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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Importance of Culture for Group A Strep Pharyngitis after a Negative Rapid Test

Study raises serious questions about current IDSA guidelines

By Richard R. Watkins, MD, MS, FACP

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Dr. Watkins reports no financial relationships in this field of study.

SOURCE: Dingle TC, et al. Reflexive culture in adolescents and adults with group A streptococcal pharyngitis. *Clin Infect Dis* 2014;59:643-650.

Pharyngitis is a very common infection resulting in more than 6 million annual office visits by adults in the United States. The ability to distinguish pharyngitis caused by group A streptococci (GAS) from other etiologies (e.g. viruses) is important because untreated GAS can have serious consequences including peritonsillar abscess and rheumatic fever. However, over-prescribing antibiotics is one of the main causes for the spread of antibiotic resistance. Several guidelines on the diagnosis and treatment of GAS pharyngitis have been published but unfortunately they disagree on the need for reflexive culture after a negative RADT. Because of this controversy, Dingle and colleagues sought to determine the utility of reflexive culture after a negative RADT in adult and adolescent patients suspected of having GAS pharyngitis.

The study was a retrospective analysis from two hospitals in Seattle, Washington. Included were all patients 13 years and older who between 1

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January 2000 and 31 December 2011 had a negative RADT and a positive GAS culture. It is the policy of both microbiology labs in the study that all negative RADTs be reflexively followed by a backup throat culture. Subjects were eliminated from the analysis if they had a missing note corresponding to the respective date or inadequate clinical symptoms. Out of 1,023 patients identified, 726 patients underwent analysis (71%).

The authors calculated the modified Centor score (0 to 4) for each patient by assigning 1 point for each of the following symptoms: swollen or tender anterior cervical lymph nodes; absence of cough; tonsillar swelling or exudate; and fever. They added 1 point for ages 13-14 and deducted 1 point for age ≥ 45. After a negative RADT, a second throat swab was anaerobically cultured and growth was scored semiquantitatively, from 1+ representing growth in the first streak area to 4+ representing growth on the whole plate.

The sensitivity of the RADTs performed during the study was 76.3%. Of the 21,284 negative RADTs that were reflexively cultured, 1023 (4.8%) were positive for GAS. RADT missed 29 patients (4.0%) with peritonsillar abscess and 2 (0.28%) with acute rheumatic fever. Moreover, RADT failed to detect some patients with high modified Centor scores; 55% of patients with negative RADT and positive GAS culture had modified Centor scores ≥ 2. Interestingly, modified Centor scores did not correlate with culture quantities of GAS and RADT missed some patients with substantial quantities of GAS, as 77% of cultures had ≥ 2+ growth.

No significant differences were found in the clinical parameters between adolescents and adults, nor were there any differences in antibiotic treatment or incidence of peritonsillar abscesses between the two groups. Finally, bacterial quantities were similar in patients with peritonsillar abscesses and the overall study population, reflecting how bacterial burden did not correlate with modified Centor scores.

COMMENTARY

The rationale for not doing a follow up culture for GAS after a negative RADT in the current IDSA guidelines is that GAS pharyngitis is rare in adults and patients with negative RADTs have both mild disease and low complication rates.1 The results of the study by Dingle and colleagues call this recommendation into serious question. Notably, RADT failed to detect 55% of patients with a modified Centor score ≥ 2. This means that many patients would likely not have been treated had a back-up throat culture not been obtained.

The authors found no differences in the clinical presentations or complication rates between adults and adolescents, which suggests that separate recommendations for the two groups are superfluous.

An important limitation to the study was its retrospective design. Also, it is difficult to ascertain how many of the positive GAS cultures represented colonization and not true infection. While all of the patients in the study had sore throat as their primary reason for seeking medical attention, it is possible other etiologies (e.g. viruses) were the true culprits for their symptoms.

It is clear that patients with GAS pharyngitis need to be identified because antibiotic therapy reduces communicability, improves symptoms and prevents both recurrences and rheumatic fever.

The present study by Dingle and colleagues is important because it raises questions about an authoritative treatment guideline. It seems reasonable for microbiology laboratories that routinely perform back up cultures for negative RADTs to continue this practice, which is the current policy at my institution. In order to remain relevant, guidelines must be a continuous work in progress.

As new evidence becomes available, the expert panels who decide guideline content should carefully consider these data and modify their recommendations when necessary. ■

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ABSTRACT & COMMENTARY

Treatment of MDR

Bedaqualine Appears to be a Major Advance in Treatment of MDR-TB

By Dean L. Winslow, MD, FACP, FIDSA

Clinical Professor of Medicine and Pediatrics Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Associate Editor of Infectious Disease Alert

Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: Bedaquiline (a unique diarylquinoline) was studied vs. placebo in a prospective randomized trial when added to a standard 5-drug regimen in the treatment of multidrug-resistant (MDR) tuberculosis. Treatment with bedaquiline when added to a preferred background for 24 weeks resulted in significantly more and faster culture conversion than placebo. There were more deaths in the bedaquline group but almost allone most occurred after treatment ended.

SOURCE: Diacon AH, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *New Eng J Med* 2014;371: 723-732.

In this Janssen-sponsored Phase 2b trial, 160 patients with newly diagnosed multidrug-resistant TB were randomized to either bedaquiline or placebo combined with a standard 5-drug background regimen. The bedaquiline or placebo was used for the initial 24 weeks of treatment followed by an additional 12-18 months of the background regimen to complete a total 18-24 month course of treatment.

Compared to placebo, bedaquiline reduced the median time to sputum culture conversion from 125 to 83 days. At 24 weeks the rate of culture conversion was 79% vs. 58% for bedaquiline vs. placebo. At 120 weeks the cure rates for bedaquiline vs. placebo were 58% and 32% respectively. The overall incidence of adverse effects was similar between the two groups but there were 10 deaths in the bedaquiline group vs. 2 deaths in the placebo group.

COMMENTARY

Bedaquiline is the first new antimicrobial specifically developed to treat TB that we have had for many years. The drug is interesting in that it has a novel mechanism of action: inhibition of mycobacterial ATP synthetase. Bedaquiline was initially approved by the FDA under the accelerated approval process based on 72-week data from this Phase 2 clinical trial. The 120-week results are reported above. Interestingly these longer-term follow up data showed that while only 2 patients in the placebo group died, 10 patients in the bedaquiline arm died.

