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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Next-generation Sequencing for Diagnosis of Cryptic Hepatitis B and E in Patients with Hepatitis of Unknown Etiology

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: Sera from patients with hepatitis of unknown etiology (HUE) were studied using next-generation sequencing (NGS). Sequences from hepatitis B virus were detected in 7 patients and hepatitis E virus in 2 patients.

SOURCE: Ganova-Raeva L, et al. Cryptic hepatitis B and E in patients with hepatitis of unknown etiology. *J Infect Dis* 2015;212:1962-1969.

Serum specimens were collected from 32 patients from both the United Kingdom and Vietnam. None of the patients had received hepatotoxic drugs and none had laboratory evidence of autoimmune hepatitis. All patients' sera tested negative by serologic tests for hepatitis A, B, C, E, CMV, and EBV, as well as by polymerase chain reaction (PCR) for HBV DNA, HCV RNA, and HEV RNA. No patients were immunocompromised or were infected with HIV. Twenty-six U.S. blood donors were used as controls.

After total nucleic acid extraction, the samples were reverse transcribed using random hexamer primers, then the cDNA product was amplified, purified, and finally used to generate shotgun libraries for sequencing.

Extraction of total nucleic acid from 12 patients with acute hepatitis and 26 controls yielded a

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sufficient amount of DNA for sequencing. Total nucleic acids from 26 acute hepatitis patient sera with insufficient nucleic acid quantity for sequencing were pooled and then used for NGS.

Sequences from HBV were detected in seven individuals with HUE and from the pooled library. HEV was detected in two individuals with HUE and from the pooled library. Both HEV patients were co-infected with HBV. HBV sequences were from genotypes A, D, and G. The HEV sequences were genotype 3. No known hepatitis viruses were detected in the tested normal sera.

■ COMMENTARY

Up to 30% of cases of presumed acute viral hepatitis have no known etiology. This study shows that NGS-based detection of HBV and HEV is more sensitive than commercial antibody and molecular assays, and that cryptic infection with these viruses is likely responsible for a high proportion of HUE. This still leaves about 40% of cases of HUE in this study in which no viral etiology was determined, suggesting that either HBV or HEV was present at levels of viremia below the threshold of detection using NGS or that yet-undiscovered pathogens were responsible.

NGS is emerging as a powerful tool to identify rare or unexpected pathogens. Fremond et al recently applied NGS to identify an astrovirus as the cause of unexplained progressive encephalitis in a child with X-linked agammaglobulinemia,[1] and Wilson et al used NGS to diagnose neuroleptospirosis in a child with severe combined immunodeficiency.[2] ■

REFERENCES

1. Fremond M-L, et al. Next-generation sequencing for diagnosis and tailored therapy: A case report of astrovirus-associated progressive encephalitis. *J Ped Infect Dis Soc* 2015;4:e53-e57.
2. Wilson MR, et al. Actionable diagnosis of neuroleptospirosis by next-generation sequencing. *N Engl J Med* 2014;370:2408-2417.

ABSTRACT & COMMENTARY

Both Azithromycin and Doxycycline Achieve a High Rate of Cure for Chlamydia

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: Although a well-conducted randomized clinical trial did not show that azithromycin was non-inferior to doxycycline for the treatment of chlamydia, both treatments resulted in a high rate of cure (97% and 100%, respectively).

SOURCE: Geisler WM, et al. Azithromycin versus doxycycline for urogenital *Chlamydia trachomatis* infection. *N Engl J Med* 2015;373:2512-2521.

Chlamydia continues to be the most prevalent bacterial sexually transmitted infection worldwide. Currently the CDC recommends treatment with either a single 1-g dose of oral azithromycin or doxycycline 100 mg twice a day by mouth for 7 days. Because of limitations to previous studies comparing the two regimens, Geisler and colleagues sought to clarify whether

azithromycin is non-inferior to doxycycline for the treatment of *Chlamydia* infection.

The study was conducted in youth correctional facilities in Los Angles and enrolled males and females between 12 and 21 years of age. A physical exam and nucleic acid amplification testing (NAAT) to screen for chlamydia is routinely performed on individuals within 96 hours of intake to the facility. All those who had a positive screen were offered enrollment in the study. Exclusion criteria included pregnancy, breast feeding, gonorrhea co-infection, allergies to tetracyclines or macrolides, photosensitivity, concomitant infection, receipt of an antibiotic within 21 days with antichlamydial activity, pelvic inflammatory disease, or epididymitis. Enrollees were randomly assigned on a 1:1 ratio to receive azithromycin or doxycycline therapy as per the CDC recommendations. On day 28, an interview and test of cure were performed using NAAT. Participants who tested negative at day 28 and were still in a correctional facility at day 67 had a second interview and test of cure done. The primary outcome was treatment failure at the 28-day follow-up. The study was designed to test the null hypothesis that the absolute rate of azithromycin treatment failure would be at least 5 percentage points higher than the absolute rate of doxycycline treatment failure against the hypothesis that there would be no difference between the two groups.

