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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Trimethoprim-sulfamethoxazole versus Placebo for Skin Abscesses After Incision and Drainage

By Richard R. Watkins, MD, MS, FACP

Dr. Watkins is with the Division of Infectious Diseases, Akron General Medical Center, Akron, OH; Associate Professor of Internal Medicine, Northeast Ohio Medical University, Rootstown, OH.

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

SYNOPSIS: A multicenter, double-blind, randomized clinical trial found that a 7-day course of trimethoprim-sulfamethoxazole following incision and drainage (I&D) resulted in a higher rate of cure for skin abscesses compared to I&D and placebo (80.5% vs 73.6%, respectively; $P = 0.005$).

SOURCE: Talan DA, et al. Trimethoprim-sulfamethoxazole versus placebo for uncomplicated skin abscess. *N Engl J Med* 2016;374: 823-832.

A skin abscess is a common presenting complaint in emergency departments, especially since the emergence of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA). Incision and drainage (I&D) is the primary treatment, and antibiotics have been considered adjunctive. Talan and colleagues aimed to clarify the role for trimethoprim-sulfamethoxazole (TMP-SMX) in treating skin abscesses after I&D and determine if this drug leads to a higher rate of cure.

The study was a double-blind, randomized clinical trial that compared a 7-day outpatient course of TMP-SMX (320 mg/1600 mg) twice a day to placebo for patients with cutaneous abscesses who received I&D in the emergency department. Patients older than 12 years of age were enrolled from five emergency departments between April 2009 and

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April 2013. They all had a skin abscess that was present for less than a week and measured at least 2 cm in diameter. The primary outcome was clinical cure of the abscess, which was determined 7-14 days after the end of the treatment period.

A total of 630 patients were randomized to receive TMP-SMX, while 617 received placebo. Their median age was 35 years (range, 14-73) and 58.2% were male. MRSA grew in 45.3% of the wound cultures, and 97.4% of the strains were susceptible to TMP-SMX. The abscess cure rate was 80.5% in the TMP-SMX group compared to 73.6% in the placebo group ($P = 0.005$) in the modified intention-to-treat population, which included all participants who took at least one dose of TMP-SMX or placebo. In the per-protocol group, which included patients who took ≥ 75% of the total doses of study drug during the first 5 days and had a test-of-cure visit, clinical cure for those who received TMP-SMX was 92.9% vs 85.7% for placebo ($P < 0.001$). TMP-SMX was superior to placebo for most of the secondary outcomes, including lower rates of subsequent surgical drainage procedures, skin infections at a new site, and infections among household members. Gastrointestinal symptoms were the most common adverse events, which occurred among 42.7% in the TMP-SMX group and 36.1% in the placebo group.

■ COMMENTARY

The decision to prescribe oral antibiotics for uncomplicated skin abscesses after I&D has been controversial. The potential benefits, including faster healing, reduced future occurrences, and decreased transmission to household contacts, need to be weighed against the risks of side effects, potentially spreading antibiotic resistance, *C. difficile* infection, and the cost of medication. The 2014 Infectious Diseases Society of America (IDSA) guidelines recommend antibiotics after I&D for patients with impaired host defenses or evidence of systemic inflammatory response syndrome (SIRS), including temperature > 38°C or < 36°C, tachypnea > 24 breaths per minute, tachycardia > 90 beats per minute, or white blood cell count > 12,000 or < 4000 cells/μL, which is based on moderate quality evidence.[1] Of the five studies cited for this recommendation, only two were conducted during the current MRSA era; one included children and one included adults. The latter was a multicenter, double-blind, randomized, placebo-controlled trial that found treatment with TMP-SMX after I&D did not reduce treatment failure but did decrease the formation of subsequent lesions.[2] However, this study and others have been criticized for being underpowered because the cure rate with I&D alone exceeds 80% and large sample sizes are necessary to test for small differences in cure rates.

The study by Talan and colleagues provides some welcome clarity to the role for antibiotics after I&D. Their study was large, well-designed, and found a significant benefit for a 7-day course of TMP-SMX. The low rate of adverse events with TMP-SMX was surprising, since this drug is one of the most frequent antibiotics to cause adverse reactions, including ones that lead to emergency room visits.[3] While the risks associated with antibiotics (as stated above) are well known, one also needs to appreciate that higher cures of primary abscesses will subsequently lead to reduced costs from fewer follow-up visits, surgeries, hospitalizations, and less spreading of infection to others in households and communities. Although it is the latest, the present study will likely not be the last on the topic. Clinicians must manage cutaneous abscesses based on careful interpretation of the available data. Therefore, after a frank discussion with the patient about the risks and benefits, a 7-day course of an antibiotic with MRSA activity (e.g., TMP-SMX or doxycycline) should be prescribed after I&D of a moderate-sized (≥ 2 cm) cutaneous abscess. ■

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ABSTRACT & COMMENTARY

Pediatric Coccidioidomycosis in California, 2000-2012

By Dean L. Winslow, MD, FACP, FIDSA

Dr. Winslow is 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: The incidence of pediatric coccidioidomycosis in California has increased significantly from 2000 until 2012, along with hospitalization for complicated disease. Latino children were most commonly infected, but African-American children were significantly more likely to be hospitalized.

