AHC Media

Vol. 34, Issue 11, August 2015
www.AHCMedia.com

Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Antibiotics for Acute Appendicitis

By Richard R. Watkins, MD, MS, FACP

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Dr. Watkins has received research support from Forest Pharmaceuticals.

SYNOPSIS: A randomized, multicenter clinical trial compared antibiotic therapy to surgery for uncomplicated acute appendicitis and found most patients who received antibiotics did not require appendectomy during the one-year follow-up period. Of those who needed surgery after treatment with antibiotics, the risk for complications was low.

SOURCE: Salminen P, et al. Antibiotic therapy vs. appendectomy for treatment of uncomplicated acute appendicitis. *JAMA* 2015;313:2340-2348.

Appendectomy has been the treatment for acute appendicitis since the late nineteenth century. During the past decade, the notion of treating acute appendicitis with antibiotics alone has been proposed and evaluated in several clinical trials. However, these trials have been criticized because of methodological limitations. Therefore, Salminen and colleagues aimed to test the hypothesis that acute appendicitis could be successfully treated with antibiotics and surgery avoided using a more robust study design that would overcome the limitations of previous trials.

The study was a randomized, open-label, non-inferiority clinical trial conducted at 6 Finnish hospitals between 2009 and 2012. Inclusion criteria were patients between 18 and 60 years of age who presented to the emergency department (ED) with clinical symptoms of acute appendicitis confirmed by CT scan. Those with complicated appendicitis including perforation, presence of an appendicolith, abscess or tumor were excluded. Randomization was performed with a 1:1 allocation ratio for either open appendectomy or antibiotic therapy. Ertapenem was given to those patients

Financial Disclosure: *Infectious Disease Alert*'s editor, Stan Deresinski, MD, FACP, FIDSA, reports no financial relationships relevant to this field of study; peer reviewer Patrick Joseph, MD, is laboratory director for Genomic Health, Siemens Corp., and CareDx; Shelly Morrow Mark's spouse works for a company that has created advertising for Uroplasty; Updates author, Carol A. Kemper, MD, FACP, and continuing education and editorial director Lee Landenberger report no financial relationships to this field of study.

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Infectious Disease [ALERT]

Infectious Disease Alert,
ISSN 0739-7348, is published monthly by
AHC Media, LLC
One Atlanta Plaza
950 East Paces Ferry NE, Suite 2850
Atlanta, GA 30326.
www.AHCMedia.com

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

GST Registration Number: R128870672.
POSTMASTER: Send address changes to *Infectious Disease Alert*, P.O. Box 550669, Atlanta, GA 30355.

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This CME activity is intended for critical care physicians and nurses. It is in effect for 36 months from the date of the publication.

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in the antibiotic treatment group for 3 days, with the first dose given in the ED. Following intravenous therapy, oral levofloxacin and metronidazole were prescribed for 7 days. The primary endpoint in the antibiotic group was resolution of appendicitis without surgery and no recurrent appendicitis over the next one year. The secondary end points were overall post-intervention complications, late recurrence (more than one year) of acute appendicitis after antibiotic therapy, length of hospital stay, length of sick leave used by the patient, and post-intervention pain issues.

Of the 530 patients randomized, 273 underwent appendectomy and 257 were assigned to antibiotic therapy. After one year, 186 patients in the antibiotic group did not require appendectomy (72.7%), while 70 patients did (27.3%). Moreover, despite having recurrent appendicitis and delayed operation, the surgical complication rate for the patients in the antibiotic group who eventually needed an appendectomy was 7% compared to 20.5% in the surgical group (P = .02). The overall complication rate was also significantly lower in the antibiotic group (2.8% vs 20.5%, P < .001). Length of hospitalization was similar between the groups (median, 3 days), while pain scores and length of sick leave (median 19.0 days vs. 7.0 days) favored the antibiotic group. At the beginning of the study, the investigators established 24% as the minimum clinically important difference between the treatment groups. The intention-to-treat analysis revealed a difference of -27%, meaning the results did not demonstrate noninferiority of antibiotic therapy relative to surgical therapy (P =.89).

■ COMMENTARY

The findings of Salminen and colleagues support the hypothesis that many patients with acute appendicitis can be treated with antibiotics alone, and even the ones who fail antibiotic therapy and eventually undergo appendectomy will likely have an uncomplicated course. A particular strength of the study was the reliance on CT scans to diagnose acute appendicitis. This has proven to be a more accurate method to diagnose appendicitis than older ones, i.e., history and physical examination. The use of CT scans minimized diagnostic uncertainty in the trial and allowed for exclusion of intraluminal appendicoliths, which can lead to complicated acute appendicitis. A potential use of these data could be to serve as the basis of a scoring system that would help clinicians determine which patients should undergo appendectomy and which should be treated with antibiotics alone.

