RELIAS MEDIA

Vol. 38, Issue 11, August 2019
ReliasMedia.com

Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Isavuconazole vs. Caspofungin for Candidemia

By Richard R. Watkins, MD, MS, FACP, FIDSA

Professor of Internal Medicine, Northeast Ohio Medical University; Division of Infectious Diseases, Cleveland Clinic Akron General, Akron, OH

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

SYNOPSIS: In a large, randomized, double-blind, multicenter clinical trial, researchers found that isavuconazole did not meet the primary endpoint of noninferiority compared to caspofungin for candidemia and invasive candidiasis.

SOURCE: Kullberg BJ, Viscoli C, Pappas PG, et al. Isavuconazole versus caspofungin in the treatment of candidemia and other invasive candida infections: The ACTIVE Trial. *Clin Infect Dis* 2019;68:1981-1989.

Isavuconazole, the newest triazole, offers a number of advantages over some older agents, including broad antifungal activity, fewer drug-drug interactions, availability of IV and oral formulations with excellent bioavailability, and less toxicity and side effects. Investigators conducted a clinical trial to determine the role of isavuconazole in treating invasive candidiasis.

The study was a multicenter, randomized, double-blind trial that compared IV isavuconazole followed by oral isavuconazole to IV caspofungin followed by oral voriconazole. Patients were eligible who were at least 18 years of age and had candidemia with a positive blood culture or tissue culture within 96 hours before randomization, along with signs and symptoms of infection. Exclusion criteria included hepatic dysfunction, *Candida* endocarditis, *Candida* osteomyelitis, *Candida* meningitis, severe immunodeficiency, or systemic antifungal therapy for more than 48 hours before randomization. Patients in the trial were randomized in a 1:1 ratio to receive isavuconazole or caspofungin.

Financial Disclosure: Peer Reviewer Patrick Joseph, MD, is a consultant for Genomic Health Reference Laboratory, Siemens Clinical Laboratory, and CareDx Clinical Laboratory. *Infectious Disease Alert*'s Editor Stan Deresinski, MD, FACP, FIDSA, Updates Author Carol A. Kemper, MD, FACP, Peer Reviewer Kiran Gajurel, MD, Executive Editor Shelly Morrow Mark, Editor Jonathan Springston, and Editorial Group Manager Leslie Coplin report no financial relationships to this field of study.

Infectious Disease [ALERT]

***Infectious Disease Alert*, (ISSN 0739-7348), is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Infectious Disease Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.**

GST Registration Number: R128870672.

SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

Editorial Email:
mmark@relias.com

Subscription Prices
United States:
Print: 1 year with free *AMA PRA Category 1 Credits*™: $349
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits*™: $299

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

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias LLC designates this enduring material for a maximum of ***3*** *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 3 MOC Medical Knowledge points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Infectious Disease Alert may contain references to off-label or unapproved uses of drugs or devices. The use of these agents outside currently approved labeling is considered experimental, and participants should consult prescribing information for these products.

This CME activity is intended for the infectious disease specialist. It is in effect for 36 months from the date of the publication.

Patients without neutropenia could be switched from IV therapy to oral therapy after day 10. Therapy was continued for a minimum of 14 days after the last positive blood culture and could be extended up to 56 days. Venous catheters were removed for all patients with candidemia. Investigators followed patients for six weeks after the end of therapy (EOT). The primary endpoint was the overall response at the end of IV therapy (EOIVT) in patients who had proven *Candida* infections who received one dose or more of the study drug (modified-intent-to-treat [mITT] population).

Of the 450 patients randomized, 400 (199 in the isavuconazole group and 201 in the caspofungin group) were included in the mITT population. Patient demographics were comparable in both groups, including baseline neutropenia (12% in each). A successful outcome at EOIVT was achieved in 120/199 (60.3%) in the isavuconazole group and 143/201 (71.1%) in the caspofungin group (adjusted difference, -10.8%; 95% confidence interval [CI], -19.9% to -1.8%).

Because the lower limit of the 95% CI for the treatment difference (-19.9%) was lower than the -15% prespecified noninferiority margin, the study results did not demonstrate noninferiority of isavuconazole to caspofungin. Secondary endpoints were comparable between the two groups, including overall response rates at two weeks after EOT and survival at days 14 and 56. For the patients with only candidemia, 110/170 (64.7%) exhibited a successful overall response at EOIVT in the isavuconazole group vs. 118/163 (72.4%) in the caspofungin group (adjusted difference, -7.7%; 95% CI, -18.3% to -2.9%). For those with invasive candidiasis, the response rates were 34.5% (10/29) for isavuconazole and 65.8% (25/38) for caspofungin (adjusted difference, -31.3%; 95% CI, -57.7% to -5.0%).

A body mass index ≥ 25 resulted in a lower response rate, with a trend toward a worse outcome with isavuconazole compared to caspofungin. Five patients in the isavuconazole group and 11 in the caspofungin group had either breakthrough, emergent, or recurrent *Candida* infection during the study. Finally, safety profiles were comparable for the isavuconazole recipients and the caspofungin-voriconazole recipients.

