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Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Skin Infections in Student Athletes

By Richmond M. Castillo and Philip R. Fischer, MD, DTM&H

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Mr. Castillo and Dr. Fischer report no financial relationships relevant to this field of study.

SYNOPSIS: Among high school and college athletes, skin infections are most common in wrestlers and football players. Bacterial infections predominate. Up to 22% of wrestlers are colonized with methicillin-resistant *Staphylococcus aureus* sometime during the season.

SOURCE: Ashack KA, Burton KA, Johnson TR, et al. Skin infections among US high school athletes: A national survey. *J Am Acad Dermatol* 2016;74:679-684.

Skin infections are known to be problematic among some high school athletes, but there had not previously been a broad review of the epidemiology of skin infections across multiple sports. Kurt Ashack and colleagues used skin infection data collected by High School Reporting Information Online (RIO), an Internet-based high school sports injury surveillance system, from fall 2009 through spring 2014. The study determined the epidemiology of skin infections across multiple high school sports. Skin infections accounted for 1.2% of all sports-related injuries/adverse events prompting a missed practice or game. There were 474 skin infections, a rate of 2.2 infections per 100,000 athlete practices/games. Wrestlers accounted for 74% of infections and football players for 18%. Skin infections were most commonly of bacterial origin (61%), followed by tinea (28%) and herpes (5%). Infections occurred most commonly on the head/face (25%), followed by a forearm (13%). Overall, 64% of affected athletes returned to play within six days.

COMMENTARY

Seven million U.S. high schoolers participate in sports each year. To decrease the risk of infection,

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there are prevention and education recommendations. For example, the National Federation of State High School Associations implemented a standardized pre-match procedure regarding having either referees performing skin checks or verifying that skin checks have been performed.[1] On the other hand, many high school athletic programs have no policies on hand hygiene or restricting participation by athletes with skin infections.[2] As noted by Ashack and colleagues, even post-practice showers can reduce infection rates and are commonly used. Understanding the epidemiology of skin infections among high school athletes can lead to awareness and can drive targeted, evidence-based prevention efforts.

There appears to be a seasonality of infections, specifically infections with *Staphylococcus aureus*. Jiménez-Truque and colleagues found that among a cohort of 377 collegiate athletes, within both contact and non-contact sports, acquisition of *S. aureus* colonization is highest during summer, especially for football players.[3] It is important for infectious disease specialists to be aware of these vacation months as a key time to implement preventive hygiene measures.

More than one-third of *Staphylococcus* infections in college athletes are due to methicillin-resistant strains (MRSA).[3] Of college athletes, 22% of wrestlers and 8% of football players become colonized with MRSA at some point,[4] and actual MRSA infection is also more common in wrestlers and football players than in other athletes.[5] Decolonization treatment with intra-nasal mupirocin for five to 10 days (with or without oral rifampicin) reduces the risk of subsequent infection by one-third.[5]

As athletes head back to school this fall, several interventions potentially could prevent participation-limiting skin infections. First, identification of colonization and subsequent decolonization treatment can reduce the risk of subsequent infection. Wrestlers could be targeted since they are at highest risk.[4,5] Further study will be needed to guide widespread policy changes. Second, athletes should shower thoroughly after practices and games. Third, pre-play skin inspection, especially of wrestlers, and removal of athletes with active infection can help reduce the spread of infecting microbes to other athletes. ■

[There appears to be a seasonality of infections, specifically infections with *Staphylococcus aureus*.]

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ABSTRACT & COMMENTARY

Evaluation of Amoxicillin Allergy in Children

By Hal B. Jenson, MD, FAAP

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

SYNOPSIS: Provocative challenge with oral amoxicillin is an accurate and safe test for confirming cutaneous allergic reactions to amoxicillin in children. The majority of children in this study, 94%, were nonallergic. Provocative challenges should be conducted by pediatric immunologists/allergists in an appropriate medical setting.

SOURCE: Mill C, Primeau MN, Medoff E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and nonimmediate reactions to amoxicillin children. *JAMA Pediatr* 2016;170:e160033.

Investigators conducted an observational cohort study of all children referred with suspected allergy to amoxicillin between March 2012 and April 2015 at Montréal Children's Hospital. A total of 818 children were assessed (median age, 1.7 years [interquartile range, 1.0-3.9 years]; 441 [53.9%] male). None of the children who received a provocative challenge had a history of anaphylaxis to amoxicillin. All children received a provocative challenge with oral amoxicillin. Among all participants, 770 (94.1%) tolerated the challenge without any reaction, 17 (2.1%) developed mild immediate reactions (all with hives only), and 31 (3.8%) developed nonimmediate reactions (maculopapular rashes and serum sickness-like reactions). The oral challenge had a specificity of 100.0% (95% CI, 90.9-100%), a negative predictive value of 89.1% (95% CI, 77.1-95.5%), and a positive predictive value of 100% (95% CI, 86.3-100%).

