococcal disease over this period.

During the six years of the study, there was an increase in ceftriaxone non-susceptibility to 22% in 2006-2007. The increase in ceftriaxone non-susceptibility was not observed to be associated with significant changes in hospitalization or mortality rates.

On February 24, 2010, a 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar 13) was licensed by the FDA for use among children six weeks-71 months of age. PCV13 succeeds PCV7, and includes the additional serotypes 1, 3, 5, 6A, 7F, and 19A conjugated to the same carrier protein. These additional six serotypes accounted for at least 44% of the non-PCV7 serotypes causing invasive pneumococcal disease in Massachusetts during 2001-2007. This underscores the significant benefit that is expected with the new 13-valent vaccine. As PCV13 becomes available in providers' offices, unvaccinated children, and children incompletely vaccinated with PCV7, should complete the immunization series with PCV13.

The results of this study demonstrate the continued need for surveillance of pneumococcal disease — incidence, serotypes, and antimicrobial susceptibilities — to guide vaccine development and also clinical management including presumptive antibiotic choices in critically ill children. ■

Increasing Herpes Zoster Among Veterans: An Unintended Consequence of the VZV Vaccine?

ABSTRACT & COMMENTARY

By Robert Muder, MD

Synopsis: *Between 2000 and 2007, the annual incidence of herpes zoster among veterans increased from 3.10 / 1000 to 5.22 / 1000. The increase was confined to veterans over 40 years of age. The authors postulate that lack of exposure to varicella, due to widespread immunization of children with VZV vaccine, may be a contributing factor.*

Source: Rimland D et al. Increasing Incidence of herpes zoster among veterans. *Clin Infect Dis*. 2010;20:1000-1005.

The Veterans Health Administration maintains a national automated information system (DSS) that contains hospital discharge and outpatient data for the entire system. It

was fully operational in 1999. Investigators at the Atlanta VA Medical center identified unique patient encounters for herpes zoster during the period of October 1999 through September 2007 (federal fiscal years 2000-2007). Inpatient and outpatient data were assessed, as were patient age and sex. Both primary and secondary diagnoses of herpes zoster were included. An individual patient could be included only once per year so that multiple visits for a single episode would not be counted.

The investigators found a steady increase in incidence of herpes zoster from 3.10 episodes per 1,000 in FY 2000 to 5.22 per 1,000 in FY 2007, a 68% increase. The increase was seen only among veterans older than 40 years. They then performed a validation study by reviewing all patients diagnosed with herpes zoster at the Atlanta VA for the same period. All cases were reviewed by an experienced infectious disease specialist, who found that 56% of cases represented an acute episode of herpes zoster. The majority of the remainder was a remote episode or a diagnosis of postherpetic neuralgia. The increase in confirmed zoster diagnoses over the period was 75.6%. The increase was significant even when patients with HIV infection, malignancy, and chemotherapy were excluded.

■ COMMENTARY

This study shows a rather striking increase in varicella zoster over a seven-year period among veterans. This investigation was possible because the Veterans Health Administration maintains a national automated information system that draws data from the VA's nationwide system of computerized medical records. Although the validation study in Atlanta found that only 56% of diagnoses of varicella zoster represented a new episode, the increase in the rate of zoster was similar to the national data. Because the VA medical record system is standardized, the Atlanta findings are highly likely to be representative of the system as a whole. One potential weakness is that patients use care outside of the VA as well, and some episodes of varicella zoster would not be captured. However, it seems unlikely that the change in rates was due to a large shift of veterans with zoster into the VA healthcare system. There is no evidence that the prevalence of diseases associated with immune dysfunction, such as HIV, is increasing among veterans.

