AHC Media

Vol. 35, Issue 4, January 2016
AHCMedia.com

Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Hospital-acquired Infections and Other Hospital-acquired Conditions — How Are We Doing?

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: There was a large decrease in the number of total hospital-acquired conditions from 2010-2014, but with no improvement from 2013-2014. While there were decreases in hospital-acquired infections, much further improvement is needed.

SOURCE: Saving Lives and Saving Money: Hospital-Acquired Conditions Update. December 2015. Agency for Healthcare Research and Quality, Rockville, MD. www.ahrq.gov/professionals/quality-patient-safety/pfp/interimhacrate2014.html.

The U.S. Agency for Healthcare Research and Quality (AHRQ) supports "projects to advance the science of hospital-acquired infection (HAI) prevention, develop more effective approaches for reducing HAIs, and help clinicians apply proven methods to prevent HAIs on the front lines of care." They have now reported preliminary estimates of the change in incidence of hospital-acquired conditions (HACs), including selected hospital-acquired infections from 2010-2014.

There was a cumulative reduction of HAC episodes of approximately 2.1 million relative to the expected number over this time, although there was no significant change from 2013-2014. (*See Figure 1.*) AHRQ also estimates that nearly 87,000 fewer patients died during hospitalization as a result of this reduction, and that approximately $19.8 billion in healthcare costs were saved from 2010 to 2014.

While the majority of this reduction in HACs

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; Updates author, Carol A. Kemper, MD, FACP, continuing education and editorial director Lee Landenberger, executive editor Shelly Morrow Mark, and associate managing editor Jonathan Springston report no financial relationships relevant to this field of study.

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.
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.

SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@ahcmedia.com
AHCMedia.com

Editorial Email:
shelly.mark@ahcmedia.com

Subscription Prices
United States:
Print: 1 year with free *AMA PRA Category 1 Credits™*: $349
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits™*: $299

Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses, or electronic distribution. For pricing information, call Tria Kreutzer at (404) 262-5482.

Back issues: Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

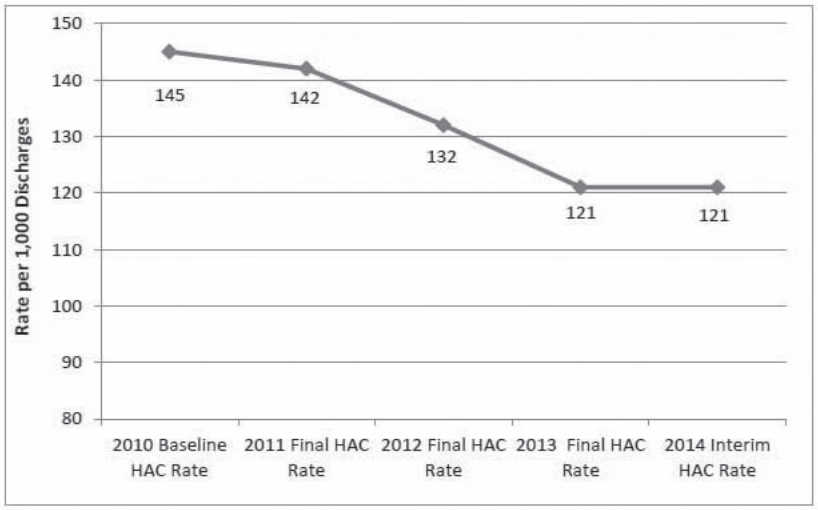
AHC Media designates this enduring material for a maximum of ***36*** *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Infectious Disease Alert may contain references to off-label or unapproved uses of drugs or devices. The use of these agents outside currently approved labeling is considered experimental, and participants should consult prescribing information for these products.

This CME activity is intended for the infectious disease specialist. It is in effect for 36 months from the date of the publication.

AHC Media

Figure 1. HAC Rates, 2010 to Interim 2014



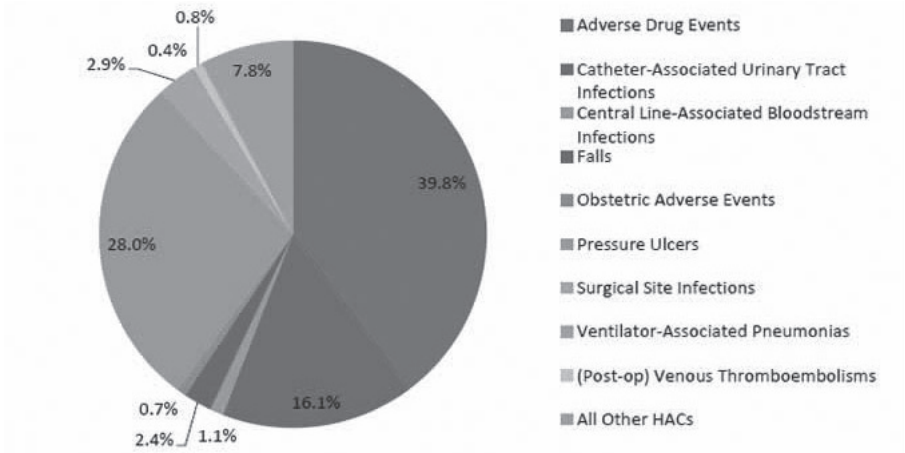
Source: Saving Lives and Saving Money: Hospital-Acquired Conditions Update . December 2015. Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/professionals/quality-patient-safety/pfp/interimhacrate2014.html.

