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INSIDE

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Ceftobiprole: MRSA Coverage Comes to β-Lactams at Last

ABSTRACT & COMMENTARY

By Brian G. Blackburn, MD

Clinical Assistant Professor of Medicine, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine

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

Synopsis: *Ceftobiprole, a novel broad-spectrum cephalosporin with activity against MRSA, was non-inferior to vancomycin plus ceftazidime in a study of complicated skin and skin-structure infections. This is the first β-lactam with reliable activity against methicillin resistant Staphylococcus aureus (MRSA) to be evaluated in advanced-stage clinical trials.*

Source: Noel GJ, et al. A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. *Clin Infect Dis*. 2008;46:647-655.

In the current era of increasing antimicrobial resistance, the need for novel antibacterial agents has become more acute than ever. While complicated skin and skin-structure infections (cSSSIs) are a common scenario, the clinician's ability to choose a single antibacterial agent with reliable activity against the most likely pathogens has become limited, particularly because of the widespread emergence of MRSA. With the exception of tigecycline, agents with anti-MRSA activity have a relatively narrow spectrum of activity, necessitating the addition of a second agent, if broader coverage is desired. Despite their otherwise broad spectrum of activity and relatively benign safety profiles, β-lactams to this point have not had anti-MRSA activity.

Ceftobiprole is a novel cephalosporin in advanced phases of clinical development. The broad-spectrum activity of this agent includes most gram-positive cocci, many aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*), and some gram--

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positive anaerobes.[1,2] Because of high-affinity binding to penicillin binding protein 2a (the major determinant of methicillin resistance in Staphylococci), ceftobiprole retains activity against MRSA, unlike all previous β-lactams.[1,2]

Clinical evaluation of ceftobiprole was undertaken in a non-inferiority trial designed to evaluate efficacy in patients with cSSSIs. The comparator arm received vancomycin plus ceftazidime; patients were allowed to receive metronidazole for 48 hours pending culture results in both arms if anaerobes were suspected. This randomized, double-blind, placebo-controlled trial was conducted internationally from 2005-2006. Patients included for enrollment had surgical wound infections, skin abscesses, cellulitis, or diabetic foot infections. Overall, 828 patients were included in the intent-to-treat analysis, randomized 2:1 into the ceftobiprole and comparator arms, respectively. Both arms received therapy for 7-14 days.

The two arms were well matched with regard to baseline characteristics, including the frequency of the infecting organisms. In each arm, methicillin susceptible *Staphylococcus aureus* (MSSA) was the most commonly identified pathogen, with MRSA second in frequency; together, these comprised 64% of infections overall. Gram-negative or mixed (gram positive plus gram negative) infections comprised 27% of the study population.

In the intent-to-treat analysis, the clinical cure rates were nearly identical in the ceftobiprole and comparator arms (82% and 81%, respectively). Among clinically evaluable patients, the clinical cure rates were also similar (91% and 90%, respectively), including among the subgroup of patients with MRSA infections (90% and 86%, respectively). Microbiological cure rates (88% vs 89%, respectively) were also similar. Cure rates were similar in both arms when analyzed with regard to type of cSSSI, receipt of adjunctive surgical therapy, and for each of the infecting organisms (although for P. aeruginosa, a non-significant trend favored the comparator arm). No significant differences were observed for any of these comparisons. In addition, there were no differences in the frequency or type of adverse events (AEs) between the two groups; though over 50% of patients experienced at least one AE in each arm (most minor).

COMMENTARY

These data support the conclusion that ceftobiprole is non-inferior to the combination of vancomycin plus ceftazidime for the treatment of cSSSIs. This supplements a recent clinical trial (which used a lower dose of ceftobiprole) that demonstrated ceftobiprole non-inferiority to vancomycin monotherapy in a study which focused on cSSSIs caused only by gram-positive organisms.[3] By including gram-negative and diabetic foot infections in the current trial, Noel and colleagues demonstrated the success of this new drug in a broader range of patients. More importantly, this trial demonstrates that monotherapy may now be possible in situations where combination therapy was previously necessary. The combination of anti-MRSA activity with a broad anti-bacterial spectrum is unique only to tigecycline and ceftobiprole to date, and only ceftobiprole among these two agents also has anti-pseudomonal activity. Clinicians are frequently confronted by the need to cover MRSA, particularly in cSSSIs. In doing this, ceftobiprole also offers the advantages of the β-lactam class, such as rapid bactericidal activity, favorable pharmacokinetics (eg, good CNS penetration), and a good safety profile.[4] The most common adverse events (AEs) associated with ceftobiprole are gastrointestinal symptoms and taste disturbance; serious AEs are rare.[5]

Pending final data review and FDA approval, ceftobiprole appears to be a welcome addition to the therapeutic armamentarium for cSSSIs. In addition, pending data to this end, it is easy to envision subsequent use of ceftobiprole in other clinical scenarios, should its safety profile and efficacy expectations remain on track. For example, given the activity against resistant gram-positive bacteria such as MRSA and penicillin-resistant

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ASSOCIATE PUBLISHER: Lee Landenberger.
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Questions & Comments