A history of a reaction occurring within five minutes of prior exposure was associated with immediate reactions to the challenge (adjusted odds ratio = 9.6; 95% CI, 1.5-64.0). A history of a rash that lasted longer than seven days (adjusted odds ratio = 4.8; 95% CI, 1.4-16.4) and parental history of drug allergy (adjusted odds ratio = 3.0; 95% CI, 1.3-6.8) were associated with nonimmediate reactions to the challenge.

Among all 346 participants eligible for annual follow-up, 250 (72.3%) responded, 55 of whom had received treatment with a full course of amoxicillin. Among these 55 participants, 49 (89.1%) reported tolerance to a full course of amoxicillin, and six (10.9%) developed nonimmediate cutaneous reactions.

COMMENTARY

Otitis media accounts for approximately 16 million visits to healthcare providers annually in the United States. Although guidelines recommend observation, more than 80% of children with otitis media receive antibiotics, with amoxicillin prescribed in approximately 40% of cases. Rashes develop in up to 10% of children receiving antibiotics, with about 6% of children labeled as allergic to penicillin. Only about 4-9% of these children have an immunologically mediated response, whether an immediate reaction (e.g., urticaria, angioedema, rhinitis, bronchospasm, or anaphylaxis) mediated by IgE, or a nonimmediate reaction (e.g., maculopapular rash) mediated by a T lymphocyte-dependent reaction. Of note, most of the children in this study referred for evaluation were described as having their reaction to amoxicillin after the first exposure, suggesting that these were nonimmune reactions, which require prior exposure. Most individuals labeled as allergic to penicillin are, in fact, not allergic, either because their reactions represented a sensitivity or adverse effect rather than an immune-mediated reaction, or because the allergy has been lost with time.

The current approach to evaluate penicillin allergy in children is with immediate-type skin tests with penicillin and the penicilloyl determinant and, if negative, followed by challenge with oral amoxicillin, which identifies allergies to minor determinants including the amoxicillin side chain. This study performed the oral challenge first. For the 17 children with an immediate reaction, skin tests two to three months later with penicillin and the penicilloyl determinant were positive in only one patient, indicating a poor predictive value of skin tests.

This study showed that 94% of children tolerated

the challenge and also showed, for the first time, that nonimmediate reactions are about twice as common as immediate reactions (3.8% vs. 2.1%). Six of 55 children with no response to the oral provocation subsequently developed late-onset rashes to subsequent exposures. This implies that a single provocation challenge may be sufficient to identify an IgE-mediated immediate reaction, but may not be sufficient to identify nonimmediate reactions.

The financial costs and obstacles for optimal management of patients labeled as allergic to penicillin are significant. It is important not to inappropriately label a patient as being allergic in the first place, and also to appropriately evaluate those who are labeled since the majority will be shown not to be allergic, greatly simplifying management of common childhood infections. Even though the children in this study with immediate reactions to oral challenge had hives only, systemic reactions requiring treatment with epinephrine are possible and have been reported. Given the risks of reactions and nuances of performing skin tests or oral challenge first, it is prudent that these children be tested by board-certified immunologists/allergists in an appropriate medical setting. ■

ABSTRACT & COMMENTARY

Screening for *Clostridium difficile* Carriers at Hospital Admission Reduces Subsequent *C. difficile* Infections

By Richard R. Watkins, MD, MS, FACP

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

SYNOPSIS: Patients admitted to a single hospital were screened for *C. difficile* carriage and those found to be positive were placed in contact isolation. This led to a significant decrease in hospital-acquired *C. difficile* infections.

SOURCE: Longtin Y, et al. Effect of detecting and isolating *Clostridium difficile* carriers at hospital admission on the incidence of *C. difficile* infections: A quasi-experimental controlled study. *JAMA Intern Med.* 2016;176:796-804.

Clostridium difficile infection (CDI) is now the leading nosocomial infection in the United States. Novel approaches are needed to decrease the CDI epidemic. Longtin and colleagues reported the results of one such strategy: identifying and isolating asymptomatic carriers of *C. difficile*.