was due to decreased incidences of adverse drug events (-39.8%) and pressure ulcers (-28.0%), there were also significant decreases in selected reported HAIs. (*See Figure 2.*) These included a 16.1% decreased incidence of catheter-associated urinary tract infection (CAUTI), a 2.9% decrease in surgical site infections (SSI), a 1.1% decrease in central line-associated bloodstream infection (CLABSI), and a 0.4% decrease in ventilator-associated pneumonia (VAP). These reductions were associated with cumulative estimated decrements in deaths of 7922, 1748, 4402, and 1150, respectively.

A number of factors likely contributed to these overall reductions, including the dissemination of evidence regarding improved patient safety developed by AHRQ, as well as their investment in tools and training for improvement and in data and measures facilitating the tracking of change. There has been, in addition, the implementation of financial incentives and required public reporting of selected conditions.

However, while the overall improvement is significant, there are some worrisome findings, not the least of which is the lack of a reduction in HAC in the last year. Furthermore, while the reduction in CAUTI was large, that of SSI, CLABSI, and VAP were de minimis. Clearly, more work is needed in the prevention of HAI. ■

Figure 2. Change in HACs, 2011-2014 (Total = 2,107,800)



Source: Saving Lives and Saving Money: Hospital-Acquired Conditions Update. December 2015. Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/professionals/quality-patient-safety/pfp/interimhacrate2014.html.

ABSTRACT & COMMENTARY

Azithromycin to Prevent Asthma Exacerbations?

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: Azithromycin helped prevent progression from upper airway infection to wheezing in a select group of preschool-age children. Further studies are needed before considering widespread use of azithromycin for young children with "colds."

SOURCE: Bacharier LB, et al. Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: A randomized clinical trial. *JAMA* 2015;314:2034-2044.

In a multi-center study, 607 preschool-age children (mean 41 months old, range 12-71) with a history of recurrent severe wheezing that had seemingly been triggered by upper respiratory infections were randomized to receive either azithromycin (12 mg/kg daily for 5 days) or placebo at the onset of their next viral upper respiratory tract illness. All children were given scheduled and as-needed doses of a bronchodilator with onset of the upper respiratory symptoms. During the 52-78 week follow-up period, 443 children had another upper respiratory illness and were included in the analysis (223 with azithromycin, 220 with placebo).

Children who received azithromycin were less likely to progress to a severe lower respiratory tract illness than were children who received placebo (hazard ratio 0.64; 95% confidence interval, 0.41-0.98= *P* = 0.04). It was necessary to treat 33 children with azithromycin to prevent one child from progressing to wheezing with the next upper respiratory infection. The rates of development of subsequent respiratory illnesses were not different between the azithromycin and placebo groups.

COMMENTARY

Macrolides have both favorable and unfavorable effects. They cure infections in individuals, but they also alter microbiomes and promote infection by resistant organisms in both individuals and populations. They improve gastrointestinal function in patients with dysmotility, but they also stimulate adherence-altering abdominal cramping in some treated subjects. In addition, macrolides impact inflammatory responses, even separate from their effects on infection.

It is not clear just how macrolides alter inflammation. Interleukin 8 is the primary chemoattractant for neutrophils, and asthma patients treated with clarithromycin have decreased neutrophilic inflammation. Thus, Bacharier and colleagues evaluated the interleukin 8 gene in their subjects but found no link to outcomes, whether treated by azithromycin or placebo. In a recent laboratory-based study of epithelial cells from patients with cystic fibrosis, azithromycin markedly reduced rhinovirus replication, possibly due to effects on the interferon pathway.[1] Bacharier had previously been involved in a study showing that other inflammation-altering agents (inhaled steroid and oral montelukast) given during upper respiratory infections did not change

[Macrolides have both favorable and unfavorable effects. They cure infections in individuals, but they also alter microbiomes and promote infection by resistant organisms in both individuals and populations.]

long-term asthma outcomes.[2] In a recent clinical study, weekly azithromycin (30 mg/kg, three total doses) did not improve outcomes in children already sick with bronchiolitis.[3]

Unfortunately, antibacterial agents are already over-prescribed for patients with apparent viral upper respiratory infections. A recent review of prescription medication use during the month following a diagnosis of presumed viral acute respiratory infection showed that 49% of patients filled an

antibiotic prescription.[4] Antibiotics were most likely used following evaluation in an urgent care center and least likely used when care was provided by a pediatrician. The recent study of anti-inflammatory effects of azithromycin in children with recurrent wheezing should not be construed as a reason to indiscriminately prescribe azithromycin for children with viral infections.