Leslie Hamlin,
Managing Editor, at (404) 262-5416, or e-mail to leslie.hamlin@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Streptococcus pneumoniae, ceftobiprole might allow monotherapy for empiric coverage in many cases of community-acquired bacterial meningitis where combination therapy with vancomycin plus ceftriaxone are currently necessary. The availability of ceftobiprole might also allow for empiric hospital-acquired pneumonia regimens which do not require the addition of a narrow-spectrum gram-positive agent (such as vancomycin or linezolid) for MRSA coverage. These advantages are significant, not only from a toxicity standpoint, but also from an efficacy standpoint, given that β-lactams are more rapidly bactericidal than these drugs. Should clinical data and peer review subsequently support use in such scenarios, ceftobiprole (or similar agents currently in development, such as ceftaroline) would be a welcome advance. ■

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Pneumococcal Vaccine has Changed the Epidemiology of Pneumococcal Meningitis

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

Chief Academic Officer, Baystate Health Professor of Pediatrics and Dean of the Western Campus of Tufts University School of Medicine

Dr. Jenson is on the speaker's bureau for Merck.

Synopsis: *Pneumococcal conjugate vaccination has resulted in significant decreases of hospitalizations for pneumococcal meningitis for both children and adults. Most cases of pneumococcal meningitis now occur among working-age and older adults.*

Source: Tsai CJ, et al. Changing epidemiology of pneumococcal meningitis after the introduction of pneumococcal conjugate vaccine in the United States. *Clin Infect Dis*. 2008;46: 1464-1472.

THE IMPACT OF 7-VALENT PNEUMOCOCCAL CONJUGATE vaccine (PCV7) was studied using the Nationwide Inpatient Sample, which is the largest source of inpatient data in the United States and drawn from about 1000 community hospitals. Pneumococcal meningitis cases and associated deaths were studied from 1994-2004, before and after the introduction of PCV7 in 2000.

From 1994-2004, there were 21,396 hospital discharges with a primary diagnosis of pneumococcal meningitis. During 1994-1999, there was an average of 2199 pneumococcal meningitis hospitalizations annually, with an average of 1572 hospitalizations annually from 2001-2004.

The average annualized rates per 100,000 population of pneumococcal meningitis hospitalizations among children < 2 years of age was 7.7 for 1994-1999, and 2.6 for 2001-2006, a 66% decrease (95% CI, 75% to 56.3%). Among children 2-4 years of age, hospitalization decreased from 0.9 to 0.5, a 51% decrease (95% CI, 66.9% to 28.9%). The hospitalization rate declined among adults 18-39 years of age from 0.4 to 0.3, a 26.1% decrease (95% CI, 38.8 to 10.7), and among adults > 65 years of age, a decrease of 33% (95% CI, 43.4% to 20.9%).

From 2001-2004, PCV7 vaccination prevented an estimated 3330 pneumococcal meningitis hospitalizations and 394 deaths among all age groups in the United States. From 1994-2004, there were 21,396 hospital discharges with a primary diagnosis of pneumococcal meningitis. During 1994-1999, there were 2199 pneumococcal meningitis hospitalizations annually, with 30% among children < 5 years of age, and from 2001-2004, there were 1572 hospitalizations annually, with only 15% among children < 5 years of age. The percentage of cases among adults > 65 years of age was constant over the entire period at 20%.

COMMENTARY

These results are encouraging, and able to be demonstrated within a relatively short period following introduction of PCV7. These results show that the epidemiology of pneumococcal meningitis decreased significantly in the United States following the adoption of PCV7 vaccination. The power of this administrative dataset is that it is sufficiently large enough to provide detection of statistically significant decreases of a relatively uncommon disease.

The changes occurred rather sharply following the introduction of PCV7 and persisted during the years 2001-2004, underscoring the role of PCV7. The decrease occurred not only among the target group of young children, but also among adults 18-39 years and > 65 years of age. Similar to the experience for *Haemophilus influenzae* type b conjugate vaccine, this likely represents reduced nasopharyngeal carriage of vaccine-type pneumococci among vaccinated children and decreased transmission to close contacts (eg, community or herd immunity).

Pneumococcal conjugate vaccines with protection against more than 7 serotypes (eg, 13 serotypes) are being evaluated and are expected to provide even greater benefit. Despite the limitation of including only 7 serotypes, and the potential that non-vaccine serotypes may replace vaccine serotypes as more common causes of pneumococcal disease, these results demonstrate that PCV7 has already earned its place as a major advance against human disease. ■

Excluding Bacteremia in Children with Central Venous Catheters

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

Synopsis: *Bloodstream infections associated with central venous catheters and caused by Gram-negative bacteria are significantly associated with an earlier time to positivity (99.2% at 36 hours) compared to other organisms (84.4% at 36 hours). The overall predicted probability for a culture being positive within 36 hours was 96.6% for catheter-associated infections.*

Source: Shah SS, et al. How long does it take to "rule out" bacteremia in children with central venous catheters? *Pediatrics.* 2008;121:135-141.