Although this was a seminal study, one limitation was that antibiotic therapy did not prove to be noninferior to surgical intervention, which is currently the standard of care. My suspicion is that this was due methodological reasons and not from a true weakness of antibiotics per se. For example, the investigators had difficulty enrolling patients in the trial necessitating a re-evaluation of the sample size that may have led to underpowering and indeterminate results. Further studies are needed to conclusively validate the findings of Salminen and colleagues.

How will this study impact clinical practice? There is now good evidence that select patients with acute uncomplicated appendicitis (i.e., nonpregnant, older than 18 years, not systemically ill) diagnosed by CT scan can be successfully treated with antibiotics (intravenous ertapenem for 3 days followed by 7 days of oral levofloxacin and metronidazole) with close follow up. While we wait on additional studies, antibiotic therapy instead of immediate appendectomy seems to be a reasonable option that can be discussed with some patients who present to the ED with acute appendicitis. ■

ABSTRACT & COMMENTARY

Polio — New Strategies as We Get Close to Eradication

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.

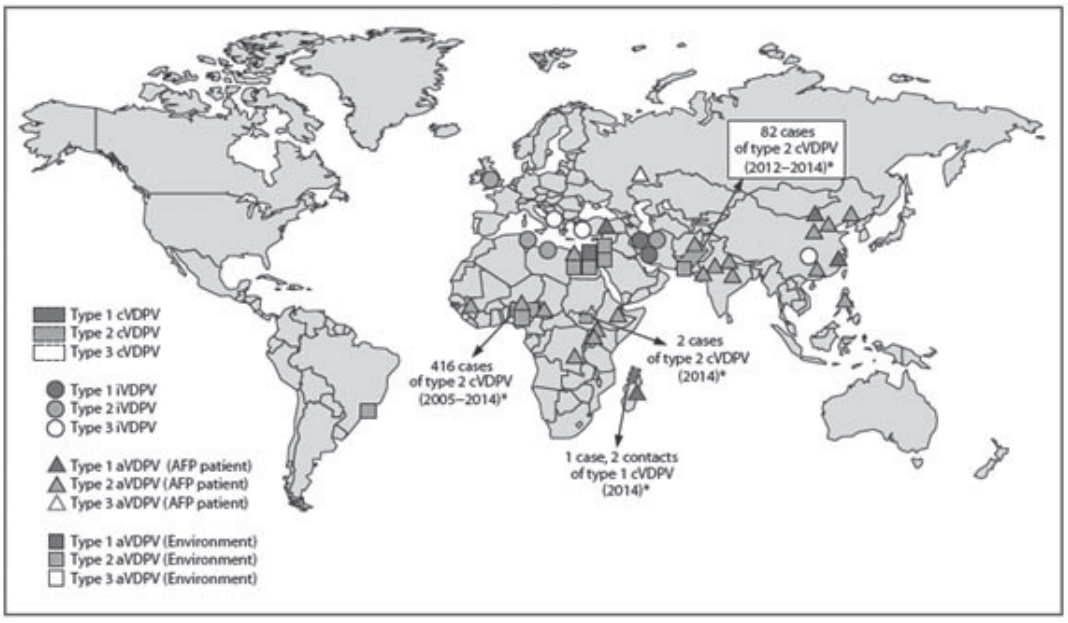
SYNOPSIS: The switch to a bivalent live attenuated oral polio vaccine by elimination of serotype 2 from it will be coordinated with the use of trivalent inactivated vaccine. The purpose is to eliminate outbreaks of polio due to vaccine serotype 2, the major cause of such events.

SOURCES: Diop OM, Burns CC, Sutter RW, et al. Update on Vaccine-Derived Polioviruses — Worldwide, January 2014-March 2015. *MMWR Morb Mortal Wkly Rep* 2015;64(23):640-646.

Immunization Systems Management Group of the Global Polio Eradication Initiative. Introduction of Inactivated Poliovirus Vaccine and Switch from Trivalent to Bivalent Oral Poliovirus Vaccine — Worldwide, 2013-2016. *MMWR Morb Mortal Wkly Rep* 2015;64(25):699-702.