This reason for this apparent increase in varicella zoster in not clear. The authors note that varicella immunization was implemented in the United States in 1995. Exposure of adults to cases of varicella elicits an immune response in those with latent varicella zoster infection, and this may provide some degree of protection against the later development of zoster. Some investigators have, in fact, predicted an increase in herpes zoster following the implementation of mass varicella immunization.[1]

It should be noted that other studies of the incidence of zoster over time have shown inconsistent results.[2] It would be quite useful to confirm an increase in varicella zoster among the general population. Zoster causes considerable morbidity, particularly among the elderly. A zoster vaccine (Zostavax, Merck) is available and recommended for the prevention of herpes zoster in those 60 and older.[3] The vaccine significantly decreases the incidence of zoster and postherpetic neuralgia, a particularly unpleasant sequela. If the rate of varicella zoster is indeed increasing, more widespread administration of the zoster vaccine is warranted. ■

References

1. Thomas SL et al. Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study. *Lancet*. 2002;360:678-682.
2. Reynolds MA et al. The impact of the varicella vaccination program on herpes zoster epidemiology in the United States. *J Infect Dis*. 2008;197:S197-S227.
3. Harpaz R et al. Prevention of herpes zoster: Recommendations of the Advisory Committee of Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008;56(RR-5):1-30.

Invasive Fungal Infections in Transplant Recipients

ABSTRACT & COMMENTARY

By Ellen Jo Baron, PhD, D(ABMM)

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Interim Director, Clinical Virology Laboratory,
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Dr. Baron reports no financial relationships relevant to this field of study.

Synopsis: *The Transplant-Associated Infection Surveillance Network (TRANSNET) conducted a multicenter, prospective, observational study of invasive fungal infections involving U.S. sites performing hematopoietic stem cell transplant (22 sites) and solid organ transplant procedures (15 sites) during five years from 2001-2006. Aspergillus was the most common agent in stem-cell transplant recipients, and Candida was most common among solid-organ recipients. The predominant species of Candida was glabrata among stem-cell recipients and albicans in the solid-organ group. Surprisingly, although the overall incidence was low (< 4%), the incidence of invasive fungal infections in both transplant recipient populations increased slightly over the time period being surveyed.*

Sources: Kontoyiannis DP, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: Overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. *Clin Infect Dis.* 2010;50:1091-1100; Pappas P, et al. Invasive fungal infections among organ transplant recipients: Results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Clin Infect Dis*. 2010;50:1101-1111.

There are approximately 16,000 hematopoietic stem cell transplants (HSCT) and > 29.000 solid-organ transplants performed in the United States each year. Invasive fungal infections are among the most serious sequelae faced by these patients. Numerous studies have been published on cumulative experiences from individual centers, such as the recent 10-year Stanford experience with yeast infections in heart and lung transplant recipients,[1] as well as an interesting study evaluating invasive fungal infections (IFI) in allogeneic HSCT recipients in St. Petersburg, Russia, carried out over approximately the same time frame as the U.S. study.[2] But such single-site experiences should not be extrapolated, since results will vary based on types of procedures, institutional practices, and environmental exposures. In fact, the role of the external environment may be more important than appreciated. A study that measured the relative numbers of *Aspergillus* spores (using molecular methods) at various locations within a pediatric hospital, during a remodeling project featuring internal construction, showed that concentrations of spores in the environment outside the hospital and heavy foot traffic in the carpeted lobby were the factors most responsible for increased *Aspergillus* spore concentrations detection inside the hospital.[3]

The data presented in the two companion papers from the TRANSNET group represent the first multicenter, longitudinal study investigating all of the invasive fungal infections seen in a large population of transplant recipients over a geographically diverse area. The results of these investigations should be useful for developing criteria for risk stratification and to inform prospective policy development regarding prevention and therapy of IFI in transplant patients. The HSCT study involved 16,200 recipients from 22 institutions over the five-year study period. Only 9% were pediatric patients; the average age was 50, and patients were primarily white (82%) and male (59%). Most recipients received autologous cells (59%), with the rest receiving matched-related allogeneic (22%), allogeneic unrelated (16%), and mismatched related (3%). Among approximately 16,500 solid-organ recipients followed in the second study, there were 39% liver, 24% renal, 20% lung, 9% pancreas, 75 heart, and < 2% small bowel transplants, some involving simultaneous transplantation of more than one organ system. Patient characteristics were very similar to those of the HSCT recipients, with a low (< 5%) prevalence of pediatric patients. In both studies, audits of non-surveyed incident cohorts showed that most infected patients (> 95%) had been detected and included.