Out of 567 enrollees, 284 were randomized to receive azithromycin and 283 were randomized to receive doxycycline. After early discontinuation, mainly due to discharge from the correctional facility, 155 participants in each group completed the first follow-up. No treatment failures occurred in the doxycycline group (0%; 95% confidence interval [CI], 0.0-2.4) and five occurred in the azithromycin group (3.2%, 95% CI, 0.4-7.4). All of the treatment failures were asymptomatic. Since the upper boundary of the CI exceeded 5 percentage points, the null hypothesis was not rejected, and the non-inferiority of azithromycin to doxycycline was not shown. Adverse reactions occurred in 23% and 27% of participants in the azithromycin and doxycycline groups, respectively, with gastrointestinal symptoms the most commonly reported.

■ COMMENTARY

One of the most interesting aspects of this study is that it was conducted in youth correctional facilities. This allowed the investigators a degree of control that is often not present in other settings. For example, the possibility of chlamydia re-exposure was far less than would have been possible with a more conventional trial. Also, the setting facilitated the adherence of the participants to therapy. Adherence would have been particularly important for the doxycycline group. As the authors mentioned in their discussion, previous studies have shown that non-adherence to doxycycline therapy contributes to treatment failure in the magnitude of 20% for those who took fewer than 10 doses. Despite a higher treatment failure rate for azithromycin compared to doxycycline, overall it was still low (3%). In 2012, a total of 1,422,976 chlamydial infections were reported to CDC in 50 states and the District of Columbia.[1] The public health implications of not successfully treating three out of every 100 individuals with chlamydia would be significant. However, this study should not be interpreted in a broad context since it was conducted in a highly controlled and regimented setting. Indeed, in the "real world," many patients are unable to complete 7 days of doxycycline, and it is far simpler for them to take a single dose of azithromycin with a strong recommendation to have a test of cure 4 weeks later.

[As the authors mentioned ... previous studies have shown that non-adherence to doxycycline therapy contributes to treatment failure in the magnitude of 20% for those who took fewer than 10 doses.]

Why is azithromycin seemingly less effective than doxycycline? One theory is that azithromycin drug levels might not be sufficient in some patients to eradicate chlamydia. Testing this hypothesis could involve giving higher doses of azithromycin (e.g., 2 g orally), although this approach would be limited by increased gastrointestinal symptoms. Another possible explanation is that azithromycin might be less efficient in eradicating chlamydia from acutely infected human epithelial cells compared to doxycycline. Further studies on azithromycin and other agents, particularly ones under development, in acute chlamydia infection are needed. ■

REFERENCE

1. Centers for Disease Control and Prevention web site. Available at www.cdc.gov. Accessed Jan. 1, 2016.

ABSTRACT & COMMENTARY

Outbreaks of Salmonellosis Associated with Turtles

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, MI.

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

SYNOPSIS: Eight outbreaks with 473 cases of salmonellosis associated with small turtles occurred in the United States from 2011-2013, despite the 1975 ban of the sale and distribution of small pet turtles. The outbreaks disproportionately affected children younger than 5 years of age (55% of case-patients) and Hispanics (45% of case-patients).

SOURCE: Walters MS, Simmons L, Anderson TC, et al. Outbreaks of salmonellosis from small turtles. *Pediatrics* 2016;137:1-9.

Using epidemiologic reports of *Salmonella* isolates to the Centers for Disease Control and Prevention, or to PulseNet, which is the national molecular subtyping network for foodborne disease surveillance, eight outbreaks of symptomatic salmonellosis were identified during 2011-2013. These included a total of 473 cases (range, 7 to 124 cases) from 41 states, Washington DC, and Puerto Rico. The median case-patient age was 4 years (range, 5 weeks to 94 years). Children younger than 18 years of age accounted for 74% of case-patients; 55% of case-patients were younger than 5 years of age; and 23% were younger than 1 year of age. Among 191 case-patients with available information, 85 (45%) were Hispanic. Knowledge of the association between Salmonella and turtles did not vary by ethnicity. Among 274 case-patients with available information, 78 (28%) patients were hospitalized, with a median duration of hospitalization of 3 days (range, 1-24 days).

[... small turtles remain a significant source of salmonellosis in humans.]