A RETROSPECTIVE, COHORT STUDY OF 200 EPISODES randomly selected from 315 episodes, during 2000-2003, at Children's Hospital of Philadelphia, of laboratory-confirmed bloodstream infections among outpatient children with central venous catheters was performed to determine the optimum duration of antibiotic therapy before infection could be reliably excluded. Blood cultures were performed using the BacT/Alert system, which automatically monitors carbon dioxide production every 10 minutes, 24-hours a day to detect bacterial growth. Patients with a single commensal organism isolated from the blood culture were excluded from the study.

The mean age of the children was 5.5 years (interquartile range, 2.7-12.1 years). The catheters included percutaneously inserted central catheters (PICC; 18), double-lumen (129), or single-lumen (22) Broviac catheters, double-lumen Medcomp catheters (12), subcutaneously implanted ports (14), and others (5). Catheters were in place for a median of 80.5 days. Among the 200 children, 134 (67%) were receiving *Pneumocystic carinii* prophylaxis, 42 (21.5%) had recently received antibiotics, 41 (20.5%) had recently received or were receiving parenteral nutrition, and 35 (17.5%) had received corticosteroids recently.

Among the 200 study patients, 127 (63.5%) had monomicrobial infections and 73 (36.5%) had polymicrobial infections, including 52 with > 1 gram-negative bacteria. The causative organisms included gram-positive bacteria (69), gram-negative bacteria (50), Candida (6), and rapidly growing mycobacteria (2). The most common gram-negative bacteria causing monomicrobial infections were Pseudomonas (16) and Klebsiella (12).

The median time to positive blood culture was 14.0 hours (interquartile range, 11.1-20.4 hours). Infections caused by gram-negative bacteria had a shorter time to becoming positive regardless of whether the infections were monomicrobial or polymicrobial. Most cultures with ≥ 1 gram-negative bacteria were positive within 24 hours of collection (94.1% predictive probability; 95% CI, 87.6-97.3%). In contrast, the predicted probability for infections caused by gram-positive bacteria or other organisms (eg, Candida and rapidly growing mycobacteria) was only 66.4% at 24 hours and 84.4% at 36 hours.

Vomiting at presentation was independently associated with an earlier time to positive blood culture, but was not associated with a specific organism.

COMMENTARY

These results are useful in the management of sus-

pected bloodstream infections among children with central venous lines by demonstrating that almost all (> 96%) bloodstream infections have positive blood cultures within 36 hours of collection. The results also show that infections caused by gram-negative bacteria are even more likely (99.2%) to have positive blood cultures within 36 hours of collection. This remained significant even after adjusting for age, catheter type, and recent treatment with antimicrobial therapy. This study was not able to assess blood culture volume, which directly influences time to positive blood culture. It is common that pediatric blood cultures, especially among very young children, include only 1-2 mL of blood, which may increase the time to becoming positive.

The results suggest that discontinuing antibiotic treatment among clinically stable children with central venous catheters is warranted if the blood cultures remain negative at 36 hours after collection. Vomiting was an independent marker of a shorter time to positive blood culture. It may be that vomiting is a sentinel marker of a more severely ill patient with higher-grade bacteremia, and should be an important part of the assessment of fever in children with central venous lines. ■

Pseudo Fever Due to Mucositis

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 Boehringer-Ingelheim and GSK.

Synopsis: *One hundred consecutive patients receiving cytotoxic chemotherapy were stratified into 4 groups of 25 each (patients with no fever and no mucositis, patients with mucositis, patients with fever and no mucositis, and patients with neutropenia and neither fever nor mucositis). Using simultaneous measurement of oral and tympanic membrane (TM) temperature, patients with mucositis had a mean oral temperature of 38.0 vs. TM temperature of 37.1° C.*

Source: Ciuraru NB, et al. The influence of mucositis on oral thermometry: when fever may not reflect infection. *Clin Infect Dis*. 2008;46:

In this study, 100 consecutive patients, who were receiving several different cytotoxic chemotherapy regimens for a variety of cancers, were self-referred on the basis of perception of mucositis, elevated temperature at home, malaise, or were referred by a nurse based on assessment of potential infection or mucositis. The patients were stratified into the following groups of 25 patients each: group A- patients with neither fever nor mucositis; group B- patients with mucositis; group C- patients with fever and no evidence of mucositis; and group D- patients with neutropenia but without fever or mucositis.

All four groups demonstrated higher mean oral temperatures than TM temperatures: group A, 36.9 vs 36.8; group B, 38.0 vs 37.1; group C, 38.7 vs 38.4; group D, 37.0 vs 36.7. A linear regression model that examined the effect of other variables on the difference in temperature found that only mucositis was a significant factor.

COMMENTARY

This is a fascinating paper that has significant potential clinical implications. Due to the high mortality rate of untreated bacterial sepsis occurring in the setting of fever and neutropenia, it has been "standard of care" since the 1970s to empirically begin broad-spectrum antibiotics in this clinical setting. It has long been recognized that this standard results in many more patients receiving antibiotics than the small number who actually have bacterial sepsis. While the empirical early use of antibiotics in febrile neutropenic patients has clearly resulted in reduction of mortality in patients with cancer and leukemia, it does come with a price tag consisting of all the complications of antibiotics therapy, including *C. difficile*-associated disease, allergic reactions, including allergic interstitial nephritis, and enhanced predisposition to fungal colonization and infection.

