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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Duration of Antibiotic Treatment for Vertebral Osteomyelitis

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: Three hundred fifty-nine patients with pyogenic vertebral osteomyelitis were randomized to 6 weeks vs. 12 weeks of antibiotic treatment in an open-label controlled trial. Six weeks of antibiotics was found to be not inferior to 12 weeks of treatment.

SOURCE: Bernard L, et al. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: An open-label, non-inferiority, randomized, controlled trial. *Lancet* 2015;385:875-882.

This open-label, randomized controlled trial enrolled patients 18 years or older with microbiologically confirmed pyogenic vertebral osteomyelitis from 71 medical centers across France from 2006-2011. The primary endpoint was the proportion of patients classified as cured at one year by a masked independent validation committee and analyzed by intention to treat. Three hundred fifty-nine patients were randomized. Sixty-eight percent of patients had bacteremia. Forty-one percent of patients were infected with *Staphylococcus aureus*, 17% with coagulase-negative Staphylococcus, 18% with Streptococci, 7% with Enterococcus, 11% with Enterobacteriaceae, and 9% with a variety of other organisms. Of the evaluable patients, 160/176 (91%) patients in the 6-week group and 159/175 (91%) of patients in the 12-week group met criteria for clinical cure and demonstrated non-inferiority. Fifty patients in the 6-week group and 51 patients in the 12-week group experienced adverse events. Antibiotic intolerance was seen in 7% of the patients

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in the 6-week group and 5% of patients in the 12-week group.

■ COMMENTARY

The famous quote commonly attributed to the legendary Dr. Maxwell Finland relates to the Boston City Hospital resident who would ask Max, "How long do you treat XYZ disease?" Max would always reply, "Long enough." Sadly, that is still the correct answer for many infectious diseases for which we don't have randomized controlled clinical trial data to support our judgment. In the 40 years that I've been treating patients with infections, I've observed a significant "creep" in duration of antibiotics prescribed for many infections.

During my residency and fellowship training, I can't think of any infections (other than tuberculosis) that we treated for more than 6 weeks, and I don't believe we had more treatment failures than we do now. Also, since we didn't have PICC lines, we often had to stop IV antibiotics when we ran out of accessible peripheral veins and either stopped antibiotic treatment early or transitioned the patient to either oral beta-lactam antibiotics, trimethoprim/sulfamethoxazole, or clindamycin (depending on the organism). This was before we had fluoroquinolones. It is quite common now to see our younger colleagues place PICC lines and treat patients for osteomyelitis and various abscesses for several months. We also now see more complications, like subclavian vein DVT and *C. difficile* infection, than we did in the old days.

This study from France may not be completely generalizable to practice in North America (or even elsewhere in Europe), since patients received many (to us) odd antimicrobial regimens including oral fluoroquinolone + rifampin (44%), rifampin + aminoglycoside (13%), and fluoroquinolone + aminoglycoside (7%). However, the convincing demonstration of non-inferiority of 6 weeks vs. 12 weeks duration of treatment that was seen in this study goes a long way toward answering that Boston City Hospital resident's question to Dr. Finland. At least for treatment of pyogenic vertebral osteomyelitis, "6 weeks is long enough!" ■

ABSTRACT & COMMENTARY

Antibiotics for Intraabdominal Infections: Less Is More

By Richard R. Watkins, MD, MS, FACP

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Dr. Watkins receives research support from Forest Pharmaceuticals.

SYNOPSIS: A multi-center, randomized trial comparing patients with complicated intraabdominal infections found no difference in outcomes between those who received 4 days of antibiotic therapy vs. 8 days after adequate source control.

SOURCE: Sawyer RG, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med* 2015;372:1996-2005.

Complicated intraabdominal infections (IAIs) cause significant morbidity and mortality, especially in the elderly. Often IAIs are treated with antibiotics until all the signs and symptoms of the systemic inflammatory response syndrome (SIRS) resolve, typically for 7 to 14 days. However, guidelines from the IDSA recommend 4 to 7 days based on clinical response.[1] Because of differences in clinical practice, Sawyer and colleagues conducted a randomized trial that compared outcomes of fixed-duration antibiotic therapy for 4 days following

source control to a traditional strategy of continuing antibiotics until 2 days after the resolution of SIRS.

The study enrolled patients aged 16 years and older from 23 centers who presented with a complicated intraabdominal infection and either fever, leukocytosis, or gastrointestinal dysfunction due to peritonitis and subsequently underwent a procedure for source control. They were randomized in a 1:1 ratio to receive 4 full days of antibiotic therapy (experimental group) following the source-control procedure or to receive antibiotic therapy until 2 days after resolution of SIRS (control group). The primary endpoint was the development of a surgical-site infection or recurrent intraabdominal infection or death within 30 days after the source-control procedure. The secondary endpoints were duration of antibiotics for the original infection, overall exposure to antimicrobial agents, rates of subsequent extraabdominal infection, and adherence to the protocol.