■ COMMENTARY

This was a large, multinational clinical trial that included sites in the United States, Europe, Israel, and Thailand. It identified a significant difference in treatment arms for the primary endpoint, with isavuconazole failing to demonstrate noninferiority to caspofungin for candidemia and invasive candidiasis. Previous studies comparing echinocandins to azoles have been criticized for methodological shortcomings, such as imbalances in treatment arms. However, that was not an issue in the current study, as both groups were similar in terms of species of *Candida*, minimum inhibitory concentrations of the drugs, severity of illness, and removal of vascular catheters. The trial also was larger than others that compared an azole to an echinocandin, which likely allowed for the detection of differences with more precision.

Furthermore, the sponsor of the trial should be commended for publishing the results despite the finding that the study drug did not meet the threshold for noninferiority. Indeed, many negative clinical trials are never published, to the detriment of science and patient care.

Although it was a well-designed and well-conducted study, there are a few limitations to mention. First, it did not include children, so the findings might not be generalizable to this population. Second, the number of patients with neutropenia was relatively small.

Finally, investigators did not perform therapeutic drug monitoring, which may have affected the results, especially for overweight patients.

How do the results of this trial affect clinical practice? The findings strengthen the recommendation from the current

guidelines for using echinocandins as empiric first-line therapy.[1] Also, isavuconazole seems to be a reasonable choice (along with voriconazole) for oral step-down therapy for fluconazole-resistant strains once clinical improvement and clearance of fungemia have been achieved.

Further investigation of isavuconazole in other settings and patient populations (e.g., prophylaxis, pediatric patients, and neutropenic patients) may help clarify its place in the antifungal armamentarium. ■

REFERENCE

1. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016;62:e1-50.

ABSTRACT & COMMENTARY

Babesiosis — Increase in Reported Cases in the United States

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: The number of cases reported to the CDC from 2011-2015 has increased and there is concern about expansion of the areas in which it is transmitted.

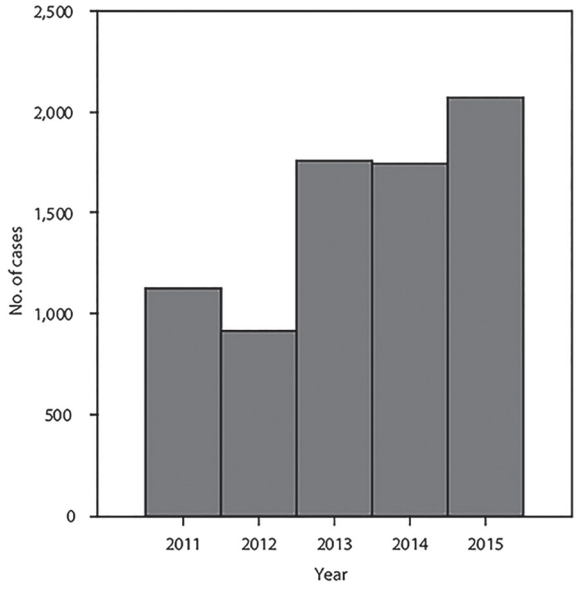
SOURCE: Gray EB, Herwaldt BL. Babesiosis Surveillance — United States, 2011-2015. *MMWR Surveill Summ* 2019;68:1-11.

Babesiosis has been a nationally notifiable condition since 2011, with 33 states reporting cases to the Centers for Disease Control and Prevention (CDC) as of 2015. During that interval, 7,612 cases were reported. The annual reports ranged from 909 in 2012 to 2,074 in 2015, with annual population-adjusted incidence rates ranging from 0.6 to 0.9 per 100,000 persons in those same years, respectively. (*See Figure 1.*) In 2015, 87.1% of cases were confirmed and 12.9% were probable.

Although 27 states reported cases from 2011-2015, 94.5% of these were reported by seven states, including five from the northeastern United States (New York, Massachusetts, Connecticut, New Jersey, and Rhode Island) and two from the Upper Midwest (Wisconsin and Minnesota). (*See Figure 2.*) The only other states reporting more than 100 cases were Maine and New Hampshire, where cases increased over the years of the study. Overall, > 70% of cases had onset during June to August.

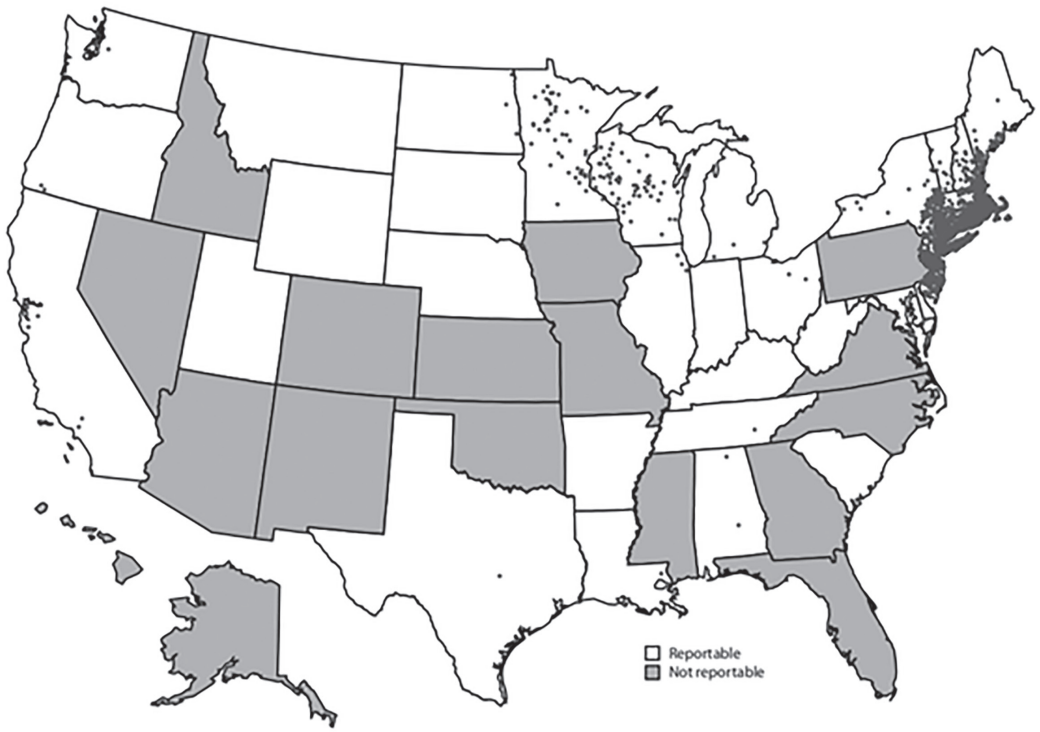
Among the 6,399 cases for which data were available, 5,343 (83.5%) had a positive blood smear while 1,056 (16.5%) were diagnosed only by serological testing, a result considered insufficient for classification as confirmation. Molecular or serologic testing allowing species level identification was available for 2,867 cases, and all but three identified *Babesia microti* as the etiology. Those