Patients were followed for development of IFI, as defined by the original European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC-MSG).[4] Although the consensus group has since refined the definitions to narrow the range of possible infections and broaden the criteria for probable infections,[5] these two TRANSNET publications were based on the original criteria. "Proven" infections require unequivocal evidence of fungi in the tissues or the bloodstream, preferably based on culture results, but histopathological findings in association with tissue damage (seen on histology or by some form of imaging) are also acceptable proof. "Probable" infections are those with a combination of patient criteria (such as prolonged neutropenia, steroid use, graft-vs.-host disease, etc.), microbiological criteria (including factors such as a positive beta-galactomannan test result, isolation of a fungus from a non-tissue site, positive fungal antigen test result, or other evidence), and two minor, or one major, clinical criteria involving signs and symptoms such as radiological or other imaging study evidence, cough with hemoptysis, skin lesions, etc. The "possible" category, which included patients with one host factor and either microbiological or clinical criteria traditionally associated with invasive fungal disease, was not included for evaluation in these surveillance data, which adds to the strength of these publications. Readers are referred to the original documents for complete original and current definitions of IFI.[4,5]

Among stem-cell transplant recipients, patients who received allogeneic grafts were more likely to develop IFI, with 78% of IFI occurring in that group. Equal numbers of those who had matched-related donors (38%) and unrelated donors (34%) became infected, but only 6% of patients receiving cells from mismatched-related donors became infected. Slightly more (56%) of these cases were proven than probable. Invasive aspergillosis was the most common infection (43%), with *A. fumigatus* comprising 44% of the cases, although 26% were unidentified, and some of those certainly also could have been *A. fumigatus*. A total of 28% of patients developed invasive candidiasis, with the most common species being *C. glabrata* (33%), followed by *C. albicans* (20%). The median time to development of infection was 61 days for *Candida* and 99 days for *Aspergillus*. The Fusarium infections (3% of total) had a median time of 125 days and the zygomycete infections (8%) developed a median of 135 days post-transplantation.

At least two positive findings emerged among the results of this study. First, the incidence of Candida infections is lower than seen in previous surveys conducted approxi-

mately 20 years ago.[6] The authors suggest that widespread use of azole prophylaxis may account for this decrease. Second, the overall incidence in this U.S. cohort is much less than the 19% of HSCT patients cared for in St. Petersburg who developed IFI over a similar time period.[2] The populations differed in that more pediatric patients were included in the Russian survey; however, 61% of the infections occurred in adults. The one note of caution based on the results of the TRANSNET study is that the cumulative incidence curves demonstrated that invasive aspergillosis disease, particularly at sites performing more of the higher-risk allogeneic transplantations, has not decreased despite broad use of prophylactic antifungal therapies and, in fact, has shown a slight increase; whereas, invasive candidiasis has remained stable. Reasons are unclear, but the authors suggest shifts in choice of patients and immunotherapeutic regimens. Another factor that should not be discounted is the possible improved ability of microbiology laboratories to detect agents of invasive fungal disease. More sites are performing beta-galactomannan studies (specific to *Aspergillus*) or, even better, beta-glucan studies (positive for many yeasts and molds), to detect antigens of fungi in the bloodstream before clinical signs and symptoms are observed.[7,8] Perhaps use of chromogenic media for yeast isolation and identification has also enhanced laboratory detection.[9] A non-controversial conclusion is that better diagnostic tests are needed. Unfortunately, overall mortality among the HSCT cohort who developed IFI was still high. For patients with Fusarium infections, the one-year mortality was highest (93%), 75% for patients with aspergillosis, 72% for patients with zygomycosis, and 66% for patients developing candidiasis.

The IFI among the solid-organ transplant recipients were assessed using the same EORTC-MSG criteria as summarized above over only the three-year period from 2002 to 2005. Solid-organ transplant recipients were also generally at low risk of developing an IFI during the surveillance period post-transplantation, with an overall one-year incidence < 4%. However, receipt of some organ systems placed patients at increased risk; for example, 8.6% of lung and heart-lung recipients (from 11 institutions) developed IFI, compared with only 1.3% for kidney transplants (15 sites). There appeared to be site-to-site variation in incidences of infections similar to those seen in the HSCT patient study. Among the 1,208 infections detected in 1,063 patients, 53% were Candida, with *C. albicans* being most common (46% of all candidiasis), followed by *C. glabrata* (25%). Invasive aspergillosis accounted for 19% of the diagnoses, with cryptococcosis next most prevalent (8% of infections). Only 2.3% of patients developed zygomycosis. Invasive candidiasis had the highest 12-month cumulative incidence estimate (1.9%), followed by invasive aspergillosis (0.7%). Median time to development of IFI was longer for the solid-organ recipients than was observed for HSCT patients, with 103 days observed for invasive candidiasis, 184 days for development of invasive aspergillosis, and 312 days for zygomycosis, with the other endemic fungal infections, such as histoplasmosis and coccidioidomycosis, appearing at a median of 343 days. An extended period of 575 days marked the median time until development of cryptococcosis.