A total of 508 patients were randomized to either the experimental or control group. The most common site of infection was the colon or rectum; one-third of the infections were managed by a percutaneous procedure, and there were no significant demographic differences between the two groups. The primary endpoint occurred in 21.8% of the experimental group and 22.3% in the control group (P = 0.92). The median duration of antibiotic therapy in the experimental group was 4.0 days compared to 8.0 days in the control group (P < 0.001). There were significantly fewer antibiotic-free days at 30 days in the control group and no differences between the two groups in rates of extraabdominal infections, *Clostridium difficile* infection, or secondary infections with resistant pathogens. The rate of nonadherence to the protocol was 18% in the experimental group.

■ COMMENTARY

The most salient finding from the study was that 4 days of antibiotic therapy after a successful source-control procedure resulted in the same outcomes as longer courses. This implies that antibiotics are most effective in the first 4 days after the procedure and there is little benefit to prolonging them beyond 4 days. There are a multitude of potential benefits from shorter antibiotic courses, including reduced collateral damage to commensal flora, less risk for developing *C. difficile* infection, fewer adverse medication events, less risk of promoting antibiotic resistance, and reduced costs. An accompanying editorial estimated the cost saving based on the antibiotics prescribed in the study would be $97 million annually in the United States.[2] Reducing the duration of antibiotic therapy is one of the central tenets of antibiotic stewardship, and the data presented by Sawyer and colleagues will likely be useful in these efforts.

However, there are important limitations of the study worth noting. First, the rate of nonadherence to the protocol was high, creating bias toward the null hypothesis of no difference between the two groups. Second, the study did not reach the calculated sample size to detect equivalence between the two groups. These methodological flaws lessen the clinical impact of the study and necessitate that further studies be conducted to elucidate the duration of therapy for IAIs.

Overall, my impression of the study is that better source control is needed for complicated IAIs, and antibiotics have an important yet secondary role to play. Notably, the rate of infectious complications was > 20% in both the experimental and control groups, most of which were recurrent IAIs. Thus, infectious disease physicians need to be strong advocates for optimal source control early in the clinical course of IAIs, along with maintaining their traditional role of promoting the judicious use of antibiotic therapy. ■

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ABSTRACT & COMMENTARY

Measles-induced Immunomodulation and Impact on Childhood Mortality

By Hal B. Jenson, MD, FAAP

Dr. Jenson is Professor of Pediatric and Adolescent Medicine, and Dean, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, Michigan.

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

SYNOPSIS: Population-level studies in high-resource countries demonstrated that fluctuations in childhood mortality from all infectious diseases are strongly associated with measles infection. The effect is likely attributable to generalized immunomodulation that follows measles infection, with a duration of two to three years.

SOURCE: Mina MJ, Metcalf JE, de Swart RL, et al. Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. *Science* 2015;348:694-699.

The effect of measles vaccination was studied using population-level data before and after the introduction of measles vaccination approximately 50 years ago in England and Wales, the United States, and Denmark. There was a strong association of measles vaccination in these countries with declines in mortality from other childhood infectious diseases; for example, the association (after transformation of the pre-vaccine data) for the United States was R^2 = 0.87. The nonspecific impact of measles vaccination was generalized and prolonged, with a duration of two to three years, with robust results across all ages studied from 1-14 years of age. The effect of immunomodulation after measles infection aligned with the risk of bacterial invasive disease in children younger than 5 years of age, with both declining along the same gamma curve (R^2 = 0.97 and 0.99, respectively). Furthermore, and confirming previous findings, there was consistently stronger association of immunomodulation for females than for males. Similar results of the adverse impact of measles on immunomodulation were found in both pre- and post-vaccine eras.

The results showed that when measles was common, it was indirectly responsible for as much as half of all childhood deaths from infectious diseases, accounting for nearly all of the interannual fluctuations in childhood infectious disease deaths. The main factor in the overall reduction of childhood mortality from infectious diseases in these countries was attributable to the implementation of measles vaccination programs. Fluctuations in childhood mortality in the United Kingdom, the United States, and Denmark were able to be explained by a simple weighted integral that described the prevalence of measles immune memory loss, capturing the generalized impact of measles infection on immune depletion.