This important observation shows that oral mucositis can result in "pseudo fever" when only oral determinations of temperature are made. Awareness of this phenomenon may result in the reduction of unnecessary empirical use of antibiotics in some patients.

While the results of this study were surprising to me, they probably should not be. When one gets a sunburn, the skin is definitely hot to touch, not just subjectively so. It is always fun these days to occasionally read a paper in the field of infectious diseases which makes use of very simple technology and does not rely on sophisticated molecular techniques to make an important observation. ■

Whither PANDAS?

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

Synopsis: *Two prospective studies of a cohort of children with pediatric autoimmune neuropsychiatric disorders associated with group A streptococcal infections (PANDAS) suggest that the role of streptococcus as a precipitant of neuropsychiatric symptom exacerbations is minor. Laboratory studies including ELISA and Western immunoblotting for antibodies to brain proteins and for inflammatory cytokines failed to identify a basis for the purported autoimmune mechanism of PANDAS.*

Source: Kurlan R, et al. Streptococcal infection and exacerbations of childhood tics and obsessive-compulsive symptoms: A prospective blinded cohort study. *Pediatrics*. 2008;121:1188-1197; Singer HS, et al. Serial immune markers do not correlate with clinical exacerbations in pediatric autoimmune neuropsychiatric disorders associate with streptococcal infections. *Pediatrics*. 2008;121:1198-1205.

A BLINDED, PROSPECTIVE, CASE-CONTROL STUDY OF 40 children meeting all of the DSM-IV criteria for PANDAS matched with 40 children with obsessive-compulsive disorder and/or a chronic tic disorder was conducted with periodic intensive laboratory testing for group A streptococcus for 2 years, especially with clinical exacerbations or acute illness. There were 10 cases and 6 controls subjects who withdrew before completing the two-year study; 4 cases and 3 controls were replaced.

PANDAS subjects were more likely than controls to have a family history of rheumatic fever ($P = 0.03$). Over the two years of the study, PANDAS subjects and control subjects had an average of 24.3 ± 6.8 and 24.3 ± 5.4 throat cultures and 13.9 ± 5.3 and 12.7 ± 4.0 serum samples, respectively. Some subjects illustrated chronic carriage of group A streptococcus, with 23 positive of 25 throat cultures (all type M/emm-77) in one subject and 24 positive of 24 throat cultures (all type M/emm-2) in a second subject.

There were 65 clinical exacerbations, including 40 cases in 21 PANDAS subjects, and 25 cases in 14 control subjects. The exacerbation rate was 0.56 per person per year for PANDAS subjects and 0.28 per person per year for control subjects. There were 43 definite or probable group A streptococcal infections, with 31 infections in 31 PANDAS subjects and 12 infections in 9 control subjects. The group A streptococcal infection rate (definite or probable) was 0.43 per person per year for PANDAS subjects and 0.13 per person per year for control subjects.

Only 5 of 64 clinical exacerbations were temporally associated (within 4 weeks) with streptococcal infection, all occurring among cases. Over 75% of clinical exacerbations in such cases had no definable temporal association with group A streptococcal infections.

Another prospective, blinded, controlled study was conducted among 12 children participating in an intensive clinical and laboratory cohort of children diagnosed with PANDAS. The mean age was 11.4 years and included 8 boys and 4 girls. Serial serum samples were obtained before (2 samples), within 2 weeks (1 sample), and after (2 samples) a well-defined clinical exacerbation. Of the 12 children, 6 had an exacerbation associated with a well-documented streptococcal infection, and 6 children had an exacerbation without streptococcal infection. Assays of antineuronal antibodies included: ELISA of antineuronal antibodies using tissue proteins from human caudate, putamen, and Brodmann's area 10 (BA10); Western immunoblotting using the same tissue proteins with emphasis on brain proteins of 40, 45, and 60 kDa; ELISA for IgM and IgG lysoganglioside GM1 antibodies; competitive inhibition assay for IgG lysoganglioside GM1; and measures of inflammatory cytokines including: T-helper (Th1) cytokines IFN-α and IL-12; CD8 releasing cytokines IFN-α and tumor necrosis factor (TNF)-α; Th2 cytokines (IL-4, IL-5, IL-6, IL-10, and IL-13); the immunomodulatory cytokine IL-1; and the chemokines macrophage chemoattractant protein (MCP)-1 and RANTES (CCL5).

There was no association of clinical worsening or streptococcal infection with quantitative measures of autoantibodies. Antineuronal antibodies did not correlate with the phenotype, phenomenology, severity, or duration.

COMMENTARY

PANDAS was first described in 1998 with 5 diagnostic criteria: 1) presence of an obsessive-compulsive disorder and/or a chronic tic disorder (Tourette disorder, chronic motor or vocal tic disorder); 2) onset at 3 years to beginning of puberty; 3) abrupt onset of symptoms or pattern of dramatic, recurrent symptom exacerbations and remissions; 4) temporal relationship between group A streptococcal infection and clinical onset of symptoms, as reported by the subject or par-

ent; and 5) neurologic abnormalities such as motoric hyperactivity, tics, or choreiform movements during an exacerbation. PANDAS was hypothesized to be a continuation of a spectrum of autoimmune-mediated responses to group A streptococcal infections that included *Sydenham chorea*, the neurologic sequela of rheumatic fever, and, furthermore, that neurological exacerbations resulted from repeated group A streptococcal infections.

