RELIAS MEDIA

Vol. 38, Issue 3, December 2018
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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Optimal Treatment of Vivax Malaria

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: In glucose-6-phosphate-dehydrogenase-sufficient individuals in Southeast Asia, combined treatment with chloroquine and primaquine provides much more lasting relief from vivax malaria than either chloroquine alone or artesunate.

SOURCE: Chu CS, Phyo AP, Lwin KM, et al. Comparison of the cumulative efficacy and safety of chloroquine, artesunate, and chloroquine-primaquine in *Plasmodium vivax* malaria. *Clin Infect Dis* 2018;67:1543-1549.

Vivax malaria is mostly a seasonal infection along the Thailand-Myanmar border. Nonetheless, it is associated with significant morbidity resulting from frequently relapsing bouts of illness. In the United States, the treatment standard for patients with *Plasmodium vivax* infection generally is the use of chloroquine to eradicate the blood phase of the pathogen, followed by primaquine (an alternative, tafenoquine, just received FDA approval) to eradicate the liver phase organisms (hypnozoites) that account for the relapses. However, in endemic countries, chloroquine alone often is used. Although chloroquine alone usually is able to achieve a cure without relapse, it has not been clear whether different medication regimens also might delay or prevent recurrent symptomatic malaria infection.

Thus, researchers prospectively studied 644 patients at least 6 months of age from May 2010 through October 2012. Glucose-6-phosphate-dehydrogenase (G6PD)-sufficient individuals were randomized to receive either artesunate or chloroquine or both chloroquine and primaquine; G6PD-deficient individuals received either artesunate or chloroquine.

Parasitemia was cleared more rapidly with artesunate than with the other treatment regimens. With artesunate, 70% had cleared their parasites within the first day of treatment, 22% did so with

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 Terrey L. Hatcher report no financial relationships to this field of study.

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***Infectious Disease Alert*, (ISSN 0739-7348), is published monthly by Relias Learning, 111 Corning Road, Suite 250, Cary, NC 27518-9238. Periodicals postage paid at Cary, NC, and additional mailing offices. POSTMASTER: Send address changes to *Infectious Disease Alert*, Relias Learning, 111 Corning Road, Suite 250, Cary, NC 27518-9238.**

GST Registration Number: R128870672.

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chloroquine alone, and 28% did so with chloroquine and primaquine.

However, recurrence of infection by 28 days after treatment initiation was more common with artesunate (50%) than with chloroquine (8%). Combined chloroquine and primaquine led to much fewer recurrences (0.5%) than did either of the other therapeutic regimens. The median time to first recurrence was 28 days in those treated with artesunate, 49 days in those treated with chloroquine, and 195 days in those treated with both chloroquine and primaquine. Using primaquine reduced total recurrences by 92%. In fact, only 3% of individuals treated with both chloroquine and primaquine experienced repeated malaria episodes during the 12 months following initial treatment.

The investigators screened patients for G6PD deficiency prior to inclusion in the study. However, they readily remarked that current G6PD screening tests do not identify G6PD-heterozygous individuals and that heterozygous females risk significant anemia with primaquine treatment. Thus, one risk of primaquine treatment would be anemia in G6PD-heterozygous females, who are not always identified by the current routine G6PD screening tests.

■ COMMENTARY

Five different species of *Plasmodium* cause malaria in humans (not just four, as some of us learned in medical school). *P. falciparum* is responsible for approximately 200 million bouts of malaria and most of the 445,000 malaria-caused deaths each year (mostly in children in sub-Saharan Africa).[1,2] *P. vivax*, the subject of this current study, is emerging as the most common cause of malaria outside Africa. *P. ovale* occurs mostly in West Africa. *P. malariae* occurs at low levels in tropical settings. The most recently recognized cause of human malaria, *P. knowlesi*, acts like *P. falciparum* clinically (causing severe disease), yet looks morphologically most similar to *P. malariae*. *P. knowlesi* is seen in Asian-Pacific areas.

P. falciparum has been markedly resistant to treatment with chloroquine for decades, but resistance has developed more recently and much less extensively for *P. vivax*. *P. vivax* can persist in a dormant state in the liver for months or even years; thus, later recurrences of symptomatic illness from the original infection still are possible. Therefore, effective treatment of *P. vivax* malaria depends not just on immediate clearance of bloodstream pathogens, but also on long-term reduction of recurrent bouts of symptomatic infection. Thus, artesunate is limited in treatment because although it can clear the initial bloodstream infection rapidly, it does not reduce or suppress subsequent release of parasites from the liver. Chloroquine persists longer in the human body than artesunate and, therefore, provides longer suppression of malaria, as noted in this new study by Chu and colleagues. Primaquine effects "radical cure" by killing the otherwise dormant liver stages of malaria.