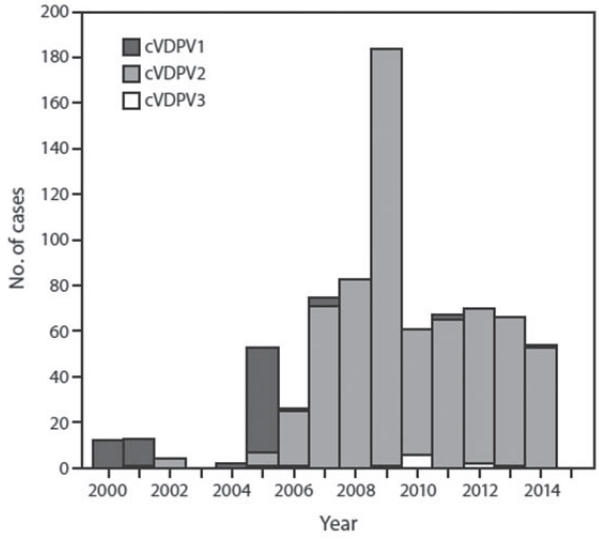
The use of live, attenuated oral polio vaccine (mostly trivalent) has been a major component of the World Health Organization (WHO) Global Polio Eradication Initiative since the resolution to eradicate poliomyelitis throughout the world that was promulgated by the World Health Assembly in 1988. The program has brought polio to its knees. Of the three serotypes of polio virus, wild-type polio virus 2 (WPV2) was eliminated in 1999, while the last time WPV3 was detected was in November, 2012, and circulation of WPV1 is currently only occurring in parts of Pakistan and Afghanistan. This success, with the world on the brink of eradication of polio, has had a downside due to the fact that it has been largely accomplished by the use of an attenuated, but nonetheless viable, virus. One risk is the very rare sporadic occurrence of reversion of the vaccine strain to neurovirulence, causing vaccine-associated paralytic polio (VAPP). More worrisome is significant genetic diversion from the vaccine strain as a result of prolonged replication and/or circulation with the development of neurovirulence. Circulating vaccine-derived polioviruses (cVDPV) resemble WPV and may cause outbreaks in areas with low coverage

FIGURE 1. Vaccine-derived Polioviruses (VDPVs) Detected Worldwide, January 2014–March 2015



Abbreviations: cVDPV = circulating VDPV; iVDPV = immunodeficiency-associated VDPV; aVDPV = ambiguous VDPV; AFP = acute flaccid paralysis. Source: Centers for Disease Control and Prevention

FIGURE 2. Circulating Vaccine-derived Poliovirus (cVDPV) Cases Detected Worldwide, by Serotype and Year, January 2000–March 2015



Source: Centers for Disease Control and Prevention

by oral polio vaccine. VDPVs may replicate in some individuals with primary immunodeficiencies who may excrete them for years — these viruses are designated iVDPV.

During January 2014 to March 2015, new outbreaks of cVDPV occurred in both Madagascar and South Sudan, but there was also a marked reduction in type 2 cVDPV in Nigeria and Pakistan. In addition, an additional 8 patients from 6 countries were found to be excreting iVDPV and, remarkably, a previously identified patient was still excreting iVDPV after more than 28 years. (*See Figure 1.*)

Since 2006, 686 cases of paralytic polio caused by cVDPV have been identified, and > 97% of these were caused by cVDV2. (*See Figure 2.*) Since WPV2 was eliminated 26 years ago, a logical step is to discontinue the use of OPV serotype type 2. WHO has, in fact, announced that this component will be withdrawn from all immunization activities and programs through a global replacement of all trivalent with bivalent OPV (bOPV) containing only types 1 and 3 polioviruses. This changeover will require careful synchronization to minimize the risk of new outbreaks due to cVDV2 during the transitional period. To further reduce the risk of such outbreaks, injectable trivalent inactivated poliovirus vaccine (IPV) is being introduced into routine immunization schedules in all countries.

Relying on IPV may, however, prove problematic. In Israel, WPV1 has recently been repeatedly isolated in the course of routine environmental surveillance despite the fact that the country has a high rate of coverage with IPV. OPV has not been used for just over a decade and this has allowed silent circulation of WPV that had been introduced into the country. This experience demonstrates the necessity of ongoing acute flaccid paralysis surveillance and high-quality environmental surveillance. Of further criticality will be rapid detection and response to cVDV2 outbreaks should they occur. ■

ABSTRACT & COMMENTARY

BCG — Back to the Future?

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: In a population-based study, neonatal vaccination with bacille Calmette-Guérin (BCG) significantly reduced rates of hospitalization for non-tuberculous respiratory infection and sepsis. BCG vaccine might provide significant protection through nonspecific immune enhancement.

SOURCE: de Castro MJ, Pardo-Seco J, Martinon-Torres F. Nonspecific (heterologous) protection of neonatal BCG vaccination against hospitalization due to respiratory infection and sepsis. *Clin Infect Dis* 2015;60:1611-1619.

In this study, de Castro and colleagues wisely made use of a "natural experiment." Some regions of Spain altered standard immunization practices in a way that left some still giving routine neonatal BCG vaccination and others forgoing that vaccine. Carefully controlling for as many other variables as they could, these investigators compared hospitalization rates for non-tuberculous respiratory infections and sepsis between Basque Country (where BCG was still routinely given) and the rest of Spain.