As seen in the HSCT recipients, the incidence of invasive fungal disease increased slightly over the surveillance period in this cohort of patients, but in the solid-organ recipients, the increase was due to Candida infections (1.4% in 2002 to 2.3% in 2005), whereas *Aspergillus* incidence remained stable.

A sad conclusion from this report is that once solid-organ transplant patients become infected, their prognosis is poor, although not as bad as that for HSCT patients. The one-year mortality after infection was 41% for patients with invasive aspergillosis, 39% for infections due to molds other than *Aspergillus*, 34% for invasive candidiasis, and 73% for cryptococcosis. Many of the observed infections occurred more than one year after transplantation, and 25% of IFI developed more than three years after the transplantation in this group. These results suggest that diagnostic studies, prevention strategies, and treatment interventions must take into consideration the long time frame required for monitoring these patients.

Another conclusion supported by the slightly increasing incidence of IFI in these patients is that the ability of diagnostic studies to detect IFI in time for caregivers to react preemptively is still limited. Studies evaluating non-invasive, usually molecular-based, assays have been published; however, the results have been less than optimal. In one report, Hebart et al used the presence of any of numerous Candida and *Aspergillus* species fungal genetic elements in whole blood, as detected with a nucleic acid amplification assay, compared with clinical criteria alone to initiate treatment with liposomal amphotericin-B in allogeneic stem-cell transplant recipients.[10] Although more patients received early treatment based on polymerase chain reaction (PCR) results and survival for the two groups was better among the PCR-based treated individuals during the first 30 days, the 90-day survival was identical and showed no benefit for patients for whom PCR diagnostic tests were performed. As have numerous studies in the last few years, these authors called for further studies on the benefits of using PCR in patients at risk for IFI.

Both of the TRANSNET studies summarized here concluded that the true incidence of IFI was likely to have been underestimated due to the imperfect capabilities of diagnostic assays at this time. To quote Kontoyiannis et al, "…the precise epidemiology of invasive mold infections will remain uncertain until validated, sensitive, and specific non–culture based diagnostic methods become available." ■

References

1. Schaenman JM, et al. Trends in invasive disease due to Candida species following heart and lung transplantation. *Transpl Infect Dis*. 2009;11:112-121.
2. Zubarovskaya NI, et al. Invasive fungal diseases in patients after allogeneic hematopoietic stem cell transplantation. *Cellular therapy and transplantation*. This is an online, open access journal. Article available at: http://ctt-journal.com/1-3-en-zubarovskaya-2009jul6.html
3. Goebes,M, et al. Effect of building construction on *Aspergillus* concentrations in a hospital. *Infect Cont Hosp Epidem*. 2008;29:462-464.
4. Ascioglu S, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis*. 2002;34:7-14.
5. De Pauw B, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis.* 2008;46:1813–1821
6. Singh N. Impact of current transplantation practices on the changing epidemiology of infections in transplant recipients. *Lancet Infect Dis*. 2003;3:156-161.
7. Koo S, et al. Diagnostic performance of the (1-->3)-beta-D-glucan assay for invasive fungal disease. *Clin Infect Dis*. 2009;49:1650-1659.
8. Leeflang MM, et al. Galactomannan detection for invasive aspergillosis in immunocompromized patients. *Cochrane Database Syst Rev*. 2008;(4):CD007394 http://mrw.interscience.wiley.com.laneproxy.stanford.edu/cochrane/clsysrev/articles/CD007394/frame.html
9. Powell HL, et al. Evaluation of CHROMagar Candida for presumptive identification of clinically important Candida species. *Diagn Microbiol Infect Dis*. 1998;32:201-204.
10. Hebart H, et al. A prospective randomized controlled trial comparing PCR-based and empirical treatment with liposomal amphotericin B in patients after allo-SCT. *Bone Marrow Transplantation*. 2009;43:553–561.