[Ninety-one countries still are endemic for malaria, and 10 of those are on track to eliminate malaria by 2020.]

Based on these new data, the authors rightly advocated for more widespread use of primaquine as part of malaria treatment, at least in areas such as Southeast Asia where malaria transmission is mostly seasonal rather than maintained throughout the year. Of course, details are important. Chu and colleagues also recently published a systematic review showing that increasing the dose of chloroquine from the current standard 25 mg/kg over three days to 30 mg/kg, at least in young children, would reduce the risk of recurrent disease substantially, even when primaquine is not given.[3]

The incidence of malaria worldwide had been decreasing for several years and then plateaued in 2015-2016.[1] Ninety percent of malaria cases are in Africa.[1,2] Still, elimination programs continue.[2] Ninety-one countries still are endemic for

malaria, and 10 of those are on track to eliminate malaria by 2020.[2]

Travelers still are at risk of malaria. There were 1,517 individuals diagnosed with malaria in the United States in 2015, the most recent year for which summary data are available; 11 of those patients died.[4] More than two-thirds of those individuals had been traveling to visit friends and relatives, and only about one-fourth of U.S. residents who returned home with malaria had been taking chemoprophylaxis.[4]

Researchers at a medical center in Washington, DC, reviewed its experience with 100 adult cases of imported malaria during this century.[5] There, 76% had *P. falciparum*, and 94% had been traveling in sub-Saharan Africa.[5] Twenty-one individuals had severe malaria (10 with cerebral malaria), but all survived (even though the pre-born child of one infected woman did not survive the infection).[5] Clearly, pre-travel prescription of appropriate antimalarial prophylaxis, focusing especially on travelers going to visit friends and relatives, still is important. ■

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ABSTRACT & COMMENTARY

Blastomycosis (But Not *That* Blastomycosis) in the Western 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: Blastomycosis occurs in western Canada and in the United States well outside the known endemic area, but it is due to *Blastomyces helicus*, not *Blastomyces dermatitidis*.

SOURCE: Schwartz IS, Wiederhold NP, Hanson KE, et al. *Blastomyces helicus*, a new dimorphic fungus causing fatal pulmonary and systemic disease in humans and animals in western Canada and United States. *Clin Infect Dis* 2018; doi: 10.1093/cid/ciy483. [Epub ahead of print].

Schwartz and colleagues described 10 blastomycosis cases in humans and five in animals (including two dogs and two cats) that were acquired in the western regions of the continental United States and Canada. However, the cases were not caused by *Blastomyces dermatitidis*, but instead by *Blastomyces helicus*. The human cases appeared to have been acquired in Alberta, Saskatchewan, Texas, Utah, Nebraska, and Northern California. Clinical information was available for seven of the human cases, with six of these occurring in immunocompromised patients. The authors recounted an instructive case that had been reported from Stanford University in 2017 that described a California snake farmer who had trapped and fed small mammals and who developed fatal pulmonary infection with dissemination shortly after undergoing liver transplantation.[1]

The most frequent sites from which the fungus was isolated in the patients, in decreasing order of frequency, were blood, bronchoalveolar lavage fluid, cerebrospinal fluid, pleural fluid, bone marrow, liver, sputum, and lung tissue. On histopathological examination, the organisms appeared as small budding yeast cells, although hyphae also were seen in lung tissue in one case. A *B. dermatitidis* DNA probe was positive in all three cases in which it was applied, while one patient had a positive urinary *Histoplasma* antigen test. A *Blastomyces galactomannan* antigen test was positive in a cat. On culture, the organism exhibited yeast-like growth at 35°C on potato dextrose agar, and the cells were pleomorphic and variably sized. Mycelial growth was notable for the absence of conidia, which usually are present (and said to resemble "lollipops") in

B. dermatitidis, and the presence of helically coiled hyphae (hence, the name *B. helicus*), especially on media with low concentrations of carbohydrates with incubation at 25°C.

Outcomes were known for six of the human cases. The infection was fatal in four of these, three of whom received antifungal therapy. Both survivors received such therapy. One animal was known to have received treatment with fluconazole and survived.

■ COMMENTARY

This report describes the occurrence of blastomycosis due to *B. helicus* in regions of North America outside those known to be endemic for *B. dermatitidis* infection. On histopathological examination, the yeasts that are observed may be mistaken not only for the latter (although the occasional observation of short yeast chains is somewhat distinctive), but also for *Histoplasma capsulatum*. Furthermore, DNA probes for *B. dermatitidis* and urinary antigen tests for this organism and *H. capsulatum* also may be positive in the presence of *B. helicus* infection. In culture, the lack of conidia as well as the presence of coiled hyphae are distinctive.