This is the first prospective cohort of patients diagnosed with PANDAS that has been studied with comprehensive clinical and immunologic testing. In this study, the PANDAS subjects showed an increased rate of exacerbations and also of streptococcal infections, though most of the clinical exacerbations could not be associated with streptococcal infections. This suggests that children with PANDAS may represent a subgroup of patients with Tourette syndrome or obsessive-compulsive disorder who are susceptible to group A streptococcal infections. Those clinical exacerbations that were temporally associated with group A streptococcus were not clinically distinct from exacerbations not associated with group A streptococcus. These studies have small study groups and so the lack of statistical significance must be interpreted cautiously.

The causal link of group A streptococcal infections to clinical exacerbations remains uncertain. These new results, which include serial antibody testing, combined with lack of specificity of previous studies of PANDAS patients at a single time point (many of which have methodologic concerns) and the failure of serum microinfused into rodent ventral and ventrolateral rodent striatum to produce changes of animal behavior, suggest that there is not a role of autoimmunity in PANDAS. ■

Serum (1 →3) β-D-glucan Assay for Diagnosis of Invasive Fungal Infection

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *A retrospective study was performed on 279 patients to evaluate the performance of a (1 →3)-β-D-glucan (BG) assay for the diagnosis of invasive fungal infection. 117 patients had probable or proven invasive fungal infection (IFI) by European Organization for Research and Treatment of Cancer (EORTC) criteria, 40 blood donors, and 122 hospitalized patients at risk for IFI, but in whom, IFI had not been diagnosed. For overall IFI diagnosis, the BG assay had 77.8% sensitivity, with specificity of 92.5% in blood donors and 70.5% specificity in patients at risk for IFI. The BG assay demonstrated 100% sensitivity in the 20 patients who had* Pneumocystis jiroveci *pneumonia (PCP).*

Source: Persat F, et al. Contribution of the (1'3)-B-D-glucan assay for diagnosis of invasive fungal infections. *J Clin Microbiol*. 2008; 46:1009-1013.

For this study, 279 patients from five groups (including 70 with proven or probable invasive pulmonary aspergillosis, 27 patients with blood cultures positive for a fungal pathogen, and 20 with PCP) were evaluated. BG levels were measured with the Fungitell test kit. Using a cutoff of ≥ 80 pg/mL, the assay showed a sensitivity/specificity of 77.8%/92.5% for diagnosis of IFI compared to blood donors. When using total patients at risk as a control, sensitivity/specificity was 77.8%/70.5%. For diagnosis of pulmonary aspergillosis vs patients at risk the sensitivity/specificity was 68.6%/73.0%. For fungemia vs patients at risk the sensitivity/specificity was 85.2%/64.4%. All 20 patients with PCP had positive BG titers.

COMMENTARY

Antemortem diagnosis of invasive fungal infection remains problematic. While the use of antifungal prophylaxis has likely reduced the frequency of yeast infections, IFI due to molds including Aspergillus, Zygomycetes, Fusarium species, and others remains problematic. Due to the high mortality rate associated with these latter infections, despite appropriate therapy and the toxicity of many antimicrobials used to treat these infections (particularly amphotericin), is high, more sensitive diagnostic methods are needed. The use of high-resolution CT scanning in febrile neutropenic patients coupled with presumptive therapy in patients with suspicious lesions on chest CT has been somewhat helpful, but this strategy also lacks sensitivity and specificity. Enzyme immunoassays to detect *Aspergillus galactomannan* and *Candida mannan* antigens have been developed but have lacked sensitivity in most studies and suffer from frequent false positive results in the presence of certain drugs, most importantly piperacillin/tazobactam.

Several colorimetric assays using horseshoe crab (Limulus or Tachypleus species) amebocyte lysate

have been developed. The Fungitell assay developed by Associates of Cape Cod has received FDA marketing clearance as a 510(k) in vitro diagnostic device. In another paper published earlier this year, the Seikagaku Corporation's Fungitec G-test MK also displayed excellent sensitivity (78%) and specificity (98.4%) using a cutoff value of 80 pg/mL in a large autopsy series.[1] Using this latter assay and a lower cutoff value of 30 pg/mL, sensitivity increased to 95.1% but specificity fell to 85.7%. An in vitro comparison of four commercially available kits using spiked serum samples demonstrated that the FDA-cleared Fungitell assay was the least sensitive, with a measurable range of 31.25-500 pg/mL, while the other three assays demonstrated lower limits of sensitivity ranging from 1.2-6 pg/mL.[1] A small in vivo study in rabbits comparing the Wako-WB003 and the Fungitec G BG assays demonstrated weak interassay correlation and greater sensitivity of the Fungitec G assay.[2]

It is unclear what the "best" assay for diagnosis of IFI is in humans due to the lack of comparative data in humans. One interesting fungal disease where absolute sensitivity of the BG assay appears to be less important than it is with invasive mold infections is *Pneumocystis pneumonia*. In the 20 patients with PCP studied in the Persat paper, the lowest BG level was 103 pg/mL and the majority of cases had BG levels of > 500 pg/mL with the Fungitell assay. A recent letter to CID reported three patients with clinical findings consistent with PCP but with negative microscopic examination results all had BG levels > 500 pg/mL.[3] This strongly suggests that BG assays will be a useful tool in the diagnosis of invasive fungal infections and have particular sensitivity in the diagnosis of Pneumocystis infection. ■

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Eosinophilia in Travelers: A Role for Empiric Antihelminthic Therapy?

