AHC Media

Vol. 36, Issue 5, February 2017
AHCMedia.com

Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Zika Virus and Risk of Congenital Abnormalities

By Hal B. Jenson, MD, FAAP

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: Two recent studies clarify the substantial risk of congenital abnormalities following maternal Zika virus infection. The risk is highest in the first trimester of pregnancy, and appears similar following symptomatic and asymptomatic maternal infection.

SOURCES: Honein MA, Dawson AL, Petersen EE, et al. Birth defects among fetuses and infants of U.S. women with evidence of possible Zika virus infection during pregnancy. *JAMA* 2017;317:59-68.

Brasil P, Pereira JP Jr, Moreira ME, et al. Zika virus infection in pregnant women in Rio de Janeiro. *N Engl J Med* 2016;375:2321-2334.

The United States Zika Pregnancy Registry, established by the Centers for Disease Control and Prevention (CDC), monitors pregnancy and fetal or infant outcomes among pregnant women or their offspring with laboratory evidence of Zika virus infection. Since February 2016, the CDC has recommended Zika virus testing for all pregnant women following possible exposure to Zika virus through travel, sexual contact, or mosquito transmission, regardless of symptoms.

Laboratory evidence of Zika virus infection includes a positive test result by RT-PCR or other nucleic acid amplification test, maternal IgM antibody, seroconversion, or immunohistochemical staining of tissues such as placenta.

A total of 442 pregnant women (median age, 28 years; range, 15-50 years) with possible Zika virus infection in the registry had completed pregnancies, with 271 (61%) asymptomatic mothers, 167 (38%)

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, Updates author Carol A. Kemper, MD, FACP, peer reviewer Kiran Gajurel, MD, senior accreditations officer Lee Landenberger, executive editor Shelly Morrow Mark, and assistant editor Jonathan Springston report no financial relationships 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
Customer.Service@AHCMedia.com
AHCMedia.com

Editorial Email:
mmark@reliaslearning.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

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.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 36 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

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.

symptomatic mothers, and 4 (1%) with insufficient information. All pregnant women had travel-associated Zika virus infections, with four cases resulting from sexual transmission from a traveler to a non-traveler.

There were 26 offspring (6%; 95% confidence interval [CI], 4-8%) with birth defects, including 21 infants with birth defects among 395 live births, and five fetuses with birth defects among 47 pregnancy losses. Twenty-two (85%) of these fetuses or infants had microcephaly (4), brain abnormalities only (4) (e.g., intracranial calcifications, corpus callosum abnormalities, abnormal cortical formation, cerebral atrophy, ventriculomegaly, hydrocephalus, and cerebellar abnormalities), or both (14). Infants with microcephaly represented 4% (18/442) of the completed pregnancies.

The proportion of infants and fetuses with birth defects was 6% for both symptomatic women (95% CI, 3-11%) and asymptomatic women (95% CI, 4-9%). No birth defects were reported among pregnancies with maternal exposure or symptoms during only the second or third trimesters.

In Rio de Janeiro from September 2015 through May 2016, a total of 345 pregnant women who tested positive for Zika virus by RT-PCR and had a rash within the previous five days were enrolled in a prospective cohort to follow pregnancy outcomes. The timing of Zika virus infection ranged from 6-39 weeks of gestation, and the predominant maternal symptoms included a descending macular/maculopapular rash, pruritus (90%), arthralgia (62%), conjunctival injection (50%), headache, and short-term, low-grade fever (27%). Zika-negative women were more likely to have nausea, vomiting, anorexia, fatigue or malaise, myalgia, respiratory symptoms, and fever than Zika-infected women, who typically had a pruritic maculopapular rash and conjunctival injection.

There were 125 completed evaluable pregnancies among Zika-infected women, and 61 evaluable completed pregnancies among Zika-negative women. Fetal death rates were 7% in both groups.