Figure 1: Number* of Reported Cases of Babesiosis, by Year — United States, 2011-2015†



* A total of 7,612 cases of babesiosis were reported (n = 1,126 for 2011, n = 909 for 2012, n = 1,761 for 2013, n = 1,742 for 2014, and n = 2,074 for 2015).
† Year as reported by the health department.
Source: Centers for Disease Control and Prevention

Figure 2: Reported Cases of Babesiosis, by Patient's County of Residence* — 33 States, 2015†



* N = 2,070; county of residence was known for all but four (< 1%) of the 2,074 total patients. Each dot represents one case; dots were placed within the patient's county of residence.
† Year as reported by the health department.
Source: Centers for Disease Control and Prevention

three were identified only by serological testing as *Babesia duncani*.

Most patients had fever and/or chills, while approximately two-thirds were thrombocytopenic. Approximately half of patients were hospitalized. At least one complication occurred in 231 of the 630 (36.7%) patients for whom the information was available, with renal insufficiency the most frequent complication, followed by hepatic injury and respiratory distress or failure. Approximately one-half of patients were hospitalized, with asplenia a strong risk factor. Eighty-three percent of patients for whom information was available received treatment with atovaquone, azithromycin, clindamycin, or quinine — alone or in combination. Seventy-one percent of patients received guideline-compliant combination therapy with either atovaquone plus azithromycin or clindamycin plus quinine. Almost half of patients received doxycycline. Forty-six patients died, but not all deaths were due to babesiosis.

Among the 3,173 patients for whom the information was available, 1,443 (45.5%) reported a tick bite in the eight weeks prior to the onset of symptoms or diagnosis, while 23.1% of the remainder reported prior outdoor activities.

Fifty-one patients had transfusion-related babesiosis.

[As with other tick-borne diseases, there is concern that the areas in which transmission occurs may be expanding.]

■ COMMENTARY

Most cases in this series were diagnosed by examination of a blood smear. The frequency of nucleic acid amplification test use is increasing. In contrast to morphologic examination, nucleic acid amplification tests allow distinction between the dominant species, *B. microti*, and the infrequently identified *B. duncani*. Babesia must be distinguished from plasmodia on blood smear. In patients with low-level parasitemia, repeated examination of blood smears may be necessary to detect the organism.

An important consideration in dealing with a patient with suspected or known babesiosis is the coinfection

with other pathogens also transmitted by *Ixodes scapularis* ticks. In the United States, these include *Borrelia burgdorferi*, *Anaplasma phagocytophilum*, *Borrelia miyamotoi*, *Borrelia mayonii*, Powassan virus, and an *Ehrlichia* species. It is likely that concern about one or more of these accounted for the fact that almost 50% of patients with babesiosis reported to the CDC received doxycycline. As with other tick-borne diseases, there is concern that the areas in which transmission occurs may be expanding, as evidenced by the increasing number of cases in Maine and New Hampshire. The main defense against infection in areas of transmission is avoiding tick-infested areas, applying tick repellent to both skin and clothing, undergoing full-body inspection for ticks after outdoor activities, and removing attached ticks with fine-tipped tweezers as soon as possible. ■

ABSTRACT & COMMENTARY

Significance of Pyuria in Children With Neurogenic Bladder

By Philip R. Fischer, MD, DTM&H

Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN

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

SYNOPSIS: Pyuria is common in asymptomatic children with neurogenic bladders, especially after bladder surgery. The simple presence of pyuria does not necessarily indicate a need for antibiotic treatment.

SOURCE: Su RR, Palta M, Lim A, Wald ER. Pyuria as a marker of urinary tract infection in neurogenic bladder: Is it reliable? *Pediatr Infect Dis J* 2019; Jun 20. [Epub ahead of print].