The FDA, in this same issue of *NEJM* published an editorial explaining their rationale for continuing to support the use of bedaquiline for drug-resistant TB while awaiting additional safety and efficacy data from ongoing confirmatory clinical trials.[1] Reassuringly only one of the deaths in the bedaquiline arm occurred during the bedaquiline treatment phase and appeared to be due to progression of TB, not side effect of medication. In fact, none of the 9 deaths observed in the bedaquiline arm during the follow-up treatment period while receiving background drug appeared to be treatment-related.

Tuberculosis remains a huge scourge worldwide with 10-year case fatality rates in HIV-negative patients exceeding 70% in the absence of effective treatment. Bedaqualine appears to be a major advance in the treatment of multi-drug resistance TB.■

Reference

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ABSTRACT & COMMENTARY

Enterovirus 68 – Rumors, Realities, Research

By Philip R. Fischer, MD, DTM&H

Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic.

Dr. Fischer reports no financial relationships in this field of study.

SYNOPSIS: A preliminary report from Missouri suggests that enterovirus 68 is responsible for a large outbreak of respiratory disease in children. Typically, there is a rapid onset of respiratory symptoms with wheezing, and intensive care is required for about 15% of affected patients.

SOURCES: Vesterling G. Respiratory illnesses due to enterovirus D68 (EV-D68) in Missouri. Missouri Department of Health and Senior Services, August 29, 2014, health.mo.gov/emergencies/ert/alertsadvisories/pdf.HA82914.pdf; Centers for Disease Control and Prevention. Severe respiratory illness associated with enterovirus d68 - Missouri and Illinois, 2014. *MMWR* 2014;63(36):798-9.

In recent months, a children's hospital in Kansas City, MO, cared for over 300 children with respiratory illness, a surprisingly large number for the summer season. Approximately 15% of these children required intensive care, but no deaths have been reported. Samples from 22 affected children were tested by the Centers for Disease Control and Prevention (CDC); 19 (86%) were positive for enterovirus D68.

Similarly, St. Louis, MO is also experiencing an increase in pediatric respiratory illnesses. There, too, many samples have tested positive for enterovirus, and more detailed testing of virus type is pending. Cases have now also been reported from as far away as the northeastern U.S.

RUMORS

Professional emails and lay news services have been lighting up with reports of unseasonable outbreaks of pediatric respiratory illness. Even the September 8, 2014, issue of AMA Morning Rounds cited reports of a "mystery virus" and "a rare virus sending kids rushing to the hospital when they can't breathe." Anecdotally, patients are usually children in the first decade of life with little or no history of asthma. They become very sick very quickly with mild upper respiratory symptoms, wheezing, and significant respiratory distress. When used, commercially available tests that identify RNA common to both enteroviruses and rhinoviruses are often positive. Many of these children, even without a prior history of asthma respond favorably to therapeutic trials of albuterol. Pressure and even ventilatory support are sometimes required for one to three days. Most of these preliminary unconfirmed reports so far are from the central United States. The Missouri report cited above was the only semi-formal documentation of an outbreak as this issue went to press. Anecdotal discussions at a meeting of Midwestern pediatric residency program directors suggested that many centers are seeing unseasonably large numbers of children with respiratory illnesses. Internet and news reports suggest that this frightening "new" disease is common in Missouri, Colorado, Ohio, Illinois, and other states. Accurately but dramatically, reports often mention that there is no specific treatment available for enteroviral infections. Personal reports suggest that CDC staff are analyzing data in order to prepare a peer-reviewed paper about relevant findings.

REALITIES

There are over 100 different enteroviruses, and several of them cause mild illnesses in children, often during summer. (Polioviruses, echoviruses, and Coxsackie viruses are in subgroups of the larger enterovirus family.) Most enteroviruses spread through personal contact and manifest infection with upper respiratory symptoms, fever, rash, and, sometimes, meningitis.

Enterovirus 68 was isolated from four California children with bronchiolitis and pneumonia in 1962. [These isolates were further studied several decades later.[1]] In recent years, this enterovirus has been reported in Asia as well.

From October 2009 through October 2010, a

laboratory in Japan evaluated 448 respiratory specimens from children with fever and respiratory tract infections.[2] Fifteen of the children had enterovirus 68, all during illnesses occurring from June through September. Children were aged 3 months to 4 years 9 months. The majority of affected children wheezed. Retrospectively, only 14 patients were found to have enterovirus 68 during the preceding four years, so investigators believed that this represented an epidemic.

Clinical respiratory specimens collected from May 2008 to May 2009 in the Philippines were later retrospectively analyzed for enterovirus using polymerase chain reactions and genetic sequencing.[3] Enterovirus 68 was identified in 21 samples, 2.6% of all samples evaluated in the study. Children were from Tacloban City and surrounding areas, and most all positive samples were from October through December. Ages of affected children ranged from 1 month to 9 years. All had cough, and two-thirds wheezed; all had retractions. Two patients did not survive the illness.

More recently, Chinese investigators studied 1565 samples obtained between 2009 and 2012; 41 (2.6%) were positive for enterovirus.[4] Seven (17%) of the enterovirus positive samples tested positive for enterovirus 68, making it the predominant type of enterovirus in children with acute respiratory infection.

Most enterovirus 68-positive subjects were ill from August through December; two were adults. Most of the infected children also tested positive for other respiratory pathogens (human bocavirus, respiratory syncytial virus, Epstein Barr virus, cytomegalovirus, Chlamydia, Mycoplasma, and influenza A).

Genetic evaluation showed similarities between the Chinese strains and previously identified strains from the Netherlands and the USA, suggesting that the Chinese viruses might have migrated from Europe and North America to China.

In 2006, the CDC reviewed clinical data associated with 52,812 enterovirus infections in the US.[5] There were only 26 cases of enterovirus 68 during the 36 studied years; most were associated with respiratory illness, but the virus was also identified from cerebrospinal fluid of a young adult with acute flaccid paralysis.