SOURCE: Sondermeyer GL, et al. Epidemiology of pediatric coccidioidomycosis in California, 2000-2012. *Ped Infect Dis J* 2016;35:166-171.

The reported rates of coccidioidomycosis have increased five-fold from 2.4/100,000 population in 2000 to 10.8 in 2012. To specifically evaluate the epidemiology of coccy in pediatric patients, three datasets were analyzed: surveillance, hospitalization, and death datasets. The total cases of coccy reported during this period in California were 35,804, including 3453 incident cases in children 17 years of age or younger. Eight hundred forty-one pediatric cases required hospitalization. In children, the overall incidence and rates of hospitalization increased six-fold, with incidence going from 0.7 to 3.9, and hospitalization rate increasing from 0.2 to 1.2 cases/100,000 population. The RR of both infection and hospitalization was slightly higher for males than females and higher in the older age group (12-17 years) than in the youngest children (0-2 years). The risk of infection was greater in Latino children, but the risk of hospitalization was greatest in African-American children when compared to white children. RR of infection was 95 times greater in children coming from endemic areas compared to less endemic areas. Of the 841 hospitalized pediatric patients, 58% had a diagnosis of pulmonary coccy, 21% had other forms of progressive coccy, and 7% had meningeal disease. African-American children had the lowest proportion of primary pulmonary coccy (40%) and highest proportion of other progressive disease (48%).

Only 11% of hospitalized pediatric coccy patients were diagnosed with an immunocompromising condition, and 1% had diabetes. Twenty percent of hospitalized patients were re-admitted at least once, with a median length of stay of 7 days. During the period of study from 2000-2012, more than $149MM in total charges related to the hospitalizations was accrued.

[This study sheds light on the epidemiology of coccy in the pediatric population.]

During the period of study, there were 11 pediatric coccidioidomycosis-associated deaths. Of the 11 children who died, eight were male, two were younger than 2 years of age, three were 3-11 years old, and six were 12-17 years of age. Six children who died were Latino, two were African-American, two were Asian/Pacific Islander, and one child was white. Of the 11 deaths, three carried a death diagnosis of disseminated coccy, two had meningitis, two had pulmonary coccy, and four had "unspecified" coccidioidomycosis.

■ COMMENTARY

The reasons for the increase in coccidioidomycosis diagnoses in California during the past decade are unclear. This study sheds light on the epidemiology of coccy in the pediatric population. While many think of coccy as being a threat in patients residing in (or traveling through) the Central Valley, those of us practicing at referral centers in California

have clearly seen many cases of coccy in patients who reside in areas of California not previously considered to be endemic for this disease. In my own limited personal experience caring for children with coccy, the diagnosis of coccy often is not considered by pediatricians early in the clinical course, and patients often have fairly severe disease by the time they are sent to us. This is certainly understandable since the initial clinical manifestations of this disease may be nonspecific. A recent review of 13 cases of coccy in infants (from Madera, in the highly endemic Central Valley) highlights the problem of delayed diagnosis of coccy in young children, even in an area where coccy is known to be endemic.[1] This case series highlighted the severity of illness and disseminated disease. Many of these young children developed pleural and pericardial effusion, hilar and mediastinal adenopathy, lung abscess, neck abscess, and intracranial abscesses. One infant even developed depressed temporoparietal skull fracture related to osteomyelitis of the skull. The paper by Sondermeyer et al should be a good reminder to at least consider coccy in the differential diagnosis of sick children in almost all areas of California, as well as in those who had visited endemic areas.

We also need better, safer, and more effective treatment for CNS coccidioidomycosis in particular. Unfortunately, experimental animal models of CNS coccy are not highly predictive of human disease. Due to the relative rarity of CNS disease, large randomized, controlled trials of various drugs and treatment modalities (such as intrathecal amphotericin B) would be very difficult to conduct. I am still haunted by the memory of a beautiful 5-year-old child, whose case I helped manage about 6 years ago at our county hospital. This little boy developed severe CNS disease complicated by hydrocephalus and intracranial vasculitis with stroke. Despite neurosurgical intervention, systemic fluconazole, intrathecal amphotericin B, and systemic corticosteroids, the child died. I would have given just about anything to have been able to save this child's life. ■

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ABSTRACT & COMMENTARY

Antibiotic Use in Treatment of Children with Uncomplicated Severe Acute Malnutrition

By Simrit K. Warring and Philip R. Fischer, MD, DTM&H

Simrit K. Warring is a Mayo Medical School student. Dr. Fischer is Professor of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

Ms. Warring and Dr. Fischer report no relevant financial relationships related to this field of study.