Nearly half a million hospitalizations from 1992 to

2011 were analyzed. BCG-vaccinated children had significantly fewer respiratory hospitalizations for all age groups than did other children (preventive fraction 41%, $p < 0.001$). The hospitalization rate for sepsis during the first year of life was also lower in BCG-vaccinated children (preventive fraction 53%, $p < 0.001$). (The hospitalization rate for tuberculosis-related illnesses was also 74% lower in the Basque Country where BCG was still used.)

The authors point out that BCG vaccine seems to stimulate a subsequently enhanced release of monocyte-derived cytokines when a child is exposed to non-tuberculous bacterial and fungal infections. Thus, they viewed their data as supporting the conclusion that BCG vaccination may provide heterologous protection against non-tuberculous infections/illnesses.

■ COMMENTARY

BCG is one of the safest and most widely used vaccines. For decades, however, most American global health professionals have advised against the use of routine BCG vaccination — with good reason. Now, mounting evidence suggests that perhaps there is still value in using BCG for newborns. Why have we said not to use BCG?

First, the incidence of TB in the United States is relatively low. Some assume the risk is low enough not to bother vaccinating. They leave the vaccine for use in developing countries where there is more tuberculosis and where early diagnosis and treatment of active infection might not be feasible.

Second, though relatively safe, the vaccine is not without risk. Some children develop adenitis after the vaccine, and children with hereditary immunodeficiencies can develop disseminated disease from the BCG germs.

Third, use of the vaccine can complicate the interpretation of subsequent tuberculosis tests. While we never really took previous BCG use into consideration when interpreting tuberculosis skin tests, we did know that BCG can "falsely" increase induration around the site of purified protein derivative (PPD) skin tests. Some argued that future diagnosis post-exposure to tuberculosis would be complicated by previous receipt of BCG.

Finally, and most importantly, the vaccine doesn't help much. There is good evidence that BCG reduces the risk of miliary and disseminated tuberculosis. But, BCG is not consistently effective in preventing pulmonary tuberculosis. Some studies have shown favorable effects, but others have not; this is perhaps due to variations if efficacy between various lots/strains of BCG.

Now, though, new data prompt us to challenge each of these aspects of our sage BCG-avoiding advice.

First, it is still true that tuberculosis is uncommon in the United States. In fact, the incidence has been steadily decreasing for two decades. However, there are still new cases each year — about 3 per 100,000 people. About 35% of the new cases are in people who were born in the United States and, thus, potentially could have been helped by an effective tuberculosis vaccine. There were more than 500 deaths due to tuberculosis in the United States in 2011 (the last year for which final data are available).[1]

Second, the risks are actually minor or very rare. Non-suppurative adenitis following BCG vaccination usually resolves without treatment.[2] HIV-exposed newborns have similar responses to BCG vaccine as do HIV-unexposed babies.[3]

Third, new interferon-based tuberculosis tests are not susceptible to confusion due to previous BCG vaccination. These tests have not yet been perfected, but they obviate much of the challenge of interpreting tuberculosis skin tests in BCG-exposed children.[4]

And, there is some value in giving BCG. The vaccine does reduce disseminated TB, might actually decrease acquisition of infection following known exposure,[5] and, as noted by de Castro, might serve as a general immune stimulant. Other recent work also affirmed the reduced risk of non-tuberculous lower respiratory infection in children who had received BCG.[6] Thoughts that BCG might also permanently reduce the risk of asthma have not be confirmed.[7]

The use of immune stimulants is not new. The "hygiene hypothesis" suggests that some inflammatory and infectious problems are less common in children who are exposed to immunity-altering poor hygiene during infancy. Silver nitrate has been put in newborns' eyes for decades, not to kill contaminating gonococci, but, rather, to stimulate the child to develop a local inflammatory response that will prevent the gonococci from initiating an infection. It is not novel to suggest that the immune stimulation of exposure to BCG might be useful in general ways beyond whatever effect it has on subsequent tuberculosis disease.

Of course, it would be premature to alter immunization strategies simply based on de Castro's

study. It could well be that there are genetic, nutritional, and environmental variations between residents of Basque Country and the residents of the rest of Spain. Other as-yet unidentified factors might have confounded the interpretation of de Castro's results in ways that overestimate the value of BCG.

Nonetheless, it is possible that the international community was correct in continuing with BCG vaccination. Perhaps with further data, we Americans might reconsider our resistance to the use of BCG (and advocate for its availability in the United States). Or, as suggested by an editorial accompanying de Castro's paper, perhaps we will use these new data as further impetus to develop a new vaccine that will be more effective against tuberculosis than is BCG and that might also provide other helpful immune enhancements.[8] ■

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ABSTRACT & COMMENTARY

Does Bacteremia Associated with Bone and Joint Infections Require Prolonged IV Antibiotic Therapy?