Further research is needed prior to generalization of the findings in this study. As Cohen and Pelton stated well in an editorial accompanying Bacharier's paper, "the consequences of widespread use of azithromycin, both known and hypothesized, outweigh the benefit for most children."[5] Nonetheless, these new data do offer optimism that some subpopulation groups with inflammatory conditions might indeed benefit from the use of azithromycin in some settings. ■

REFERENCES

1. Schögler A, et al. Novel antiviral properties of azithromycin in cystic fibrosis airway epithelial cells. *Eur Respir J* 2015;45: 428-439.
2. Bacharier LB, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008;122:1127-1135.
3. McCallum GB, et al. Three-weekly doses of azithromycin for indigenous infants hospitalized with bronchiolitis: A multicentre, randomized, placebo-controlled trial. *Front Pediatr* 2015;3:32.
4. Ebell MH, Radke T. Antibiotic use for viral acute respiratory tract infections remains common. *Am J Manag Care* 2015;21: e567-575.
5. Cohen RT, Pelton SI. Individual benefit vs societal effect of antibiotic prescribing for preschool children with recurrent wheeze. *JAMA* 2015;314:2027-2029.

ABSTRACT & COMMENTARY

Differences Between Older and Younger Adults with Viral Respiratory Infections

By Dean L. Winslow, MD, FACP, FIDSA

Dean Winslow is Professor of Medicine, Division of General Medical Disciplines, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine.

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

SYNOPSIS: A prospective study of acute respiratory illness was conducted between 2009 and 2013. Coronavirus and rhinovirus/enterovirus were the most common viral pathogens. Among patients older than age 60 with chronic lung and heart disease (vs healthy adults 18-40 years old), dyspnea, more prolonged illness, and treatment with prednisone and antibiotics were more commonly seen. Myalgia was more common in younger patients.

SOURCE: Gorse GJ, et al. Coronavirus and other respiratory illnesses comparing older with young adults. *Am J Med* 2015; (e-pub 1251: e11-e20).

This paper reports on the results of a prospective study conducted during 2009-2013, which assessed acute respiratory illness (ARI) soon after onset of symptoms and 3-4 weeks later in adults 60 years of age and older with chronic lung and heart diseases (group 1, n = 100) and in healthy adults 18-40 years old (group 2, n = 101). Samples of respiratory secretions were tested by polymerase chain reaction (PCR) for multiple pathogens (including several human coronaviruses, respiratory syncytial virus, influenza A and B, parainfluenza, metapneumovirus, enterovirus/rhinovirus, adenovirus, and bocavirus). In addition, some subjects' serum was later tested by an EIA for coronavirus antibodies. ARI symptoms were assessed and severity was scored.

Illnesses more commonly occurred during fourth and first quarters of all years. Of virus-associated illnesses, coronavirus was seen in 19% of group 1 and 22% of group 2 patients. Enterovirus/rhinovirus was seen in 19% of group 1 and 31% of group 2 patients. Virus coinfection occurred in 10 patients. Group 1 patients more commonly experienced multiple symptoms and symptoms of greater severity; they experienced longer duration of symptoms, and dyspnea was more commonly seen in this cohort than in group 2 patients. In addition, more group 1 patients received treatment with antibiotics and prednisone. Of various symptoms recorded in patients with coronavirus-associated illness, myalgia was more commonly seen in group 2 patients (68% vs 21% in group 1 patients), whereas dyspnea was

more commonly seen in group 1 patients (71% vs 24% in group 2 patients). Other symptoms, such as chills, headache, malaise, cough, sputum production, sore throat, and nasal congestion, were seen in similar percentages of group 1 and group 2 patients.

■ COMMENTARY

This is an interesting paper that prospectively evaluated a good-sized cohort of adults with ARI over 4 years in a rigorous manner. The study showed that coronaviruses and enteroviruses/rhinoviruses were responsible for the largest number of infections. Older, chronically ill adults had more severe illness and experienced a longer duration of symptoms than young, healthy patients. Dyspnea was more commonly seen in older adults with underlying cardiac and pulmonary disease. Lastly, older and chronically ill adults were more likely to receive antibiotics and steroids. This latter observation is particularly important since the use of antibiotics in patients with viral ARIs (in the absence of bacterial co-infection) may be harmful. ■

ABSTRACT & COMMENTARY

Encephalitis from Chikungunya Virus: An Increasingly Recognized Syndrome

By Richard R. Watkins, MD, MS, FACP

Dr. Watkins is in the Division of Infectious Diseases, Akron General Medical Center, Akron, OH; Associate Professor of Internal Medicine, Northeast Ohio Medical University, Rootstown, OH.