COMMENTARY

Measles infection is accompanied by a transient general immunosuppression lasting a few weeks to a few months. Beyond the immediate benefits of prevention of mortality from measles directly, the World Health Organization recently concluded that measles vaccination is associated with significant reductions in overall childhood mortality from all causes.

Recent studies showed that measles infection results in rapid expansion of predominantly measles-specific B and T lymphocytes, essentially replacing the memory cell population. This has been postulated to result in "immune amnesia" to non-measles pathogens.

This study supports this hypothesis that measles infection results in loss of immunological memory cells by demonstrating that this effect on the mortality associated with other childhood infectious diseases is demonstrable. Measles vaccination had demonstrable impact to reduce overall childhood mortality and improve childhood survival. This was shown in high-resource settings where mortality from opportunistic infections associated with acute measles infections is low. It would be expected that studies of morbidity would also show the generalized adverse impact of measles infections. Measles vaccination may also contribute to preserving effective herd or community immunity to non-measles pathogens. Vaccinations are the most important measure in reducing mortality from infectious diseases. These

results underscore the reach of measles vaccine beyond reducing the morbidity and mortality directly attributable to measles illness, to a generalized and significant adverse effect on immune function that has far-reaching impact not previously appreciated. ■

Infectious Diseases Grand Rounds — Stanford University

By Carlos A. Gomez, MD

Dr. Gomez is Infectious Disease fellow, Stanford University, CA.

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

CASE: 55-year-old male with an atypical cause of osteo-articular infection

CASE HISTORY

A 55-year-old caucasian male, with a history of chronic HCV infection and ongoing injection drug use, was admitted due to severe bilateral wrist infection. The patient presented due to purulent drainage from several open wounds and multiple skin soft-tissue abscesses that emerged from prior sites of skin-popping with heroin in both wrists. Superficial wound culture grew methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas putida* for which the patient received two weeks of IV vancomycin and oral ciprofloxacin.

Three weeks after ceasing therapy, he re-presented for progressive bilateral wrist wound drainage, swelling, and wrist motion restriction. He denied any systemic signs of infection. Following admission, the patient underwent bilateral wound debridement at the OR. He had extensive skin soft-tissue compromise that extended deep into the radial bone and R-wrist joint. Wrist arthrotomy and radial bone biopsy was performed. MRSA grew from multiple tissue cultures, while acid fast and fungal staining was negative. Radial bone histopathology examination revealed acute osteomyelitis with surrounding suppurative soft-tissue inflammation. Periodic acid-Schiff (PAS) and Grocott-Gomori's methenamine silver (GMS) stains were negative for fungal elements. The patient was started on IV vancomycin and piperacillin-tazobactam empirically, but the latter was discontinued when culture results showed only MRSA. He was transferred to the long-term rehabilitation unit of our institution to continue IV vancomycin therapy for six weeks.

PAST MEDICAL HISTORY

His medical conditions include gout, chronic HCV infection, alcohol abuse, history of injection drug use, methamphetamine abuse, smoking dependency, and a history of septic arthritis of the left knee for which he underwent arthrotomy and washout two years prior to presentation. One year prior to the current admission, the patient developed right-wrist swelling, motion restriction, synovitis, and bone erosion changes at X-rays. A rheumatoid factor (RF) test was positive and the patient was started on low-dose prednisone (5 mg daily) for presumed rheumatoid arthritis (RA). Nonetheless, his symptoms progressed and he was evaluated by Rheumatology, who decided to initiate anti-TNF blocking therapy with etanercept (Enbrel) and later with adalimumab (Humira), five and two months prior to the initial presentation, respectively. His family history was contributory for cardiovascular disease. The patient lived in a trailer house in central California. He worked as a mechanic for many years. He denies any sick contacts, animal exposures, gardening, or agricultural work. His home medication included colchicine, indomethacin, trazodone, and omeprazole.

PHYSICAL EXAMINATION

Upon admission, the patient seemed in good general condition, appeared uncomfortable, slightly disheveled, and hyperactive. His vital signs were normal. He had swelling and erythema over both wrist areas, and active purulent discharge from several ventral and lateral wounds.

LABORATORY TESTING AND IMAGING

Laboratory investigation revealed a WBC (13700/mm^3, 75% neutrophils); hemoglobin was 8.3 g/d. Sedimentation rate (ESR) was 70 mm/h and C-reactive protein (CRP) was 1.65 mg/dL. Two sets of peripheral blood culture drawn upon admission were negative. X-rays of the right wrist revealed interval development of severe erosive change with extensive fragmentation and disorganization of the distal radius, ulna, and proximal/distal carpal rows. Severe soft-tissue swelling bilaterally with likely joint

effusions was present.