By Dean L. Winslow, MD, FACP, FIDSA

Dr. Winslow is Chairman, Department of Medicine, Santa Clara Valley Medical Center, Clinical Professor of Medicine and Pediatrics (Affiliated), 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: Two hundred sixty-five children with culture-proven acute bone or joint infections were studied. All patients received 2-4 days of IV antibiotics followed by PO antibiotics. Clinical outcomes and resolution of inflammatory biomarkers were the same whether the patient had positive blood cultures or not on admission.

SOURCE: Pääkkönen M, et al. Does bacteremia associated with bone and joint infections necessitate prolonged parenteral antimicrobial therapy? *J Pediatric Infect Dis Soc* 2015;4:174-177.

Two hundred sixty-five previously healthy children with culture-proven acute bone or joint infection (age range 3 months to 15 years) were studied. Cultures were obtained from the affected bone or joint and from blood. Clindamycin or a first-generation cephalosporin were given according to randomization for a total of 20 or 30 days in osteomyelitis and 10 or 30 days in septic arthritis. Patients with *Haemophilus influenza* type B arthritis were given IV ampicillin followed by PO amoxicillin. Treatment was always instituted IV and given for 2-4 days at the discretion of the treating clinicians. The switch to PO was made once the patient was felt to be clinically responding and CRP began to decline. One hundred thirty-one patients had osteomyelitis with or without adjacent septic arthritis, and 134 had

septic arthritis alone. Blood cultures were positive in 59% of cases. *Staph. aureus* (MSSA) was isolated in 199 cases, *Haemophilus influenza* type B in 26 cases, *Streptococcus pyogenes* in 25 cases, *Streptococcus pneumonia* in 12 cases, and other organisms in 3 cases. Mean duration of IV antibiotics was 4 days in both the no bacteremia and bacteremia groups; CRP normalized in 10 days in both groups; and ESR normalized in 23 days in patients with no bacteremia and in 24 days in the patients with bacteremia. There were no relapses or treatment failures in the entire series.

■ COMMENTARY

I found this to be a very interesting paper, which supports one of my biases regarding over-treatment of many infections, especially in adult infectious disease. While one needs to be careful about extrapolating treatment of a largely pediatric disease to adult infections, the take-home point still applies: There is nothing magical about IV antibiotics despite the common perception of patients, generalist physicians, and even infectious disease subspecialists that there is. Despite the potential for even more adherence issues in children than in adults, the fact that serious bacteremic infections can be successfully treated with very short courses of IV antibiotics (followed by PO) should be reassuring to infectious disease specialists. Since the introduction of PICC lines in the 1980s, there has clearly been a "duration creep" in the lengths of IV treatment of many infections. In most cases, there is no justification for this but it is often done because of "fear of failure" by the treating physicians and there is often the attitude, "because we can" since PICCs are so easy to insert. What is often forgotten is that PICC lines can be complicated by subclavian vein thrombosis and line sepsis, and the prolonged duration of IV antibiotics is likely driving both increased *C. difficile* infection rates and increased prevalence of antimicrobial-resistant bacteria, as well as dramatically increased costs. ■

ABSTRACT & COMMENTARY

When Profiling Is a Good Thing: Distinguishing Bacterial from Viral Infection

By Joseph F. John, Jr., MD, FACP, FIDSA, FSHEA

Dr. John is Clinical Professor of Medicine, Medical University of South Carolina, Charleston.

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

SYNOPSIS: Transcriptional analysis outperformed serum procalcitonin in distinguishing viral from bacterial infections.

SOURCE: Suarez NM, Bunsow E, Falsey AR, et al. Superiority of transcriptional profiling over procalcitonin for distinguishing bacterial from viral lower respiratory tract infections in hospitalized adults. *J Infect Dis* 2015;212:213-222.

Procalcitonin predicts, to a degree, the likelihood of a bacterial versus a viral infection. Dependence on a single variable like procalcitonin has made clinicians uneasy, particularly if such a single test is used to guide continued use of antimicrobials. Hospitalized adults with pneumonia is a population that can benefit from markers that distinguish between bacterial and viral infection. If the infection is associated or not with certain biomarkers, then antibiotics can be stopped when they are not useful, such as with viral infections.

This study was performed using patients from Rochester General Hospital in Rochester, NY. During respiratory infection seasons, 118 patients with lower respiratory tract infections (LRTIs) and 20 healthy controls were included in the study. Very broad culture and polymerase chain reaction (PCR)-based diagnostics were used for traditional identification of bacterial and viral pathogens. Those identifications were used as the gold standard. A large set of transcriptional modules that group together genes with shared expression were the basis of the transcriptional array analysis. A method known as the K-nearest neighbor (K-NN) algorithm was used to identify top-ranked genes which discriminated between viral and bacterial infection.