CME Questions

31. Which of the following is correct?

a. Topical ivermectin is superior to topical malathion in the eradication of head lice.

b. Topical ivermectin is superior to oral malathion in the eradication of head lice.

c. Eradication of head lice requires administration of a second dose of effective therapy 7 to 11 days after the initial dose.

d. Ivermectin administration is associated with a significantly greater risk of adverse events than is malthion therapy.

32. Which of the following is correct?

a. Pre-operative skin preparation with povidone-iodine is associated with a significantly lower risk of surgical site infection than is preparation with chlorhexidine-alcohol.

b. Pre-operative skin preparation with chlorhexidine-iodine is associated with a significantly lower risk of organ-space infection than is preparation with povidone-iodine.

c. Chlorhexidine-alcohol has a rapid onset of bactericidal action and prolonged antibacterial activity.

d. Pre-operative skin preparation with povidone-iodine is associated with a significantly lower risk of superficial incisional infections than is preparation with chlorhexidine-alcohol.

33. Which of the following is correct?

a. The incidence of herpes zoster is increasing among U.S. veterans older than 40 years.

b. The incidence of herpes zoster is decreasing among U.S. veterans older than 40 years.

c. The changing epidemiology of herpes zoster is the result of increased exposure to varicella in children.

d. The changing epidemiology of herpes zoster is the result of routine varicella vaccination of veterans.

Answers: 31. (c); 32. (c); 33. (a)

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:

Piperacillin/Tazobactam

UPDATES

Treating Chronic HEV with Interferon-α

Source: Kamar N et al. Pegylated interferon-α for treating chronic hepatitis E virus infection after liver transplantation. *Clin Infect Dis*. 2010;50:e30-e33.

As recently discussed in *Infectious Disease Alert* (January 2010), chronic Hepatitis E virus (HEV) infection has been described in solid-organ transplant recipients, and uncommonly in persons with HIV. This report describes three solid-organ transplant recipients with chronic HEV infection treated with 12 weeks of pegylated interferon-α.

All three patients had received cadaveric liver transplants, the first two for chronic HBV infection, and the third for sclerosing cholangitis. The first patient developed acute hepatitis at 130 weeks post-transplantation. Liver biopsies showed acute hepatitis not consistent with rejection, and studies for HBV were negative. However, blood and stools were positive for HEV RNA. His immunosuppressive therapy was decreased, but nearly a year later, he continued to have abnormal transaminases, progressive disease on liver biopsy, and persistently positive HEV RNA test results. He received Peg-IFN-α at 135 micrograms/week for 12 weeks. Within one week, his liver enzymes improved, and serum HEV RNA levels became undetectable, and remained undetectable six months later.

The second patient also had a cadaveric liver transplant for chronic HBV. About 65 weeks post-transplantation, he developed acute hepatitis, with progressive liver disease on biopsy without evidence of rejection or recurrent HBV infection. Although serum and stool specimens were subsequently found to be positive for HEV RNA, these results, and the diagnosis, were not made for another three years. His immunosuppressive therapy was decreased, but his liver disease worsened. Nearly eight years after transplantation, studies for HEV were still positive, and it was elected to treat him with Peg-IFN-α. Within one week, RNA levels dropped nearly one log, and were undetectable by completion of 12 weeks of therapy. He remained free of any evidence of HEV five months later. The third patient had a similar story, and demonstrated good virologic suppression during Peg-IFN-α therapy, with negative serum HEV RNA at the end of 12 weeks of therapy, but unfortunately relapsed 15 days after completion of therapy.

These data suggest that pegylated-interferon therapy may be effective in chronic HEV infection in immunosuppressed persons. The first and third patient had hepatitis E genotype 3c, the most prevalent genotype identified in developing countries, while the second patient had genotype 3f. Further study is warranted to examine the optimal duration of therapy and safety in solid-organ recipients. Whether different HEV genotypes respond more favorably to treatment is not known.

Night of the Iguana?

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

Did you hear the one about dogs in southern Florida gnawing on dead iguana carcasses and developing possible botulism? Florida has had a bitter cold winter, and iguanas — which are poikolotherms, and cannot store body heat — are either freezing up and shutting down their metabolism, or dying. TV reports described cold, immobilized iguanas falling out of trees and residents telling tales of rotting carcasses on their lawns. Dogs apparently think they are large chew toys! One resident described how their dog was gnawing on a dead iguana one day, and developed progressive hindleg paralysis the next. At first, veterinarians were stumped when dogs began developing progressive paralysis and respiratory failure. Several dogs, whose owners could not afford intubation and critical care, have died. Botulism is the most likely diagnosis, pending laboratory confirmation.