In the 7 days preceding illness, 68% (187 of 273) of case-patients who were interviewed reported turtle exposure, defined as direct contact (61%; 54 of 88 case-patients) or in the same room as a turtle. Among these, 88% (124 of 141 case-patients) described small turtles (shell length less than 4 inches). Turtle exposure by outbreak ranged from 47% to 74%. Water samples from turtle habitats linked to human illness were cultured for *Salmonella*, with outbreak strains isolated from turtle habitats linked to human cases in seven outbreaks. Turtles were owned for a median of 84 days before illness onset (range, 1-1278 days). Turtles from one outbreak were traced to a Louisiana turtle farm.

COMMENTARY

In the United States each year, *Salmonella enterica* causes an estimated 1 million cases, 19,000 hospitalizations, and 400 deaths. Salmonella are normal intestinal flora in turtles and other reptiles and may be shed throughout their lifetime. Human exposure to reptiles (e.g., turtles and snakes) and amphibians (e.g., frogs) is associated with about 6% of human cases. During 1970-1971, exposures to turtles accounted for an estimated 280,000 human cases annually. In 1975, the U.S. Food and Drug Administration banned the sale and distribution of small pet turtles in the United States except for turtles for exhibition, education, or export. Although the federal ban remains in place, household turtle ownership has increased from 0.6% in 2001 to 1.1% in 2011.

Since the 1975 ban, five outbreaks of *Salmonella* were reported from 2006 to 2011. This report describes eight additional outbreaks from 2011 to 2013.

Despite the federal ban, and additional bans in some states and local jurisdictions, small turtles remain a significant source of salmonellosis in humans. Physicians should be aware of this resurgent risk in evaluating acute illness, and also educate families about the risk of turtles in households, especially households with children. ■

ABSTRACT & COMMENTARY

Bronchiolitis

By Philip R. Fischer, MD, DTM&H

Dr. Fischer is Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

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

SYNOPSIS: Bronchiolitis is a common infection caused by several different viruses; 20% of children in the United States seek medical care for respiratory syncytial virus (RSV), a common cause of bronchiolitis, during the first year of life. Supportive care is effective, but many children still receive pharmacologic treatments that have been proven to be ineffective.

SOURCE: Meissner HC. Viral bronchiolitis in children. *N Engl J Med* 2016;374:62-72.

Bronchiolitis is a common problem caused by respiratory syncytial virus (RSV) and other viruses. Each year in the United States, approximately 20% of children younger than a year of age require medical care for RSV infection, and 2-3% (about 100,000) of children are hospitalized with bronchiolitis. Globally, bronchiolitis accounts for up to 200,000 pre-school-aged deaths each year.

While clinical presentations of bronchiolitis vary, there are usually a few days of nasal congestion, runny nose, and low-grade fever, followed by worsening cough. Respiratory distress can manifest as tachypnea and retractions. Wheezing is often heard on auscultation. Apnea can be seen early in the course of the illness, especially in prematurely born children. Severe bronchiolitis requiring hospitalization is most common at 1 to 3 months of age, likely related to declining levels of protective antibodies that had been acquired trans-placentally. Prematurely born babies and infants with congenital heart disease are at increased risk of severe bronchiolitis.

Severe bronchiolitis is associated with a subsequent risk of developing asthma. It is not known, however, whether the infection prompts the development of asthma or whether lungs destined to get asthma are already altered in ways that make them more likely to develop severe bronchiolitis.

RSV is the most common viral cause of bronchiolitis and accounts for more than half of cases; it is most common in November through April in North America. Especially in autumn and spring, rhinovirus and parainfluenza virus cause bronchiolitis. The peak incidence of human metapneumovirus-related bronchiolitis is usually a month or two after the peak of RSV bronchiolitis. Coronavirus, adenovirus, influenza, and enterovirus can also cause bronchiolitis.

The treatment of bronchiolitis is largely supportive in nature. Good studies have demonstrated the inefficacy of several interventions, including diagnostic radiographs, viral testing, bronchodilators such as albuterol, glucocorticoids, antimicrobial agents, chest physiotherapy, and supplemental oxygen when the oxygen saturation is still at or above 90%.

COMMENTARY

Bronchiolitis is a global problem. In eastern Kenya, RSV accounts for 20% of hospitalizations for severe respiratory infection during the first six months of life.[1] In Thailand, RSV accounts for 29% of lower respiratory tract infections during the first year of life, but the season is usually from July to October.[2]

[As noted by Dr. Meissner in this new review article ... aggressive interventions do not usually help children with bronchiolitis recover any better than does supportive care.]