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

SYNOPSIS: A retrospective cohort study of a major chikungunya virus outbreak found a significant incidence of central nervous system disease, with patients < 1 year of age and > 65 years of age at most risk for chikungunya virus-associated encephalitis.

SOURCE: Gerardin P, et al. Chikungunya-virus associated encephalitis. *Neurology* 2016;86:1-9.

Chikungunya virus (CHIKV) is a mosquito-borne alphavirus that emerged in the islands of the Indian Ocean about a decade ago and has become widely disseminated. Clinically similar to dengue fever, CHIKV is generally considered a nonfatal disease with spontaneous recovery, although some patients have arthralgias that persist for months. Gerardin and colleagues reported their experience of central nervous system (CNS) involvement after a large CHIKV outbreak that occurred on Reunion Island between September 2005 and June 2006.

The study was a retrospective cohort that included all patients hospitalized at a single hospital on Reunion Island with CHIKV infection and neurological symptoms who had a lumbar puncture. Patients with a positive cerebral spinal fluid (CSF) CHIKV PCR or anti-CHIKV IgM were used to fulfill the specific case definition. The investigators followed the International Encephalitis Consortium criteria to classify patients according to a current definition of encephalitis. These combine the major criterion of change in mental status with several minor criteria, including fever within 72 hours of presentation; seizures not related to epilepsy; new onset of focal neurological deficits; CSF leukocyte count ≥ 5/mm^3; brain parenchyma on neuroimaging suggestive of encephalitis; and EEG consistent with encephalitis and not attributable to another cause. Probable CHIKV-associated encephalitis was defined as the major criterion and at least three minor criteria; possible CHIKV-associated encephalitis was defined as the major criterion and two minor criteria. Every patient with CHIKV CNS disease was followed for 3 years to assess for neurological sequelae.

During the CHIKV outbreak, 129 patients developed neurological signs, of which 57 were enrolled in the study after various exclusions. The cohort contained 21 adults (age range 33-88 years, mean age 63.9 years) and 36 infants (age range 4 days-5.4 months, mean age 1.6 months). The adults were more likely to have experienced decreased consciousness, coma, focal neurological signs, seizures, or death, while the infants were more likely to have experienced fever, behavior changes, rash, and survival. The cumulative incidence rate of CHIKV-associated encephalitis was 8.6 per 100,000 persons (95% confidence interval [CI], 6.9-10.4) with a U-shaped distribution pattern that affected mostly those younger than 5 years old and older than 65 years. Six adult patients died during hospitalization, and eight were discharged with oral neurologic sequelae. Of the 10 adults

available for follow up at 3 years, three of them had neurologic sequelae attributable to CHIKV. Of the 17 infants available for follow up at 3 years, one had severe cerebral palsy and blindness after a full-term normal gestation, and four had poor neurodevelopmental performance. Because of the high attrition in the follow-up period, the burden of neurologic sequelae could not be precisely calculated. However, poor prognosis (i.e., death or sequelae) was more prominent in adults compared to children (52.6% vs 18.2%, respectively; $P = 0.020$).

■ COMMENTARY

This report adds to the increasing body of evidence that CHIKV can cause severe neurological disease. The finding of a number of cases of CNS involvement and encephalitis in the Reunion Island cohort questions the conventional belief that CHIKV infection causes a painful yet self-limited illness. Notably, the cumulative incidence rate of CHIKV-associated encephalitis in the cohort was higher than what has been observed with West Nile virus. The outcomes data were similar to what has been reported for other virus-associated encephalitides, dispelling hope that CHIKV-associated encephalitis might lead to less neurological sequelae. Further research is needed to elucidate the neurological tropism mechanisms of CHIKV, which could possibly be targets for antiviral therapy.

[This report adds to the increasing body of evidence that CHIKV can cause severe neurological disease.]

What are the clinical implications of the study? CHIKV should be considered in the differential diagnosis of travelers with fever and neurological symptoms, especially in those returning from tropical and subtropical regions. This is illustrated by a recent case report of a 57-year-old man from the island of Tonga who presented to Stanford Hospital with 1 day of fever and altered mental status after a week of diffuse joint pains, headache, abdominal pain, and rash.[1] Initial testing for HIV antibody/antigen, IgM for dengue virus, West Nile virus, measles and rubella, syphilis immunoassay, and CSF PCRs for enterovirus, herpes simplex virus, Epstein-Barr virus, varicella-zoster virus, and cytomegalovirus were negative. These were followed by nucleic acid amplification tests for dengue virus, *Plasmodium* species, Zika virus, and *Leptospira* species, which were also negative. Next, serum and plasma specimens were tested for CHIKV, yellow fever virus, dengue virus, and Rift Valley fever virus using a multiplex, real-time reverse transcriptase PCR, which detected CHIKV RNA. On the second hospital day, the patient defervesced and improved with supportive care, including antiepileptic drugs and IVIG. After his discharge, anti-CHIKV IgM was detected in serum from hospital day 2 by the Division of Vector-Borne Infectious Diseases at the CDC. ■

REFERENCE

1. Nelson J, et al. Encephalitis caused by chikungunya virus in a traveler from the Kingdom of Tonga. *J Clin Microbiol* 2014;52: 3459-3461.