CLINCAL COURSE

The patient completed six weeks of IV vancomycin therapy as an inpatient in the rehab ward. Close to the antibiotic therapy termination, his left-wrist wounds were almost healed, with significant interval decrease of inflammatory changes and no limitations for range of motion. However, over the right wrist he developed a sinus tract that emerged from the wrist joint toward the skin. This was associated with chronic sero-purulent discharge and restricted range of motion. This finding triggered the investigation of the results of the fungal tissue culture from the surgical specimens taken upon admission. This culture was retrieved from an external reference laboratory and it showed the growth of the dimorphic fungus, *Sporothrix schenckii*. Unfortunately, the external reference laboratory failed in communicating to our institution, in a timely manner, the results of the fungal culture. A new fungal culture was sent from the R-wrist sinus tract, and confirmed, in less than a week, the presence of *Sporothrix schenckii*. A repeated chest X-ray was clear. At examination, there were no signs of extra-articular disease.

DIAGNOSIS

Wrist septic arthritis and radial osteomyelitis caused by *Sporothrix schenckii*

DISCUSSION

Sporotrichosis — or "rose gardener disease" — is primarily an infection that affects the skin and subcutaneous tissue from the extremities. It is caused by the traumatic inoculation of the dimorphic fungi *Sporothrix schenckii*. Sporotrichosis has global distribution, but most cases are reported in tropical and subtropical areas in the Americas.[1] In the environment, *Sporothrix schenckii* exist in hyphal form at temperatures < 37°C, whereas in-vivo adopts the forms of oval or cigar-shaped budding yeast. The acquisition occurs through traumatic contact with a variety of environmental sources, including soil, plants, plant products such as timber, straw, sphagnum moss, hay, thorny plants (e.g., roses and barberry bushes); and from animal contact (armadillos, cats, and squirrels). Sporotrichosis manifests primarily as lymphocutaneous disease: an ulcerated, verrucous or erythematous papule-nodular lesion arises initially at the site of inoculation, which can be followed by multiple secondary lesions through lymphangitic spread. Extra-cutaneous forms of sporotrichosis occur infrequently and generally affect immunocompromised patients. The most common forms of extra-cutaneous disease are osteoarticular, followed by pulmonary (usually cavitary), sinusitis, CNS disease, and endophthalmitis. The diagnosis of sporotrichosis relies on culture methods or through direct visualization by histopathology, but the yeast may remain difficult to detect unless multiple sections are examined. After 5 to 7 days of incubation at 25°C, filamentous hyaline colonies start to grow in Sabouraud dextrose agar. Isolation of the *Sporothrix schenckii* from any site is considered diagnostic of infection. To date, no standard method of serologic testing is available.

Osteoarticular sporotrichosis occurs by contiguous spread from cutaneous foci or hematogenous dissemination. The most common joints involved by *Sporothrix schenckii* include (in descending order): knee, wrist, elbow, and ankle. Tenosynovitis, effusion, bursitis, and synovial cyst formation with or without sinus tract may develop in the affected joint.[2] In one case series, failure to consider the diagnosis resulted in an average delay of 25 months, resulting in joint damage and increased need for arthrodesis.[3]

In a case review series that include 84 cases of osteoarticular sporotrichosis since 1970, 49% of the patients had ≥ 1 comorbidities (diabetes, hematological malignancy, AIDS, alcohol abuse, or long-term corticosteroid use).[4] In comparison with other causes of dimorphic-fungi osteoarticular infection (e.g. *C. immitis*, *B. dermatitidis*, *H. capsulatum*, *P. brasiliensis*, *P. marneffei*), osteoarticular sporotrichosis is less likely to be diagnosed by histopathology (< 10% of the cases) but it has the highest rate of isolation by fungal culture (90%) compared with other dimorphic fungi.[4]

The Infectious Disease Society of America (IDSA) updated the clinical practice guidelines for the management of sporotrichosis in 2007.[5] Oral forms of itraconazole (usually 200 mg/ twice per day) are recommended for lympho-cutaneous disease, with a length of therapy of 3-6 months necessary for complete resolution. In localized osteoarticular disease, itraconazole remains the first line of therapy but it should be extended for 12 months.[5] Lipid formulations of amphotericin B are recommended as an alternative to itraconazole in cases of disseminated disease or treatment failure with itraconazole.