Different enteroviruses are known to be associated with acute flaccid paralysis,[6] but there have been two paralyzed children in California since 2012 who were infected (or, at least, colonized) with enterovirus 68.[7]

RESEARCH REQUIRED

Thus, the currently evolving outbreak of pediatric respiratory illness in the central United States seems similar to reported outbreaks of pediatric respiratory infections in Asia. However, associations and anecdotes do not prove causality. Especially as news agencies sound alarms over "mystery" illnesses that "rush" children to hospitals, we should show some restraint as we await the results of peer-reviewed studies.

Earlier this year, Swedish investigators reported on viral studies of 151 children with acute respiratory infections.[8] They compared positive results in patients to positive results in controls. Interestingly, asymptomatic control children were as likely to test positive for enterovirus as were sick patients! As in the Chinese study noted above[4], many sick children carry several potential pathogens, and it is not clear just which of multiple identified pathogens is etiologically related to their symptoms.

Rhinoviruses are commonly identified in both sick and asymptomatic children.[8] The virus previously identified as rhinovirus 87 is actually the same virus as enterovirus 68.[5] There is overlap between rhinovirus and enterovirus RNA, and current commercial polymerase chain reaction tests do not distinguish between rhinovirus and enterovirus. Thus, future studies will need to not only compare findings in symptomatic patients with controls but also to accurately identify strains of specific viruses.

While awaiting further research and peer-reviewed reports, however, clinicians should be aware that the current summer-fall viruses now circulating in the United States might include an enterovirus that can cause severe respiratory infections. While effective specific anti-viral therapy is not available, supportive care seems to be effective. ■

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ABSTRACT & COMMENTARY

ID Grand Rounds-Stanford University: Woman with Neutropenic fever, Ab Pain

By Susanna Tan, MD

Fellow, Division of Infectious Diseases, Stanford University

Dr. Tan reports no financial relationships in this field of study

CASE HISTORY

A 44-year old woman with a history of acute myelogenous leukemia (AML) who recently completed a third-cycle of consolidation chemotherapy with idarubicin and cytarabine presented with fever and abdominal pain. Two days prior to admission, she developed mild, diffuse abdominal pain followed by fever and non-bloody vomiting. In the emergency department, she was found to be neutropenic, anemic, and thrombocytopenic. She was started on cefepime and given a unit of platelets. She was initially conversant, but then developed somnolence, hypotension, tachypnea, and hypoxia requiring intubation two hours after her initial presentation.

PAST MEDICAL HISTORY

She has a history of fibroids. She was diagnosed with AML five months prior to presentation and was currently in clinical and cytologic remission. Six weeks prior to presentation, she was hospitalized for neutropenic fever, typhlitis, bacteremia due to *Klebisella pneumoniae* and viridans streptococcus with a liver abscess and was treated with a four-week course of ceftriaxone and metronidazole. She was taking voriconazole for pulmonary nodules that were presumed to be fungal in etiology and she was also receiving acyclovir for prophylaxis.

SOCIAL HISTORY

She is originally from Eritrea and moved to the United States 20 years ago. She has not traveled outside the country in the past several years. She does not have pets. She works as an office assistant.

PHYSICAL EXAMINATION

Her temperature was 37.3C, blood pressure 126/61mmHg on norepinephrine and vasopresssin, heart rate 110 beats per minute, respiratory rate 35 beats per minute, oxygen saturation 90% on maximal vent settings. She was minimally responsive and intubated with frank blood within her endotracheal tube. Her sclera was icteric. She had bilateral coarse breath sounds. Her abdomen was distended, tympanic, and there were minimal bowel sounds. She had blood at the urethral meatus and within the foley catheter and there was mild bruising of her upper extremities bilaterally, but no petechiae or purpura. Several of her intravenous line sites were oozing blood.

LABORATORY RESULTS AND IMAGING

Repeat blood work done at the time of her clinical decline was significant for a white blood cell count of 0.1 cells/μL, hematocrit 12.0%, and platelets 226 cells/μL. She had a potassium of 6.6 mmol/L, bicarbonate 6 mmol/L, blood urea nitrogen 40 mg/dL, creatinine 1.4 mg/dL, anion gap 24, and lactate

>15 mmol/L. Total bilirubin was 20.0mg/dL with a conjugated bilirubin of 1.7mg/dL, AST 1770 U/L, ALT 954 U/L. Uric acid was 7.9 mg/dL and LDH >4000 U/L. Her INR was 3.3, PTT 95 seconds, D-dimer >20K ng/mL, and fibrinogen 525 mg/dL. Respiratory virus PCR panel was negative. CT of the chest, abdomen, and pelvis showed extensive ground glass opacities and consolidative opacities throughout the lungs and extravasation of contrast into the third portion of the duodenum concerning for a gastrointestinal bleed. Uterine fibroids were stable compared to prior imaging.

CLINICAL COURSE

She was admitted to the intensive care unit. Meropenem, vancomycin, clindamycin, levofloxacin, osteltamivir, and liposomal amphotericin B were started at doses appropriately adjusted for hepatic and renal impairment. Acyclovir was continued.

She was also started on methylprednisolone sodium succinate 60mg IV Q6 hours because of concern for diffuse alveolar hemorrhage and received numerous units of packed red blood cell, platelet, and fresh frozen plasma products. Blood cultures were positive for Clostridium perfringens, *Rothia mucilanginosa, Streptococcus equinus, Streptococcus gordonii, Enterococcus gallinarum*, Herpes simplex virus, cytomegalovirus, and adenovirus PCR testing as well as galactomannan, strongyloides IgG antibody, and cryptococcus antigen tests were negative.

She developed worsening respiratory status with inability to adequately oxygenate and ventilate despite maximal ventilatory support and died 18 hours after initial presentation. Her family declined an autopsy.

DISCUSSION

C. perfringens is an anaerobic, gram positive rod that is implicated in asymptomatic bacteremia, gastroenteritis, gas gangrene, shock and death. Septicemia with massive intravascular hemolysis is a rare but well-known complication, occurring in 7% to 15% of *C. perfringens* bacteremias. *C. perfringens* produces an alpha-toxin that damages red blood cell membranes by means of phospholipase activity, leading to spherocytosis and coombs-negative hemolysis. Peripheral smears classically demonstrate spherocytosis without schistocytes and may occasionally show ghost cells which are red blood cells that appear empty because they have a leaky membrane and no longer contain hemoglobin. *C. perfringens* can also produce streptolysin O and perfringolycin O toxins which have been implicated in the development of disseminated intravascular coagulation.