SYNOPSIS: Universal antibiotic use in the community-based treatment of uncomplicated severe acute malnutrition in children likely is not necessary in regions where suitable access to healthcare facilities is available.

SOURCE: Isanaka S, et al. Routine amoxicillin for uncomplicated severe acute malnutrition in children. *N Engl J Med* 2016;374:444-453.

Malnutrition continues to be a major public health problem in the developing world, with severe acute malnutrition affecting approximately 19 million children younger than the age of 5 years worldwide. The classification of malnutrition may be mild, moderate, or severe based on clinical assessment, anthropometry, and biochemistry. Severe acute malnutrition is defined by weight-for-height more than three z-scores below the mean (i.e., more than three standard deviations below the mean), and/or malnutrition with edema of both feet.[1] Uncomplicated severe acute malnutrition is defined as severe acute malnutrition without edema and without anorexia, fever, hypothermia, vomiting, severe dehydration, severe anemia, altered consciousness, altered respiration, or moderate to severe skin infection. Severe acute malnutrition is a life-threatening condition that substantially increases mortality and disease burden among children, therefore requiring specialized medical attention.

In 1999, the World Health Organization (WHO)

introduced guidelines in the *Management of Severe Malnutrition: A Manual for Physicians and Other Senior Health Workers*.[2] The manual includes a 10-step ordered approach of three treatment phases to improve the identification and treatment of severe acute malnutrition. The first phase includes the initial treatment to stabilize the child's condition. The second phase includes rehabilitation involving increasing energy content and volume of feeds to recover the lost weight. The third phase includes follow-up after discharge to ensure proper development.

Children with severe acute malnutrition are especially susceptible to infections. Unlike well-nourished children who respond to infection with an inflammatory or febrile response, malnourished children with serious infections may just seem apathetic or drowsy.[2] The infection therefore can be hidden from clinical presentation. The WHO 10-step approach recommends the routine use of broad-spectrum antibiotics because data indicated that early treatment of bacterial infections with effective antibiotics improved the nutritional response to feeding, preventing septic shock and reducing mortality. More recently, the WHO and the United Nations in 2007 supported a community-based model in which children with uncomplicated severe acute malnutrition were treated at home.[3] There is limited evidence to support that the same medical protocol of routine antibiotics within the inpatient care setting be used in community-based treatment.

The double-blind, placebo-controlled trial, organized by Dr. Sheila Isanaka and her colleagues, was conducted at four health centers in the rural health district of Madarounfa, Niger. Children between 6 and 59 months of age with uncomplicated severe acute malnutrition were randomly assigned to receive amoxicillin or placebo for 7 days. Each child also received the standard care of ready-to-use therapeutic food (RUTF) (170 kcal per kilogram per day; Plumpy'Nut Nutriset) for outpatient treatment of uncomplicated severe acute malnutrition. A total of 2412 children underwent randomization, and 2399 children included in the analysis. Nutritional recovery at or before 8 weeks, identified as the primary outcome, occurred in 65.9% (790 of 1199) of children in the amoxicillin group vs 62.7% (752 of 1200) in the placebo group.

The study determined that there was no significant difference in the likelihood of nutritional recovery (risk ratio for amoxicillin vs placebo, 1.05; 95% confidence interval [CI], 0.99-1.12; $P = 0.10$). Secondary evaluation showed that amoxicillin decreased the risk of hospitalization by 24% and the risk of transfer to inpatient care by 14%. There were no between-group differences in the mean length of stay among hospitalized patients or rate of recovery, as children in both groups recovered quickly given adequate inpatient care, mitigating any risk associated with the absence of amoxicillin treatment inclusion. Overall, this study found no significant benefit of routine amoxicillin use with respect to nutritional recovery among children with uncomplicated severe acute malnutrition in Niger.

■ COMMENTARY

The notion that routine antibiotic therapy in the treatment of uncomplicated severe acute malnutrition is always necessary or beneficial is called into question by this study. Eliminating routine antibiotic use in community-based treatments would simplify treatment and result in cost savings with regard to medications, staff, and infrastructure for delivery. Furthermore, a decreased risk of antibiotic use might minimize the risk of resistant microbial strain emergence, fostering responsible antibiotic stewardship. Research providing evidence that antibiotics should be used routinely in community-based treatments for uncomplicated severe acute malnutrition is limited. This valuable study brings into consideration the elimination of routine use of antibiotics in the protocol for uncomplicated severe acute malnutrition community-based treatment, specifically for children in regions where access to appropriate healthcare facilities and services is available. Notably, access to adequate healthcare services is not universal to all children with malnutrition, especially in rural regions of the developing world where malnutrition rates are the highest. Additionally, not all children with uncomplicated malnutrition have a similar clinical presentation, as some children will have comorbid illnesses that require special attention.