The infections were disseminated frequently, with two involving the central nervous system. Most patients with disseminated *B. dermatitidis* infection do not have underlying immunocompromise identified, while most cases in this short series occurred in immunocompromised patients.

[*B. helicus* infections are not as new as one might suspect.]

In addition, none of the patients were described as having skin lesions, which is a frequent finding in patients with disseminated *B. dermatitidis* infection. *B. helicus* infections are not as new as one might suspect. Instead, this story represents an example of the general effects of changing nomenclature, something that has become a Tower of Babel for clinicians. When first reported, this organism was called *Emmonsia helicus*. More recently, *E. helicus* has been included, along with several other *Emmonsia*, in the genus *Blastomyces*. The Stanford case involving a snake farmer with a liver transplant mentioned earlier was reported in 2017 by Kappagoda et al as a case of infection due to *Emmonsia* sp. ■

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ABSTRACT & COMMENTARY

Factors Associated With Urinary Tract Infections Caused by Multidrug-resistant Gram-negative Bacteria

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

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Dr. Watkins reports that he has received research support from Allergan.

SYNOPSIS: A multicenter, retrospective, cohort study from southern and eastern Europe identified predictive factors for multidrug-resistant complicated urinary tract infections (cUTI), which included male sex, cUTI acquisition in a healthcare facility, presence of a Foley catheter, having a UTI in the previous year, and receiving an antibiotic in the preceding 30 days.

SOURCE: Gomila A, Shaw E, Carratalà J, et al. Predictive factors for multidrug-resistant gram-negative bacteria among hospitalised patients with complicated urinary tract infections. *Antimicrob Resist Infect Control* 2018;7:111.

Hospitalized patients with suspected complicated urinary tract infection (cUTI) often are treated initially with broad-spectrum antibiotics. Having a model to predict which patients are at high risk for multidrug-resistant (MDR) pathogens would be useful to help make better antibiotic choices, thereby leading to improved antibiotic stewardship. Gomila et al conducted a retrospective cohort study

from hospitals in southern and eastern Europe, Turkey, and Israel. They defined MDR as nonsusceptibility to at least one drug in three or more antimicrobial categories. The investigators obtained data from patients who were admitted for a cUTI and from those who were admitted for other reasons and developed a cUTI during hospitalization. Each hospital contributed 50 to 60 consecutive patients to reduce selection bias. Inclusion criteria were age > 18 years; patients with a UTI with an indwelling Foley catheter, a neurogenic bladder, urinary retention, renal impairment with a glomerular filtration rate < 60 mL/min, a renal transplant, pyelonephritis, or an ileal loop/pouch; signs or symptoms of a UTI; and a urine culture with > 10^5 colony-forming units of a uropathogen or at least one positive blood culture growing a possible uropathogen and no other evident site of infection (e.g., an intra-abdominal source or pneumonia).

Patients were excluded if they had a polymicrobial urine culture, a culture with *Candida* spp. as the sole isolate, a diagnosis of prostatitis, or an uncomplicated UTI. The primary outcome was the presence of an MDR cUTI. The secondary outcomes included estimates of the prevalence of MDR in each country, definition of the cUTI microbiology, and assessment of the resistance rates of the uropathogens to different classes of antibiotics.

A total of 948 patients met inclusion criteria, from which investigators obtained 1,074 bacterial isolates. Most patients (56%) were female, and the mean age was 65.8 years. The most frequent isolates were *Escherichia coli* (52%), with 14.5% MDR; *Klebsiella pneumoniae* (15.6%), with 54.2% MDR; *Pseudomonas aeruginosa* (9%), with 38.1% MDR; *Proteus mirabilis* (7%), with 24.1% MDR; and *Enterococcus* spp. (3%), with no MDR rate given. Carbapenem resistance occurred in 2.3% of *E. coli*, 19.6% of *K. pneumoniae*, and 32.6% of *P. aeruginosa*.

The MDR rate was < 20% in Hungary and Spain and approximately 60% in Bulgaria and Greece. In a final predictive model, factors that predicted MDR were male sex (odds ratio [OR], 1.66; 95% confidence interval [CI], 1.20-2.29), acquiring a cUTI in a healthcare facility (OR, 2.59; 95% CI, 1.80-3.71), presence of a Foley catheter (OR, 1.44; 95% CI, 0.99-2.10), having a UTI during the previous year (OR, 1.89; 95% CI, 1.28-2.79), and receiving an antibiotic in the preceding 30 days (OR, 1.68; 95% CI, 1.13-2.50).