The study was conducted at a single institution in Quebec City, Canada, that had been experiencing a high burden of hospital-acquired CDI (HA-CDI). Patients admitted through the emergency department underwent screening for *C. difficile* by rectal swabs that identified the tcdB gene by polymerase chain reaction. *C. difficile* carriers then were placed into modified isolation similar to what is done for cases of CDI but with some modifications, including not requiring healthcare workers to wear isolation gowns and allowing carriers to share a room with non-carriers. For logistical reasons, patients admitted directly to the wards and those who stayed less than 24 hours were excluded. The primary outcome was the change in incidence rate of HA-CDI per 10,000 patient-days after implementation of the intervention. Secondary outcomes included changes in the proportion of HA-CDI cases with complications and changes in strain types causing CDI. The control used for the study was the HA-CDI incidence rates from other institutions in Quebec during the same time course.

The average incidence rate of HA-CDI before the intervention was 8.2 per 10,000 patient-days. After the intervention, the incidence rate decreased to 3.0 per 10,000 patient-days ($P < 0.001$). Out of 7,599 eligible patients who were screened, 368 (4.8%) were found to be asymptomatic carriers. There were no significant differences in complications (i.e., 10- and 30-day all-cause mortality, admission to the intensive care unit, need for colectomy, or readmission for recurrent CDI) between the pre-intervention and post-intervention periods ($P > 0.05$ for all). Forecast modeling estimated that the intervention prevented 63 of 101 expected cases of HA-CDI, while there was no significant change detected in the control group. Furthermore, there was a significant decrease in the proportion of NAP1 strains after the

intervention compared to beforehand (2 of 10 strains [20%] vs. 45 of 76 [59%], respectively; $P < 0.049$). No corresponding decrease in NAP1 strains was observed in the other hospitals in Quebec City during the intervention period (80% of *C. difficile* strains were NAP1). Notably, there also were outbreaks of influenza, viral gastroenteritis, and carbapenemase-producing *Enterobacteriaceae* during the intervention period at the study institution. Efforts to improve hand hygiene were introduced to mitigate the outbreaks. Consequently, the hand hygiene rate improved from 36.6% to 49.7%.

COMMENTARY

This study showed how a relatively simple intervention (i.e., rectal swabs that detect *C. difficile* followed by isolation of carriers) could have a significant impact on the burden of CDI in an inpatient setting. Before the intervention, the study institution had a high burden of HA-CDI. Afterward, it had the lowest incidence rate of HA-CDI among the 22 academic hospitals in Quebec. Experts believe that despite not having diarrhea, asymptomatic carriers of *C. difficile* still shed spores that contaminate the environment and get on caregivers' hands. This environmental contamination is particularly troublesome for institutions that do not have all private rooms.

Although the results were impressive, the study raises important economic questions. For example, do the cost savings from preventing HA-CDI exceed the cost of the intervention? The investigators attempted to address this issue by noting that each case costs $3,427 to $9,960 and since it was calculated that the intervention prevented 63 cases, the savings from averting HA-CDI ($216,000 to $627,000) exceeded the cost of the intervention ($130,000). However, further cost-analysis studies that include multiple sites are needed to determine if these savings can be replicated in other settings. Another issue to be elucidated is whether the intervention would have a significant impact at an institution that does not have a high incidence of HA-CDI. In this setting, the cost of the intervention might not be justified, although the public reporting of HA-CDI rates might nonetheless motivate hospital administrators to pay for it.

There were a couple of limitations to the study worth mentioning. The authors did not assess how many of the asymptomatic carriers had a previous history of CDI. Also, the institutional hand hygiene compliance improved during the study, which may have falsely inflated the benefit of the intervention. On the other hand, the improvement was quite modest, going from 37% to a rather dismal 50%. Institutional antibiotic stewardship also might have played a confounding role by limiting antibiotics that are most associated with HA-CDI, such as clindamycin and quinolones. Despite these limitations, isolating asymptomatic carriers of *C. difficile* seems like a promising strategy that should be investigated with larger clinical trials. ■

ABSTRACT & COMMENTARY

Newly Recognized Rickettsial Infection in Eastern Central China

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: Fifty-six of 733 patients in China who were evaluated for suspected Severe Fever with Thrombocytopenia Syndrome (SFTS) were shown by polymerase chain reaction (PCR) to be infected with Candidatus Rickettsia tarasevichiae (CRT). Fever, myalgia, cough, gastrointestinal symptoms, and hemorrhagic manifestations were common. Rash was rarely seen, and eschar was observed in 16% of cases. Thrombocytopenia, leukopenia, and abnormal LFTs were commonly observed. Co-infection with SFTS virus was seen 66% of patients, and eight patients died.