A study done in Malawi in 2013 evaluating the use of routine antibiotic therapy for "uncomplicated" severe acute malnutrition demonstrated that amoxicillin significantly reduced the risk of treatment failure and death as compared to placebo.[4] It is important to note that this study included a high-risk study population, characterized by a high burden of kwashiorkor and human immunodeficiency virus (HIV) infection, in contrast to the study done in Niger, which predominately included malnutrition due to marasmus and a population with low prevalence of HIV infection.

Continued surveillance of regions that have access to adequate healthcare facilities and resources would be required before we could eliminate the routine antibiotic regimen in community-based treatment for

uncomplicated severe acute malnutrition. Isanaka's study nicely showed that routine antibiotic use may not always be necessary, but essentially the application of this study should be limited only to settings with excellent outpatient follow-up and access to inpatient care (since more children in the placebo group required subsequent transfer to inpatient care). In regions with limited follow-up and access to adequate healthcare facilities, children with uncomplicated severe acute malnutrition should be admitted and given antibiotics to avoid deterioration or illness from hidden infections. This well-designed study illustrates that there is a need for further investigation to support the continued practice of widespread use of antibiotics in uncomplicated severe acute malnutrition. ■

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ABSTRACT & COMMENTARY

Saccharomyces Cerevisiae var *boulardii* (*S. boulardii*) and Antibiotic-associated Diarrhea

By Stan Deresinski, MD, FACP, FIDSA

Dr. Deresinski is Clinical Professor of Medicine, Stanford University.

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

SYNOPSIS: *Saccharomyces boulardii* administration failed to prevent antibiotic-associated diarrhea in a large randomized trial.

SOURCE: Ehrhardt S, Guo N, et al. *Saccharomyces boulardii* to prevent antibiotic-associated diarrhea: A randomized, double-masked, placebo-controlled trial. *Open Forum Infect Dis* (Winter 2016) 3 (1): doi: 10.1093/ofid/ofw011.

Ehrhardt and colleagues randomized adults who were prescribed systemic antibiotics while hospitalized at 15 hospitals in Germany to receive either placebo or *Saccharomyces boulardii* administered as a commercial preparation (Perenterol) containing at least 1.8 x 10^{10} live cells/gram of lyophilisate. The test preparation was started a mean of 0.5 days after the administration of the first dose of antibiotic and was to be continued for 7 days after antibiotic(s) discontinuation. If antibiotic therapy was resumed during this period (phase II), there was a return to phase I.

The incidence of antibiotic-associated diarrhea (AAD), defined as first appearing ≥ 3 days after antibiotic initiation, was analyzed according to two definitions of diarrhea: the World Health Organization (WHO) definition requiring three or more loose or liquid stools within 24 hours; and a modified WHO definition requiring at least 2 days of diarrhea. A third definition with the WHO criteria and diarrhea for 5 days occurred in only one patient. Of the 2444 patients screened, only 477 were randomized (1:1). While a power calculation had indicated that 686 patients would be needed in each group to achieve an 80% power to detect a 5% difference in the between-treatment group incidence of AAD, the study was stopped early because of futility — i.e., further enrollment would not be likely to alter the overall results. The mean age of the participants was 58.4 years, and 56.4% were male. The mean duration of antibiotic administration was 7.6 ± 6.5 days. Approximately four-fifths received a beta-lactam and the majority received combination antibiotic therapy. A nitroimidazole (presumably metronidazole) was administered to 15.5% and 13.0% in the *S. boulardii* and placebo arms, respectively. A total of 40 cases of AAD occurred in the 425 subjects whose total time at risk was 19,165 days. Of the total, 21 and 19 AAD episodes occurred in the *S. boulardii* and placebo recipients, respectively. The hazard ratio of AAD in the *S. boulardii* group compared with the placebo group was 1.02 (95% confidence interval [CI], 0.55–1.90;

$P = 0.94$). There were 2 cases of *Clostridium difficile* infection in each arm of the study.

■ COMMENTARY

The authors cite data indicating that sales of probiotics are predicted to be $48 billion by 2017. There is a remarkably broad array of microorganisms that have been suggested to have favorable effects when administered to subjects. *S. boulardii* is very closely related both metabolically and genetically to common brewer's yeast, *Saccharomyces cerevisiae*, to the extent that some have suggested they are basically the same organism. In fact, it should probably be formally referred to as *Saccharomyces cerevisiae* var *boulardii* (*S. boulardii*).