Most of us reading this article at the time of its publication are working in North American settings where many children are being treated for bronchiolitis. As noted by Dr. Meissner in this new review article and as detailed in late 2014 by the American Academy of Pediatrics,[3] aggressive interventions do not usually help children with bronchiolitis recover any better than does supportive care. For instance, strong scientific evidence suggests

that several common measures should not be routine in the care of children with bronchiolitis. Chest X-rays are associated with overtreatment with antibiotics, since atelectasis seen with viral infections masquerades as focal infiltrates. Viral testing is costly without altering isolation measures, treatment, or outcome. Bronchodilators and steroids are ineffective. Antimicrobial agents do not help. Oxygen does not improve outcomes in children with at least 90% saturation on room air. Even continuous testing of pulse oximetry delays hospital dismissals without reducing complications in patients.

Nine years ago, a commentary in the *New England Journal of Medicine* pointed out that more than half of patients with bronchiolitis were treated with interventions known not to be effective. Clearly, we still find that withholding therapy is much more difficult than giving it; we tend to want to "do something" rather than "just" provide supportive care. Evidence should guide our decisions to use and not to use specific interventions.

Now, it is time to manage bronchiolitis based on scientific evidence. Doing so, "less is more" in that provision of less intervention will actually best help most young children with bronchiolitis. ■

REFERENCES

1. Nokes DJ, Ngama M, Bett A, et al. Incidence and severity of respiratory syncytial virus pneumonia in rural Kenyan children identified through hospital surveillance. *Clin Infect Dis* 2009;49: 1341-1349.
2. Suntarattiwong P, Sojisirikul K, Sitaposa P, et al. Clinical and epidemiological characteristics of respiratory syncytial virus and influenza virus associated hospitalization in urban Thai infants. *J Med Assoc Thai* 2011;94:S164-S171.
3. Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: The diagnosis, management, and prevention of bronchiolitis. *Pediatrics* 2014;134:e1474-e1502.
4. Hall CB. Therapy for bronchiolitis: When some became none. *N Engl J Med* 2007;357:402-404.

ABSTRACT & COMMENTARY

Posaconazole Dosing — Beware!

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: The availability of two different oral formulations of posacozaole (oral suspension, delayed release tablets) with differing bioavailability and dosing requires great care by both prescribers and dispensing pharmacists in their use.

SOURCE: FDA Drug Safety Communication: FDA cautions about dosing errors when switching between different oral formulations of antifungal Noxafil (posaconazole); label changes approved. www.fda.gov/drugs/drugsafety/ucm479352.htm.

In the United States, posaconazole (Noxafil) is available for intravenous administration, but also as two distinct oral formulations — an oral suspension and a delayed-release tablet. The former was approved in 2006, and the latter in November 2013. The recommended dosing differs. The formulations also differ in how they should be taken relative to food. The bioavailability of the oral suspension is improved when it is taken during or within 20 minutes of a full meal or liquid nutritional supplement; it can also be taken with an acidic carbonated beverage such as ginger ale. Although bioavailability is not significantly improved, taking the tablet with food reduces gastric irritation.

The tables list recommended dosing for FDA-approved indications, but higher doses are generally used for some unapproved indications, such as the treatment of infections due to filamentous fungi. Since the approval of the delayed-release tablet, the FDA has received 11 reports of errors due to prescription and/or dispensing of the wrong formulation, with one patient requiring hospitalization and another dying as a result.

The patient who died was receiving posaconazole delayed-release tablets for antifungal prophylaxis when the pharmacy substituted the oral suspension without attention to proper dosing. The bioavailability of the tablets is significantly superior and more reliable than that of the oral suspension. Presumably under-dosed, the patient died of a stroke "related" to *Aspergillus* infection.

In the other 10 cases, the switch was in the other direction, i.e., from the oral suspension to delayed-

release tablets and also occurred without dose adjustment. One example was provided: A patient was given two 100-mg delayed-release tablets 3 times daily — twice the recommended prophylactic dose of three 100-mg tablets once daily. The most frequently reported adverse effects were nausea and vomiting, which, in one case, was associated with hypokalemia.

Available evidence indicated that the errors were due to a lack of knowledge among healthcare professionals that the oral formulations may not be substituted for each other without appropriate dose adjustment. As a consequence, the FDA has issued a caution about the potential for dosing errors occurring when the oral formulations of posaconazole are prescribed:

- Prescribers should specify the dosage form, strength, and frequency on all prescriptions they write for Noxafil.
- Pharmacists should request clarification from prescribers when the dosage form, strength, or frequency is not specified.
- Use caution when switching between Noxafil delayed-release tablets and Noxafil oral suspension, as the dosing is different for the two oral formulations. The delayed-release tablet has a higher bioavailability than the oral suspension. As a result, the dose and frequency of administration for Noxafil depend on the particular formulation used and the indication for use.
- Prescribers should follow the specific dosing instructions for each formulation. Incorrect dosage and administration can lead to subtherapeutic levels and potential for treatment failures, or higher levels and potential for adverse reactions.