For children with neurogenic bladder due to myelomeningocele or other congenital abnormalities, urinary tract infection accounts for significant hospitalization and healthcare utilization. Unfortunately, there is not a consistent standard to guide the diagnosis of urinary tract infection in children with neurogenic bladders. Asymptomatic bacteriuria is common in this population, and the degree of pyuria is, at best, a controversial marker of urinary tract infection. Thus, the authors sought to determine the prevalence of pyuria in asymptomatic individual children with neurogenic bladders and how much the extent of pyuria varied over time. Presumably, if one knew the intensity of pyuria in asymptomatic children with neurogenic bladders, one would be better able to determine when pyuria is suggestive of an actual infection.

Potential study subjects were all children who enrolled in the spina bifida clinic at the University of Wisconsin from January 2004 through January 2015. There, the children underwent microscopic urine exams during each routine clinic visit. Symptoms were noted, and only samples taken from asymptomatic children were included. Thus, samples that coincided with fever, abdominal pain, abnormal urine odor, and altered urine function were excluded from the study. Researchers also excluded urine samples from the study if the patient received antibiotics for a presumed urinary tract infection during the two weeks before and after the time of sampling. When urine cultures were conducted, bacterial growth of more than 50,000 colony-forming units per milliliter was assumed to represent true bacteriuria. Investigators noted the use of intermittent catheterization and whether the child had undergone a surgical intervention that would introduce contact between the bladder and a usually non-sterile site (such as the creation of an appendiceal fistula for catheterization [Mitrofanoff procedure] or bladder augmentation).

The researchers included valid data for 305 urine samples from 50 different patients. Forty-eight of the patients had myelomeningocele, one had caudal regression syndrome, and one had cloacal exstrophy with a tethered spinal cord. Fourteen of the children had undergone surgical interventions.

Of the 305 urine samples, 70% contained fewer than five white blood cells per high power field. Of the total of 50 patients, 94% had at least one urine sample with less than five white blood cells per high power field. Sixteen patients had more than 50 white cells per high power field at least once and also had zero white cells at least once. Thus, there was a wide range of variability in the amount of pyuria, even within individual patients.

Age, gender, and whether the patient underwent routine intermittent catheterization were not significantly associated with pyuria, but a significant association occurred between pyuria and previous bladder surgery. More variability in the extent of pyuria occurred within a certain patient over time than occurred between different patients.

Overall, clinicians sent 36% of urine samples for bacterial culture; 75% of those were positive. *Escherichia coli* accounted for 48% of positive cultures. *Klebsiella* (23%) and gram-positive species (18%) were among the other bacteria isolated.

Thus, pyuria is common in asymptomatic children with neurogenic bladders and was seen in about 30% of samples. However, the presence and extent of pyuria varies significantly between, and especially within, individual patients at any given time. Significant bacteriuria also is fairly common, with about 27% of samples from these asymptomatic children showing growth of a pathogen.

■ COMMENTARY

Determining which children with neurogenic bladders actually have urinary tract infections that would benefit from treatment often can be difficult.[1] A landmark study in 1995 followed urinary findings in asymptomatic children with neurogenic bladders without antibiotic treatment.[2] Then, neither the presence of pyuria nor the finding of bacteriuria was associated with deterioration in renal function. An actual symptomatic infection developed in only a few cases.[2] Now, the authors of this study have provided updated evidence that pyuria comes and goes in individual patients and is not necessarily indicative of a significant infection that requires antimicrobial treatment.

In a 2018 study of urine tests in children with neurogenic bladders (including symptomatic children), *Enterococcus* often was found in cultures even when pyuria or leukocyte esterase were not present in the urine.[3] In that study, significant growth of *Proteus* usually was associated with the presence of both pyuria and leukocyte esterase. *Pseudomonas* was associated with leukocyte esterase positivity but not with pyuria.[3] Thus, pyuria may be present with or without bacteriuria, and significant, even symptomatic, bacteriuria may be present even without pyuria.

Nearly two decades ago, asymptomatic children with neurogenic bladders who underwent routine intermittent catheterization were reviewed.[4] Then, 81% of urine samples were abnormal: 51% with bacteriuria and pyuria, 26% with bacteriuria alone, and 5% with pyuria alone.[4] Interestingly, interleukin-8 (IL-8) levels were elevated in 54% of the abnormal urine samples and in none of the normal samples; IL-8 was most likely to be elevated with pyuria.[3] This prompted speculation that IL-8 was a marker for significant inflammation and, thus, for a true infection that might require antimicrobial treatment. Subsequently, elevated levels of urinary IL-8 were found to correlate with pyuria and bacteriuria in infected children,[5] but it is not clear that IL-8 actually indicates that antimicrobial therapy would help asymptomatic patients with bacteriuria and/or pyuria.

What do clinicians do when faced with a child who has a neurogenic bladder and urinary findings? It depends. A recent scenario-based survey of hospitalists, nephrologists, and urologists revealed significant heterogeneity in how bacterial colonization (requiring no treatment) is distinguished from infection (and the need for antibiotic treatment).[1] Although symptoms (incontinence between episodic catheterization, flank pain, fever) and urine findings (pyuria, heavy growth of a potential pathogen) tended to push toward considering the patient to be infected, broad variation occurred in both the diagnosis and the confidence with which the clinician made the diagnostic determination.[1] The number of years in practice and the physician's specialty accounted for some of the diagnostic variability.[1]

The authors have advanced knowledge by reminding us that pyuria is not necessarily abnormal in asymptomatic children with neurogenic bladders. For now, urinalyses are not needed to screen for urinary tract infection in asymptomatic children with neurogenic bladders. If for some reason pyuria is identified in an asymptomatic child, antibiotic treatment is not required. For children with symptoms of possible urinary tract infection, discretion is needed in interpreting clinical data. ■