Adventure Racers Get Too Wet and Wild

Source: Stern EJ, et al. Outbreak of Leptospirosis among adventure race participants in Florida, 2005. *Clin Infect Dis*. 2010;50: 843-849.

The United States Adventure Racing Association National Championships, which took place November 4-5, 2005, ended up wilder than expected. This endurance race, which took place over about 24 hours, covered a distance of more than 100 miles and involved paddling canoes, portaging, trekking, and orienteering, including portaging and swimming in the Hillsborough River and nearby creeks and swamps.

About 11 days after the event, a 32-year-old male participant developed fever, headache, and muscle aches, requiring hospitalization in New York. Although initial Leptospirosis antibody tests were negative, other racers began complaining on the net of similar symptoms, and one California racer tested positive for Leptospirosis.

Investigation revealed that 44 (23%) of 192 racers available for testing met the case definition for acute Leptospirosis, including fever plus two or more signs or symp-

toms of infection (e.g., headache, myalgia, eye pain, conjunctival suffusion, jaundice, dark urine, or unusual bleeding). Symptoms included fever (100%), headache (91%), chills (69%), sweats (68%), muscle or joint pain (68%), and eye pain or photophobia (39%). The mean incubation time to onset of symptoms was two weeks (2-32 days); three patients required hospitalization. Risk factors associated with infection included swallowing river or swamp water, being submerged in water, and eating wet food. Cuts on the legs and wearing shorts were not statistically significant in univariate analysis, but most of the racers had wicked cuts on the legs from tree stumps and sharp saw palmetto leaves.

Testing at the CDC discovered a unique serovar of Leptospirosis, *L. noguchii*, which has been found in rodents, possums, toads, dogs, and sheep in the southern United States. Environmental samples collected six weeks later failed to find evidence of Leptospirosis.

Two other adventure races, including a triathlon in Illinois in 1998 and the 2000 Borneo Eco-Challenge, resulted in outbreaks of Leptospirosis in participants. Since many of these types of races include significant water exposure, event directors should consult specialists in advance regarding the risk of Leptospirosis, and the need for possible chemoprophylaxis or empiric post-exposure treatment.

New Money, Old Parasite

Every year about this time, I see a couple of unhappy local residents who present with an intensely pruritic, erythematous papular mystery rash. In contrast to flea bites, which are simple raised papules, the lesions seem umbilicated or have a central bite mark. The patient is typically floored when I explain they have rat mite bites, and they need to go home and set traps — I mean, this is Palo Alto! It is estimated that half the homes in this area have resident roof rats, or *Rattus norvegicus*, especially at this time of year, when they are looking for a warm, dry place to nest. The spiny rat mite, *Laelaps echidnina*, is the most common ectoparasite found in large rodents.

Chiggers and mites are a frequent cause of dermatosis in patients referred to the ID clinic, especially in travelers,1 where the rash must be distinguished from those of sand flies and other parasites. Chiggers and non-human mites typically cause an intensely pruritic, red bumpy rash. Non-human mite dermatosis can result from animal or plant infestations, including animal habitats, dens, bird nests, fruits, trees, and furniture. Mites cannot jump, but they can crawl about 1 inch per hour on warm dry skin. Just like scabies, female mites burrow under the skin, where they lay their eggs. A sampler of different mites is as follows:

• Chiggers are free-living ectoparasites, meaning the larvae feed for a few hours, and then drop to the ground, before maturing into nymphs (including the trombiculid chigger species Leptotrombidium, which can transmit scrub typhus). Chigger bites are initially painless but, within hours, become intensely pruritic, followed by an erythematous papular eruption, called prurigo, which lasts a day or two. The bites are commonly found in areas where clothing is tighter, such as around waistbands, underwear, thighs, and ankles.