ABSTRACT & COMMENTARY

Antibiotic Therapy for Pediatric Parapneumonic Empyema

By Hal B. Jenson, MD, FAAP

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

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

SYNOPSIS: In a retrospective review of 391 children with parapneumonic empyema, the safety and effectiveness of oral antibiotic therapy was comparable to outpatient parenteral antibiotic therapy for antibiotic management following hospitalization.

SOURCE: Stockmann C, Ampofo K, Pavia AT, et al. Comparative effectiveness of oral versus outpatient parenteral antibiotic therapy for empyema. *Hospital Pediatrics* 2015;5:605-612.

A retrospective review was conducted at Primary Children's Hospital of patients younger than 18 years of age hospitalized from 2005 to 2014 with a diagnosis of pediatric parapneumonic empyema and who were discharged with either oral therapy or outpatient parenteral (intravenous) antibiotic therapy (OPAT). The primary outcome was any complication, including both pneumonia-related complications (e.g., any unplanned hospital readmission or emergency department/urgent care visits within 30 days of discharge from the index hospitalization where the primary reason was related to pneumonia) and treatment-related complications (e.g., adverse drug effects or catheter-related complications).

A total of 391 children were hospitalized with parapneumonic empyema, of which 337 children (86%) received OPAT. The median age was 3.8 years (IQR 2.2–7.5 years) and the median length of stay during the initial hospitalization was 8.8 days (IQR 6.9–11.3 days). The most common etiology in the cohort was *Streptococcus pneumoniae*.

Antibiotics commonly used for OPAT were ceftriaxone or cefotaxime (299 children, 89%) and clindamycin (23 children, 7%). Antibiotics commonly used for oral therapy included amoxicillin alone (27 children, 50%), clindamycin (13 children, 24%), amoxicillin/clavulanate (7 children, 13%), and levofloxacin (4 children, 7%). Children discharged with oral antibiotics were more likely to be admitted to the ICU (57% vs 32%, $P < 0.001$) and have longer length of stay (median 10.0 days vs 8.7 days, $P = 0.01$). Other demographic and baseline characteristics were comparable between the two treatment groups.

A total of 35 children (9%) experienced a complication, including 30 children (8.9%) who received OPAT, and five children (9.3%) who received oral therapy. The annual proportion of patients who experienced a complication did not change over time ($P = 0.53$). Two patients (0.6%) treated with OPAT had treatment failure. Catheter-related complications occurred in 5% of patients who received OPAT. After adjusting using propensity score weighting, the frequency of complications was similar between oral therapy and intravenous therapy (adjusted odds ratio 0.97; 95% confidence interval, 0.23–4.65).

[After adjusting using propensity score weighting, the frequency of complications was similar between oral therapy and intravenous therapy ...]

■ COMMENTARY

Parapneumonic empyema is an uncommon though serious complication of pneumonia in children and young adults, usually requiring prolonged antibiotic therapy for 2–4 weeks after hospitalization. Evidence suggests that the incidence of parapneumonic empyema in children is increasing nationally over the last decade. Partly because of the lack of controlled clinical trials, there is considerable practice variability in the management of these patients.

[Partly because of a lack of controlled clinical trials, there is considerable practice variability in the management of these patients.]

This is the first study comparing outcomes between oral and intravenous therapy following hospitalization for parapneumonic empyema in children. Oral therapy has been successfully used for prolonged therapy of children with bone and joint infections. In general, children tolerate well the high doses of antibiotics that are most often used in these circumstances — amoxicillin, amoxicillin/clavulanate, and clindamycin. This study shows that the frequency of complications following hospital discharge for children with parapneumonic effusion was similar for oral therapy and intravenous therapy.

Oral antibiotics appear to be safe and effective for children with parapneumonic effusion who will complete antibiotic therapy in an outpatient setting. This finding is consistent with recent guidelines from the Infectious Diseases Society of America and the Pediatric Infectious Diseases Society, both of which recommend oral therapy instead of OPAT for completing therapy for parapneumonic empyema. ■

ABSTRACT & COMMENTARY

Malaria: Getting Better, but Still a Long Way To Go

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: While significant progress has been made in the control of malaria, the number of cases remains huge — an estimated 198 million cases and 584,000 deaths in 2013.

SOURCE: World Health Organization. World Malaria Report 2014. Available at: www.who.int/malaria/publications/world_malaria_report_2014/en/.