REFERENCES

1. Forster CS, Jackson E, Goldstein SL. Variation among subspecialists in the diagnosis of urinary tract infection in children with neurogenic bladders. *J Pediatr Urol* 2018;14:567.e1-567.e6.
2. Schlager TA, Dilks S, Trudell J, et al. Bacteriuria in children with neurogenic bladder treated with intermittent catheterization: Natural history. *J Pediatr* 1995;126:490-496.
3. Forster CS, Shaikh N, Hoberman A, Jackson E. Uropathogens and pyuria in children with neurogenic bladders. *Pediatrics* 2018;141:e20173006.
4. Szucs K, O'Neil KM, Faden H. Urinary findings in asymptomatic subjects with spina bifida treated with intermittent catheterization. *Pediatr Infect Dis J* 2001;20:638-639.
5. Zaki Mel S. Interleukin 8 is a surrogate marker for rapid diagnosis of bacteriuria. *Immunol Invest* 2008;37:694-703.

ABSTRACT & COMMENTARY

Checkpoint Inhibitors: The First Effective Therapy for Progressive Multifocal Leukoencephalopathy?

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Enhancing the immune response with checkpoint inhibitors may be beneficial in the management of progressive multifocal leukoencephalopathy, a viral disease previously recalcitrant to therapy.

SOURCE: Cortese I, Muranski P, Enose-Akahata Y, et al. Pembrolizumab treatment for progressive multifocal leukoencephalopathy. *N Engl J Med* 2019;380:1597-1605.

Progressive multifocal leukoencephalopathy (PML) is a rare infection caused by the John Cunningham virus (JCV) that is most often lethal. The authors of the studies reviewed here set out to evaluate the potential of checkpoint inhibitors in the treatment of PML. Checkpoint inhibitors are enhancers of the immune response that have been demonstrated to be effective in the treatment of some malignancies.

Cortese and colleagues administered a maximum of three doses of pembrolizumab, given at four- to six-week intervals, to eight adults with PML. Two patients had HIV infection, two had chronic lymphocytic leukemia, two had idiopathic lymphocytopenia, and one each had non-Hodgkin's lymphoma and a remote history of Hodgkin's lymphoma. With pembrolizumab treatment, all eight patients exhibited reduced expression of the target of the drug, programmed cell death protein 1 (PD-1), on both peripheral blood and cerebrospinal fluid (CSF) lymphocytes. Researchers observed a clinical response (improvement or stabilization) in five patients, each of whom also experienced stabilization or reduction (but not elimination) of lesions seen on brain MRI. In all five patients, clinical response was associated with increased in vitro antiviral activity directed at JCV of CD4+ and CD8+ lymphocytes in association with a reduction in JC viral load in CSF. Investigators observed no such findings in the three patients who failed to improve clinically.

The same issue of the journal contained two individual case reports: one of a patient without evident immunosuppression and one with diffuse large B-cell lymphoma, with clinical responses to nivolumab and pembrolizumab, respectively.[1,2]

■ COMMENTARY

Most adults are chronically infected with JCV. Infection with this polyomavirus ordinarily remains confined to the kidneys, and infected individuals suffer no ill consequences. However, in the presence of immunosuppressive disease or therapy, the virus may undergo genetic rearrangements in noncoding regions of its virome, which lead it to become neurotropic, potentially causing fatal brain disease. Other than reversal of the immunosuppressed state by reducing immunosuppressive therapy or by providing effective antiretroviral treatment to patients with AIDS, no therapy has demonstrated effectiveness. However, recommended treatment of PML associated with natalizumab treatment of multiple sclerosis also involves plasma exchange in addition to discontinuation of the drug.

Present on the surface of T lymphocytes, PD-1 is a negative regulator of the immune response. Blocking its expression with an inhibitor of this immune checkpoint has proven effective in treating several malignancies in which PD-1 expression is elevated. In patients with PML, PD-1 expression also is increased on both CD4+ and CD8+ T cells. This is especially the case for CD8+ T cells specifically directed at JCV.[3]

The experiences reviewed here raise hope that checkpoint inhibitor therapy may be effective in treating PML. However, the assessment is muddied somewhat by the complexity and variety of underlying diseases in the 10 patients described. As noted in an accompanying editorial, two of the five responders in the report by Cortese et al had HIV infection for which effective antiretroviral therapy frequently is an effective modality in dealing with PML.[3] The authors of the editorial also pointed out that another of the

responders may have been improving already at the time of the intervention. The editorial authors rightly called for a randomized clinical trial — not an easy task given the rarity of this disease. ■

REFERENCES

1. Rauer S, Marks R, Urbach H, et al. Treatment of progressive multifocal leukoencephalopathy with pembrolizumab. *N Engl J Med* 2019;380:1676-1677.
2. Walter O, Treiner E, Bonneville F, et al; Immune Checkpoint Inhibitors in PML Study Group. Treatment of progressive multifocal leukoencephalopathy with nivolumab. *N Engl J Med* 2019;380: 1674-1676.
3. Koralnik IJ. Can immune checkpoint inhibitors keep JC virus in check? *N Engl J Med* 2019;380:1667-1668.