■ COMMENTARY

Antibiotic misuse is the main culprit driving the global spread of antimicrobial resistance. UTIs commonly are diagnosed in hospitalized patients in Europe and North America. Many patients receive inappropriately broad empiric antibiotic therapy. Thus, the study by Gomila et al is significant and useful because it helps define which patients are at risk for a cUTI due to an MDR pathogen and inform antibiotic choices. Therefore, hospitalized patients at high risk for an MDR pathogen might be started empirically on a broader agent (e.g., a carbapenem, ceftazidime/avibactam, or meropenem/vaborbactam), while those at intermediate or low risk might receive a narrower spectrum drug (e.g., third-generation cephalosporin or a quinolone).

[Deciding about empiric antibiotic therapy requires balancing the need for having an active drug with the risks associated with coverage that is too broad, such as promoting antimicrobial resistance and *Clostridioides difficile* infection.]

De-escalation is appropriate when culture data become available except in a few circumstances, such as septic shock or neutropenic fever. A recent study showed many of the same risk factors also to be associated with MDR in healthy young adults with community-acquired UTIs.[1] Of note, nitrofurantoin was an effective choice and had a low risk for inducing MDR.

There were some limitations to the study by Gomila et al. First, it included hospitals in several countries that had higher rates of MDR pathogens compared to the United States. Therefore, further validation of the results for different regions is needed. Second, not all important risk factors, such as history of an MDR pathogen, were included in the analysis. Finally, because of the retrospective observational design, the study may have been influenced by unmeasured confounding variables.

The predictive factors identified by Gomila et al could serve as the basis for developing a risk score to identify patients at high risk for MDR cUTIs. Deciding about empiric antibiotic therapy requires balancing the need for having an active drug with the risks associated with coverage that is too broad, such as promoting antimicrobial resistance and *Clostridioides difficile* infection. The

study by Gomila et al is a significant contribution to the evidence for treating cUTIs and should help clinicians choose appropriate empiric antibiotic therapy. ■

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ABSTRACT & COMMENTARY

Oral Linezolid for *Staphylococcus aureus* Bacteremia

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: Investigators evaluated 135 patients with *Staphylococcus aureus* bacteremia (SAB) in a prospective cohort study comparing early switch to oral linezolid to continued treatment with standard parenteral therapy (SPT). Patients with complicated SAB and osteoarticular infection were excluded. Early switch to oral therapy yielded similar outcomes to continued SPT and allowed earlier hospital discharge.

SOURCE: Willekens R, Puig-Asensio M, Ruiz-Camps I, et al. Early oral switch to linezolid for low-risk patients with *Staphylococcus aureus* bloodstream infections: A propensity-matched cohort study. *Clin Infect Dis* 2018; doi:10.1093/cid/ciy916. [Epub ahead of print].

The authors conducted a prospective cohort study of *Staphylococcus aureus* bacteremia (SAB) in adult patients at a university hospital in Spain over four years. Investigators compared the efficacy, safety, and hospital length of stay for patients who received standard parenteral therapy (SPT) for the duration of their treatment course and for patients who switched from SPT to oral linezolid between days 3-9 of treatment. The researchers excluded patients with complicated SAB and osteoarticular infections from the study.

The researchers analyzed 45 patients in the linezolid group and 90 patients in the SPT group. Sources of SAB included IV catheter-related (50%), unknown origin (20%), and skin and soft tissue (17%). Patients in the groups were comparable, although less chronic renal disease was seen in the linezolid-treated patients. There were no differences in 90-day relapse rate (2.2% in the linezolid group and 4.4% in the SPT group) or the 30-day mortality rate (2.2% for linezolid and 13.3% for SPT; $P = 0.08$). The median hospital length of stay was significantly shorter in the group that received linezolid than in the group that received SPT (eight days vs. 19 days; $P < 0.01$).

■ COMMENTARY

In selected patients with SAB, an early switch from IV antibiotics to oral linezolid until treatment completion results in similar clinical outcomes and allows for earlier discharge from the hospital. The outcomes should be convincing to physicians that the strategy of switching early from IV to oral treatment of SAB is appropriate, with the caveat that patients in this study were highly selected.

Exclusions for "high risk" SAB included patients with persistent positive blood cultures after three days or more of appropriate SPT, septic thrombophlebitis, endocarditis, vascular graft or other endovascular infection, metastatic foci of infection, device-related infection, and osteoarticular infection. The exclusion of osteoarticular infection from this study was a bit surprising since pediatricians have been comfortable for years with early switch from IV vancomycin or IV beta-lactam to oral antibiotics (often clindamycin) in bacteremic bone and joint infections due to *S. aureus*. The safety and efficacy of this has been demonstrated in large studies.[1] (In one study cited below, researchers studied 265 children with acute bone or joint infections proven by cultures. All of the patients received two to four days of IV antibiotic treatment followed by oral antibiotics. Whether the patients had positive blood cultures on admission or not, researchers found that the clinical outcomes and inflammatory biomarker resolution were the same.)