[Prescribers should follow the specific dosing instructions for each formulation. Incorrect dosage and administration can lead to subtherapeutic levels and potential treatment failures, or higher levels and potential for adverse reactions.]

- Advise patients to seek medical attention right away if they:
  – develop severe diarrhea or vomiting.
  – notice a change in heart rate or heart rhythm, or have a heart condition or circulatory disease.
  – have a potentially proarrhythmic condition, as posaconazole should be administered with caution in these patients.
  – notice swelling in an arm or leg, or experience shortness of breath.
  – have liver disease or develop itching, nausea or vomiting, their eyes or skin turn yellow, they feel more tired than usual, or feel like they have the flu. ■

Table 1. Dosage for Noxafil Delayed-release Tablets

Indication	Dose and Duration of Therapy
Prophylaxis of invasive *Aspergillus* and *Candida* infections	Loading dose: 300 mg (three 100 mg delayed-release tablets) twice a day on the first day. Maintenance dose: 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day. Duration of therapy is based on recovery from neutropenia or immunosuppression.

Table 2. Dosage for Noxafil Oral Suspension

Indication	Dose and Duration of Therapy
Prophylaxis of invasive *Aspergillus* and *Candida* infections	200 mg (5 mL) three times a day. The duration of therapy is based on recovery from neutropenia and immunosuppression.
Oropharyngeal Candidiasis	Loading dose: 100 mg (2.5 mL) twice a day on the first day. Maintenance dose: 100 mg (2.5 mL) once a day for 13 days.
Oropharyngeal Candidiasis Refractory to Itraconazole and/or Fluconazole	400 mg (10 mL) twice a day. Duration of therapy should be based on the severity of the patient's underlying disease and clinical response.

CORRECTION

In the January 2016 issue, a sentence in the third paragraph of the article on "Encephalitis from Chikungunya Virus" should have said: "Of the 10 adults available for follow up at 3 years, three of them had neurologic sequelae attributable to CHIKV."

ABSTRACT & COMMENTARY

Clinicians Are Skeptical of Early Warning Systems for Sepsis

By Elaine Chen, MD

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

SYNOPSIS: While early warning systems for sepsis lead to clinical action, clinicians are skeptical and do not perceive them to be beneficial.

SOURCE: Guidi JL, et al. Clinician perception of the effectiveness of an automated early warning and response system for sepsis in an academic medical center. *Ann Am Thorac Soc* 2015;12:1514-1519.

Severe sepsis is very common, with high morbidity and mortality. Early recognition and intervention improves mortality. However, the diagnosis may often be missed in early sepsis. An academic health system developed an electronic early warning and response system (EWRS) for sepsis in 2012, monitoring real time vital signs and laboratory data for hospitalized, non-ICU, acute care patients and notifying clinicians when specific criteria were met. This EWRS accurately identified patients at increased risk for deterioration and death, resulting in more timely sepsis care and ICU transfer, and possibly reducing sepsis mortality.[1]

All non-ICU medical and surgical inpatients were screened continuously for systemic inflammatory response syndrome (SIRS) criteria as well as criteria suggesting organ dysfunction. Whenever a patient fulfilled four or more criteria, a text page was sent to the covering provider (physician or advanced practice provider) and rapid response coordinator, and the bedside nurse received a pop-up notification in the electronic health record (EHR). Clinicians were instructed to meet at the bedside within 30 minutes to evaluate the patient and make any management changes. A patient could only trigger the alert once during hospitalization.

[That most patients were perceived to be stable both before and after the alert may be a sign of low signal-to-noise ratio, which has a risk of leading to alert fatigue.]

Successful implementation of new clinical systems includes clinician acceptance. The authors hypothesized that clinicians would perceive the EWRS as useful and effective. They tested their hypothesis by surveying clinicians immediately after receiving the EWRS alert to evaluate their perception of the value of the alert. A 16-item questionnaire examined the utility of implementation of the EWRS. The rapid response coordinator distributed paper surveys within 2 hours of an EWRS alert for 6 weeks. Subjects included providers and bedside nurses in a single academic medical center. Anonymously completed surveys were returned to a designated envelope.