SOURCE: Liu W, Li H, Lu QB, et al. Candidatus Rickettsia tarasevichiae infection in Eastern Central China: A case series. *Ann Intern Med* 2016;164: 641-648.

From April until November 2014, patients with suspected SFTS were recruited for prospective study at a People's Liberation Army sentinel hospital in Eastern Central China. Seven hundred thirty-three patients were admitted to the hospital and had specimens collected. Blood specimens were analyzed

by PCR for spotted fever group (SFG) rickettsiae, *Anaplasmataceae*, *Borrelia*, and *Babesia*. Candidatus Rickettsia tarasevichiae (CRT) infection was confirmed by sequencing of the ompA-coding gene.

All 56 patients with CRT infection presented with a febrile illness. Other common manifestations included gastrointestinal symptoms, nonspecific neurologic symptoms, hemorrhagic signs, and plasma leakage. Lymphadenopathy was present in 29% of patients. Rash was present in only 4% of patients and eschar in 16%. Sixty-six percent were co-infected with SFTSV, and 14% died. Leukopenia was present in 59%, thrombocytopenia in 70%, lymphopenia in 45%, elevated transaminases or LDH in 54-82%, elevated CK in 46%, and elevated BUN in 20%. Laboratory abnormalities peaked in most patients about 10 days after symptom onset.

Only 27% of patients reported a history of tick bite, but 100% worked as farmers. A total of 397 adult *Haemaphysalis longicornis* ticks were captured, and 8.3% tested positive for CRT, while 9.3% had positive SFTSV test results. Peak numbers of cases occurred in June, July, and August.

■ COMMENTARY

"New" tick-associated rickettsial pathogens are being increasingly recognized around the world. In China, eight emerging *Rickettsia* species have been identified. CRT, *R. sibirica*, *R. raoultii*, and *R. heilongjiangiensis* are known to cause human disease.[1] In 2009, a novel tick-borne viral infection associated with severe fever and thrombocytopenia was recognized in Central Eastern China.[2] SFTS virus is a bunyavirus of the genus Phlebovirus and has resulted in thousands of cases of human disease in 19 of 32 Chinese provinces. While the clinical and laboratory manifestations of patients shown to be infected with CRT are nonspecific, many of the patients appeared to be as ill as patients with Rocky Mountain Spotted Fever, and more ill than most patients with *R. conorii* SFG rickettsial disease. The clinical overlap with SFTSV and the common occurrence of co-infection with SFTSV and CRT in patients in China should be appreciated. Use of rapid molecular diagnostic methods to diagnose CRT (and other rickettsioses) and empiric use of doxycycline should be considered in appropriate patients. ■

["New" tick-associated rickettsial pathogens are being increasingly recognized around the world.]

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ABSTRACT & COMMENTARY

Diagnosis and Management of Invasive Aspergillosis in 2016

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: This updated guideline takes into account newer diagnostic methods and therapeutic agents and their use in the treatment of aspergillosis.

SOURCE: Patterson TE, Thompson III GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* doi: 10.1093/cid/ciw326. First published online: June 29, 2016.

Invasive aspergillosis continues to be a lethal infection in many patients with hematologic malignancy as well as in transplant recipients. This update to the 2008 Infectious Diseases Society of America (IDSA) guidelines provides current recommendations for the diagnosis and management of invasive aspergillosis (IA), chronic (and saprophytic) forms of infection, as well as

allergic forms of aspergillosis. The following is a partial summary of the recommendations regarding pulmonary IA.

Prophylaxis

In patients with prolonged neutropenia at risk of IA, prophylaxis with posaconazole (strong recommendation, high-quality evidence), voriconazole (strong, moderate), or micafungin (weak, low) is recommended. Caspofungin is also believed to probably be effective. Prophylaxis with posaconazole in allogeneic hematopoietic (HSCT) recipients with graft-versus-host disease at high risk of IA is recommended. While voriconazole is commonly used, the evidence is of lower quality than that for use of posaconazole.

In lung transplant recipients, prophylaxis with either a systemically administered triazole or inhaled amphotericin B is recommended for the first three to four months after transplantation. The former is weakly recommended based on low-quality evidence over inhaled amphotericin B in a variety of circumstances, such as those colonized with a mold, those with a mold infection of an explanted lung, fungal infection of paranasal sinuses, or single lung recipients. Antifungal prophylaxis after the initial three-to-four-month window should be reinitiated in those with augmentation of their immunosuppressive therapy with thymoglobulin, alemtuzumab, or high-dose corticosteroids.