Antibiotics such as linezolid and clindamycin are particularly attractive in bone and joint infections

since they have nearly 100% oral bioavailability. Both drugs also are lipophilic, so they achieve good tissue levels in bones, joints, and other tissues. Linezolid can be problematic when used for > 2-3 weeks because it displays mitochondrial toxicity. Thrombocytopenia, peripheral neuropathy, and lactic acidosis can be seen with prolonged use.

I also found it interesting that in this trial from Europe, median antibiotic treatment duration was 15 days in both arms of the study. Relapse rates also were incredibly low in both arms (4.4% and 2.2%). Treatment of low-risk SAB for just 14-15 days was a common practice when I trained in the late 1970s. However, I have noticed progressive "duration creep" of IV antibiotic courses for SAB over my career, with SAB patients commonly receiving four to six weeks IV antibiotics even when endocarditis and other high-risk conditions have been excluded. This study should reassure clinicians that short-course oral therapy of low-risk SAB often is appropriate. I also hope that the IDSA practice guideline currently under development will help provide clinicians with better guidance in selecting duration of treatment regimens and early conversion of SPT to oral antibiotics. ■

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ABSTRACT & COMMENTARY

Healthcare-associated Infections — Better, But Not There Yet

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: One-day prevalence studies demonstrated that there has been a 16% reduction in the risk of healthcare-associated infections from 2011 to 2015.

SOURCE: Magill SS, O'Leary E, Janelle SJ, et al. Changes in prevalence of health care-associated infections in U.S. hospitals. *N Engl J Med* 2018;379:1732-1744.

Using the Emerging Infections Program, researchers at 10 participating sites recruited as many as 25 hospitals (general, women's, and children's) in their areas to participate in a one-day prevalence of healthcare-associated infections (HCAI). Each hospital selected a study date from May 1, 2015, through Sept. 30, 2015. The survey included 12,299 patients in 199 hospitals, and the results were compared to a 2011 survey involving a similar number of hospitals and patients. The patients in the two surveys were similar regarding the proportion in critical care units (15%), the median interval from hospital admission to the survey (three days), and the proportion with an HCAI who died (approximately 11%). However, in 2015, the percentages with a urinary catheter were lower (18.7% vs. 23.6% in 2011), as were those with a central venous catheter (16.9% vs. 18.8%).

In 2011, 452 of 11,282 (4.0%; 95% confidence interval [CI], 3.7-4.4) patients had one or more HCAI. In 2015, using the same definition, this was true of only 394 of 12,299 (3.2%; 95% CI, 2.9-3.5), a difference that was significant ($P < 0.001$). Pneumonia was the most frequently identified infection, followed by gastrointestinal (mostly due to *Clostridioides difficile*) and surgical site infections. Just more than three-fourths of the latter were deep incisional or organ-space infections.

The most frequently isolated pathogens were *C. difficile*, *Staphylococcus aureus*, and *Escherichia coli*. Of the 47 isolates of *S. aureus* for which susceptibility test results were available, 21 (45%) were methicillin-resistant. Carbapenem resistance was detected in only three of 66 (5%) isolates of *E. coli*, *Klebsiella* spp., and *Enterobacter* spp.

After multiple adjustments, it was determined that the risk of acquiring an HCAI was 16% lower in 2015 than it had been in 2011 (risk ratio, 0.84; 95% CI, 0.74-0.95; $P = 0.005$). Without adjustment for the presence of a ventilator, central venous catheter, or urinary catheter, there was a 24% reduction in HCAI during the interval.

■ COMMENTARY

This study demonstrates that national activities, locally applied, have had great success in reducing the prevalence of HCAI in the United States. The investigators estimated that in 2015 there were 633,300 (95% CI, 216,000 to 1,912,700) patients with an HCAI, a number that translates into a reduced prevalence since 2011.The largest improvement was seen in surgical site and urinary tract infections. The authors suggested that the former may be related to improved surgical antibiotic practices and, possibly, MRSA decolonization procedures. The decreased use of bladder catheters may have been responsible, at least in part, for a corresponding decrease in urinary tract infections despite adjustments in the multivariate analysis. In contrast, there was no evidence of a decrease in the prevalence of healthcare-associated pneumonia cases, most of which were not associated with mechanical ventilation, or of *C. difficile* infection. The latter presents some difficult issues in interpretation because of the introduction of PCR testing for the presence of the *toxinB* gene, which, if used alone, may overestimate the frequency of infection by this organism, possibly by a factor of 2. Although the diagnostic methods were not examined, such confounding may have masked an actual decrease in *C. difficile* infection.