The EWRS generated 247 alerts; 494 surveys were distributed, and 232 were returned (127 from providers and 105 from nurses) for an overall response rate of 47%. Both providers and nurses reported that patients were medically stable both before and after the alert in approximately 80% of cases and did not commonly perceive the presence of a new critical illness. Sepsis was the suspected trigger in one-third of cases and volume depletion in one-fifth. In one-third of cases, clinicians perceived the values to be erroneous at baseline or inconsequential.

Management changed in approximately half of patients, most commonly by way of closer monitoring, basic diagnostic testing, or therapies such as intravenous fluids and antibiotics. Less than half of providers or nurses found the alert helpful and less than one-third thought it improved patient care. Nurses thought more favorably about the EWRS than providers.

Overall, clinicians were lukewarm in their support of the EWRS. The authors noted that users received no formal education regarding the importance

of early sepsis recognition and treatment. The authors suggested that the alert may have resulted in behavioral modifications that improved clinical outcomes, but that clinicians may not have appreciated that the tool was a catalyst to better patient care. Alternatively, the alert may have caused pressure to order tests or escalate care in patients who did not truly require it. That most patients were perceived to be stable both before and after the alert may be a sign of low signal-to-noise ratio, which has a risk of leading to alert fatigue. Further investigation can focus on acceptability, resource allocation, and system improvement.

COMMENTARY

Previously, the article by Umscheid et al described with great enthusiasm some potential benefits of the EWRS.[1] In contrast, this article tempers that enthusiasm, with only moderate clinician support. While clinicians are often initially skeptical of any changes that disrupt their usual work flow, the benefits may be borne out over a longer time period before clinicians recognize them. Thus, I would be hesitant to discount the results of lukewarm clinician support to a potentially beneficial early warning system.

However, as three clinicians were required to evaluate and communicate about each alert, this alert is highly personnel-intensive. EHRs have the potential to (and do) provide alerts at many points of contact. I have watched clinicians ignore myriad alerts in order to proceed with their work. Additionally, I would be hesitant to warmly welcome a system that identifies stable patients 80% of the time because it has the potential to overburden busy clinicians with low-yield clinical data. While I am optimistic about the EWRS and its potential to improve outcomes in sepsis, this system needs some improvements prior to widespread adoption. ■

REFERENCE

1. Umscheid JA, et al. Development, implementation, and impact of an automated early warning and response system for sepsis. *J Hosp Med* 2015;10:26-31.

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Diagnostic Puzzle? Solved by *The New York Times*

Donald G McNeil, Jr. Fighting hepatitis by slashing drug price, in lab size of Egypt. *The New York Times*, Dec. 16, 2015, A1; Progress toward prevention and control of hepatitis C virus infection — Egypt, 2001-2012. *MMWR* 2012;61:545-549.

A fascinating consult crossed my path a few weeks ago. A 70-year-old Egyptian man was referred by Oncology for hepatic microcalcifications to rule out schistosomiasis or granulomatous infection. He was to receive Rituxan and high-dose corticosteroids for lymphoplasmocytic lymphoma. *Schistosoma hematobium* and *mansoni* are both endemic in Egypt, and it has been argued whether the building of the Aswan Dam in the 1960s exacerbated the problem.

The patient was born in Cairo, came from an educated, middle-class family, and immigrated to the United States about 15 years ago. He was on the rowing team in high school, and practiced frequently on the Nile, although he knew to avoid the shallow areas. He was diagnosed with prostate cancer in 2008 and received high-dose radiation therapy and adjuvant hormonal therapy. Small foci of slowly progressive hepatic microcalcifications were observed on serial CT scans from 2008 to 2015, although there was no evidence of calcium deposition in the spleen, lymph nodes, or lung. Blood and urine studies for *Schistosoma mansoni*, tuberculosis, coccidioidomycosis, histoplasmosis, cystercercosis, and strongyloides were all negative. But he was positive for HBV-core IgG antibody, negative for HBV surface Ag and core IgM, and HBV DNA was undetectable; and his HCV Ab was positive. Further studies demonstrated HCV genotype 4 with a viral load of approximately 600,000. His liver function studies had consistently been normal for years. The patient had no apparent risk factors for HBV or HCV infection, and he merely shrugged when I asked the usual questions, stating that "everybody" in Egypt has hepatitis. Pending further laboratory results, I imagined that micronodular cirrhosis from his HCV was the most likely explanation for his microcalcifications.

What was the answer to this case?