Although extraordinary efforts have led to decreases in cases of malaria, the number of cases remains very high. It is estimated that 3.3 billion people live in areas that put them at risk of malaria, and that the risk is high (defined as having an incidence of > 1 per 1000 population annually) for 1.2 billion of these. An estimated 198 million cases occurred in 2013, resulting in approximately 584,000 deaths. The World Health Organization (WHO) Africa region accounted for 90% of the deaths; children 5 years of age accounted for 78% of all deaths.

PREVENTION

Vector control activities have significantly increased so that by 2013, 49% of at-risk populations in sub-Saharan Africa had access to insecticide-treated mosquito nets in their household, an increase from only 3% in 2004. WHO estimated that, by the end of 2014, the number of such nets delivered to countries in the region since 2012 would total 427 million. On the other hand, the proportion of at-risk populations who were protected by the use of indoor residual spraying decreased in sub-Saharan Africa from 11% in 2010 to 7% in 2013. Globally, only 4% were protected. Unfortunately, vector resistance to insecticides is increasingly widespread.

[Thirty-five countries have adopted intermittent preventive treatment in pregnancy and, in 2013 in those countries, 57% of pregnant women received at least one dose.]

Thirty-five countries have adopted intermittent preventive treatment in pregnancy and, in 2013 in those countries, 57% of pregnant women received at least one dose. However, only 17% received the recommended greater than three doses in the nine countries reporting this information. WHO has recommended to 13 countries that they institute seasonal malaria chemoprophylaxis for infants and children younger than 5 years of age, but only six had done so for children and only one was administering prophylaxis to infants by 2013.

DIAGNOSIS, TREATMENT, RESISTANCE

More than 160 million rapid diagnostic tests were distributed by national malaria control programs in 2013 — an increase from less than 200,000 in 2005. The WHO Africa Region accounted for 83% of these.

[Artemisinin-based combination therapy was the national policy by the end of 2013 in 79 of 88 countries in which *Plasmodium falciparum* infection is endemic.]

Artemisinin-based combination therapy (ACT) was national policy by the end of 2013 in 79 of the 88 countries in which *Plasmodium falciparum* infection is endemic. In that year, enough ACT was available in public heath facilities to treat more than 70% of malaria cases. Nonetheless, WHO estimates that only 9-26% of children with malaria received ACT. Resistance of *P. falciparum* to artemesinin is present

in Cambodia, Laos, Myanmar, Thailand, and Vietnam. Furthermore, in areas along the border between Cambodia and Thailand, *P. falciparum* is now resistant to most available antimalarials. The emergence of this resistance is likely the result of artemisinin monotherapy, which is contraindicated. Fortunately, at the urging of WHO, there has been a rapid decease in the number of countries that allow marketing of oral artemisinin-based monotherapies, so that this was allowed in only 8 countries as of November 2014. India, where 24 pharmaceutical companies still market oral artemisinin-based monotherapies, is an important outlier.

PROGRESS

A total of 64 countries are on track to meet the Millennium Development Goal target of reversing the incidence of malaria, and 55 of these are on track to meet Roll Back Malaria and World Health Assembly targets of reducing malaria case incidence rates by 75% by 2015. However, these countries are not the ones with the largest at-risk populations — these 55 countries accounted for only 13 million (6%) of the total estimated cases of 227 million in 2000. Nonetheless, the mean malaria prevalence in children 2–10 years of age decreased by almost one-half from 26% to 14% in 2000 and 2013, respectively. The total number of infected individuals in Central Africa decreased from 173 million to 128 million during this time period.

Estimates of global malaria indicate that between 2000 and 2013, despite a 25% increase in at-risk population (43% in the WHO Africa region), the number of cases decreased from 227 million to 198 million, representing a 30% decrease in cases per 1000 population (34% in the WHO Africa region). There was a concomitant decrease in mortality such that at the current rate, it is projected that a global 55% decrease relative to 2000 will be reached in 2015, with a 62% decrease in the WHO Africa region. Overall, an estimated 4.3 million deaths were averted between 2000 and 2013, and 92% of these were in children younger than 5 years of age in sub-Saharan Africa.

[A total of 64 countries are on track to meet the Millennium Development Goal target of reversing the incidence of malaria ...]

This WHO report is simultaneously encouraging and disturbing. While important progress has been made, the path ahead is long and arduous, made all the more so by inadequate resources. Thus, although there was a three-fold increase in funding for malaria control between 2005 and 2013, there remains significant underfunding. ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

A Deadly Funeral

SOURCE: ProMED-mail post; Contaminated beer, fatal – Mozambique(03): (TETE) *Burkholderia gladioli* pathovar cocovenenans toxin. Nov. 9, 2015; www.promedmail.org.

We're so lucky in this country — our water is clean, the food supply is generally reliable, and the beer won't kill you. That was not the case in Mozambique last month. A home-made beer drunk by hundreds of people attending a funeral in Chitima, Mozambique, affected 232 people, causing 75 deaths. Many went to the hospital with diarrhea and severe muscle cramps, while some were simply found later that day dead in their homes. The woman who brewed the beer and her family were among the dead.