Overall, these results point to the remarkable progress that has been made in reducing HCAI in the United States, but they also demonstrate that there is a long way to go. ■

ABSTRACT & COMMENTARY

Severe Sepsis and Septic Shock Early Management Bundle

By Kathryn Radigan, MD, MSc

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

SYNOPSIS: When the Severe Sepsis and Septic Shock Early Management Bundle was used to identify patients with severe sepsis or patients in septic shock, delays in lactate measurements for patients with abnormal lactate levels were associated with delayed initiation of antibiotic therapy and increased mortality.

SOURCE: Han X, Edelson DP, Snyder A, et al. Implications of Centers for Medicare & Medicaid Services Severe Sepsis and Septic Shock Early Management Bundle and initial lactate measurement on the management of sepsis. *Chest* 2018;154:302-308.

Sepsis remains the top cause of in-hospital death. Early recognition and timely treatment of sepsis through care bundles has become a priority. The Centers for Medicare & Medicaid Services (CMS) introduced the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) in October 2015. SEP-1 pinpoints patients with "severe sepsis" by selecting patients who meet two of four systemic inflammatory response syndrome (SIRS) criteria, demonstrate a documented suspicion of infection within a six-hour period, and exhibit one new organ dysfunction. Compliance with the bundle is measured by obtaining blood cultures, initiating antibiotics, and checking serum lactate between six hours before and three hours after presentation with a repeat lactate six hours later if elevated on initial draw. To characterize those who were affected and to analyze the implications of SEP-1 on patient care and outcomes, Han et al conducted a retrospective trial including 5,762 adult patients admitted to the University of Chicago from November 2008 through January 2016. All patients met one of the International Classification of Diseases, Ninth Revision (ICD-9) codes specified by SEP-1. Time to lactate draw, along with antibiotic and IV fluid administration, were measured. Additionally, researchers assessed in-hospital mortality.

Lactates were checked within the appropriate period 32% of the time on the ward (n = 505), 55% in the ICU (n = 818), and 79% in the ED (n = 2,144). Mortality increased with higher initial lactate levels across all locations. If lactate measurement was delayed, these patients exhibited the highest in-hospital mortality (29%) and were associated with an increased time to antibiotic administration (median time, 3.9 vs. 2.0 hours). The odds of death increased with every additional hour delay in lactate measurement for patients with initial

lactate > 2.0 mmol/L (odds ratio [OR], 1.02; 95% confidence interval [CI], 1.0003-1.05; *P* = 0.04). Delays in initial lactate measurement that were found to be elevated were associated with delayed fluid administration, delayed antibiotics, and increased mortality.

■ COMMENTARY

Severe sepsis accounts for almost 10% of all deaths.[1] Sepsis bundles have been implemented to decrease mortality. Despite the SEP-1 criteria, little is known regarding the consequences of delayed lactate measurement, especially in areas of the hospital outside the ED.

Interestingly, the Han et al study revealed that lactate measurement may make a significant difference for patients with sepsis and septic shock. This is not surprising, as lactate clearance has remained a fundamental goal in sepsis management. Patients with elevated values often receive more aggressive and timely resuscitation. Delayed lactate measurement not only affects length of stay (LOS), but more importantly, it affects overall mortality.

Patients who underwent a lactate draw within the SEP-1 window experienced the shortest LOS (median, 11 days; interquartile range [IQR], 7-19 days; *P* < 0.01). LOS was longest for patients who never received a lactate measurement (median, 18 days; IQR, 11-32 days), followed by those patients who experienced a delay in lactate measurement (median, 15 days; IQR, 9-26 days). As for mortality, patients with delayed lactates demonstrated the highest in-hospital mortality (29%), followed by those with lactate samples drawn within the CMS window (27%) and those without a lactate sample (23%; *P* < 0.01).

Although the authors did not address it specifically, it is interesting to note that there was a significant decrease in mortality and longer LOS for patients who never underwent a lactate draw. As opposed to the patients who underwent a lactate draw early and those with delayed lactate, one may infer that the severity of illness for patients who never underwent a lactate draw was less. Since these patients experienced decreased mortality, they are not dying early and, therefore, are in the hospital longer. The longer LOS also may be related to the fact that most of these patients were identified on the wards. Many of the events could have occurred later in the hospital stay.

Although the importance of early and appropriate antibiotics is known, many often forget that every hour delay in antimicrobial administration is associated with a 7.6% average decrease in survival.[2] Within this study, there was a significant increase in mortality for every hour of delay in initial lactate draw > 2.0 mmol/L, which was associated with a 2% increase in the odds of death in an adjusted analysis (OR, 1.02; 95% CI, 1.0003-1.05; *P* = 0.04). When these numbers were adjusted for time to antibiotics and IV fluids, the association no longer was significant (*P* = 0.51). There was a two-hour delay in receiving antibiotics and 1.3-hour delay for IV fluid bolus for those who received lactate measurement within the time frame. This, compared to 3.9 hours to antibiotics and 4.8 hours for IV fluid bolus for those who were measured later. Based on these data, the difference in mortality was associated with earlier interventions that included antibiotics, fluids, and source control.