After identification of *Sporothrix schenckii* in tissue-wound culture, our patient was started in oral itraconazole (oral suspension) 200 mg BID with a planned length of therapy for one year. Therapeutic drug levels were confirmed two weeks after initiation of anti-fungal therapy. After three weeks of therapy, the patient started noticing reduction in the amount of discharge form the R-wrist sinus tract. The

most common mode of acquisition of *Sporothrix schenckii* in this case could have been environmental contamination of the needles used by the patient for skin-popping in the affected area. ■

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Travel Medicine: News You Can Use

By Philip R. Fischer, MD, DTM&H

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

In May this year, 1296 travel medicine specialists gathered in Quebec City, Canada, for the 14th biannual conference of the International Society of Travel Medicine. Several of the topics discussed are practically relevant to readers of *Infectious Disease Alert*, so we offer this "Top Ten" list of news items.

10. Big numbers imply big opportunity.
There were reportedly 3.5 billion air travelers last year and 1.14 billion international arrivals around the world in 2014. People traveled a total of 2.3 trillion air miles last year, with more than half of that being on international flights. Increasingly, travel originates in less-wealthy countries rather than from "developed" nations in Europe and North America. People are traveling from many places to many other places, and that means germs are on the move as well.

9. Ebola can be a sexually transmitted disease.
It seems that infectious Ebola virus can persist for months in semen. As reported in the May 8, 2015, *MMWR*, Ebola virus has been isolated from semen 82 days after the onset of symptoms, and viral RNA has been identified in semen up to 101 days after symptom onset. The "final" case of Ebola in Liberia presented 30 days after the prior "last" case — with the only identified risk factor being unprotected vaginal intercourse with someone who had long since recovered from Ebola virus disease.

8. Malaria is still an issue for nearly half of the people on our planet.
Worldwide, 3.3 billion people in 97 countries live at risk of getting sick with malaria. However, the numbers of cases and deaths due to malaria have dropped to just 30-40% of what they were 15 years ago. Still, though, millions of people living in malaria-free areas travel to malarial areas each year and come home with risks of being sick and/or introducing malaria to viable vectors still living in their home areas. In many areas, up to half of commercially available antimalarial medications are either substandard or blatantly falsified (containing little or none of the labeled product); labeling is also falsified and difficult to identify as counterfeit.

7. A popular vacation site in France is now endemic for schistosomiasis.
Tourists enjoy swimming in the Cavu River on the French island of Corsica. Unfortunately, the water is now contaminated with schistosomes. Of approximately 30,000 local residents, "only" 110 were seropositive for schistosomiasis, but half of the positive subjects were children. While control measures are being implemented, it is safer to enjoy the scenery of the Cavu River without getting wet.

6. Dengue vaccines are progressing down the development "pipeline."
But, you already knew that if you have been reading *Infectious Disease Alert* regularly (see March 2014 issue). Huge phase 3 studies are in progress in South America and Asia. Licensing applications could be submitted during the current calendar year.

5. Europeans are not the same as Americans.
This has been clear for years as we watch our European colleagues support routine BCG vaccination for tuberculosis prevention. And, it is

clear as we discuss malaria chemoprophylaxis for travelers to some "low"-risk areas such as parts of the Caribbean. European travel medicine specialists are more likely than their American counterparts to forego prophylaxis and send travelers off with a curative dose of a stand-by treatment for presumptive use.

4. Technology helps.
I'd missed it, but data reported last year showed that nano-bubble technology is leading toward a malaria test that requires no blood drawing and no reagents. The test is said to "detect and screen malaria in seconds," and "can be realized as a compact, easy-to-use, inexpensive, and safe field technology." (Lukianova-Hleb EY, et al. *Proc Natl Acad Sci USA* 2014;111:900-905)

3. Microbiomes matter.
For whatever reasons, 10% of irritable bowel syndrome (IBS) is linked to previous gastrointestinal infection, and 4-31% of acute gastroenteritis is followed by IBS. This seems to be a particular problem for travelers. Adding multiply-resistant Gram-negative rods to the intestinal flora is common with travel.

2. Vaccine refusers might not keep refusing.
Recent data suggest that the main reason international travelers who decline vaccines do so is because they are not convinced that they are personally at risk of the diseases for which vaccines help. There is less concern about safety or other "evils" of vaccines. We need to continue to provide culturally acceptable education about risks and benefits of travel.

1. You are "essential"!
Even when the CDC suggests that non-essential travel be limited to countries with active Ebola outbreaks, humanitarian aid-related travel is considered essential. The world needs you! ■

MERS: From the Middle East to East Asia

By Stan Deresinski, MD, FACP, FIDSA

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

Dr. Deresinski reports that he has served as a one-time consultant for Cubist and Bayer.