ABSTRACT & COMMENTARY

By Brian G. Blackburn, MD

Synopsis: *A retrospective review of ill returned travelers in Israel revealed that almost 9% had eosinophilia. Although half with eosinophilia were diagnosed with schistosomiasis, a confirmed parasitologic diagnosis was rare in the remainder. Empiric albendazole therapy led to clinical improvement in 90% of patients with non-schistosomal eosinophilia.*

Source: Meltzer E, et. al. Eosinophilia among returning travelers: a practical approach. *Am J Trop Med Hyg*. 2008; 78:702-709.

Ill travelers returning from the developing world represent a unique patient population, given the broad range of possible diagnoses. Eosinophilia is thought to be a relatively common finding in this group, and although many medical conditions cause eosinophilia, infectious etiologies are more likely in such patients. Despite the knowledge that helminths are the infectious agents responsible for the majority of such cases, a microbiologic diagnosis remains elusive in many patients with eosinophilia

Meltzer and colleagues undertook a retrospective review of travelers to the developing world that presented (after returning home) to a medical center in Israel. The study spanned a 12-year period, and immigrants from developing countries were excluded. Patients presented a median of 6 weeks after returning from travel. Of the 955 patients reviewed, 82 (9%) had eosinophilia (> 500 eosinophils/µL or > 6% of the total white blood count). Forty-four (54% of those with eosinophilia) of these were diagnosed with schistosomiasis. Although all were seropositive, Schistosoma ova were found in the stool or urine in only 23% of those tested. Thirty-eight (46%) patients had non-schistosomal eosinophilia (NSE), and a parasitological diagnosis was confirmed in only 24% of these persons. Although patients with NSE did not undergo uniform evaluation, of the 30 who submitted at least one stool sample for ova and parasite examination, 3 (10%) were positive for helminths (hookworm in three; one coinfected with Ascaris). One additional patient had hook-

worm in a sputum sample. Of the 11 tested serologically for Strongyloides, 5 (45%) were positive. Although protozoa were found in 4 patients, these organisms were not considered explanatory of eosinophilia.

Of the 38 patients with NSE, 36 (95%) were symptomatic; most had gastrointestinal symptoms, and many had dermatologic and respiratory symptoms. The median eosinophil count among these patients at presentation was 1700 cells/μL. Of the 30 patients treated empirically with albendazole (most commonly 400 mg twice per day for 5 days) that had follow-up information available, symptoms subsequently resolved in 77% and improved in 13%, with no response in only 10%. The median eosinophil count decreased to 400 cells/μL among the treated NSE patients. In addition, patients diagnosed with schistosomiasis were treated with praziquantel.

COMMENTARY

This study demonstrates the relative frequency with which ill travelers returning from the developing world present with eosinophilia. Previous work focusing on refugees has demonstrated similar findings,[1] but less data are available on non-immigrant travelers. Also notable is the frequency of schistosomiasis in travelers with eosinophilia, particularly when there is a history of travel to Africa (95% of patients with schistosomiasis-associated eosinophilia in the study had traveled to Africa). Ill-returned travelers from endemic areas with eosinophilia should be tested for schistosomiasis, probably both by serology and direct examination of stool or urine; if positive, treatment with praziquantel will cure most patients.[2] In patients with non-schistosomal eosinophilia, establishing a parasitological diagnosis is difficult given that stool ova and parasite examinations are insensitive for many helminths and serological testing suboptimal.

Given the increased likelihood of helminthic infection and the difficulty of establishing a diagnosis in this population, empiric albendazole is an attractive strategy in returned travelers with NSE. Empiric albendazole has been shown to significantly decrease the prevalence of intestinal helminths in refugees resettling to the United States,[3,4] but evaluation in travelers is less established. The current study demonstrated clinical improvement and decreased eosinophil counts in almost all patients with NSE who were treated with albendazole. Although limited by the retrospective nature of the study, this suggests a helminthic cause in most of these patients, even though few had a confirmed parasitological diagnosis. Of particular importance is the issue of strongyloidiasis, given the lifelong nature of untreated infection and subsequent possibility of the fatal hyperinfection syndrome in certain hosts. Although the antiparasitic regimen used in this study is a second-line option for *Strongyloides stercoralis*, it has been shown to cure many patients.[5] Treatment directed at this parasite has also previously been shown to decrease eosinophil counts within months of treatment,[6] and given the high strongyloidiasis prevalence among tested persons in this study, suggests that many of the patients with NSE were responding to treatment for *S. stercoralis*. Although Meltzer et al also raise the issue of testing and possible treatment of filariasis, exposure history should be considered heavily when considering this diagnosis in casual travelers, given the relative rarity in this population.[7] .Overall, it seems reasonable to screen ill-returned travelers as appropriate for eosinophilia, and proceed with a rational workup, including schistosomiasis testing, if the patient has traveled to an endemic area, stool ova and parasite examination, and serologic testing for strongyloidiasis. If negative, and no other diagnosis is suggested, these data suggest that empiric albendazole followed by clinical and laboratory reassessment might be a reasonable initial strategy in this patient population. ■