ABSTRACT & COMMENTARY

Trimethoprim Sulfamethoxazole Plus Clindamycin for Treatment of *Staphylococcus aureus* Endocarditis

By Dean L. Winslow, MD, FACP, FIDSA

Professor of Medicine, Division of General Medical Disciplines, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine

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

SYNOPSIS: A before-and-after intervention study compared 170 patients treated with either oxacillin IV or vancomycin IV for six weeks (plus gentamicin IV given during the first five days) to 171 patients who were treated with TMP/SMZ IV plus clindamycin IV for the first week followed by TMP/SMZ PO (without clindamycin) to complete a six-week course. Mortality and hospital length of stay were significantly less in the TMP/SMZ-treated patients.

SOURCE: Tissot-Dupont H, Gouriet F, Oliver L, et al. High-dose trimethoprim-sulfamethoxazole and clindamycin for *Staphylococcus aureus* endocarditis. *Int J Antimicrob Agents* 2019, June 8. doi.org/10.1016/j.ijantimicag.2019.06.006. [Epub ahead of print].

This prospective study was conducted from 2001-2017 with the control group of either oxacillin (for methicillin-susceptible *Staphylococcus aureus* [MSSA]) or vancomycin (for methicillin-resistant *S. aureus* [MRSA]) prescribed from 2001-2011 and the trimethoprim sulfamethoxazole (TMP/SMZ) plus initial clindamycin (T&C) regimen given from 2012-2017. The groups were well-matched at baseline, with the T&C patients slightly older than the control patients (64.4 vs. 59.4 years). Underlying diseases (diabetes, hypertension, chronic kidney disease, dialysis, coronary artery disease, etc.) were similar between the groups. Fifty-seven percent of patients in both groups had native valve endocarditis. Twenty-five of the T&C patients and 20% of the control patients had prosthetic valve endocarditis, and 28% of patients in both groups had cardiac devices. Twelve percent of the T&C patients and 11% of the control patients had MRSA.

Although septic failures were not significantly different between the arms in the ITT analysis, the on-treatment analysis showed that six patients in the control group and three patients in the T&C group failed to clear their blood cultures despite the addition of other antibiotics. Although not statistically different, 13 patients in the control group and eight patients in the T&C group experienced a relapse of infection. By ITT analysis, in-hospital death was seen in 18% of control patients and 10% of T&C patients. Although the investigators did not directly compare nephrotoxicity rates, acute kidney injury was seen in nine T&C patients and in only one control patient. Allergic reactions were similar in both groups.

■ COMMENTARY

I have always loved TMP/SMZ. Trimethoprim was just one of the many life-saving antimetabolites discovered by Trudy Elion and George Hitchings in their laboratory at Burroughs-Wellcome in North Carolina. TMP/SMZ also is > 90% orally bioavailable and is bactericidal against most sensitive organisms, including *S. aureus* and *Listeria*.[1] Current U.S. and European guidelines recommend four to six weeks of IV antibiotics to treat *S. aureus* endocarditis.

This study differs from other trials of TMP/SMZ for *S. aureus* endocarditis and bacteremia in

that investigators used high-dose IV TMP/SMZ (960/4,800 mg daily) and IV clindamycin (1,800 mg/day) for the initial seven days of treatment, followed by monotherapy with oral TMP/SMZ (320/1,600 mg or 2 DS tabs) three times per day to complete a six-week course. They also allowed the addition of IV rifampin (1,800 mg/day) and IV gentamicin (180 mg/day) in both groups if patients had persistently positive blood cultures or if they had a cardiac abscess. By this liberal definition of "persistent bacteremia," 28% of the T&C patients were noted but the number in the control arm was not mentioned. (All members of the control group also received IV gentamicin during their first seven days of treatment.) The study also seemed a bit unusual in that 67% of the control patients and 52% of the T&C patients underwent surgery at some point in their treatment courses.

Although the results of this study are a bit difficult to interpret, it reassures me that high-dose TMP/SMZ is a reasonable choice for the treatment of *S. aureus* endocarditis. My friend, Norm Markowitz, published a highly cited study back in the early 90s using standard dose TMP/SMZ that appeared to show that TMP/SMZ may have been inferior to vancomycin for the treatment of MSSA, but not MRSA endocarditis.[1] However, many have questioned this interpretation because of the small number of patients studied from his largely injection drug use patient population in Detroit and the low dose of TMP/SMZ used in his trial.

The Tissot-DuPont et al study throws another confounding factor into the mix: the use of clindamycin "to inhibit toxin production" during the first seven days of treatment. Many of the patients in this study were very sick (including 14% in the T&C arm who were in septic shock), so the use of clindamycin may have been reasonable in these cases. Although I usually do not get too concerned if a patient with *S. aureus* endocarditis does not clear the bacteremia in 48 hours, I suspect the antagonism of the bactericidal effect of TMP/SMZ by clindamycin played a role. Others have shown both in vitro and in vivo antagonism of the bactericidal activity of cell wall active antibiotics by rifampin in patients with *S. aureus* bacteremia.[2] Years ago, we showed that rifampin and other bacteriostatic antibiotics antagonize the bactericidal action of cell wall active antibiotics and TMP/SMZ against *Listeria*,[3] so I suspect clindamycin is doing the same thing.

The authors did not give a lot of detail about the nephrotoxicity encountered in this study (which resulted in dose reduction rather than discontinuation of TMP/SMZ in most cases they listed). My suspicion is that the direct effect of TMP on reducing the tubular secretion of creatinine may have caused some "over-calling" of nephrotoxicity. However, having said that, I am cautious in using TMP/SMZ, particularly in patients with mild underlying renal insufficiency in the setting of diabetes since TMP/SMZ not infrequently causes the serum potassium to rise a bit (possibly related to underlying type IV RTA, which is common in patients with diabetes).