On May 20, 2015, a 68-year-old Korean man with fever and cough who had returned eight days previously from a trip to Saudi Arabia and the United Arab Emirates was found to be infected with Middle East Respiratory Syndrome (MERS) coronavirus. The patient, unfortunately, had visited three different clinics before being admitted to St. Mary's hospital in Pyeongtaek, South Korea. While hospitalized, he shared a room with another patient, who, as a consequence, contracted MERS. Additional cases occurred and, after 29 of the first 36 were found to have been contracted at the Pyeongtaek hospital, the hospital was closed and its staff was quarantined.[1] Cases nonetheless continued to occur elsewhere, with most being acquired in health care facilities. Eventually, a second facility, Medi Heal hospital in Seoul, was closed. As of June 12, South Korea had recorded 126 cases and 14 deaths from MERS. The median age of the patients was 56 years old (16 to 84 years) and the majority were men (59%). Ten (7.9%) are health care professionals.

All cases to date have been linked to a single chain of transmission and, except for the index case, were associated with health care facilities. Investigation identified 44 hospitals at which either transmission had occurred or a confirmed case of MERS had visited prior to their diagnostic confirmation.[2,3] The transmission chain has included at least one fourth-generation case — an ambulance driver who had transported a third-generation case to a hospital. As of June 12, 3680 contacts have been identified. Globally, since September 2012, the World Health Organization (WHO) has been notified of 1289 laboratory-confirmed cases of infection with MERS-CoV, including at least 455 related deaths.

MERS was first identified in 2012 in Saudi Arabia. Including the outbreak in South Korea, MERS has infected nearly 1200 people and led to 442 deaths.

Human cases have recently been reported in Oman, Qatar, Saudi Arabia, and the United Arab Emirates, as well as an imported case in Germany. Strains of the virus that are identical to human strains have been isolated from dromedary camels in several countries, including Egypt, Oman, Qatar, and Saudi Arabia. While transmission of MERS in health care facilities in the Middle East occurs, the experience

in South Korea has been extraordinary. Genomic sequencing of a limited number of viruses indicates that the Korean virus is most closely related to a virus detected in 2015 in Saudi Arabia. Preliminary analysis has failed to find evidence that the transmissibility of the virus has increased.

The Korean experience has increased the level of concern about the importation of cases into the United States, where the CDC has recommended the following criteria for deciding which patients should be evaluated for MERS:[4]

A. Fever AND pneumonia or acute respiratory distress syndrome (based on clinical or radiologic evidence) AND EITHER:

- a history of travel from countries in or near the Arabian Peninsula[1] within 14 days before symptom onset; OR
- close contact with a symptomatic traveler who developed fever and acute respiratory illness (not necessarily pneumonia) within 14 days after traveling from countries in or near the Arabian Peninsula; OR
- a history of being in a health care facility (as a patient, worker, or visitor) in the Republic of Korea within 14 days before symptom onset; OR
- a member of a cluster of patients with severe acute respiratory illness (e.g., fever and pneumonia requiring hospitalization) of unknown etiology in which MERS-CoV is being evaluated, in consultation with state and local health departments;

OR

B. Fever AND symptoms of respiratory illness (not necessarily pneumonia; e.g., cough, shortness of breath) AND being in a health care facility (as a patient, worker, or visitor) within 14 days before symptom onset in a country or territory in or near the Arabian Peninsula in which recent health care-associated cases of MERS have been identified.

OR

C. Fever OR symptoms of respiratory illness (not necessarily pneumonia; e.g., cough, shortness of breath) AND close contact with a confirmed MERS case while the case was ill.

The Korean experience illustrates the critical importance of early recognition of potential MERS cases and rapid implementation of strict infection control measures. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Point-of-Care Syphilis Testing

Cause LM, et al. Novel syphilis test distinguishes active vs past infections. *Clin Infect Dis* 2015; Doi:10.1093/cid/civ243.

Not only has the introduction of the "reverse paradigm testing" for syphilis improved our ability to detect syphilis infection, especially acute primary infection, it has confused many — and has caused undue stress for some individuals who were surprised to learn their blood tests are consistent with "previously treated" syphilis infection. Often, screening EIA or CEA tests for syphilis antibodies do not reflex to confirmatory tests, leaving days of uncertainty for a patient regarding the true nature of the result and whether the disease is active or inactive. I've had sobbing 20- and 80-year-olds in my office, who would have preferred never to know they've had previous (treated) syphilis infection; the information can also be distressing for couples. There are times when I wish we could return to the previous testing methods, which screened only for active infection.