Diagnosis

The firmest diagnoses are based on histological and cultural analysis with use of molecular techniques for species identification when cultural identification is uncertain or not possible. The role of PCR for diagnosis remains uncertain. Measurement of galactomannan in serum and bronchoalveolar lavage (BAL) fluid is recommended for diagnosis in at-risk populations, i.e., those with hematologic malignancy and HSCT cell transplant recipients. Measurement of (1 → 3)-β-D-glucan is also of use in these patient groups. Galactomannan screening is not recommended in solid organ transplant recipients (or in those with chronic granulomatous disease).

Thoracic computerized tomography (CT) should be performed whenever there is suspicion of pulmonary IA; contrast should not be used unless a nodule or mass abuts a large vessel. Chest CT should not be repeated for at least two weeks unless the patient deteriorates, although earlier repeat CT may be considered if a nodule or mass abuts a large vessel. Bronchoscopy with BAL should be performed when pulmonary IA is suspected if deemed safe. If feasible, percutaneous or transbronchial biopsy should be considered when one or more peripheral nodular lesions are present.

Treatment

Voriconazole is the treatment of choice for IA. Treatment should be initiated as early as possible, even prior to completion of the diagnostic evaluation in patients in whom the suspicion of this infection is high. Alternative antifungals include liposomal amphotericin B and isavuconazole. Lipid formulations of amphotericin B other than the liposomal product are another alternative, although the evidence for their use is deemed to be of low quality. A weak recommendation based on moderate-quality evidence is given for the use of voriconazole and an echinocandin in combination in selected patients. Echinocandins should not be used for primary therapy unless alternatives are contraindicated. Treatment should be continued for at least six to 12 weeks. For patients who require subsequent immunosuppressive therapy, secondary prophylaxis should be initiated after completion of the treatment course. The serial measurement of GM can be used to monitor the response to therapy.

[The firmest diagnoses are based on histological and cultural analysis with use of molecular techniques for species identification when cultural identification is uncertain or not possible.]

Therapeutic drug monitoring of voriconazole, as well as other azoles if used (itraconazole, posaconazole and, possibly, isavuconazole), should be performed, as should monitoring of interacting drugs such as cyclosporine, tacrolimus, and sirolimus.

In addition to antifungal therapy, immunosuppressive therapy should be reduced or eliminated, if feasible. Although a weak recommendation based on low-quality evidence, colony stimulating factors in neutropenic patients or, in highly selected patients, administration of granulocyte transfusions may be considered. Recombinant interferon-γ is a recommended prophylactic agent for patients with chronic granulomatous disease. Surgical intervention is recommended for some types of localized infection. ■

ABSTRACT & COMMENTARY

Diagnosis and Management of Acute Infectious Diarrhea in 2016

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: The American College of Gastroenterology has developed a guideline dealing with the management of immunocompetent adults with acute infectious diarrhea, other than that due to *Clostridium difficil*e infection.

SOURCE: Riddle MS, DuPont HL, Connor BA. ACG clinical guideline: Diagnosis, treatment, and prevention of acute diarrheal infections in adults. *Am J Gastroenterol* 2016;111:602-622.

A practice guideline for the management of infectious diarrhea was published by the Infectious Diseases Society of America (IDSA) 15 years ago — an update is in progress. In the meantime, the American College of Gastroenterology (ACG) has now produced its guideline on the subject. This guideline focuses on immune-competent adults and does not consider *Clostridium difficile* infection.

Prophylaxis. Probiotics, prebiotics, and synbiotics (which are a combination of both) are not recommended. This recommendation is "conditional," meaning that uncertainty exists regarding the risk-benefit ratio, and based on low-level evidence. Based on high levels of evidence, a strong recommendation is made that bismuth subsalicylate or antibiotic chemoprophylaxis may be considered, with the latter limited to short-term use in high-risk travelers.

Diagnosis. An attempt at etiologic diagnosis is recommended for epidemiologic purposes (e.g., with concern about transmission and during outbreaks) and in circumstances in which antimicrobial treatment may be indicated. The latter include patients with dysentery, those with moderate to severe disease, and those whose illness has persisted for more than seven days. Since culture, microscopy, and antigen testing frequently fail to detect a pathogen, other culture-independent techniques, such as the use of FDA-approved nucleic acid amplification tests, should be considered. When bacterial pathogens are recovered in culture, antibiotic susceptibility testing is not recommended. Note that while most of these recommendations are graded as strong, they are all based on low or very low levels of evidence.