In any case, this is a very interesting large study that eventually may change practice (and spare patients the expense and complications from PICC lines), but it should be replicated in a larger, prospective, randomized, controlled trial. ■

REFERENCES

1. Winslow DL, Pankey GA. In vitro activities of trimethoprim and sulfamethoxazole against *Listeria monocytogenes*. *Antimicrob Agents Chemother* 1982;22:51-54.
2. Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of *Staphylococcus aureus* infection. *Ann Intern Med* 1992;117:390-398.
3. Riedel DJ, Weekes E, Forrest GN. Addition of rifampin to standard therapy for treatment of native valve infective endocarditis caused by *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2008;52:2463-2467.
4. Winslow DL, Damme J, Dieckman E. Delayed bactericidal activity of beta-lactam antibiotics against *Listeria monocytogenes*: Antagonism of chloramphenicol and rifampin. *Antimicrob Agents Chemother* 1983;23:555-558.

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Surgeons Really Are Different

SOURCES: Charani E, Ahmad R, Rawson TM, et al. The differences in antibiotic decision-making between acute surgical and acute medical teams: An ethnographic study of culture and team dynamics. *Clin Infect Dis* 2019;69:12-20.

Szymczak JE. Are surgeons different? The case for bespoke antimicrobial stewardship. *Clin Infect Dis* 2019;69:21-23.

The success of antimicrobial stewardship (AS) is based on the timely and appropriate use of antibiotics. And yet, feedback and education

generally focus on the patient and the type of infection, not the physician or surgeon making the antibiotic choice. It turns out that physicians and surgeons make decisions — including decisions about antibiotics — in very different ways. For AS to succeed, the authors argued that education and feedback — and the guidelines that govern antibiotic choices — need to take these "cultural differences" into account.

To understand the decision-making process for choosing an antibiotic regimen, the authors at the Imperial College, London, performed an ethnographic study of their surgical and medical teams at work on the wards. (An ethnographic project means the internists and surgeons were observed in their own habitats). The results were based on 500 direct observations of antibiotic decision-making, which were interpreted based on current antimicrobial stewardship policy and guidelines, as well as 23 face-to-face interviews with key healthcare professionals. The professionals included 14 surgeons and nine internists and pharmacists.

The researchers' observations yielded some important differences between medical physician teams and surgical teams:
• Medical teams function in a collaborative capacity, with multiple individuals involved in the decision process. Ward rounds are more discussion-based and less pressured by time to make decisions. This multidisciplinary approach often provides a rational basis for antibiotic choices.
• On the other hand, the authors observed that the collaborative nature of the medical team's decisions means that no one person "owns" the decision, which sometimes means the decisions are deferred, or that the person with the most knowledge is over-ridden. This can lead to more prolonged use of broad-spectrum antibiotics.
• For similar reasons, empirical antibiotics started in the emergency department (ED) often are not re-evaluated immediately by the admitting medical team, who may be reluctant to disturb the initial physician's choice of antibiotic. Thus, a gap of > 24 hours may occur before the ward team tackles the process of re-evaluating antibiotics the following day. This problem is compounded by the new urgency for starting antibiotics in the ED for any patient with suspected infection or sepsis (which is probably not necessary in one-third of cases). Thus, many patients continue to receive unnecessary antibiotics for their first day of hospitalization.
• The surgical team functions very differently, with early morning rounds quickly occurring before morning surgery, sometimes in advance of micro data. Generally, decisions are made by one individual — the lead surgeon.
• However, surgeons consider decisions about antibiotics to be a low priority. Therefore, antibiotics simply are not addressed during the more pressured surgical rounds.
• Rather, "lesser" decisions (like antibiotics) are delegated to a junior member of the surgical team. The junior member of the surgical team is more worried about negative outcomes of making the wrong decision or changing antibiotics. Difficult decisions often are deferred, again leading to more prolonged use of antibiotics.
• Medical ward rounds included a dedicated pharmacist, who often prompts discussions about antibiotic stewardship and encourages consideration of de-escalation to narrower spectrum or oral antibiotic choices. The same pharmacist is not available for early morning surgical rounds. Decisions about antibiotics end up being delayed when key surgical decision-makers are unavailable in the operating suite later in the day. Further, any discussion about antibiotics tends to occur by phone or text, rather than through an open conversation or an opportunity for education and feedback.

Interventions to improve antibiotic use need to consider the differences in culture between medical and surgical teams, and how to frame educational opportunities and feedback to the different specialties. Pharmacists specializing in antibiotic stewardship need to better engage in surgical ward rounds.

Short-Course Atovaquone/Proguanil for Malaria Prophylaxis

SOURCE: Lau CL, Ramsey L, Mills LC, et al. Drug-free holidays: Compliance, tolerability, and acceptability of a 3-day atovaquone/proguanil schedule for pretravel malaria chemoprophylaxis in Australian travelers. *Clin Infect Dis* 2019;69:137-143.