Of the 118 patients, 71% had a viral infection and 22% had a bacterial infection. A set of patients' blood samples was used as a "training" set, which identified the transcriptional signature of LRTI. These signatures were then validated further in a "test" set of blood samples. There were 3986 "differentially

expressed transcripts" showing a consistent gene expression pattern in the patients with bacterial compared to viral LRTIs. Test set samples correctly grouped gene expression patterns in 53 of 59 (90%) bacterial infections.

Bacterial LRTI showed significant overexpression of genes related to innate immunity (inflammation and neutrophil modules) and underexperssion of genes related to adaptive immunity, such as B- and T-cell activation, particularly interferon expression. The authors went even further and constructed a set of "classifier" genes. A K-NN algorithm found 10 classifier genes that did differentiate between bacterial and viral LRTI. Classifier genes group correctly 22 or 23 new patients' samples and repeated this analysis again in 23 patients with the same findings. There were patients with coninfections whose transcripts patterns were functionally between pure bacterial and pure viral infection.

■ COMMENTARY

Severe pneumonia meets big data. It is hard to imagine 10 years ago when studies showing the promise of procalcitonin to differentiate bacterial from viral pneumonia that just a decade later that massive molecular arrays could be utilized economically and rapidly to differentiate at a much more sensitive level. Surely the implication of this study is that we are at the beginning of a new revolution in microbial diagnostics. The data points are numerous, their analysis is highly technical, but the amount of information is extremely helpful, not only in differential diagnosis but also in understanding basic pathophysiology. For example, in the current study, we see that array technology identifies that multiple interferon genes are overexpressed in viral LRTIs and not in bacterial infections. The finding itself is not so surprising in view of long-standing knowledge about the nature of interferon responses. What is surprising is that a huge array can pinpoint what the authors call "classifier genes" that themselves can be used for a very practical differentiation between a bacterial and viral pneumonia and, moreover, suggest by an expanded transcript pattern when the infection may be mixed.

We have entered a brave new molecular diagnostic world where DNA array applications are just a part of the emerging technology to facilitate microbial diagnosis and treatment. ■

ABSTRACT & COMMENTARY

Decreasing Cross-Transmission of Carbapenemase-Producing Enterobacteriaceae

By Elaine Chen, MD

Dr. Chen is Assistant Professor, Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Section of Palliative Medicine, Rush University Medical Center, Chicago, IL.

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

This article originally appeared in the July 2015 issue of Critical Care Alert.

SYNOPSIS: A bundled infection control intervention was shown to decrease cross-colonization, prevalence, and bloodstream infection of *Klebsiella pneumonia* carbapenemase-producing Enterobacteriaceae in long-term acute care hospitals, which may have far-reaching effects into the ICU.

SOURCE: Hayden MK, et al. Prevention of colonization and infection by *Klebsiella pneumonia* carbapenemase-producing Enterobacteriaceae in long-term acute care hospitals. *Clin Infect Dis* 2015;60:1153-1161.

Carbapenem-resistant Enterobacteriaceae (CRE) are highly resistant to multiple classes of antibiotics and pose a serious threat to our ability to control infections. *Klebsiella pneumonia* carbapenemase-producing Enterobacteriaceae (KPC) are the most common in this group. Colonization usually precedes infection, and colonization is frequently acquired by cross-contamination in healthcare settings, particularly high-prevalence areas. Because prevalence is higher in long-term acute care hospitals (LTACHs) than elsewhere, this study was undertaken to try to decrease the incidence and prevalence of KPC in LTACHs.

This quality improvement project was implemented in 4 LTACHs in a single metropolitan area. Baseline prevalence of KPC was measured before the intervention was initiated. The KPC intervention bundle included rectal swabs for KPC for all patients on admission and every 2 weeks thereafter during their hospitalization, contact isolation, geographic separation of KPC-positive patients, chlorhexidine (CHG) baths, and healthcare worker hand hygiene education and monitoring. All healthcare workers underwent a series of mandatory educational sessions. Adherence to all measures but one, including collection of admission and periodic surveillance swabs, geographic isolation of KPC-positive patients, hand hygiene at room exit, and donning gloves and gown before room entry, was greater than 70% during the intervention; adherence to hand hygiene at room entrance was low at 24%.

In the pre-intervention period, average KPC prevalence was 45.8% (95% confidence interval [CI], 42.1-49.5%). In the post-intervention period, following an initial decline, prevalence plateaued at 34.3% (95% CI, 32.4-36.2%; P < 0.001 for exponential decline). Admission prevalence remained stable at 20.6%, but incidence rate of KPC colonization decreased from four to two acquisitions per 100 patient-weeks (P = 0.004 for linear decline). Rates of KPC in any clinical culture, KPC bloodstream infection, bloodstream infection due to any pathogen, and contaminated blood cultures all decreased significantly during the intervention period.