A review of 40 cases of *C. perfringens* septicemia with massive intravascular hemolysis found that most cases involved immunocompromised patients with underlying hematological disorders (22.5%), pancreatic or gastric cancer (12.5%) and/or diabetes (30.0%). The focus of infection was most commonly hepatobiliary (45.0%), intestinal or gynecological after invasive procedure.[2] 80% percent of cases did not survive. The median time between admission and death was only eight hours. In many cases, the patient had already gone into shock or died before a diagnosis could be made.[2]

'A REMARKABLY RAPID DETERIORATION'

Treatment involves the use of IV penicillin and removal of the focus of infection (i.e. by drainage of liver abscess, cholecystectomy, hysterectomy, or ERCP). One retrospective review found mortality benefit with the combination of clindamycin to penicillin.[3]

This patient presented with extensive intravascular hemolysis, sepsis, and DIC that is classic for *C. perfringens*. The etiology of the polymicrobial bacteremia is unclear, but was likely from an abdominal source. There was no obvious source that would have benefited from drainage. This case highlights the remarkably rapid deteriorationnd mortality that can be associated with *C. perfringens* septiciemia.

Diagnosis - Polymicrobial septicemia with extensive intra-vascular hemolysis due to *C. perfringens*. ■

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Infected American Doc knew He Faced a 'Tsunami' of Ebola in Liberia, Kept Working

4th health care worker with Ebola comes to U.S.

By Gary Evans, Executive Editor

In an August 30, 2014 blog post, **Rick Sacra**, MD, worried about the "many people in Liberia who are at risk because of the Ebola tsunami that swept through an already fragile healthcare system."

"The healthcare system in Liberia has had to go through a complete reboot after every single hospital in the city of Monrovia closed down to be decontaminated with bleach water as a result of Ebola cases landing in emergency rooms, outpatient clinics and medical wards," he continued.

"We hope to gradually increase our services over the next couple of weeks to include children and adults, but we must first make some changes to our building to allow us to triage everyone before they enter the hospital grounds to check for any signs of Ebola. A large shipment of personal protective gear arrived yesterday from our partner, Samaritan's Purse. This has been one of the key issues in reopening — ensuring that we have adequate protective equipment."

Shortly after that post, the 51-year-old family Ob/Gyn physician began exhibiting signs and symptoms of Ebola, which he probably contracted working long hours in the previous three weeks treating pregnant women and literally saving lives.

"When the patients started arriving, they had often been to several other hospitals and traveled for hours seeking care," Sacra wrote in his blog. "More than 35 cesarean sections were performed to save women and their babies in the first 20 days—sometimes two or three a day. "

Sacra was flown back to the states and admitted Sept. 5th to a specially designed 10-bed biocontainment unit at the Nebraska Medical Center in Omaha. Two of his colleagues with Samaritan's Purse had undergone successful treatment for Ebola at a similar biocontainment unit at Emory Hospital in Atlanta. By late August, each had recovered and was discharged. As this issue went to press, Sacra was making some progress but doctors said it was too early to give a definitive prognosis. Meanwhile, a fourth health care worker infected with Ebola in Africa was admitted to the Emory biocontainment unit on Sept 9th, though few details were being released.

STAFF CONSISTS OF VOLUNTEERS ONLY

The biocontainment units at Emory and Nebraska have had years to train and prepare staff to handle infectious disease cases that might overwhelm some hospitals. They were designed according to federal guidelines for handling CDC category A diseases, which include Ebola, plague, anthrax, hemorrhagic fever and smallpox.

"There is anxiety amongst hospital staff in ordinary hospitals about handling Ebola cases," says **Philip Smith**, MD, professor in the division of infectious diseases at the Nebraska Medical Center. "We have people volunteer to work in this unit and to receive special training. They're mentally prepared for something like this."

Emory uses a similar system, with a team of volunteers from various specialties ready if the alarm is sounded. "Staff involved in the direct care of these patients received extensive training with demonstrated competency verification," says **Nancy Feistritzer**, DNP, RN, vice president of patient care services at Emory. "Members of the team all volunteered to care for these patients. Even so, care of acutely ill patients at their most vulnerable can be stressful under any circumstances."

Emory provided staff and physicians caring for the Ebola patients with support through daily team huddles, leader rounding, and hospital chaplains. "The staff support team was present through-out these challenging and stressful times in order to provide emotional and spiritual support for staff," she says.

'WE WANT ROCK STARS ON THIS UNIT'

Even during the ongoing Ebola outbreak in West Africa, more hospital staff have applied to join the Nebraska unit, says **Shelly Schwedhelm**, MSN, RN, director of emergency trauma and emergency preparedness at the medical center.

"People say, 'Sign me up — I want to do this,'" she says. "It's a professional development opportunity and they see it as an opportunity to enhance their skills in other ways."

Schwedhelm doesn't hire every person who applies. First, she speaks with their managers to learn more about their clinical skills, energy, and ability to be self-directed. "We want rock stars on this unit," she says.

Volunteers have to be experts in their disciplines because they'll need to learn special skills involving high level of infection control, adds **Kate Boulter**, RN, lead nurse of the biocontainment unit in Nebraska. The ideal worker in a biocontainment unit is someone who is very detail oriented and a critical thinker, she says. Employees have to follow rules and instructions precisely, as shortcuts and mistakes could lead to exposures and injuries. Team-work is a top priority.

"Each person has a partner who watches them put on their personal protective equipment and take it off," Schwedhelm says. "They hold each other accountable."

The biocontainment team functions as one unit, and everyone involved agrees on decisions and steps taken, says **Uriel Sandkovsky**, MD, an infectious disease physician and medical director for employee health at Nebraska Medical Center.
Biocontainment team volunteers also have to be eligible to receive the smallpox vaccination in the event of an exposure. "With smallpox you have a four-day window to get vaccinated after exposure, so if we had a smallpox or monkeypox case we could vaccinate them," Smith says.