A recent meta-analysis of 21 randomized clinical trials with a comparison to placebo or no treatment concluded that *S. boulardii* administration was associated with a reduction in the incidence of AAD from 18.7% to 8.5% (risk ratio [RR], 0.47; 95% CI, 0.38-0.57) with a number needed to treat of 10 (95% CI, 9-13).[2] It also appeared to significantly reduce the risk of *C. difficile* infection (CDI) in children, but not in adults.

In contrast, quasi-experimental experience at a large hospital, also recently reported, also argues against the usefulness of *S. boulardii* in the prevention of CDI. The hospital discontinued the use of an automatic order linking the administration of this organism to the prescription of selected broad-spectrum antibiotics and, at the same time, the preparation was removed from the hospital formulary.[2] During a 13-month period while the protocol was active, the incidence of hospital-onset CDI for all inpatients was 0.99 per 1000 patients, compared to 1.04 per 1000 patient days ($P = 0.10$) after the removal of *S. boulardii* from the formulary. Limiting the analysis to those patients receiving the linked broad-spectrum antibiotics, the occurrence of CDI was 1.25% while the protocol was active and 1.51% ($P = 0.70$) after its abolition.

Once again, the role of probiotics remains unclear. In the study by Earhardt and colleagues, the incidence of AAP and of CDI was lower than that usually reported and than that anticipated by the investigators. This was likely due, at least in part, to the exclusion criteria, which resulted in a healthier, younger group of hospital inpatients than those at greatest risk of complications of antibiotic therapy. Thus, e.g., immunocompromised patients were excluded because of admonitions against the use of probiotics in this group.

The argument goes on, but right now I am on the "con" side. ■

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ABSTRACT & COMMENTARY

Early Chest CT Can Improve Treatment for Community-acquired Pneumonia

By Samuel Nadler, MD, PhD

Critical Care, Pulmonary Medicine, The Polyclinic Madison Center, Seattle; Clinical Instructor, University of Washington, Seattle

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

SYNOPSIS: In patients with suspected community-acquired pneumonia, early chest CT significantly changed management decisions.

SOURCE: Claessens YE, et al. Early chest computed tomography scan to assist diagnosis and guide treatment decision for suspected community-acquired pneumonia. *Am J Respir Crit Care Med* 2015;192:974-982.

Community-acquired pneumonia (CAP) is a very common diagnostic consideration. Early diagnosis and administration of antibiotics can save lives. However, the clinical diagnosis is often uncertain and misdiagnosis is frequent. This leads to inappropriate treatment with unnecessary antibiotics and may obscure the real underlying diagnosis. Even chest radiographs (CXRs)

demonstrating abnormalities can be misleading, and the concordance of interpretations of these infiltrates is poor, regardless of practitioner experience.[1] Thus, reliance on clinical factors and CXRs may lead to misdiagnosis and mistreatment of many patients presenting with respiratory disease.

This study hypothesized that the use of early computed tomography (CT) of the chest would improve the diagnosis and subsequent management of CAP. This was a prospective, interventional study in four tertiary teaching hospitals between November 2011 and January 2013. Enrolled in this study were 319 adults > 18 years of age who presented to the emergency department (ED) with suspicion of CAP. The criteria for CAP included: new onset of systemic symptoms (sweats, chills, aches, temperature > 38°C or < 36°C) and symptoms of lower respiratory tract infection (cough, sputum, dyspnea, chest pain, or altered breath sounds). Exclusions included: pregnancy, hospice patients, inability to complete the study, CURB-65 score of 3 or higher, or the need for ICU admission. A local radiologist performed CXRs and reported findings in a standardized fashion. Multi-detector chest CT using a low-dose protocol was performed as soon as possible afterward and was similarly interpreted. At this point, the ED physician completed a clinical report assigning a pneumonia probability and treatment plan.

Three independent evaluators who were experts in pulmonary medicine, infectious disease, or radiology subsequently adjudicated each assessment and defined the likelihood of CAP based on clinical and radiographic data and assigned a probability of CAP (definite, probable, possible, or excluded). Each case was then re-evaluated using data from the time of clinical discharge up to day 28 and assigned a final probability category.