Overall, this study showed that the implementation of a bundled infection control intervention was able to significantly decrease cross-transmission of a multi-drug-resistant pathogen and decrease healthcare-associated infections in an LTACH population.

■ COMMENTARY

Drug-resistant organisms have been increasing morbidity and mortality in healthcare settings. They are more common in LTACHs than in short-term acute care hospitals, and the chronically critically ill population is particularly at risk due to their high frequency of transfer among healthcare facilities. CRE (including KPC) colonization and infection are an increasing concern in ICUs, and have been associated with significantly longer ICU length of stay and higher mortality.[1] By decreasing KPC cross-transmission and infection in high-prevalence settings, there may be potential to decrease length of stay as well as mortality in both long-term and short-term care units.

This study presents a comprehensive infection control bundle, which was shown to decrease colonization and infection by KPC. Due to the bundled nature of the intervention, individual components of the bundle leading to improvement could not be identified. The authors speculate that the CHG baths were the intervention most responsible for the decrease in bloodstream infection, and that the bundled intervention is necessary to control cross-colonization. This bundle, as applied in LTACHs, has the potential to slow the regional spread of KPC and to decrease morbidity and mortality in both lower-acuity settings (such as skilled nursing) and higher-acuity settings (such as short-term ICUs). Potential drawbacks to the technique include high cost/benefit ratio and selection of further resistance with CHG baths. The authors propose further testing, including simulation modeling and molecular epidemiologic methods, to evaluate long-term and regional effects of the intervention. ■

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ABSTRACT & COMMENTARY

Squirrels as the Source of a New Viral Cause of Encephalitis

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: Evidence indicates that a newly discovered bornavirus caused infection in squirrels and was transmitted from them to three

humans who developed encephalitis and died.

SOURCE: Hoffmann B, Tappe D, Höper D, et al. A variegated squirrel bornavirus associated with fatal human encephalitis. *N Engl J Med.* 2015; 373:154-162.

Three men, ages 62-72 years from the same region of Germany had onset of symptoms of encephalitis in late 2011. MRI revealed hyperintense cortical and basal ganglia lesions. Cerebrospinal fluid (CSF) white blood cell count ranged from 11-168 cells/μL with 79% lymphocytes (mostly atypical) in the only one with a cell differential. Lactate was elevated in each, the serum/CSF glucose ratios were normal, and protein was elevated. Their illness progressed over the next 2-4 months when it ended in their deaths at a time when extensive investigation had failed to identify an etiology. Of note is that during the course of their illness, all three developed deep venous thrombosis, and two suffered pulmonary embolism.

Epidemiological investigation found that all three men bred variegated squirrels and frequently met and exchanged breeding pairs. Pathogen-specific screening of a squirrel from the breeding population of one of the patients failed to detect an etiology, leading to metagenomic sequencing of a number of samples from the animal. This led to identification of sequence fragments with homologies to Mammalian 1 bornavirus, and targeted screening led to the detection of additional sequencing reads related to both mammalian and avian bornavirus. The investigators named the virus variegated squirrel 1 bornavirus (VSBV-1). Using derived primers, RT-PCR, VSBV-1 was detected in the squirrel and in samples from all three patients, including in brain tissue. Testing of samples from multiple controls, both with brain disease and healthy individuals, were all negative. Immunohistochemical staining of brain tissue from one of the patients was positive, and high antibody titers to the virus were present in CSF and serum of one patient tested.

■ COMMENTARY

This is yet another example of the power of modern science to detect new viral pathogens. The problem now has become the more difficult one of unequivocally demonstrating that the novel organisms are actually causal. In the cases described by Hoffman and colleagues, while Koch's postulates have not been completely fulfilled, the evidence is overwhelming that this newly described bornavirus caused fatal encephalitis in these three individuals and that squirrels were the source of the virus.

Each of the individuals had intense exposure to the squirrels they were breeding, with each patient reporting having been scratched or bitten by them. Of note is that variegated squirrels are native to southern Mexico and Central America, so it is possible, if the virus has entered that population, that similar infections may be occurring in residents and visitors to those regions, assuming that the local squirrels are affected. Whether similar viruses are present in other squirrels is unknown.

Borna disease, originally known as "Hitzige Kopfkrankheit der Pferde" ("heated head disease of horses") was first described in the 18th century and affects sheep, rabbits, and a variety of other animals in addition to horses. In addition, related avian bornaviruses cause disease in psittacines and have also been detected in other avians. Two decades ago, the possibility that bornavirus was associated with psychiatric disease in humans was examined and apparently rejected. ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

HPV on that Ultrasound Probe?