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CME Questions

25. Which of the following is correct?

a. Ceftobiprole has in vitro activity against MRSA and many *Pseudomonas aeruginosa* isolates.
b. Ceftobiprole inhibits MRSA by a mechanism that does not involve interaction with penicillin-binding proteins.
c. Ceftobiprole has in vitro activity against MRSA, but has no activity against aerobic Gram-negative bacilli.
d. Ceftobiprole was shown to be inferior to the combination of ceftazidime and vancomycin in the treatment of patients with complicated skin and skin structure infections.

26. Which of the following is correct with regard to the bacteriological diagnosis of bacteremia in children with central venous catheters?

a. It is reasonable to discontinue empiric antibiotic therapy if blood cultures have remained negative for 12 hours.
b. It is reasonable to discontinue empiric antibiotic therapy if blood cultures have remained negative for 24 hours.
c. It is reasonable to discontinue empiric antibiotic therapy if blood cultures have remained negative for 36 hours.
d. It is never reasonable to discontinue empiric antibiotic therapy.

27. Which of the following is correct?

a. Assays for serum (1 →3) β–D-glucan are specific for the detection of Candida species.
b. Assays for serum (1 →3) β–D-glucan are specific for the detection of Aspergillus species.
c. Assays for serum (1 →3) β–D-glucan are non-specific with regard to the species of fungus detected.
d. Assays for serum (1 →3) β–D-glucan are not sensitive in the detection of Pneumocystis infection.

Answers: 25. (a); 26. (c); 27. (c)

CME Objectives

The objectives of *Infectious Disease Alert* are to:

• discuss the diagnosis and treatment of infectious diseases;

• present current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• present the latest information regarding the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy. ■

In Future Issues:

Practicing Renal Dosing Considerations and Drug Interaction Monitoring

UPDATES

By Carol A. Kemper, MD, FACP

Transmission of STD's: The defense rests

Source: Mohanty K. Transmission of Chlamydia and genital warts during sleepwalking. *Int J STD AIDS*. 2008;19:129-130.

SLEEPWALKING IS A FORM OF PARASOMNIA, which may be exacerbated by alcohol and drug use, is typically associated with non-rapid eye movements or nREM activity on electrophysiologic studies. Sexual activity during these periods of nREM activity — and during sleepwalking — has been well described, leading to variety of usual and unusual sexual behaviors, including indecent exposure, sexual assault, and rape, which may be associated with total amnesia respective to the events. This variant of parasomnia is not-so-euphemistically referred to as 'sexomania." Sexomania has been successfully used as a criminal defense in rape trials in both Canada and Great Britain.

In this unusual case, a 15-year-old was accused of repeatedly sexual abusing his 13-year-old stepsister over a 4-year period of time, resulting in transmission of two sexually transmitted diseases. The abuse began with digital penetration but had recently progressed to insertive vaginal intercourse. The 15-year-old admitted to alcohol use.

The abuse first came to light when the 13-year-old presented with complaints of vaginal discharge and was found to have chlamydia and genital warts. Further investigation confirmed the likely source was her stepbrother, who was also found to have infection with gonorrhea, chlamydia, and penile warts. However, he denied any knowledge of sexual contact or abuse of his stepsister. Once experts confirmed that he was sleeping during sex with his stepsister, all charges were dropped.

MRSA in Pig Farmers

Source: van Rijen MM, et al. Increase in a Dutch hospital of methicillin-resistant *Staphylococcus aureus* related to animal farming. *Clin Infect Dis* 2008;46:261-263.

JUST LIKE HUMANS, ANIMALS CAN become colonized or infected with MRSA. About three years ago, the presence of MRSA in horses and trainers at several large horse breeding and training facilities in Northern California contributed to an outbreak of MRSA infection in the equine inpatient unit at UC Davis, leading to the death of one horse from MRSA bacteremia (line sepsis) and another from MRSA osteomyelitis.

An increase in MRSA infection in persons hospitalized in the Netherlands from 2002-2006 is likely related to the emergence of a novel strain of MRSA in farm animals. This new clone of non-typable MRSA, which was first identified in the Netherlands around 2004, has since been found in nearly one-fourth of patients hospitalized with MRSA in the Netherlands. Physicians at the hospital surveyed patients with farm animal contact, and found that 32% of persons reporting exposure to calves or pigs were positive for MRSA. These included farmers, their wives, a farmer's daughter, an agricultural student, as well as an inseminator.

Household or professional animal contact can be a risk factor for persons with MRSA infection, and should be included in the patient history, especially in persons with recurrent infection.

Abacavir and DDI Linked to Heart Disease in HIV

Source: Sabin CA, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet.* 2008;371:1417-1426.