A WATCHFUL EYE FOR SYMPTOMS

Emory University developed a comprehensive surveillance program consistent with CDC guidelines to monitor physicians and staff caring for the Ebola patients, Feistritzer says.

"Inclusion criteria were defined as individuals who were involved in direct patient care or those involved in the handling of contaminated blood or body fluids," she says.

The surveillance protocol included taking employees temperature twice daily for 21 days — the outer limits of the incubation period — after their last episode of care for Ebola patients. Also, each employee tracks their own symptoms, including headache, joint or muscle aches, weakness, diarrhea, vomiting, stomach pain, or lack of appetite. They use a log to document and track results and follow a protocol to report any symptoms.

ADRESSING WORKER, PATIENT CONCERNS

Emory also addressed concerns among patients and other employees through hospital-wide education and communication. The hospital educated staff about infection control practices and the Ebola protocols.

They held town hall meetings to provide accurate information and to have clinical experts and hospital leaders answer any questions staff might have, she explains. "Physician and nurse executive teams rounded on each patient care unit to answer questions staff or patients might have had," Feistritzer says.

The Emory website posted educational material with frequently asked questions and regular updates, available to both staff and patients.
As other hospitals prepare for the possibility of admitting an Ebola patient, it's a good idea to regularly train on the proper use of isolation precautions and personal protection equipment.

"One of our colleagues in the unit has an innovative educational approach where people get into gowns and take care of mock patients," Smith says. "It's recorded, and supervisors go over the video with employees to reinforce compliance." ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Upgraded recommendations for gonorrhea: A reminder

In 2012, the CDC upgraded their recommendations for treatment of pharyngeal, anorectal, and urogenital gonorrhea to include ceftriaxone (CFTX) 250 mg IM plus either a single dose of azithromycin 1 gram orally or doxycycline 100 mg twice daily orally. This dose of ceftriaxone is believed to be effective for all anatomic sites of involvement, although personal experience with 1 individual as well as individual case reports document failure of treatment for pharyngeal disease, even for

isolates with MICs below the resistant breakpoint (0.5 micrograms per mL). It is conceivable that gonorrhea (GC) involving the pharynx may be less responsive to treatment than urethral infection. In one report of 4 cases with oropharyngeal GC who failed single dose cephalosporin therapy, all 4 subsequently responded to CFTX 1 gram intramuscularly or CFTX 250 mg IM plus azithromycin 1 gram orally. Because most pharyngeal infections are asymptomatic, test of cure is essential.

In contrast to the United States, the European gonorrhea guidelines recommend CFTX 500 mg plus azithromycin 2 gram orally for uncomplicated GC. How rigorously these recommendations are being followed and dual treatment is being used in the U.S. and Europe is not known. But evolving resistance in GC isolates around the world continues to threaten our ability to treat this infection – and dual therapy should be mandated.

Also remember that revised CDC guidelines now recommend routine laboratory screening for GC and chlamydia of all genital and extra-genital sites for sexually active men who have sex with men (MSM) using the newer NAAT laboratory screening tests for all 3 anatomic sites. While earlier non-culture tests based on DNA or RNA sequences frequently failed to detect a good number of infections (especially chlamydia), the newer tests are much more sensitive and specific than earlier screening laboratory STD tests.

Treatment options for GC in cephalosporin allergic

Kirkclady RD, et al. The efficacy and safety of gentamicin plus azithromycin and gemifloxacin plus azithromycin as treatment of uncomplicated gonorrhea. *Clin Infect Dis* 2014;doi10.10903/cid/ciu521.

There is an urgent need for a back-up regimen for the treatment of gonorrhea (GC), especially for patients allergic to cephalosporins or intolerant, or for patients with treatment failure from suspected resistant isolates.

The effectiveness of two different combination regimens for the treatment of uncomplicated GC in persons 15 to 60 years of age was determined in a non-comparative treatment trial at 5 clinical sites across the United States. The two regimens were either gentamicin 240 mg IM (or 5 mg/kg for those < 45 kg body weight) plus azithromycin 2 gram orally, or gemifloxacin 320 mg orally plus azithromycin 2 grams orally. While it remains effective in the treatment of GC for most isolates, azithromycin is generally not recommended as monotherapy because of the risk of emergent macrolide resistance.

On the other hand, gentamicin is very effective in the treatment of GC, and has been used successfully as monotherapy in some countries, although infrequently used for this purpose in the United States. Gemifloxacin is an oral fourth-generation fluoroquinolone with in vitro activity against ciprofloxacin-resistant strains of GC.

A total of 614 patients were randomized to one of the two regimens; cultures were negative in 117 of these, and these individuals were excluded from the analysis. More than one-third (38%) reported sex between the initial and follow up study visits; 15% did not use a condom.

Microbiologic cure was achieved in 100% of the patients receiving gentamicin/azithromycin, and 97.6% of patients treated with gemifloxacin/azithromycin. All 25 patients with oropharyngeal GC and all 6 with rectal gonorrhea responded to treatment.

The single patient who failed therapy (with gemifloxacin/azithromycin) reported unprotected sex without a condom between visits. His initial isolate was sensitive to all agents tested with an MIC to gemifloxacin of .004; a post-therapy isolate was not available for testing.

Between the two regimens, 26% and 40% of participants reported nausea, and 17% and 22% experienced diarrhea; 7% vomited within an hour of receiving gemifloxacin and azithromycin combined.

Thus, these two regimens appear to be represent reasonable alternatives in patients intolerant/allergic to cephalosporins, although resulted in frequent gastrointestinal side-effects. A total of 421 isolates were available for susceptibility testing. None of the isolates were resistant to gentamicin.

Azithromycin MICs were elevated (breakpoint >2.0 micrograms/mL) in 0.5% of isolates, while gemifloxacin MICs were higher than the breakpoint (> 1.0 micrograms/mL) in 17% of isolates. Most of these MICs were similar or only 1-2 dilutions lower than those for ciprofloxacin.
Thus, gemifloxacin did not appear to provide a significant advantage for ciprofloxacin-resistant isolates as hoped.

Aggressive treatment of MDR TB worth the effort

Velasquez GE, et al. Improving outcomes for multidrug-resistant tuberculosis: aggressive regimens prevent treatment failure and death. *Clin Infect Dis* 2014;59(1):9-15.