Daily atovaquone/proguanil (A/P) is one of the more commonly used regimens for malaria prophylaxis in travelers. The usual regimen is one tablet (250 mg/100 mg A/P) daily beginning one to two days before arriving in a malaria risk area and continuing for seven days following departure. This means that travelers, some of whom are young and healthy and otherwise taking no medication, are taking a pill every day of their trip. Needless to say, studies have found compliance with malaria prophylaxis to be poor. In one study, researchers observed that only 59% of Australian travelers took their A/P, and less than one-third of these were fully complaint.

The pharmacokinetics of A/P suggest a different approach. Both drugs have long elimination half-lives

(two to three days and 14-20 hours, respectively). Larger treatment doses have provided malaria protection for more than four weeks.

The compliance and tolerability of treatment dose A/P (four tablets daily × three days), completed at least one day prior to departure, was observed in 233 adult travelers recruited from four different travel medicine clinics in Australia. Travelers were visiting countries with low-to-medium malaria risk for four weeks or less. The average age of the travelers was 44 years, and 51.2% were female. Compliance with the three-day regimen was remarkably good at 97.7%.

Side effects were common (43%), but generally mild to moderate and limited to the first or second day of medication. In descending order of frequency, side effects included nausea (25%), diarrhea (17%), fatigue (9%), headache (6%), and dizziness (6%). The median duration of side effects was two days, and no one experienced side effects lasting more than four days. Side effects limited daily activities for three people, although only two individuals failed to complete the three-day regimen because of side effects.

Follow-up phone calls to 205 participants (88%) revealed that none of the participants developed malaria during or after their trip.

A three-day malaria prophylaxis regimen — taken before departure — appears to be a perfect solution. Given the efficacy and improved compliance, fewer travelers would develop malaria, and many travelers would have the blessing of a medication- and side-effect-free trip at a lower cost.

The High Cost of Chronic Lyme Treatment

SOURCE: Goodlet KJ, Fairman KA. Adverse events associated with antibiotics and intravenous therapies for post-Lyme disease syndrome in a commercially insured sample. *Clin Infect Dis* 2018;67:1568-1574.

The researchers evaluated a large, commercially insured group of "chronic Lyme disease" patients, now characterized as post-Lyme disease syndrome (PLDS) for prolonged antibiotic use and complications. Investigators derived the data from medical and pharmacy claims from a large database (Truven Health Market Scan), based on ICD 9/10 codes and DRG hospital codes. They based observations on the 90-day incident rates for adverse events for PLDS patients at least six months following their initial Lyme diagnosis. Researchers compared data for patients receiving parenteral, oral, or no antibiotic therapy at least six months following their initial diagnosis. Oral antibiotics prescribed within a period 14 days before to 14 days following a Lyme diagnosis were not included in the analysis. Of the 123,687 unique patients with at least one claim for Lyme, 13,444 (10.9%) met criteria for PLDS with available data at least six months later.

Composite adverse event incident rates were significantly higher for patients receiving either parenteral or oral antibiotic therapy compared to the no-treatment group (18.7%, 16.8%, and 13.4%; $P = 0.019$). The three most common adverse events were infection, gastrointestinal side effects, and electrolyte abnormalities. The prevalence of infection was significantly higher in the parenteral antibiotic group (22%), compared with the oral group (17.7%), although the prevalence of *Clostridium difficile* enterocolitis was similar. Emergency room visits and hospital stays also were significantly higher in the parenteral treatment group. When treatment was given intravenously, the all-cause incidence of emergency room visits was 11.3% compared with 2.2% for the oral antibiotic group and 3.4% for the no-treatment group. Seven percent of those receiving parenteral antibiotics required hospitalization, generally for infection and/or electrolyte abnormalities.

The authors admitted this study may be limited by the observation that patients with more compelling symptoms may be more likely to receive parenteral therapy and, thus, also may have more complications. Also, it is possible that patients in this parenteral group received antibiotics for reasons other than Lyme disease. However, the results of this study are consistent with other clinical studies of chronic Lyme disease treatment, although the authors believe their data to be more robust and more "real world," based on a larger, commercially insured patient group. ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
1. Read and study the activity, using the provided references for further research.
2. Log onto ReliasMedia.com and click on My Account. *First-time users must register on the site.*
3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%. Tests are taken with each issue.
4. After successfully completing the test, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be emailed to you.

CME QUESTIONS

1. In a randomized trial comparing isavuconazole to caspofungin in the treatment of patients with invasive candidiasis with or without a positive blood culture, Kullberg and colleagues found which of the following?

a. Isavuconazole was noninferior to caspofungin regarding the primary endpoint (overall response at the end of intravenous therapy).

b. Isavuconazole was superior to caspofungin for all secondary endpoints.

c. Isavuconazole and caspofungin had comparable safety profiles.

d. When the analysis is limited to just those patients with invasive infection in the absence of detected candidemia, isavuconazole was superior to caspofungin.

2. Which of the following is correct regarding babesiosis in the United States from 2011-2015?

a. Most cases occurred in the southwestern part of the country.

b. Most cases occurred from October to March.

c. Two-thirds of patients were thrombocytopenic.

d. Ninety-eight percent of patients for whom the information was recorded recalled a tick bite in the eight weeks prior to the onset of symptoms.

3. Which is correct regarding management of an asymptomatic child undergoing intermittent catheterization with a neurogenic bladder?

a. Routine urinalysis should be performed at regular intervals.

b. Routine urine culture should be performed at regular intervals.

c. The presence of pyuria indicates a need for immediate antibiotic therapy.

d. Urinalysis and/or urine culture are not indicated.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis 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.