Treatment. Fluid and salts can be replaced in most individuals with juice, sports drinks, water, and salted crackers. Balanced electrolyte solutions are recommened for elderly individuals with severe diarrhea and in any traveler with cholera-like watery diarrhea. Probiotics and prebiotics are not recommended in the acute stage of illness, but bismuth subsalicylate may provide benefit in those with mild to moderate illness. Adjunctive loperamide is recommended for travelers receiving antibiotic therapy for acute diarrhea. However, antimicrobial administration is not routinely recommended except for travelers in whom the likelihood of a bacterial etiology is "high enough to justify the potential side effects of antibiotics." In contrast, antibiotic administration is discouraged in patients with community-acquired diarrhea — which is most often caused by viral pathogens. All the treatment recommendations are graded as strong and are based on moderate to high levels of evidence.

Evaluation When Symptoms Persist. Laboratory testing and endoscopic evaluation is not recommended for those with persistent diarrhea (defined as lasting for 14-30 days). While this is a strong recommendation, it is based on very low levels of evidence.

■ COMMENTARY

This guideline is useful, but it will be interesting to see the degree to which the IDSA guideline currently under development differs — especially with regard to diagnostics. While most of the ACG recommendations are graded as strong, it is discouraging that the majority are made based on low levels of evidence. ■

ABSTRACT & COMMENTARY

Too Much of a Good Thing

By Seema Gupta, MD, MSPH

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

SYNOPSIS: In the United States in 2010 and 2011, an estimated 30% of outpatient oral antibiotic prescriptions may have been inappropriate, a finding that supports the need for establishing a goal for outpatient antibiotic stewardship.

SOURCE: Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotic prescriptions among U.S. ambulatory care visits, 2010-2011. *JAMA* 2016;315:1864-1873.

Antimicrobials are perhaps one of the most successful forms of chemotherapy in the history of medicine. Since their discovery in the early 1900s, antibiotics have contributed significantly to the control of communicable diseases that have been the leading causes of human morbidity and mortality throughout human history. However, as their popularity and utilization expanded, antibiotic resistance has become a significant public health issue, both in the United States and across the world, potentially creating infectious diseases that may become unresponsive to antibiotic treatments.

In the United States, at least 2 million people become infected with antibiotic-resistant bacteria, and at least 23,000 people die each year as a direct result of these infections.[1] According to the CDC, antibiotic resistance in the United States costs an estimated $20 billion a year in excess healthcare costs, $35 billion in other societal costs, and results in more than 8 million additional days in the hospital. The primary driver of antibiotic resistance is the overuse and misuse of antibiotics. In 2011, healthcare providers prescribed 262 million courses of antibiotics, equating to more than five prescriptions written for every six residents.[2] It is also estimated that approximately 50% of antibiotic prescriptions written in the outpatient setting and 30-50% of antibiotics prescribed in hospitals may be unnecessary or inappropriate.[3] Therefore, decreasing inappropriate use is essential to reducing both antibiotic resistance and adverse events.

Despite the release of a national action plan for combating antibiotic-resistant bacteria that sets a target of reducing inappropriate antibiotic use in the outpatient setting by 50% by 2020, the precise degree to which antibiotic use is inappropriate and amenable to reduction is unknown.[4] Additionally, previous goals and measures for the appropriate use of antibiotics have focused on targeted, specific age groups and conditions.

Fleming-Dutra et al established a baseline of the current rate of outpatient, oral antibiotic prescriptions by age and diagnosis and estimated the overall rate of appropriate, outpatient antibiotic prescriptions in the United States.

Using the 2010-2011 data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, researchers estimated the baseline annual numbers and population-adjusted rates with 95% confidence intervals (CI) of ambulatory visits with oral antibiotic prescriptions in the United States by age, region, and diagnosis. Researchers found that in 2010 and 2011, of the 184,032 sampled ambulatory care visits, 12.6% of visits (95% CI, 12%-13.3%) resulted in antibiotic prescriptions, with an estimated 506 antibiotic prescriptions (95% CI, 458-554) per 1,000 population annually. The number of antibiotic prescriptions varied geographically across the United States, ranging from 423 antibiotic prescriptions (95% CI, 343-504) in the West to 553 antibiotic prescriptions (95% CI, 459-648) in the South, per 1,000 population. The annual antibiotic prescription rate was found to be highest among children younger than two years of age at 1,287 antibiotic prescriptions (95% CI, 1,085-1,489) per 1,000 population.