Beginning in 2000, treatment of multidrug resistant (including XDR)-TB in Tomsk, Russia was assisted by the creation of a public-private partnership between the Tomsk public health, the Tomsk Penitentiary TB Hospital, and private funding sources, including the Bill & Melinda Gates Foundation.

A retrospective cohort analysis was performed for 614 patients with MDR/XDR TB who began treatment through this partnership between 2000 and 2004. A multivariate analysis, adjusting for XDR-resistance (resistance to fluoroquinolones plus resistant to an injectable agent) and other risk factors was performed.

Treatment regimens were based on standard algorithms, an assessment of prior treatment history, and the results of drug susceptibility testing, including testing for first- and second-line agents. Most of the patients were treated as inpatients during the first 6-9 months of treatment, and then continued treatment as outpatients for 18 months post culture-conversion. All treatment was administered as directly observed therapy.

A total of 614 patients with confirmed MDR TB were included in the analysis. All but 3 had received prior therapy. One-third had prior exposure to parenteral therapy and 15% had prior exposure to a fluoroquinolone. Half presented with bilateral and cavitary disease. Of these, 92% received what was considered an aggressive regimen, defined as 5 more likely effective agents for the first 6-9 months, followed by at least 4 effective drugs till completion of therapy. First-line drugs at maximal dosages were continued whenever feasible. Patients with resistance to fluoroquinolones nonetheless received treatment with ofloxacin or levofloxacin. The group had limited access to linezolid and imipenem.

The mean duration of treatment was 19 months, with 54 failures and 30 deaths. The median survival for treatment failures was 18 months (range, 11 – 28 months).

Treatment failure was associated with XDR-resistance, as well as a history of 2 or more previous treatment regimens, HIV disease, low BMI at baseline, and severe pulmonary disease at baseline. Extra-pulmonary disease was also a negative risk factor, and increased the risk of death by > 10%.

Monthly exposure to an aggressive regimen was significantly associated with treatment success (hazard ratio .52, p = .03). Although expensive and intensive to administer, and more likely to create problems in terms of compliance and side-effects, a treatment regimen with at least 5 likely effective agents seems to be well worth the effort and expense in these patients at high risk of mortality from their disease.

Screening for hepatocellular carcinoma — an empty proposition?

Kansagara D, et al. Screening for hepatocellular carcinoma in chronic liver disease: A systemic review. *Ann Intern Med* 2014;161(4):261-269.

Public health authorities report a trend in increasing numbers of cancers; one of these is hepatocellular carcinoma (HCC). Current guidelines recommend routine screening of persons at higher risk for HCC with periodic tumor markers and radiological studies.

These authors contend there is little evidence these measures have an affect on mortality from HCC. An extensive review of the literature was conducted, identifying 22 (English) studies that met criteria. Eighteen observational studies and 2 clinical trials provided little evidence in support of routine screening, using either tumor markers or periodic radiologic screening, in the reduction of mortality. One study of persons with chronic HBV infection found that routine periodic radiological screening was able to identify patients with HCC, with improved mortality rates, but the authors believe the study was flawed. One other study found that periodic alpha-fetoprotein screening was able to identify patients with earlier disease but found no survival benefit.

Perhaps the caveat to this argument is not that routine screening was unable to identify patients with earlier disease, potentially amenable to treatment, but that current treatments for HCC are woefully inadequate. But how are we to know which treatments may, in the future, be effective, if we fail to recognize patients who may be potentially salvageable. Because we don't have uniformly effective therapies at present, should we stop looking? ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
1. Read and study the activity, using the provided references for further research.
2. Scan the QR code to the right or log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. Which of the following is correct with regard to bedaquiline?

A. It is a novel aminoglycoside.

B. It inhibits ATP synthetase

C. Its use is associated with prolongation of the time to sputum culture conversion in tuberculosis.

D. Its use in clinical trials has been associated with reduced mortality.

2. Which of the following is correct with regard to the study by Dingle et al of reflex throat culture for Group A streptococcus (GAS) when rapid testing has been negative in subjects >13 years of age?

A. The sensitivity of the rapid test was >96%.

B. Rapid testing detected all cases in patients with high Centor scores.

C. Rapid testing failed to detect GAS in 29 patients with peritonsillar abscess and 2 with acute rheumatic fever.

D. Bacterial burden closely correlated with modified Centor scores.

3. Which of the following is correct?

A. Enteroviruses often cause respiratory infection in children.

B. There are only six enterovirus types.

C. Patients may shed enterovirus in the absence of symptoms.

D. Enterovirus 68 was first identified in 2014.

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 latent 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

TIPPING POINT

"[Consider the] possibility ... that the Ebola virus spreads from West Africa to megacities in other regions of the developing world. ... It is much easier to control Ebola infections in isolated villages. But there has been a 300% increase in Africa's population over the last four decades, much of it in large city slums. What happens when an infected person yet to become ill travels by plane to Lagos, Nairobi, Kinshasa or Mogadishu — or even Karachi, Jakarta, Mexico City or Dhaka?"

--Michael Osterholm, PhD, New York Times Sept 11, 2014

Antibiotic Stewardship: Advances in Practice

[ASAP: Protecting Patients by Preserving Antibiotic Efficacy]

Antibiotic Stewardship – the Time is Now!

By **Stan Deresinski**, *MD, FACP, FIDSA*

Clinical Professor of Medicine, Stanford University, Editor of Infectious Disease Alert

The problem of antibiotic resistance was recently dramatized by Dame Sally Davies, the Chief Medical Officer of the UK, when she called it a "catastrophic threat," which was followed by issuance of a "Threat Report" by the U.S. Centers for Disease Control and Prevention.[1]

On this side of the Atlantic, in recognition of this threat — which results from the confluence of rising resistance and a lack of development of new antibiotics — the President's budget request announced some months ago included $30 million for the CDC's "Detect and Protect Against Antibiotic Resistance Initiative."[2]

The emergence of antibiotic resistance is closely tied to antibiotic use. As stated by the U.S. Acting Surgeon General, preserving antibiotics is key to protecting patients.[3]

In concert with the related statements, the CDC published the results of a national study of antibiotic use in U.S. hospitals.[4] Among the findings were that almost three-fifths of patients received an antibiotic and that 37.2% of uses were, at a minimum, suboptimal. In addition, there was as much as 3-fold variability in antibiotic prescribing between institutions. It was estimated that a 30% reduction in use of broad-spectrum antibiotic therapy would result in a 26% reduction in *Clostridium difficile* colitis.