After the initial clinical assessment and chest radiograph, the percentages of patients assigned to the CAP probability categories of definite, probable, possible, or excluded were 44.9%, 36.9%, 16.9%, and 1.2%, respectively. After chest CT, these categories shifted to 50.9%, 10.9%, 9.4%, and 28.8%, respectively. Adjudicating committee assignments were 47%, 8.7%, 11.3%, and 32.9%, respectively. At the 28-day final adjudication, the distribution was 47%, 4.1%, 10.7%, and 38.2%, respectively. Interestingly, of the 120 patients without parenchymal infiltrates on CXR, 40 had infiltrates on CT that conventional CXR missed. Conversely, of the 188 patients with parenchymal infiltrates on CXR, CT scans excluded CAP in 56 patients. Based on these CT findings, the ED physician modified the probability of CAP diagnosis in 187 of the patients (58.6%; 95% confidence interval, 53.2-64.0). Of these patients, 59 were upgraded and 128 downgraded based on CT, including 11 of 36 patients previously considered as definite CAP by CXR.

COMMENTARY

This was an intriguing study that clearly showed the limitations of clinical factors and CXRs to diagnose CAP. More than half (58.6%) of the pre-CT probabilities of CAP were altered after chest CT. Prior to chest CT, 64.7% of patients were intended to start antibiotic therapy and after chest CT, researchers ended the administration of antibiotics in 29 patients. Furthermore, 51 patients who did not receive antibiotics after CXRs were then administered therapy after receiving a CT scan. Three pulmonary emboli were discovered, and cardiac failure was diagnosed in 11 patients. Furthermore, 45 patients had a change in level of care, including 22 outpatients being admitted and 23 admissions changed to discharges. Overall, modifications of antibiotics or site of care occurred in 60.8% of patients.

[Ultimately, the decision to use CT scanning for the diagnosis of CAP will require a thorough analysis of the cost of care and the outcomes data.]

It appears that most of the changes in diagnostic probability were in marginal cases. The percentage of "probable" CAP cases decreased with progressive assessments from 36.9% with CXR and clinical suspicion alone, to 10.9% after CT, to 8.7% after committee adjudication, and to 4.1% at 28 days. The number of "possible" cases decreased from 16.9% to 9.4% with chest CT. In a univariate secondary analysis, among 188 out of 308 patients with an infiltrate on CXR, CT excluded CAP in 56 patients. These patients, compared to the 132 with infiltrates confirmed on CT, tended to be older (71.1 vs 63.2 years of age; $P = 0.0131$), have lower white blood cell (WBC) counts (10.2 vs 12.6 x $10^3/mm^3$; $P = 0.283$) and lower C-reactive protein (CRP) levels (78 vs 163.3 mg/L; $P = 0.0074$). Conversely, among 120 patients without infiltrates on CXR who also had a CT, 40 patients had CT infiltrates compatible with CAP. Compared to the 80 patients without CT infiltrates, those 40 patients with CT infiltrates were more likely to have crackles on exam (48.7% vs 26.6%; $P = 0.0169$), higher WBC counts (12.3 vs 10.2 x $10^3/mm^3$; $P = 0.0387$), and higher CRP levels

(138.1 vs 59.9 mg/L; $P = 0.0037$). Thus, clinical factors such as lung auscultation and CRP still seem to have a good predictive value for CAP.

Ultimately, the decision to use CT scanning for the diagnosis of CAP will require a thorough analysis of the cost of care and the outcomes data. It may very well be that the improved diagnostic accuracy of CT scanning will reduce the cost of care enough to offset the cost of additional CT scans. Furthermore, earlier administration of antibiotics with CT-confirmed CAP and prevention of unnecessary antibiotics in those without CAP might also improve health outcomes. Both these factors should be prospectively examined before entertaining the widespread adoption of routine CT for the diagnosis of CAP. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

TB in Captive Elephants in the United States

SOURCE: Diagnosis of tuberculosis in three zoo elephants and a human contact — Oregon, 2013. *MMWR Morbid Mortal Wkly Rep* 2016;64:1398-1402.

Animal-to-human transmission of tuberculosis (TB) has been well-documented for a number of mammalian species, including deer, dogs, and even cats. Transmission of TB from circus elephants to humans occurred in the United States in the 1990s, and was reported in *Infectious Disease Alert* many years ago. It has since been recognized that TB is endemic in captive elephants in the United States (~5% are infected with TB based on truncal washings or necropsy), prompting the U.S. Department of Agriculture's Animal and Plant Health Inspection Service in 1998 to develop guidelines for screening and diagnosis of TB in captive elephants, as well as contact precautions. These included recommendations for three consecutive truncal washings for AFB smear and culture for each elephant every year.

The problem is, no one really knows how to detect latent TB in elephants (imagine the skin test). The use of gamma-interferon assays is controversial and believed to result in too many false-positives. Nor is it clear how to effectively screen those with latent disease for active infection. Data for 2011 indicated that about 270 Asian and 220 African elephants were living in the United States, many of them at refuges for the old or infirm — and all of these are screened with trunk washings on an annual basis.

[... TB is endemic in captive elephants in the United States.]