Before I had a chance to investigate further, *The New York Times* lead article the next morning provided the answer. Indirectly, schistosomiasis was the culprit but not the cause of his problem. Egypt has the highest burden of HCV infection in

the world, with seroprevalence studies demonstrating that 15% of the population has HCV antibody, and 10% are actively infected. This amounts to ~6 million Egyptians with active HCV infection. Ironically, this epidemic is largely owing to a mass campaign to control schistosomiasis in Egypt from 1960-1980 using parenteral antischistosomal therapy (e.g., praziquantal). The patient confirmed that he and his school buddies were lined up and sequentially injected using non-sterile syringes. The boys were more frequently "vaccinated" than girls, because the boys were more athletic and more likely to get infected. And, indeed, seroprevalence studies in Egypt confirm that 12% of men and 8% of women are HCV-infected. Poor infection control practices, unsafe medical injections, and bad dental practices only exacerbated the problem for the next few decades.

As a response to this epidemic, National Egyptian Guidelines for the prevention of transmission of HCV and Infection Control practices were published in 2003; a National Committee for the control of viral hepatitis was established in 2006; and a National Strategy for Control for Viral Hepatitis developed in 2008. This involves a complex treatment campaign, costing approximately $200 million per year, about 40% of which is supported by public health dollars (about 20% of the Egyptian healthcare budget). The government's goal is to treat 300,000 cases of HCV infection per year, driving down the prevalence of HCV infection to less than 2% of the population by 2025.

Licensing of technologies for the manufacture of antiviral medications has been a key part of the strategy. Gilead Sciences, based in California, licenses the rights to manufacture and market sofosbuvir (Solvaldi) to 11 Indian companies and two Egyptian companies, in exchange for 7% of the royalties. There were plans to begin manufacturing Harvoni, a combination pill containing sofosbuvir and ledipasvir, in December 2015. The result is that sofosbuvir costs about $10 per day per pill for a 3-month course in Egypt, while the same medication costs about $1000 per day in the United States. This strategy makes treatment affordable for developing countries and those who are impoverished. In an attempt to cut down on the black market for these drugs, sofosbuvir is dispensed through Egyptian pharmacies, through a tightly controlled system, where patients receive directly observed therapy, often for free. Interestingly, about 90% of HCV infections in Egypt are genotype 4, which more readily responds to antiviral therapy.

Glucometers as Culprit

Lee EH, et al. Healthcare–associated transmission of *Plasmodium falciparum* in New York City. *Infect Control Hosp Epidemiol* 2016;37:113-115.

Person-to-person transmission of malaria is rare but has been reported as the result of contaminated blood products, needle sticks, saline flushes, multi-dose vials, and contact with non-intact skin. Injection drug use in some countries may be the more frequent route for this unusual event. While sexual transmission of malaria does not occur, congenital transmission may. In a review of malaria cases at our county facility in 1991, one case of *P. vivax* was identified as the result of congenital transmission in a 1-month-old.

Investigation at a New York City hospital points to a break in infection control practices resulting in occult person-to-person transmission of P. falciparum to a 40-year-old woman, hospitalized for acute cholecystitis, requiring cholecystectomy. She was admitted 2 weeks later to a different facility with fever and thrombocytopenia, with evidence of *P. falciparum* ring forms on blood smear.

The problem was, there was no plausible explanation for her malarial infection. She had no history of travel, she lived in a group home, which she seldom left, she had received no injections, did not live near an airport, and had no international visitors (making "suitcase" malaria unlikely, with spare mosquitos hitching a ride in airplanes or in luggage).

No cases of malaria had been reported by the first hospital. While all cases of malaria must be confirmed by an outside laboratory, and reported to local health authorities, investigation revealed that the initial hospital had, indeed, cared for a woman with acute malaria, just returned from Nigeria. Her blood smears were never reviewed for confirmation, nor was the case reported to local health authorities, and she was presumptively treated for falciparum malaria with mefloquine. Light microscopy and real-time polymerase chain reaction (PCR) testing of both patients' blood smears confirmed *P. falciparum*. In addition, sequencing revealed 11 of 12 common genetic markers. Pyrosequencing demonstrated 10 identical drug resistance mutations in three genes consistent with an African origin for the organism.

Review of procedures could not pinpoint a certain break in infection control practices at the hospital. Both patients were in the emergency department (ED) at the same time, although in different areas of the ED, and treated

by different staff. They were hospitalized on the same ward. Blood draws were performed by different phlebotomists, individual saline flushes were used, and parenteral therapies were administered with fresh tubing and bags. The only suspect source was the glucometers. Both patients had blood sugar checks, although documentation was lacking to directly compare staff and devices used between patients. Further investigation revealed that glucometers were not routinely nor adequately cleaned after use.