THYMIDINE ANALOGUES FOR THE treatment of HIV infection have been implicated as long-term risk factors for cardiovascular disease. However, in contrast to the investigators' reported expectations for this study, abacavir and didanosine, and not stavudine (d4T), zidovudine (AZT), and lamivudine (3TC), were found to be independently associated with an increased risk of myocardial infarction in persons with HIV infection. In this long-term analysis of persons enrolled in the D:A:D study, risk factors for cardiovascular disease were extensively examined, including the recent and cumulative use of nucleoside-reverse transcriptase inhibitors (NRTI's).

A total of 517 myocardial infarctions occurred in 33,347 persons during a total of 157,912 person-years. Recent use of abacavir (relative risk 1.90, $P = .0001$) and didanosine (relative risk 1.49, $P = .003$) were each independently associated with an increased risk of

cardiovascular events, though the cumulative use of either agent, or use > 6 months earlier, was not significant. The cardiovascular risk of protease inhibitor therapy vs non-PI-based therapy was not clear in this study.

Investigators stressed that other factors, such as hypertension, smoking, and hyperlipidemia, are much more significant for myocardial infarction, and should be aggressively addressed. The benefits of effective virologic suppression, especially in persons in need of antiretroviral therapy, even if it involves the use of abacavir or didanosine, outweigh the long-term potential risks of therapy.

Interestingly, from another study recently reviewed in *Infectious Disease Alert*,[1] this argument may be appropriate for younger HIV-infected patients who initiate antiretroviral therapy, regardless of stage of disease or viral load. But the benefits of HIV treatment may be more limited by increasing non-HIV-related mortality as patients age, especially if therapy is started "too early" at lower HIV viral loads. In such patients, attempts to reduce the toxicities and risks of treatment may be more important, and have greater impact on the risk-benefits of treatment. Other factors, not expressly examined in the article reviewed here, include other drug-related toxicities and quality-of-life issues, such as drug-related pancreatitis, peripheral neuropathy, and lactic acidosis.

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Marijuana Increases Risk of Steatosis

Source: Hezode C, et al. Daily cannibas use: a novel risk factor of steatosis severity in patients with chronic hepatitis C. *Gastroenterology*. 2008;134: 432-439.

Multiple factors contribute to the development of non-alcoholic steatosis ("fatty liver") in patients with HCV and HIV, which are known risk factors for progression of fibrosis and chronic liver disease. Some of these factors include diabetes, hyperlipidemia, and obesity, often associated with insulin resistance and metabolic syndromes. Interestingly, endocannabinoids, found in marijuana, are stimulants of CB1 and CB2 receptors, the former of which mediate some of the psychoactive properties and appetite stimulus of marijuana upon the central nervous system. However, CB1 receptors also play an important role in energy metabolism (eg, liver, placenta), where stimulation of these receptors can contribute to insulin resistance and an increase in obesity and steatosis. CB1 receptor antagonists have been developed (not available in the United States) which can lead to a reduction in weight and prevent the development of steatosis, regardless of caloric intake. Such agents may be especially useful in patients prone to diabetes and obesity.

These authors examined whether the regular use of marijuana increases the risk of hepatic steatosis in persons with chronic HCV infection. A total of 315 HCV-infected patients, who were undergoing liver biopsy as part of another clinical trial, were assessed for cannabis, alcohol, and tobacco use, as well as HCV genotype and plasma viral load, lipids, and Body Mass Index (BMI). The mean age was 45 years; 71% were male and the average BMI was 24.8 kg/M^2. Approximately two-thirds of the patients were HCV genotype 1 and 21% were genotype 3. About 24% were daily cannabis smokers (with an average use of 84 cigarettes per month), 12% were occasional users, and 64% were classified as non-users. Approximately 13% were defined as regular alcohol abusers (> 30 grams of alcohol per day); regular cannabis users were more likely to abuse alcohol than non-cannabis users.

Liver biopsies were evaluated independently by two pathologists and scored according to METAVIR criteria, assessing for inflammatory grade, fibrosis, and steatosis. Marked steatosis was defined as > 30% of hepatocytes containing fat vacuoles. Significant fibrosis and activity grade ≥ 2 were found in 36% and 59% of biopsy specimens, respectively. Steatosis was observed in approximately half of the specimens, which was considered marked in 19%.

In multivariate analyses, risk factors for steatosis included the activity factor identified on liver biopsy, HCV genotype 3, hyperglycemia or diabetes, BMI > 27 kg/M^2, and serum HCV viral load, as well as daily cannabis use. Adjusting for alcohol intake and HCV genotype, daily cannabis use was a significant risk factor for marked steatosis compared with those with occasional use (P = .03) and no use (P = .008).

This study implicates daily cannabis use as a significant predictor of steatosis and the severity of progression of liver disease in persons with HCV infection, independent of alcohol consumption and HCV genotype. Daily cannabis use appears to alter energy metabolism in the liver, and other organ systems, via CB1 receptors, thereby increasing the likelihood and severity of steatosis. (This article and the accompanying editorial also suggest that the active ingredient in oral pill form delta-9-tetrahydrocannabinol (THC) may have the same effect.) Although comorbidities are common in this group of patients, limiting marijuana use may be beneficial in patients with steatosis and chronic HCV infection. ■