Evidence suggests, however, this approach may not be sufficiently sensitive for the detection of active TB. From 2004 to 2006, a non-profit reserve in Tennessee, which cares for retired or sick elephants within a 2700-acre reserve, received two Asian elephants with active TB and eight elephants with TB exposure. Infection control and treatment protocols were established, and the sick elephants were quarantined. Sadly, one the elephants died of TB, but the other was cleared of infection at 1 year of treatment.

The remaining elephants were trained to provide their own trunk washing samples (install 30-60 cc of saline, lift and lower, lift and lower, and exhale into a plastic bag) for regular screening. In addition, environmental samples from the elephants and their excrement were cultured. From 2006 to 2009, all trunk washings, as well as environmental samples, were negative. Despite these measures, 13 of 46 employees converted their PPD. Five were elephant caregivers, two were maintenance workers, and several were administrative staff who worked in an adjacent two-story building (which shared a ventilation system). Employees who converted their skin tests admitted to less rigorous use of N95 masks, in part because trunk washings from elephants in the main barn had been consistently culture-negative, yielding a

general laxity regarding infection control (IC) precautions.

More recently, public health officials in Portland, OR, have confirmed an outbreak of TB in elephants at the Oregon Zoo, likely resulting in one human case of active TB and seven cases of latent infection, despite appropriate precautions. The investigation, which has been ongoing since 2013, focused on three bull elephants — including Packy, his son Rama, and Tusko (ages 51, 20, and 44 years, respectively) — each of whom developed active TB in 2013-2014. The first elephant TB case was detected in Rama, with a positive annual trunk washing in May 2013. This prompted zoo officials to increase the frequency of trunk washings in the other seven elephants, including monthly washings in those with positive TB antibodies and quarterly washings in those without TB antibodies.

[This information suggests that episodic excretion and transmission of TB from elephants is possible, despite culture-negative trunk washings.]

Within 6 months, Rama's father, Packy, who had positive antibiodies to TB, had a positive trunk culture. And in January 2014, a third male elephant was found with active infection. All sick elephants were appropriately quarantined and treated (elephants with TB are not euthanized).

An initial public health investigation of 19 close contacts began in 2013, and six new latent TB infections and one previously positive PPD were identified, none of whom had evidence of active infection. Close contacts were defined as persons with any presence within the 8300 square foot elephant barn or within 15 feet of any of the eight elephants in the enclosed outdoor space within the previous 12 months. Based on these results, the investigation was expanded to 59 casual contacts, including 20 people who had attended a special event where Rama painted a canvas by spraying paint with his trunk. None of these individuals were positive. Somewhat after the fact, an individual treated for TB in 2012 in Portland was recognized as having volunteered at the facility in 2012. This fact was not initially recognized, but a review of patients' genotypes found no match for his isolate anywhere in Oregon. Whole genome sequencing at the CDC confirmed that the volunteer's isolate and Rama's isolate were a match, indicating likely transmission of TB between the two. While it seems more likely that transmission occurred from the elephant to the volunteer, the direction of transmission is still "up in the air." Further screening of 18 other individuals who worked with elephants in 2012, before the outbreak was recognized, screened negative.

This information suggests that episodic excretion and transmission of TB from elephants is possible, despite culture-negative trunk washings. The practice of annual trunk washings for screening should be re-evaluated, and IC practices should be more strictly enforced for employees with contact with high-risk elephants.

TB Skin Testing and IGRA: An Ongoing Source of Confusion

SOURCE: Collins LF, et al. Diagnosis of latent tuberculosis infection: Too soon to pull the plug on the tuberculin skin test. *Ann Intern Med* 2016;164:122-124.

Variations in results between TB skin testing (TST) and gamma-interferon-release assays (IGRA) continue to stump providers, who are unsure which test to believe and how to proceed. It is increasingly recognized that TST and IGRAs are not uniformly correlated, and they measure different "arms" of the immune system response. To confuse matters further, the three IGRAs currently approved for use in the United States (the QuantiFERON-TB test, the QuantiFERON TB Gold In-Tube test, and the T-Spot.TB test) each employ different antigens, with different interpretative cut-offs, and the interpretative cut-offs used in published studies often differ from those used by the FDA for approval.

In low-risk populations, e.g., healthcare workers (HCWs), discordance between TST and IGRA results occurs at least 17% of the time. In household contacts with recent exposure, discordant results may occur up to 21% of the time. In part, this is related to the vagaries of IGRA testing in those at lower risk — 52% to 65% of HCWs at low risk for TB who had an initially positive IGRA result "reverted" to a negative result on repeat testing. For those with low-level positive test results, 75% to 80% reverted their test on repeat testing. For this reason, in those at low risk with low positive results, it is becoming commonly accepted practice to repeat a positive IGRA test in 2-8 weeks. In contrast, documented conversion of a TST is generally accepted

as a true positive. In individuals at high risk, both tests can be used, and a positive for either test should prompt appropriate chemoprophylaxis.