Gallay C, et al. Human papillomavirus (HPV) contamination of gynaecological equipment. *Sex Trans Infect* 2015:1-5.

HPV has been identified from a variety of sources, including the underwear and under the fingernails of persons with genital HPV, as well as on medical equipment, such as vaginal probes and cryoguns. Because HPV (a

non-enveloped capsid virus) can resist routine cleaning with such agents as glutaraldehyde and ethanol, it has been theorized that transmission other than sexual may occur.

In order to investigate the frequency of HPV contamination of gynecological equipment, these authors collected specimens from fomites twice a day for two days at two University Hospital and four private gynecology offices in Geneva and Lausanne, Switzerland, in 2013. In total, 179 samples were collected from glove boxes, lamps, tables, gel tubes, speculums, and colposcopic equipment from both colposcopic rooms and private examination rooms. Samples were processed, DNA was extracted and stored at -20 C, and then real-time amplification and genotyping was performed with the Anyplex II HPV28 test kit.

Overall, 32 (17.9%) of the fomite samples were contaminated with HPV DNA. Contamination was higher at private offices than at University facilities (27.5 vs 11.8%, p = .38). The two most frequently contaminated sites were the colposcopic handle (43.8%) and the lamp (37.5%) — with the latter most likely because the operator reaches to adjust the lamp. Other sites of less frequent contamination included the glove box (9.4%), and gel tubes (6.2%). One of 24 speculums (3.1%) was contaminated. Speculums were sterilized between patients, so this speculum could have been contaminated from the tray table or contaminated gloved hands. There was no difference in the observed frequency of contamination between samples collected in the morning or the evening.

Twenty different HPV genotypes were detected, including 13 different high-risk genotypes found in 20 locations, and 7 lower-risk genoptypes found in 24 locations. The number and viability of virus detected using these techniques could not be determined.

These authors propose changes in procedures for gynecologic exam — including enhanced cleaning procedures. Once the exam begins, gloved hands of the examiner should not touch other equipment or surroundings; and lights should be adjusted by an assistant. The use of disposable speculums should further reduce the risk of contamination.

Saving Elephants from Herpesviruses

Akst J. A plague on pachyderms. *The Scientist*. June 1, 2015.

At least seven genetically distinct herpesviruses, called elephant endotheliotropic herpesvirus (EEHV), can infect elephants, resulting in a devastating hemorrhagic infection with a high rate of mortality, especially in non-immune calves. Between 1978 and 2008, nearly 20% of the United States-born Asian elephant calves died from EEHV. Since then, there's been a considerable effort to save these youngsters.

Most recently, a 5-year-old Asian elephant named Sampson at the Maryland Zoo in Baltimore began behaving poorly, and his caretaker quickly initiated a diagnostic and therapeutic protocol developed at other centers — including large volumes of oral fluids (15-20 gallons of Gatorade-spiked water), supplemental enemas as needed, anti-inflammatories, pain medications, and famciclovir — at doses about 40 times the human dose (administered 15 mg/kg per day) for one month. Since Sampson weighs around 3500 pounds, it is estimated he took around 2500 tablets of Famvir during his treatment course. The Houston zoo protocol also includes the use of a single dose of ganciclovir 5 mg/kg in 1 liter of fluid.

Since 2005, steps have been taken to routinely screen zoo elephants for the viruses, which can be isolated from trunk washings (as well as genitals and eyes) of healthy elephants, using ELISA screening. Evidence suggests that, similar to human herpesviruses, EEHV can intermittently reactivate, causing a localized head and neck infection. Originally thought to cause a more benign infection in wild African elephants, these viruses appear to present a greater risk to non-immune elephants born in captivity — and so contact between Asian and African elephants is discouraged. Further work is occurring, using DNA fingerprinting, to identify differences between the species/types — which appear to have evolved as distinct viruses many years ago — and to track transmission of infection between animals. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following is correct with regard to patients with uncomplicated acute appendicitis treated with antibiotics alone?

A. The majority ultimately required appendectomy.

B. Their overall complication rates were greater than in those who immediately underwent appendectomy.

C. Among those who ultimately underwent appendectomy, they had a lower surgical complication rate than those with immediate appendectomy.

D. Their pain scores and length of sick leave were each higher than in those who underwent immediate appendectomy.

2. Which of the following is true of the BCG vaccine?

A. It is not widely used.

B. It is ineffective in preventing tuberculosis.

C. It causes disseminated tuberculosis in HIV-exposed newborns.

D. It is associated with reduced risk of non-tuberculous respiratory infection.

3. In the study by Pääkkönen and colleagues, what was the mean duration of intravenous antibiotic administration in the children with bacteremia and bone or joint infection?

A. IV antibiotics were not administered.

B. 4 days

C. 14 days

D. 6 weeks

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