At least some of this problem could be resolved with

more rapid confirmation or point-of-care testing. A newer point-of-care test, called a dual path platform (DPP) immunochromatographic screening assay, provides both treponemal and non-treponemal testing at once, using whole blood, serum, or plasma (Chembio Diagnostic Systems, Medford NY). Such tests are often referred to as lateral flow tests or strip tests, which are user-friendly, relatively inexpensive to perform, are stable for long periods without refrigeration, and provide rapid results. They are especially useful in rural areas or third-world countries.

In a high-risk population, based on tests of 1005 samples, the sensitivity of the DDP treponemal test was 89.8% and the specificity was 99.3%. For the non-treponemal portion of the test, the sensitivity was 94.2% and the specificity was 62.2%. Concordance of the test, with reference RPR and immunoassays, was 94.3% for high titre infections and 90% for low titre infections. Concordance of the DDP assay for past/treated infection was only 27.5%, but half of inactive infections were accurately recognized as inactive — and 22.8% were not recognized at all.

This method of screening would be easier for clinicians to interpret, and prevent unnecessary treatment of some inactive infections. While a small number of active infections would be missed, some individuals would be saved from the embarrassment and stigma of finding out they have treated infection. The advantages of this test, which has not been approved by the United States Food and Drug Administration, in terms of ease of use and cost, would need to be balanced against the somewhat lower test accuracy.

Revised Urinary Catheter Use Guidelines

Meddings J, et al. The Ann Arbor Criteria for appropriate urinary catheter use in hospitalized medical patients: Results obtained by using the RAND/UCLA Appropriateness Method. *Ann Intern Med* 2015;162 (9) S:S1-S34.

Every day on ward rounds, many hospitals apply daily use criteria for urinary catheters based on recommended guidelines. These include such criteria as critical illness, bladder outlet obstruction, and monitoring fluid status. While these criteria seem reasonable, they are not entirely evidence-based, and are sometimes ambiguous or loosely applied by day-shift nursing staff evaluating daily Foley use. For example, patient request for comfort or for incontinence, especially in patients with limited mobility (or an unwillingness to get out of bed), remains a gray area for nursing staff, who simply do no wish to tussle with a patient's expressed wishes. A 15-member multi-disciplinary panel has submitted a revised guideline for Foley catheter use in hospitalized medical patients, based on a review of the literature for 299 potential scenarios for catheter use. Several recent U.S. and European guidelines, and an extensive literature review, informed this process, and a risk-benefit analysis was developed for the different uses. Scenarios for both continuous use catheters and intermittent straight catheters were evaluated — both for the inpatient and the outpatient setting. Many common uses for catheters — especially intermittent catheterization — were debunked, and others for indwelling Foley use were clarified, including the use in critical care settings, the appropriate use for urine collection and measurement, and comfort care.

Areas of controversy were resolved using the RAND/UCLA method — which does not require a consensus or a majority vote, but rather a weighted recommendation based on the opinions of the committee members or, at times, outside clinical experts.

Specifically, for 105 possible uses for Foley catheterization in hospitalized patients, only 43 were found to be appropriate, 48 were inappropriate, and 14 were uncertain. Some of these scenarios and patient characteristics were sufficiently similar, allowing consolidation of the recommendations — providing a list of 12 appropriate indications for catheter use and 9 inappropriate recommendations for Foley catheter use in hospitalized patients. A summary of these criteria follows, with justification for each, footnotes, and clinical examples provided in the body of the article :

- Acute urinary retention without bladder outlet obstruction; bladder outlet obstruction due to non-infectious, non-traumatic diagnosis; or chronic urinary retention with bladder outlet obstruction;
- Stage 3 or 4 or unstageable pressure ulcers or similarly severe wounds of other types that cannot be kept clear of urine despite other management strategies;
- Urinary incontinence in patients for whom nurses find it difficult to provide skin care despite other urinary management strategies — e.g., such as temporary immobility for a procedure or weight greater than 300 pounds;
- Hourly measurement of urine volume required to provide treatment;
- Daily (not hourly) measurement of urine volume that is required to provide treatment and cannot be assessed by other volume and urine collection strategies;
- Single 24-hour urine sample for diagnostic test that cannot be obtained by other means;

• Improvement in comfort when urine collection by catheter addresses patient and family goals in a dying patient;
• Reduce acute, severe pain with movement when other urine management strategies are difficult;
• Management of gross hematuria with clots;
• Clinical condition for which intermittent or external catheter use would be appropriate but placement by an experienced nurse or practitioner was difficult or patient for whom bladder emptying was inadequate with non-indwelling strategies during this admission.

HIV and Meningococcal Vaccination Revisited

Miller L, et al. Elevated risk for invasive meningococcal disease among persons with HIV. *Ann Intern Med* 2014;160:30-37.