Sinusitis was the diagnosis associated with the most antibiotic prescriptions per 1,000 population (56 antibiotic prescriptions [95% CI, 48-64]), followed by suppurative otitis media (47 antibiotic prescriptions [95% CI, 41-54]), and pharyngitis (43 antibiotic prescriptions [95% CI, 38-49]). Overall, acute respiratory conditions per 1,000 population led to 221 antibiotic prescriptions (95% CI, 198-245)

annually, but only 111 antibiotic prescriptions were estimated to be appropriate for these conditions. Researchers also found that among all conditions and ages combined in 2010 and 2011, an estimated 506 antibiotic prescriptions (95% CI, 458-554) per 1,000 population were written annually, and, of these, only 353 antibiotic prescriptions were estimated to be appropriate.

■ COMMENTARY

In the United States, an estimated 154 million prescriptions for antibiotics were written in ambulatory care settings annually from 2010-2011. In this study, researchers found that almost half of antibiotic prescriptions for acute respiratory conditions may have been unnecessary, representing 34 million antibiotic prescriptions annually. It is even more astounding to consider that collectively, across all conditions, an estimated 30% of outpatient, oral antibiotic prescriptions may have been inappropriate, although this is likely a conservative estimate. Although these findings offer a critical starting point to understand prescribing practices in the ambulatory care setting, it is equally vital that clinicians consider national, regional, and local approaches to address this challenge in view of geographic variances. However, there will be some elements common to all strategies, which include altering clinician behavior and practice culture as well as educating patients and families regarding the role of antibiotics in medical care.

The Fleming-Dutra et al study also establishes baseline estimates about outpatient antibiotic prescribing. Targeting interventions at both clinician and patient/community levels would enable reaching the national goal of reducing outpatient antibiotic use by 50% by 2020. As there are a number of antibiotic stewardship activities ongoing in outpatient settings across the nation, it is critical clinicians do their part to ensure appropriate antibiotic prescribing. This includes a consideration of displaying informational posters in patient waiting rooms to encourage active conversations around the need for antibiotics. Studies demonstrate most patients will be satisfied without antibiotics if physicians communicate why an antibiotic is unnecessary, what patients can do to feel better, what to expect with their illnesses, and when they should return if they are not improving or are getting worse.[5] After all, antibiotic resistance is one of the most urgent public health threats of our time, and by rethinking each time we consider prescribing an antibiotic, we can treat patients appropriately while sustaining the efficacy of existing agents. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

C. diff. Risk in Veteran's Long-term Care

Source: Brown KA, Jones M, Daneman N, et al. Importation, antibiotics, and *Clostridium difficile* infection in veteran long-term care: A multi-level case-control study. *Ann Intern Med* 2016;164:787-794.

While the risks for *Clostridium difficile* infection (CDI) are well-recognized, the basis for the significant variation in CDI incidence found in long-term care across the United States is poorly understood. These authors examined regional risk factors for CDI across Veteran Health Administration long-term care facilities (LTCF) from 2006 to 2012. VHA is divided into 86 different regions, and there are significant differences between them in the risk of CDI.

Cases of CDI were defined by a positive toxin test three or more days after admission to LTCF or a positive toxin test eight or more weeks after a previous positive result. Various risk factors were included in the analysis, including patient age and comorbidities, use of antibiotics within 28 days, and use of proton pump inhibitors. Estimates of importation of cases were based on the prevalence of CDI within the local acute care facility within the previous eight weeks.

A total of 6,012 CDI were identified across the VHA regions, ranging from a minimum of 0.6 cases per 10,000 days to a maximum of 31.0 cases per 10,000 days. In unadjusted analyses, the strongest predictors for CDI were total antibiotic use within an LTCF (incidence risk ratio [IRR] 2.86, R2 = 0.63) and importation of cases from the acute care setting (IRR 1.59, R2 = 0.5). Both of these factors varied considerably: Estimated importation of cases varied 100-fold and antibiotic use varied six-fold across regions. Not surprisingly, individual use of antibiotics within the previous 28 days also was a significant risk factor. Other risk factors examined, including age, comorbidity, and proton pump inhibitor use, had little effect on the variability of CDI across regions.

In complex weighted analyses, antibiotic use and importation of cases explained 75% of the regional variability in the incidence of CDI in LTCF. Regional differences in antibiotic use suggested that not only was antibiotic use associated with an increased risk of CDI, but with an increased risk of spreading CD. The authors surmised that the remaining 25% of geographic variability, which was unexplained by their data, may be due to factors such as improved infection control practices and environmental measures at specific facilities.