• Zoonotic (or non-human) scabies from any number of mammalian and bird species can infect humans, who are essentially dead-end hosts; the larvae never develop in humans, although symptomatic infection from mites burrowing under the skin may still respond to 5% pyrethrine or ivermectin. Common mites in this category include the poultry mite (seen in poultry handlers, typically on the hands); bird mites (in bird fanciers, breeders, and pet shop owners), various rodent mites, such as the rat mite and the common house mouse mite (the latter can transmit Rickettsialpox (R. akari), resulting in a typical eschar). Pigeon mites have been known to cause infestations in apartment buildings, where they roost outside of windows — and one hospital experienced a nosocomial outbreak of pigeon mites in patients and nurses.[2] Bird-mite bites are usually self-limited and can be managed with antihistamines and topical corticosteroids.

• Plant mites are more unusual, but include the North American and European straw itch mites, which can cause infestations in caned furniture, straw baskets, and straw rugs; they are most typically seen after hay rides in the fall. A characteristic "comet tail" has been described, which is literally the track of the mite moving away from the bite site. Other Pyemotes (plant mites) relatives can occasionally cause outbreaks, such as a large outbreak of North American oak leaf gall mite in residents in Pittsburg, KS. Plant insect mites can also occur in back packers, campers, and resort-goers, especially during the summer months, when mites breed and feed.

In travelers, chigger and mite bites must be distinguished from sand flea bites, such as those from *Tunga penetrans* (found in sub-Saharan Africa and South America) and *Tunga trimamillata* (found in Ecuador and Peru), which infect both animals and man. The pregnant sand flea females burrow under the skin, causing inflammation and ulceration — the legs and feet can become so swollen as to be painful to walk. A recent consult was just this — a young woman who took a brief Easter jaunt to Machu Pichu and presented with severe tungiasis with dramatic lower extremity swelling and multiple small black eschars just above her sock line — quite different from mite bites.

Patient never seem as excited or intrigued as I am when they present with one of these dermatoses, but at least they are relieved to have an answer, even it means going home and setting rat traps. ■

References

1. Diaz JH. Mite-transmitted dermatoses and infectious diseases in returning travelers. *J Travel Med*. 2009;17:21-31.
2. Bellander AP, et al. Nosocomial dermatitis caused by *Dermanyssus gallinae*. *Infect Control Hosp Epidem*. 2008;29:282-283.

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.*

Finding ACCORD in the Management of Type 2 Diabetes?

In this issue: Examining the three arms of the ACCORD trial; and FDA Actions: clopidogrel, dexlansoprazole, and tamsulosin.

ACCORD and type 2 diabetes

Every once in a while a medical study comes along that turns medical dogma on its ear. The Multiple Risk Factor Intervention Trial (MRFIT), published in 1982, was such a study, so was the Women's Health Initiative (WHI), published in 2002. Both studies challenged conventional wisdom and changed practice. MRFIT caused us to take a hard look at risk factor intervention especially hypertensive treatment, while WHI established that combination hormone therapy in postmenopausal women should no longer be routinely recommended because of the risk of breast cancer and heart disease.

The Action to Control Cardiovascular Risk in Diabetics (ACCORD) trial, published in March in the *New England Journal of Medicine*, is also such a study, and is destined to change medical practice in the treatment of type 2 diabetes. ACCORD looked at three aspects of care in type 2 diabetes, the first was the effects of intensive glucose lowering, the second was the effect of intensive blood pressure control, and the third was the effect of combination lipid therapy.

The intensive glucose lowering study was published early in 2008 when it was found that the intensive therapy group (targeting hemoglobin A1c < 6.0%) reported a higher mortality than the standard therapy group (targeting A1c 7.0%-7.9%). At the same time, intensive therapy did not significantly reduce major cardiovascular events (*N Engl J Med* 2008;358:2545-2559).

The second and third wings of the ACCORD trial were published on-line March 14, and the results were similarly discouraging for aggressive care. A total of 4733 participants with type 2 diabetes were enrolled in the intensive blood pressure control wing and were randomized to intensive therapy, targeting a systolic pressure < 120 mmHg, or standard therapy targeting a systolic blood pressure < 140 mmHg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, mean target blood pressures were met in both groups. The annual rate of the primary outcome was 1.87% in the intensive therapy group and 2.09% in the standard therapy group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.73-1.06; P = 0.20). The annual rates of death from any cause were 1.28% in the intensive therapy group and 1.19% in the standard therapy group (HR, 1.07; 95% CI, 0.85-1.35; P = 0.55). There was a slightly reduced risk of stroke in the intensive therapy group (0.32% vs 0.53%; P = 0.01); however, serious adverse events were more than double in the intensive therapy group. The authors conclude