Discordance seems to occur more commonly with newly exposed individuals and for those individuals with low-intensity exposure. While the generally accepted window period between exposure and a measurable immune system response is 8 weeks, some individuals may take longer to convert their skin test or IGRA. This may be the result of a dose-dependent relationship between the intensity of the exposure and the immune system response.

One Ugandan study found that while 41% of household exposures had skin test conversion by 3 months, an additional 10% of conversions occurred at 6 months or later. Compared to those with a baseline positive TST, those with TST conversions at 3 months or later had slowly increasing gamma-interferon production that took 3-12 months following exposure to reach detectable levels. In a group of soldiers with TB exposure, 78% had positive skin tests within 1 month, but only 63% had a positive IGRA at that time. Serial IGRA testing showed that conversions continued to occur up to 14-22 weeks after exposure.

On the basis of these studies, Collins and colleagues have proposed a hypothetical model for TST and IGRA responses. With high-intensity exposure, some individuals may have already developed a positive TST response with baseline testing (within 2 weeks after a known exposure), while few would have a positive IGRA. Over the next 2-10 weeks, conversion of the IGRA is delayed relative to the TST, although both tests will capture the majority of infected persons by 10 weeks post-exposure. However, with low-intensity exposure, conversion of both tests may be delayed beyond 10 weeks, with even further delay of the IGRA test compared with the TST.

Interpretation of IGRA results, therefore, may require not only risk stratification but consideration of exposure history. And skin testing still may prove to be more reliable and efficient than IGRA in evaluating household exposures or other exposures, especially low-intensity exposures.

LASIK, Humidifiers, and *Mycobacterium chelonae* Ocular Infections

SOURCE: Notes from the field: *Mycobacterium chelonae* eye infections associated with humidifier use in an outpatient LASIK clinic — Ohio, 2015. *Morbid Mortal Wkly Rep* 2015;64:1177.

Approximately 600,000 LASIK surgeries are performed annually in the United States. In February 2015, public health authorities were notified of the occurrence of four cases of eye infection secondary to *M. chelonae* in persons who had undergone LASIK surgery at an ambulatory surgery clinic in Toledo, OH. Two infections had occurred in six patients undergoing LASIK in January, and an initial investigation was unrevealing. Two additional infections occurred in February, prompting further investigation.

It turns out that the manufacturers of LASIK equipment recommend the use of humidified air to maintain 40-50% relative humidity during procedures. The clinic employed two consumer-grade cold air humidifiers for this purpose, which were filled with tap water and located near the patient procedures. The humidifiers each had an internal reservoir, and one provided a cold air mist. Samples taken from the misting humidifier reservoir were positive for *M. chelonae*, which was identical to three of four patient isolates and closely related to the fourth (> 95%) by pulsed-field gel electrophoresis.

Currently, the CDC environmental infection control guidelines prohibit the use of reservoir-style humidifiers in healthcare facilities, and state that only steam humidification should be used with appropriate precautions. The clinic subsequently upgraded its ventilation system to provide appropriately humidified central air. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. For children with acute severe malnutrition, an initial course of antibiotic treatment:

a. is currently advised by the World Health Organization.

b. reduces the risk of death due to complicated malaria.

c. is associated with increased death due to multi-drug resistant Gram-negative bacteremia.

d. is considered wasteful.

2. Which of the following is correct regarding the prospective study by Claessens et al of plain chest radiography vs CT scanning in patients with suspected community-acquired pneumonia?

a. The radiologist's reading of the presence of parenchymal infiltrates on conventional radiography was confirmed in all cases by CT.

b. The radiologist's reading of the presence of parenchymal infiltrates on conventional radiography was confirmed in 132 of 188 cases by CT.

c. The radiologist's reading of the presence of parenchymal infiltrates on conventional radiography was confirmed in 186 of 188 cases by CT.

d. The radiologist's reading of the presence of parenchymal infiltrates on conventional radiography was confirmed in 43 of 188 cases by CT.

3. Which of the following is correct regarding the study of the use of *Saccharomyces boulardii* to prevent antibiotic-associated diarrhea (AAD) in the study by Ehardt et al?

a. *S. boulardii* administration virtually eliminated the occurrence of AAD relative to placebo administration.

b. The incidence of *Clostridium difficile* infection was greater in *S. boulardii* recipients than in placebo recipients.

c. *S. boulardii* administration did not have a statistically significant effect on the incidence of AAD relative to placebo administration.

d. The study was prematurely discontinued because of serious adverse events related to *S. boulardii* administration.

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.