The culprit was a home-made beer, made from contaminated cornmeal flour. At first, it was thought the beer had been intentionally poisoned by crocodile bile. However, tests conducted in the United States identified Flavitoxin A, which is produced by lethal strains of *Burkholderia gladioli*. *B. gladioli* is a plant pathogen that rarely causes opportunistic infection in humans (e.g., cystic fibrosis patients), but some strains produce a potentially lethal toxin called bongkrekic acid, which, by spectrographic analysis, has been shown to be identical to Flavitoxin A. While the nomenclature for these organisms has been shifting around for years, microbiologists like to distinguish between non-toxin and toxin-producing strains,

the latter of which have been renamed *B. gladioli* pathovar cocovenenans.

Bongkrekic acid took its name from the Indonesian practice of fermenting plant material, such as soybeans and coconut. Tempe bongkrek is made by fermenting coconut cake with *Rhizopus oligosporus*, which is naturally found in coconut. If it's not adequately fermented, bacterial overgrowth can occur — similar to beer. A friend used to say that brewing beer was much harder than making wine, because of the risk of bacterial contamination. While we generally think of beer as produced from fermented barley (flavored with yeast and hops), people in developing countries make use of other starches, such as rice, corn, millet, sorghum, and cassava. Heat processing does not destroy the toxin. Food-related outbreaks of Flavitoxin A poisoning were reported in 2007 from fermented soybean cakes in Indonesia, and contaminated corn flour sacks in rural China.

Increase in Congenital Syphilis

SOURCE: ProMED-mail post Syphilis – USA: Pregnant women, congenital, rising incidence. Nov. 14, 2015. www.promedmail.org.

Syphilis is popping up everywhere these days. I've never seen so many cases. ProMED-mail has been doing a nice job of summarizing the rising incidence of syphilis in a number of states, including California, Texas, Florida, New York, Ohio, and Indiana — even in rural areas. What (re)emerged in the gay community, largely affecting men who have sex with men (MSM), has predictably begun to move into the heterosexual community. While most of my recent patients with syphilis are MSM, a recent patient was a 19-year-old woman (astounded to learn she had syphilis). I include syphilis screening on anyone being screened for STDs, as well as those with an unexplained sore throat, tonsillitis, cervical or inguinal lymphadenopathy, or any kind of unexplained rash — regardless of their sexual history.

The national congenital syphilis (CS) rate reached an all-time low in 2010-2012, with 8.4 cases per 100,000 live births. Since then, the national rate has increased 38%, closely tracking with the national increase in syphilis cases in women. A few years ago, there were at most one or two annual cases of CS in the San Francisco Bay Area. In 2012, CS cases in California jumped to 35, and, in 2014, rose to 99 cases. So many cases have occurred in Fresno, CA, that the county public health officer has required all pregnant women to be screened three times during their pregnancy.

[The national congenital syphilis rate reached an all-time low in 2010-2012. ... Since then, the national rate has increase 38%, closely tracking with the national increase in syphilis cases in women.]

Many of these cases are occurring in immigrant and poor women, with delays in seeking prenatal care. While all pregnant women in California are eligible for MediCal, many don't know how to access the care, and prenatal care and STD screening are often delayed, after permanent fetal damage has already occurred. Although syphilis in adults is readily treatable with penicillin, congenital syphilis is a severe deformative disease, with a high frequency of blindness and deafness; approximately 40% of affected infants die. Early detection in pregnancy is essential. Clinicians are being urged to screen for syphilis with the first prenatal visit. In addition to weekly reviews of syphilis cases, and more aggressive contact tracing, public health authorities are being urged to prioritize female contacts of reproductive age. (Although this comes after many local health departments and STD clinics were gutted in 2008-2012; even our own county STD clinic and lab was closed for a few years. Does anyone see a correlation?)

I would recommend including RPR screening with any STD screening. Maybe we should return to the days of mandatory syphilis screening when applying for a marriage license, and RPRs should be included with hepatitis and HIV as part of "universal" screening.

That Is Not Strep Throat!

SOURCE: Smith JRM, et al. Tonsillar syphilis: An unusual site of infection detected by *Treponemal pallidum* PCR. *J Clin Microbiol* 2015;53:3089-3081.

Syphilis has been called the "Great Imitator" for a reason. Pick a symptom or a physical finding, and syphilis could be the cause. While older physicians (yikes, me) have had their share of exposure to this fascinating infection, many younger physicians have never seen a case.