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that in patients with type 2 diabetes targeting systolic blood pressure < 120 mm Hg as compared to < 140 mm Hg did not reduce the rate of the composite outcome of fatal and nonfatal major cardiovascular events (*N Engl J Med* published on-line March 14, 2010). While these results are somewhat surprising, they may not change the general recommendation for more aggressive blood pressure management in type 2 diabetes to systolic blood pressure ≤ 130/80 mm Hg, which is consistent with most current guidelines (including JNC VII).

In the third wing of ACCORD, 5518 patients with type 2 diabetes who were being treated with the statin simvastatin were randomized also to receive fenofibrate or placebo. The primary outcome was first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, the annual rate of primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group (HR 0.92; 95% CI, 0.79-1.08; P = 0.32). There were also no significant differences between the two study groups with respect to any secondary outcomes or death rate. Subgroup analysis suggested slightly higher benefit for men vs women and perhaps a benefit for those with high baseline triglycerides (> 204 mg/dL) and low HDL (≤ 34 mg/dL). The authors conclude that the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared with simvastatin alone (*N Engl J Med* published on-line March 14, 2010). This study does not in any way diminish the known benefit from aggressive statin therapy in type 2 diabetics, but does suggest that targeted treatment of triglycerides with fenofibrate is of no value. The FDA is reviewing the ACCORD data, but as of this time they have "made no new conclusions or recommendations regarding the use of simvastatin or other statin drugs and fenofibrate."

Do statins increase the risk of type 2 diabetes? It has been suggested that lipophilic statins may cause unfavorable metabolic side effects such as reduction of insulin secretion and worsening of insulin resistance. In a small single-blind, placebo-controlled parallel study, 40 to 44 patients were randomized to receive placebo, or atorvastatin 10, 20, 40, and 80 mg during a 2-month period. While atorvastatin significantly reduced LDL and apolipoprotein B levels, the drug was also associated with significantly increased fasting plasma insulin levels, as well as hemoglobin A1c levels (mean changes in fasting insulin levels, 25%, 42%, 31%, and 45%, respectively, for increasing dose; A1c increases of 2%, 5%, 5%, and 5%, respectively; P < 0.05 by paired t-test). Atorvastatin also decreased insulin sensitivity in a dose-responsive fashion. The authors conclude that atorvastatin resulted in significant increases in fasting insulin, hemoglobin A1c consistent with increased insulin resistance (*J Am Coll Cardiol* 2010;55:1209-1216). Previous studies have shown similar results with lipophilic statins including atorvastatin, rosuvastatin, and simvastatin, while pravastatin seems to reduce the risk of diabetes.

FDA Actions

The FDA has issued a warning to health care providers regarding the antiplatelet drug clopidogrel (Plavix®). It is recently been found that up to 14% of the population did not metabolize the drug effectively and may not fully convert the drug to its active form. Clopidogrel is dependent on CYP2C19 and those that genetically lack the enzyme may not convert the drug to its active form. Recent studies have suggested that reduced CYP2C19 activity was associated with higher risk for cardiovascular outcomes. A test is available to identify genetic differences in CYP2C19 function and the FDA is recommending that health care professionals consider use of other antiplatelet medications or use alternative dosing if patients are poor metabolizers. The manufacturer of Plavix is being asked to add a black box warning to the drug labeling to this effect. Previously, it was discovered that some proton pump inhibitors including omeprazole may also inhibit metabolism to the active drug. Meanwhile Eli Lilly's prasugrel (Effient®), a direct competitor to clopidogrel, is not affected by CYP genetic variants.

The FDA has approved Takeda Pharmaceutical's request to change the name of its proton pump inhibitor dexlansoprazole from Kapidex® to Dexilant™. The change is being made due to several dispensing errors that occurred between Kapidex and the prostate cancer drug Casodex® (bicalutamide) and the analgesic Kadian® (morphine).

The FDA has approved a generic version of Boeringer Ingelheim's tamsulosin (Flomax®) for the treatment of benign prostatic hyperplasia in men. Generic tamsulosin should be available later in 2010.