A number of fatal cases of invasive meningococcal disease (IMD) in men who have sex with men (MSM) in 2010 and 2012 in New York City and Los Angeles raised concerns about the risk for IMD in MSM and in persons with HIV/AIDS. Estimates of the incidence of IMD in NYC in 2012 were as high as 50-fold that of the general population (age-adjusted data); and the case-fatality rate for these cases was remarkably high (32%). More than half of the cases (54%) were HIV positive, although their average CD4 count, when available, was 525 cells/mm^3, and 70% were virologically suppressed. Many of these cases occurred after hanging out in crowded bars and large social gatherings. Molecular studies suggest that the outbreak was caused by a common strain of meningococcal serogroup C. It is now believed that a more virulent strain of meningococcus began circulating among MSM, resulting in higher death rates.

The question remains whether the risk of IMD in MSM is due more to their social behaviors (frequent clustering in large groups, similar to the Haj) or to the presence of HIV-infection. Limited data suggested that HIV-infection may contribute to an increased risk of IMD, similar to the observed increased risk for pneumococcal infection (another encapsulated organism).

Miller and colleagues have provided some answers. Using surveillance data collected between 2000-2011 for persons aged 15 to 64 years, rates of IMD in NYC were compared between HIV positive and non-HIV positive. Cases were matched to vital statistics registry, and immunological data were collected. A total of 265 persons with IMD were reported during the study period, 45 of whom were HIV positive. Two patients were excluded from the analysis, as their IMD preceded their HIV diagnosis, and 3 were re-classified as HIV-non-infected. Thirty of these were male and 10 were female. Four of the 40 case patients with IMD and HIV died (10%) compared with 51 of 223 non-HIV-positive case patients (23%).

During this study period, the average annual incidence of IMD in NYC was 0.39 cases per 100,000. The relative risk of IMD for persons with HIV/AIDS was 10.0 (95% CI, 7.2 to 14.1). When the study period was broken into three-year intervals and analyzed, this increased relative risk remained fairly uniform, ranging from 8.2 to 11.8, with an average annual incidence ranging from 0.23 in 2009-2011 to a peak of 0.41 in 2000-2002. During the interval from 2000 to 2011, the relative risk for IMD was slightly higher for HIV-positive men than HIV-positive women (12.2 vs 7.6). When CD4 data was analyzed, the odds of IMD was 5.3 higher for persons with CD4 counts less than 200/mm^3 compared with their HIV-positive counterparts with higher CD4 counts.

Thus, the risk of IMD in persons with HIV/AIDS in NYC since 2000 has been consistently higher than the age-matched non-HIV-positive population — and therefore the cases that received such dramatic attention the past 2-3 years were part of a pattern of increased risk for persons with HIV-infection.

While the CDC Advisory Committee on Immunization Practices states that "HIV infection is not an indication for routine vaccination with MenACWY,"[1] the risk for IMD in persons with HIV-infection is clearly increased, especially for those with more advanced disease. Observations of microbiologic data for NYC cases found that 74% were vaccine-preventable serogroups (A, C, Y, and W), and that 87% of the cases in HIV/AIDS were potentially vaccine-preventable. It is known that meningococcal quadravalent vaccine is immunogenic in HIV-positive persons, at least as demonstrated in HIV-positive adolescents. Two doses administered at least two months apart are recommended for persons with HIV infection, if you choose to administer vaccine to your patients. ■

REFERENCE

1. Recommended Adult Immunization Schedule, United States — 2015, CDC; http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf.

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following is correct regarding the duration of antibiotic treatment for pyogenic vertebral osteomyelitis?

A. Twelve-week treatment is significantly superior to 24 weeks.

B. Twelve weeks is significantly superior to 6 weeks.

C. Twelve-week and 6-week treatment results in very similar cure rates.

D. Six weeks is superior to 12 weeks.

2. Which of the following is correct regarding the duration of antibiotic therapy for intraabdominal infections after source control?

A. Outcomes after 4 days of treatment do not significantly differ from those after treatment continuation for 2 days after resolution of SIRS.

B. Treatment may be stopped after 4 days, but only if there has been resolution of SIRS symptoms for at least 2 days.

C. Treatment should never be stopped until SIRS symptoms have been resolved for at least 2 days.

D. Treatment continuation until SIRS has been resolved for at least 2 days is significantly superior to alternative strategies with shorter duration of antibiotic administration.

3. Which of the following is correct?

A. Sporothrix appears as filaments in tissue and is readily visualized.

B. Sporothrix cultures generally require 4-6 weeks to become positive.

C. Itraconazole is a recommended treatment for the lymphocutaneous form of the disease.

D. Sporothrix has only one morphological growth phase.

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