Critically, clinicians need to give special attention to patients already admitted to the hospital. This study demonstrates that many patients develop sepsis on the wards. It is time to broaden our focus outside the ED. Although not addressed in this study, the identification of sepsis is paramount. Often, doctors and nurses on general medicine floors and in the ICU miss sepsis. Even though 60% of patients with severe sepsis underwent serum lactate measurements within the mandated period, timelines varied based on location of patient. For instance, 32% of patients met the standard SEP-1 timeline on the wards, compared with 55% in the ICU and 79% in the ED.

Regarding the patients who did not receive lactate within the mandated time frame, 14% received delayed lactates (between three and 24 hours after the time of first suspicion of sepsis). More than one-quarter had no lactate measurements at all. Since patients with initial lactate levels > 2.0 mmol/L were at an increased odds of death by 2% for each hour in lactate delay, it is important that recognition of sepsis and lactate measurements improve.

Systematic, timely lactate measurements in sepsis patients may be useful in prompting earlier, potentially life-saving interventions, including IV fluids and antibiotics. Clinicians also should focus on early resuscitation efforts that include lactate measurements in those populations in which there often is delay, especially those on the wards and ICU.

Despite the obvious benefits, researchers also were concerned that mandating lactate measurements for all sepsis patients may lead to many unwarranted lactate measurements and excessive resource use. More studies are needed to further improve patient outcomes. ■

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Metagenomics for Prosthetic Joint Infection

SOURCE: Thoendel MJ, Jeraldo PR, Greenwood-Quaintance KE, et al. Identification of prosthetic joint infection pathogens using a shotgun metagenomics approach. *Clin Infect Dis* 2018;67:1333-1338.

A good proportion of prosthetic joint infections (PJI) are culture-negative, necessitating prolonged courses of empiric antibacterial therapy. Even more frustrating are those cases of suspected PJI in which infection cannot be confirmed, and the role of infection in chronic hip or knee pain or aseptic loosening remains a concern.

These authors compared culture data derived from sonication of resected hip and knee components with a shotgun metagenomics approach. In this case, "shotgun" simply means that all nucleic acid in a sample is extracted and sequenced by next-generation sequencing techniques, and the sequences are read and identified.

From 2011-2016, a total of 408 cases were selected sequentially from a database of orthopedic cases in which sonication for culture was used, although the decision to use sonication for any particular case was at the discretion of the individual surgeon. These cases included 213 patients with PJI and 195 without infection in whom surgery was performed for other reasons (e.g., aseptic loosening). A positive culture was defined as isolation of the same organism from two or more intra-operative specimens, with at least ≥ 20 colony-forming units of growth.

Of the 213 subjects with suspected PJI, 115 (54%) were culture-positive by sonication and 98 (46%) were culture-negative. Metagenomics identified the same bacterial pathogen as sonication cultures in 109 of 115 (94.8%) cases. Additionally, metagenomics identified probable pathogens in 11 of these culture-positive cases (9.6%) not previously detected by culture, suggesting polymicrobial infection. Potential pathogens also were identified in 43 of 98 (43.9%) culture-negative cases of PJI. While most of the organisms identified by metagenomics were organisms common to PJI, one unique pathogen picked up in metagenomic testing, not identified by culture, was *Mycoplasma salivarium*.

However, when comparing all available culture results, including the results of blood culture or any cultures obtained prior to surgery, metagenomics identified pathogens in 121 of 146 culture-positive cases (82.9%), plus additional pathogens detected in 12 cases. Sixteen cases had at least one pathogen isolated in culture that was not detected in joint specimens by metagenomics; 14 of these had received antibiotics prior to surgery, and seven also had negative sonification cultures.

In only six of the 115 PJI cases (5.2%), an organism was detected by sonication culture but was not detected by metagenomics. These included the isolation of *Pseudomonas aeruginosa* infection in two cases (which may be more susceptible to DNA degradation), *Candida albicans* in two cases, and *Escherichia coli*, *Enterobacter cloacae*, and *Mycobacterium abscessus* in one case each.

Sonicated specimens from (presumably) uninfected prosthesis or components were submitted for metagenomic testing in 195 cases. Seven (3.6%) were positive for potential pathogens, all organisms recognized to cause PJI.

The authors acknowledged that a limitation to the use of metagenomics for PJI is the ability to distinguish background "noise" and contaminants from true pathogens. Many of the organisms contributing to PJI generally would be considered contaminants in other clinical specimens (e.g., skin organisms). Higher "read counts" provided an inference as to the likelihood of a true pathogen, but generally those specimens that were negative in culture also gave fewer "read counts." Further, although metagenomics may provide information about the presence of a potential pathogen, susceptibility data still are lacking.