Certainly a "community burden" of CD must play a significant role in the risk of active CDI within a facility. Our acute care hospital, with two campuses located 17 miles apart, screens all high-risk hospital admissions with rectal swabs for CD PCR (e.g., admissions from SNF or other facilities, dialysis patients, anyone with a history of CDI). The prevalence of CD colonization on admission between the two campuses is 19% vs. 9.7%, and the difference in CD colonization for SNF admissions between the two campuses is 18% vs. 6%. Despite the use of the same infection control and environmental procedures at both facilities, significant differences in CD rates between the two facilities are frequently observed.

Survival in Acute Liver Failure

Source: Reuben A, Tillman H, Fontana RJ, et al. Outcomes in adults with acute liver failure between 1998 and 2013: An observational cohort study. *Ann Intern Med* 2016:164:724-732.

As infectious disease consultants, we are frequently involved in cases of severe liver failure (ALF). My recent experience, involving a young Asian Indian man with acute severe hepatitis E virus infection, who required formal consultation with a liver transplant service but was not placed on the transplant list and survived, was more positive than others. Patients with acute hepatic deterioration from acute injury receive the most urgent ranking for organ transplantation, and it's important to know when and whom to call when such events occur. Fortunately, infectious causes of acute liver failure are responsible for a minority of cases, although antimycobacterial and antifungal medications may contribute.

From 1998 to 2005 and from 2006 to 2013, these authors examined the U.S. experience with ALF patients enrolled in the Acute Liver Failure Study Group (ALFSH), including the severity of liver failure, patient characteristics, and the transplant-free and transplant-related outcomes at 21 days. During this 16-year period, 2,070 patients (median age, 39 years) were enrolled in the registry, 461 (22%) of whom received a liver transplant. Of these, there were sufficient data to examine characteristics and outcomes in 1,410 individuals.

During the 16-year study period, causes of ALF did not significantly differ. Acetaminophen (AC) toxicity remained the leading cause of ALF in nearly half of the cases, although the majority of these cases were from unintentional overuse rather than suicidal overdose. Other causes included other non-AC drug-induced ALF (10.8%), autoimmune hepatitis (7%), ischemia (5.7%), and mushroom toxicity (0.6%); hepatitis B virus infection (7.2%) and hepatitis A virus (1.8%) were less common — and ALF due to other viruses even less common (0.9%). Only three cases were due to HCV infection and three due to HEV infection. Only the role of hepatitis A appeared to decrease over time, from 2.8% during the first eight years to 0.8% during the second eight-year study period, probably from improved immunity from vaccination.

Most of the patients registered on the transplant list had critical liver failure, and 50% had grade 3 or 4 hepatic encephalopathy. Even though the causes for ALF did not significantly differ between the two study periods, both transplant-free and transplant survival significantly improved. Overall survival steadily improved during the 16-year study period from 58.8% in 1998 to 75% in 2013 ($P < 0.001$). Transplant-free survival improved from 32.9% in 1998 to 61% in 2013 ($P < 0.001$). Overall survival for AC-related ALF with grade 1 or 2 hepatic encephalopathy improved from 34.5% to 43.7% ($P = 0.019$), although there was no significant change in mortality with more severe AC-related injury. This was believed to be related to

improvements in critical care and the administration of *N*-acetylcysteine. The 21-day transplant survival improved from 88.3% in 1998 to 96.3% in 2013 (P = 0.002).

Causes of death included multi-organ system failure (20%), neurologic causes (13.9%), multifactorial causes (10.8%), general "liver-related causes" (10.8%), sepsis and infection (7.9%), and cardiac causes (5.3%). Thirty-one liver transplant centers participate in the ALFSH project, five of which have been operating for the entire 16 years. There were no apparent differences in survival between those five transplant centers and the remaining facilities. ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
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CME QUESTIONS

1. Among student athletes:

a. Wrestlers are at the greatest risk of skin infection.

b. Skin infections are usually viral in origin.

c. MRSA is usually acquired during winter.

d. All of the above are correct.

2. Which of the following is among the 2016 Infectious Diseases Society of America recommendations for treatment of invasive pulmonary aspergillosis?

a. The treatment of choice is amphotericin B deoxycholate.

b. The treatment of choice is itraconazole.

c. The treatment of choice is fluconazole.

d. The treatment of choice is voriconazole.

3. Which of the following is among the 2016 American College of Gastroenterology recommendations for acute infectious diarrhea?

a. Antibiotic therapy is strongly recommended for all patients with traveler's diarrhea.

b. Antibiotic therapy is discouraged for patients with community-acquired diarrhea.

c. Probiotics are the treatment of choice.

d. Loperamide should never be administered to patients with acute infectious diarrhea.

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.