These authors describe a young

man with a steady male partner who had 2 weeks of sore throat and otalgia. He denied any outside sexual contact. His exam was remarkable for a large, shiny red tonsil and tender tonsillar adenopathy. Screening for group A strep was negative. He returned a week later, now anxious that maybe he had forgotten about an episode of oral sex with a stranger at a party several weeks earlier. His throat was still red, the tonsil now covered by a thin white exudate, and his adenopathy was still tender. Throat and urine NAAT studies for GC/chlamydia were performed, along with blood tests for an RPR, and a swab for *T. pallidum* DNA was obtained and sent to the National Microbiology Laboratory in Winnepeg, Canada. The RPR was positive at 1:16, and the PCR test (using three different gene targets) was positive. Sequencing revealed the A2058G mutation associated with macrolide resistance. Remarkably, by the time the studies came back and he was seen back in clinic for treatment, he was asymptomatic and his exam was unremarkable.

Put syphilis on your list for causes of exudative tonsillitis (I would have also included HSV culture). With the reported increase in oral sex, apparently favored by teens and young adults, be prepared to spot those cases of oropharyngeal and tonsillar syphilis. Primary syphilis may present in the oropharynx, with tonsillar erythema and exudative tonsillitis and often boggy, tender neck nodes. Fever may or may not be present. Children with syphilis (usually from kissing or pre-masticated food) also frequently present with oral findings and bulky tender nodes.

Another lesson here: Never believe a patient's sexual history (at least not entirely); people "forget" their risk factors. If it's appropriate to perform an STD test, don't be dissuaded by a patient's apparent lack of risk factors. And it's reasonable to do RPR screening of high-risk patients on a regular basis.

Increase in Ocular Syphilis

MMWR. Notes from the field: A cluster of ocular syphilis cases — Seattle, Washington, and San Francisco, California, 2014-2015. Oct. 16, 2015;64:1150-1151.

In 2014-2015, ocular syphilis was reported in four people from King County, WA, and in eight people from San Francisco County, CA. The first four cases, all of which occurred during a two-month period in late 2014, prompted a Clinical Advisory to medical providers and West Coast health departments. The median age of these four cases was 39 years (range, 29–52 years), three were HIV-positive, and their RPRs ranged from 1:252–1:4096. Among the three HIV-positive cases, the median CD4 count was 111 cells/mm^3, and the median HIV RNA viral load was 34,740 copies/mL. All four patients presented with blurry vision, bright flashing lights and visual loss, and all four were diagnosed with uveitis. Three of the patients were believed to have early latent disease, and one had late latent disease, at least based on their histories.

Cerebrospinal fluid analysis was performed in three patients, and CSF FTA was positive in two. Despite treatment, two patients became legally blind during the next 5 months, and one patient had a permanent blind spot. The fourth patient was lost to follow-up. As the result of the advisory, San Francisco County identified eight cases of ocular syphilis, occurring from December 2014 through March 2015. The median age of these cases was 52 years (35-58 years), and seven of the cases were HIV-positive, including one female sex worker. The median CD4 count was 291 cells/mm^3, and the median HIV-RNA was 84,500 copies/mL. Ocular presentations included uveitis, optic neuritis, and one case of retinal detachment. Four of the cases had CSF analysis, three of which were positive for neurosyphilis. Following treatment, one patient had permanent visual loss in one eye.

RPRs ranged from 1:256–1:8192; two of the patients initially had negative RPRs because of the prozone affect.

Ocular syphilis — another great imitator — is an important cause of uveitis and optic neuritis, and is frequently associated with neurosyphilis. While it generally occurs during early syphilis infection, it is frequently associated with invasion of the central nervous system. These patients deserve cerebrospinal fluid analysis, especially if they are HIV-positive. Ocular syphilis should be managed just like neurosyphilis, regardless of the CSF results. ■

[Ocular syphilis — another great imitator — is an important cause of uveitis and optic neuritis, and is frequently associated with neurosyphilis.]

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 at right or log onto AHCMedia.com and click on My Account. *First-time users must register on the site.*
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 test, a credit letter will be emailed to you instantly.
5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

CME QUESTIONS

1. **Based on new data about azithromycin in children with recurrent wheezing, which of the following is true?**

   a. Children with viral upper respiratory infections should be treated with 5 mg/kg azithromycin daily for 5 days.

   b. Children with viral upper respiratory infections should be treated with 12 mg/kg azithromycin daily for 5 days.

   c. Children with acute asthma exacerbations should be treated with 12 mg/kg azithromycin daily for 5 days.

   d. There should be no widespread change in the management of either upper respiratory infections or asthma.

2. **Which of the following is correct with regard to the percentage change in incidence of catheter-associated urinary tract infections (CAUTI) in the United States between 2010 and 2014?**

   a. It increased by 7.2%.

   b. It remained unchanged.

   c. It decreased by 2.7%.

   d. It decreased by 16.1%.

3. **Which of the following is correct?**

   a. There has been no evidence of resistance *Plasmodium falciparum* to artemisinin antimalarials.

   b. Resistance of *Plasmodium falciparum* to insecticides has emerged as a significant problem.

   c. Despite all efforts, mortality from malaria in Africa continues to rise.

   d. As a result of their widespread free distribution, almost all children with malaria in sub-Saharan Africa receive artemisinin-based combination therapy.

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.