Helicobacter pylori: A Mini Primer

SOURCE: Siddique O, Ovalle A, Siddique AS, Moss SF. *Helicobacter pylori* infection: An update for the internist in the age of increasing global antibiotic resistance. *Am J Med* 2018;131:473-479.

Like every other infection we deal with, *Helicobacter pylori* (HP) is increasingly drug resistant. Estimated failure rates are 5-10%, even after receipt of two different antimicrobial regimens. Failures most often are due to resistance to clarithromycin (which may be as high as 30% in some countries and in some parts of the United States) and levofloxacin (which also may be approaching resistance rates of 30% in some parts of the United States). Physicians need to keep pace with the consequences of this development and newer recommendations. Although the prevalence of HP seems to be decreasing in the United States, at least in higher socioeconomic strata, HP remains a problem for lower-income groups, travelers to developing countries, and the rest of the world. The prevalence of HP is believed to be > 50% in some parts of the world, especially in Central Asia, Central America, and Eastern Europe.

There are multiple barriers to appropriate testing and treatment:

- The first barrier is the promotion of testing for HP in patients at risk. HP screening is indicated for anyone with recurring epigastric discomfort, chronic use of nonsteroidal anti-inflammatory drugs, unexplained iron deficiency anemia, and ITP. Any of the "alarm symptoms," such as recurrent vomiting, weight loss, and dysphagia, especially with a family history of gastric cancer, should prompt endoscopy with biopsy and examination for HP.
- The second barrier is the type and timing of testing. Tests for active infection include stool antigen testing and the urea breath test (both ≥ 95% sensitive, ≥ 95% specific). But they must be performed more than four weeks after the use of any bismuth-containing product or antibiotic, and all proton pump inhibitors (PPI) must be stopped for more than two weeks. Serologic testing is not recommended, as it may remain positive for many years after successful eradication and is associated with a higher false-positive rate.
- When selecting a first-line regimen, the patient should be queried about antibiotic use in the past one to two years. Prior treatment with macrolides or levofloxacin may increase the risk of resistance, and a regimen without the respective agent should be selected. In contrast, resistance to amoxicillin, tetracycline, and metronidazole is uncommon (< 2%).
- Patients should be counseled that strict adherence to the regimen is necessary. Missed doses may increase the risk of developing resistance during treatment, especially with clarithromycin; and completion of the entire regimen is important to successful eradication.

[There are multiple barriers to appropriate testing and treatment for *H. pylori*.]

- In those who fail a first-line regimen, consider whether the patient has a penicillin allergy and whether clarithromycin or levofloxacin was used in the first regimen. There are two or three options depending on the answers to these questions. For example, for patients who fail a first-line regimen containing clarithromycin, a regimen without clarithromycin should be selected (e.g., amoxicillin, levofloxacin, PPI × 14 days).
- The management of patients who have failed two regimens is not straightforward. Endoscopy with biopsy and culture for susceptibility testing is recommended, although the organism does not always grow well in culture, and susceptibility testing is not widely available. Empiric treatment with a non-clarithromycin-based regimen (e.g., rifabutin, amoxicillin, PPI × 10 days) in those previously treated with clarithromycin can be attempted. A levofloxacin-containing regimen can be used in those not previously treated with fluoroquinolones. Increasing the dose of the PPI, or using newer, more potent PPIs, may be helpful.
- Finally, confirming eradication four weeks or more following completion of treatment is mandatory. ■

ABIM CME MOC ACCREDITED

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following statements is true regarding vivax malaria?

a. It is increasingly common in Africa.

b. It requires "radical cure" with primaquine only if the person is leaving the endemic area.

c. It clears more quickly with chloroquine than with artesunate.

d. It recurs less frequently with chloroquine than with artesunate.

2. Which of the following is correct?

a. The western United States is endemic for *Blastomyces dermatitidis*.

b. In culture, *Blastomyces dermatitidis* is characterized by a lack of conidia and the presence of helical mycelia.

c. The majority of reported human cases of *Blastomyces helicus* infection have occurred in immunocompromised hosts.

d. Almost one-half of reported cases of *Blastomyces helicus* infection have been acquired in the mid-Atlantic states.

3. Which of the following is correct regarding a comparison of the adjusted risk of acquiring a healthcare-associated infection in the United States in 2011 vs. 2015?

a. The risk was 16% lower in 2015 compared to 2011.

b. The risk was 16% higher in 2015 compared to 2011.

c. The risk did not change between 2015 and 2011.

d. The risk could not be calculated because of changes in reporting.

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.