In the end, a definitive source for transmission was not identified, but in the absence of any other explanation, a breach in Infection Control practice probably related to poorly cleaned glucometers was believed to be responsible. Ironically, a recent investigation of transmission of an MDR organism in our hospital led to the conclusion that glucometers may have been the source. Observations of ATP testing of glucometers at our site revealed that these devices are well cleaned on the top, bottom, back, and front, but both sides (where they are being held) can have high ATP readings, despite apparently adequate cleaning. How can you hold a device and clean it at the same time?

Shorter Isolation Times for TB

Floe A, et al. Shortening isolation of patients with suspected tuberculosis by using polymerase chain reaction analysis: A nationwide cross-sectional study. *Clin Infect Dis* 2015;61;1365-1373.

Patients with suspected tuberculosis are frequently masked and placed on voluntary home isolation — or hospitalized — until serial sputum AFB smears are negative and the patient has been cleared to return to work. Patients may miss work or school, may be removed from their family as a precautionary measure, or require prolonged hospital stays in isolation until cleared.

In an effort to determine whether a single sputum sample for polymerase chain reaction (PCR) testing for *M. tuberculosis* can guide the need for isolation, more than 53,000 sputum samples from 20,928 individuals were assessed. A total of 1630 had culture-confirmed MTb. Of these, 1274 had more than three sputums obtained; 856 had a positive AFB sputum smear obtained 14 days before or after a culture-positive specimen; and 486 had PCR testing performed on more than one sample. Of the 722 patients with either a positive smear or PCR test, 74.1% were smear-positive and 81.4% were PCR-positive.

Only 9 people (2.5%) with culture-confirmed MTb who had provided three or more sputum specimens, at least one of which was smear-positive, had a negative PCR. Eight of these smear-positive/PCR-negative cases had only one sputum that was smear-positive, and five had very low-grade smears. In addition, while most of the concordant smear-positive/PCR-positive samples were obtained within 1 day, there was a trend for the discordant samples to be obtained farther apart (median 4 days, range 1-6 days). In those people who provided only two sputum specimens, at least one of which was smear-positive, seven patients (0.9%) were smear-negative.

Sixty-five patients with one or more PCR-positive samples were culture-negative. Of these, various other mycobacterium were isolated, including *M. avium* (n = 1), *M. gordonae* (n = 2), *M. bovis* (n = 1), and nine others that were untypeable (but could feasibly have been poorly growing MTb). Many of these patients had begun antituberculous therapy.

MTb PCR was positive for more than 97.5% of the smear-positive, culture-confirmed cases, who had provided three or more sputums. MTb PCR testing of sputum specimens may provide rapid confirmation of those patients with MTb, allowing a larger number of patients without MTb to be quickly cleared and returned to work and their families. A small percentage of patients (2.5%) may yet prove to have MTb, but these data suggest that most will have low-grade smears, and are not as likely to be contagious. Whether smear-positive/PCR-negative being ruled out in-hospital should be removed from isolation seems less certain; our hospital still requires patients with confirmed MTb to remain in isolation for a full 2 weeks of therapy and three negative sputum smears.

Discordant smear-positive/PCR-negative results in this study may have been the result of poor-quality specimens submitted for PCR testing. This suggests that only those smear-positive specimens be submitted for PCR testing. This is something our laboratory has attempted but finds limiting because of the larger volume required to perform both tests. Perhaps two negative PCRs obtained on good induced sputums in suspect cases would be adequate for removal of respiratory precautions in-hospital. These data also highlight the importance of submitting quality samples to the laboratory for AFB smear and PCR testing. Unless patients can readily produce productive phlegm, I prefer sending patients to the respiratory therapy lab for good induced specimens. Suspect patients, generally with smaller infiltrates, who are unable to produce good specimens are referred to pulmonary for bronchoalveolar lavage. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following is effective as standard care for children with bronchiolitis?

a. Oxygen supplementation if the oxygen saturation is less than 93%

b. Albuterol as a bronchodilator

c. Glucocorticoids as anti-inflammatory agents

d. All of the above

e. None of the above

2. Which of the following is correct?

a. *Salmonella* are part of the normal intestinal flora of turtles.

b. Because of their association with human cases of salmonellosis, individuals in the United States are allowed to purchase only one pet turtle at a time.

c. Only households with children younger than 2 years of age are banned from purchasing small turtles in the United States.

d. All sales of large turtles (shell length > 4 cm) are permanently banned in the United States.

3. Which of the following is correct?

a. The two formulations of posaconazole available for oral administration in the United States are identically dosed.

b. Posaconazole oral suspension has improved bioavailability when administered while fasting.

c. Posaconazole delayed-release tablets are less bioavailable than the oral suspension.

d. Prescriptions for posaconazole must specify the dosage form, strength, and frequency of 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.