In recognition of the problem of antibiotic misuse and its consequences, CDC has made antibiotic stewardship a focus of its activities, as indicated in their following statement: "Antibiotics save lives, but poor prescribing practices are putting patients at unnecessary risk for preventable allergic reactions, super-resistant infections, and deadly diarrhea. Errors in prescribing decisions also contribute to antibiotic resistance, making these drugs less likely to work in the future."[5]

In addition, there are increasing calls for the Centers for Medicare & Medicaid Services to regulate antibiotic stewardship programs with fiscal penalities and pay-for-performance incentives.

For now, the CDC and the Acting Surgeon General recommend that hospitals dedicate necessary human, financial and IT resources to overcome these patient safety challenges. More specifically, CDC recommends that all hospitals implement antibiotic stewardship programs (required by law in California) that include, at a minimum, 7 core elements:

- Support and commitment of hospital leadership with dedication of necessary human, financial, and information technology resources;
- Accountability through a single physician lead responsible for program outcomes;

ASAP: New IDA Supplement makes a Timely Debut

Antibiotic Stewardship: Advances in Practice (ASAP) debuts at a critical time, as stewardship programs to carefully monitor and control drug use have become a top public health priority. There are now infections resistant to all available antibiotics, as vanishing drug efficacy and a "post-antibiotic" era are no longer theoretical threats. The CDC is calling for stewardship programs in all health care settings. CMS regulatory action on antibiotic stewardship is widely seen as a foregone conclusion. Look to future issues of ASAP for clinical insights into successful programs, news updates and keys to compliance with guidelines and regulations.

• Appointing a single pharmacist leader responsible for working to improve antibiotic use;
• Implementation of at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e., "antibiotic time out" after 48 hours);
• Monitoring of prescribing and resistance patterns;
• Regular reporting of information on antibiotic use and resistance to doctors, nurses and relevant staff members.
• Educating clinicians about resistance and optimal antibiotic prescribing.

Antimicrobial resistance is a global public health emergency. In fact, the World Health Organization takes this a step further in calling it a "global health security threat that requires concerted cross-sectional action by governments and society as a whole."[6] Antimicrobial stewardship is an important part of that action. ■

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ABSTRACT & COMMENTARY

Reducing Antibiotics for Asymptomatic Bacteriurias

By Timothy C. Jenkins, MD

Assistant Professor of Medicine, Denver Health and University of Colorado School of Medicine

Dr. Jenkins reports no financial relationships in this field of study.

SYNOPSIS: In hospitalized patients without a urinary catheter for whom urine cultures were ordered, routine reporting of positive culture results was replaced by a modified report asking providers to call the microbiology laboratory for the results if they clinically suspected urinary tract infection. Antibiotic treatment of asymptomatic bacteriuria decreased from 15 of 31 (48%) cases before the intervention to 4 of 33 (12%) of after the intervention.

SOURCE: Leis JA, et al. Reducing antimicrobial therapy for asymptomatic bacteriuria among noncatheterized inpatients: a proof-of-concept study. *Clin Infect Dis* 2014:58 980-83.

Leis and colleagues previously demonstrated that in hospitalized patients, positive urine cultures from non-catheterized specimens typically represent asymptomatic bacteriuria.[1] In this follow-up pilot study, the authors modified urine culture reporting from the microbiology laboratory in an attempt to reduce antibiotic prescribing for asymptomatic bacteriuria.

In hospitalized patients for whom urine cultures were ordered, positive results from non-catheterized specimens were no longer reported automatically. Instead, the following message was posted, "The majority of positive urine cultures from inpatients without an indwelling urinary catheter represent asymptomatic bacteriuria. If you strongly suspect that your patient has developed a urinary tract infection, please call the microbiology laboratory."

Results of positive cultures were provided to any clinician who called the laboratory. For catheterized urine specimens, culture results continued to be routinely reported, thereby serving as a control group. Urine cultures sent from the Emergency Department for patients who presented to the hospital with signs and symptoms of UTI were also excluded from the intervention.

Over 16 weeks, 415 urine cultures from non-catheterized inpatients and 231 urine cultures from catheterized inpatients were ordered by clinicians. Of 151 total positive cultures, 134 (89%) did not meet Centers for Disease Control and Prevention (CDC) criteria for UTI and were classified as asymptomatic bacteriuria. Among non-catheterized patients, prior to the intervention, asymptomatic bacteriuria was treated with antibiotics in 15 of 31 (48%) cases.

After the modified reporting was introduced, asymptomatic bacteriuria was treated in 4 of 33 (12%) of cases ($p = .002$). In catheterized patients (the control group), the rate of antibiotic treatment of asymptomatic bacteriuria was similar before and after the intervention (42% vs. 41%, respectively).

A total of 37 non-catheterized patients had positive culture results during the modified reporting period; clinicians called the laboratory to obtain the culture and susceptibility results for 5 (14%) of the modified reports.

Of these 37 patients, 4 met the CDC definition for UTI, and all 4 of them had been started on appropriate

empiric antibiotic treatment when the urine cultures were ordered.
In addition, none of the 37 patients developed sepsis within 72 hours of urine culture collection

COMMENTARY

Despite calls for reductions in the overuse of antibiotics for asymptomatic bacteriuria,[2] inappropriate prescribing for this condition remains all too common.[3] Providers frequently order urine cultures in hospitalized patients who develop fever even though the pre-test probability for UTI is very low, especially in patients without a urinary catheter. Moreover, when these cultures subsequently turn positive, providers often reflexively start antibiotic therapy. Both of these factors contribute to the inappropriate treatment of asymptomatic bacteriuria.
The current study by Leis and colleagues represents a novel intervention to help circumvent these factors that contribute to unnecessary antibiotic use for asymptomatic bacteriuria. First, the modified laboratory report educates providers that the likelihood of developing a UTI in a non-catheterized patient in the hospital is low. Second, by not displaying the positive culture result, providers may not feel compelled to treat. This simple intervention was highly effective at reducing antibiotic use, leading to a 36% absolute reduction in antibiotic treatment of episodes of asymptomatic bacteriuria. Furthermore, the intervention appeared to be safe as no patients where the modified report was displayed developed sepsis or went untreated if they met CDC criteria for UTI.
Although this intervention only addresses the problem of overtreatment of asymptomatic bacteriuria in a subset of patients where this occurs (this is also common in those with indwelling urinary catheters), it is nevertheless a creative approach to a challenging antimicrobial stewardship problem where previous interventions have been relatively ineffective.
This study also serves as an excellent example of the ability of antimicrobial stewardship programs to improve prescribing through collaboration with the microbiology laboratory. Although the results of this study demonstrate a new and promising approach to a long-standing problem, additional studies are needed before this intervention can be recommended for widespread implementation. ■

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Antibiotic Stewardship as A weapon against *C. diff*

By Gary Evans, Executive Editor

A compelling new incentive is being brought into the role of antibiotic stewardship programs: preventing deadly *Clostridium difficile i*nfections (CDI).
"The impact of antibiotic stewardship ideally is reducing antimicrobial resistance but also very importantly — and probably realized faster — would be a reduction in C. diff rates," says **Sara Cosgrove**, MD, MS, FSHEA, FIDSA, director of the antimicrobial stewardship program and associate hospital epidemiologist at Johns Hopkins Hospital in Baltimore.
Indiscriminate antibiotic use can wipe out commensal bacteria in the patient's gut, clearing the way for *C. diff* to proliferate. Overall, *C. diff* causes some 250,000 infections in hospitalized patients and 14,000 deaths every year among children and adults. Taking antibiotics is the most important risk factor for developing CDIs for both adults and children, the Centers for Disease Control and Prevention reported. In particular, the use of antibiotics that have a high risk of triggering C. diff led to a three-fold increase risk of hospital-onset and post-discharge CDI.[1,2] The antibiotic classes considered to be high-risk were 3rd/4th generation cephalosporins, fluoroquinolones, and beta-lactam/beta-lactamase inhibitor combinations. The CDC conducted a retrospective study of the relative risk of CDI in two large academic medical centers located in New York and Connecticut. The academic center in NY has approximately 700 beds and 40,000 discharges per year while the academic center in Connecticut has approximately 1,000 beds and 58,000 discharges per year. The risk of CDI among those exposed to the aforementioned high-risk antibiotics was three times higher compared to persons with low-risk or no antibiotic exposure, the CDC reported.
"Decreasing the use of antibiotics that most often lead to CDIs by 30% (5% of overall antibiotic use) could lead to 26% fewer of these deadly diarrheal infections," the CDC concluded. "Reductions in CDI of this magnitude could also have additional positive effects in reducing transmission of *C. difficile*

throughout the community."
In a separate CDC study, investigators reported that the majority of pediatric CDIs infections occurring among children in the community were in those who recently took antibiotics prescribed in doctor's offices for other conditions.[3] The study showed that 71% of the CDIs identified among children were community-associated and did not involve an overnight stay in a health care facility.
Among the community-associated pediatric cases whose parents were interviewed, 73% were prescribed antibiotics during the 12 weeks prior to their illness, usually in an outpatient setting such as a doctor's office. Most of the children who received antibiotics were being treated for ear, sinus, or upper respiratory infections. Previous studies show that at least 50% of antibiotics prescribed in doctor's offices for children are for respiratory infections, most of which do not require antibiotics, the CDC noted. ■

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Obama orders fed agencies to combat antibiotic resistance

By Gary Evans, Executive Editor

In what could be a prelude to future federal regulations, President Obama has issued an executive order to reduce the threat of antibiotic resistant bacteria and protect what remains of the nation's endangered drug formulary.
The sweeping order will empower the push for antibiotic stewardship programs, as the rise of drug-resistant pathogens was describe as a "national security priority." The federal government will "work domestically and internationally to detect, prevent, and control illness and death related to antibiotic-resistant infections by implementing measures that reduce the emergence and spread of antibiotic-resistant bacteria and help ensure the continued availability of effective therapeutics for the treatment of bacterial infections," the Sept. 18 executive order stated.
Indeed, the executive order includes establishing a task force that doesn't quite sound like the proverbial blue ribbon panel. Homeland Security has a seat at the table and one of the three co-chairs is the Secretary of Defense. The other two chairs in this triumvirate are the Secretary of the Department of Health and Human Services and the Secretary of Agriculture.
The task force mission is to "identify actions that will provide for the facilitation and monitoring of implementation of this order and the National Strategy for Combating Antibiotic-Resistant Bacteria. … By February 15, 2015, the Task Force shall submit a 5-year National Action Plan to the President that outlines specific actions to be taken to implement the Strategy. The Action Plan shall include goals, milestones, and metrics for measuring progress, as well as associated timelines for implementation."
After years of warnings and pleas to use antibiotics judiciously, this is what we've come to: a crisis big enough to stir the full mechanization of federal power. An overreaction? There are now infections resistant to all available antibiotics, as vanishing drug efficacy and a "post-antibiotic" era are no longer theoretical threats.
At this year's conference of the Association for Professionals in Infection Control and Epidemiology (APIC) there were gram negative infections described that were even resistant to colistin, a bottom-of-the-barrel antibiotic that has maintained its efficacy primarily because it's typically worse for the patient than anything they are infected with.
In addition to pushing for new drug development and reaching out to international partners facing a similar, global problem, the executive order calls for a more aggressive role in "actively identifying and responding to antibiotic-resistant outbreaks; preventing outbreaks and transmission of antibiotic-resistant infections in healthcare, community, and agricultural settings through early detection and tracking of resistant organisms; and identifying and evaluating additional strategies in the healthcare and community settings for the effective prevention and control of antibiotic-resistant infections. …. DoD, HHS, and the VA shall review and, as appropriate, update their hospital and long-term care infectious disease protocols for identifying, isolating, and treating antibiotic-resistant bacterial infection cases." ■

Editor's note: For the full executive order go to: http://www.whitehouse.gov/the-press-office/2014/09/18/executive-order-combating-antibiotic-resistant-bacteria*)*