Small size for gestational age was seen in 9% of Zika-exposed newborns and in 5.3% of offspring of uninfected mothers. Central nervous system abnormalities on physical examination, imaging, or both were observed in 49 newborns (42%) among Zika-infected mothers, and in three newborns (5.3%) among uninfected mothers. Microcephaly was seen in four (3.4%) of the Zika-exposed newborns, and none of the offspring of uninfected mothers. A total of 31 of the 49 infants (63%) among Zika-infected mothers had grossly abnormal neurologic examinations, including hypertonicity, clonus, hyperreflexia, spasticity, contractures, and seizures.

[The significant impact of Zika virus as a cause of central nervous system congenital abnormalities is becoming more clear, and is substantial.]

Adverse outcomes occurred among Zika-infected mothers throughout pregnancy, affecting 55% (11 of 20) infected in the first trimester, 52% (37 of 71) in the second trimester, and 29% (10 of 34) in the third trimester.

One of the first-trimester miscarriages occurred in a Zika-infected mother who was also coinfected with chikungunya virus. Three of the seven adverse outcomes among the Zika-uninfected mothers were among mothers who were diagnosed with chikungunya virus.

■ COMMENTARY

The significant impact of Zika virus as a cause of central nervous system congenital abnormalities is becoming more clear, and is substantial. Microcephaly is an extreme finding, occurring in 3-4% of pregnancies following maternal infection, with central nervous system imaging and clinical abnormalities also occurring. These studies likely underestimate the complete risk of abnormalities with Zika virus infection. Entry criteria for both

studies included having a positive test for Zika virus infection, which likely was performed because of the finding of maternal symptoms, and the Brazilian study also specifically included a maternal rash within five days. The U.S. study showed that the risk of congenital abnormalities was similar (6%) among both symptomatic and asymptomatic mothers. Outcomes in both studies were the immediate and severe sequelae in fetuses and newborns, and not the subtler potential long-term effects, such as learning deficits, which may not be seen until late childhood.

The Brazilian study found that the risk of congenital abnormalities was present throughout pregnancy, though with higher risk in early pregnancy. Microcephaly was found in four infants of mothers infected at 8, 12, 30, and 38 weeks of gestation, although disproportionate microcephaly was seen only in infants of mothers infected in the first trimester of pregnancy. These outcomes are perhaps analogous to other congenital infections, such as rubella, where the risk is significantly higher during the first 20 weeks of gestation and minimal later in pregnancy.

The best steps currently to manage Zika virus infection are preventive: counseling pregnant women to wear long-sleeves and use repellants to minimize exposure to mosquitos, including voluntarily limiting travel to Zika-endemic areas, and delaying conception after potential Zika virus exposure, for eight weeks for women and six months for men, and using barrier protection with sexual partners who potentially have been exposed. ■

ABSTRACT & COMMENTARY

Intrauterine Zika Virus Infection — Not Just Microcephaly at Birth

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Manifestations of intrauterine Zika infection may not be clinically apparent at birth, warranting the use of early neuroimaging and careful follow-up.

SOURCE: van der Linden V, Pessoa A, Dobyns W, et al. Description of 13 infants born during October 2015–January 2016 with congenital Zika virus infection without microcephaly at birth — Brazil. *MMWR Morb Mortal Wkly Rep* 2016;65:1343-1348.

Van der Linden and colleagues assessed 13 infants (nine male) with documented intrauterine Zika virus infection but who did not appear to have microcephaly at birth. All had birth weights appropriate for gestational age; two of the 13 were preterm, having been born at 35 and 36 weeks gestation. Six of the mothers reported having had a skin rash that appeared between the second and fifth months of pregnancy. Six infants had craniofacial disproportion, three had redundant scalp skin, and three had hip dysplasia (one of whom with arthrogryposis had bilaterally dislocated hips). Three had chorioretinal abnormalities, while all 11 tested had intact hearing. Subsequent evaluation found that 10 of the infants had dysphagia and seven had epilepsy, while 12 had pyramidal and extrapyramidal findings with dystonic movements.

Despite having normal head circumferences at birth, neuroimaging demonstrated brain abnormalities in all 13 infants. Findings included diminished brain volume, ventriculomegaly, and malformations of the cortex. Follow-up demonstrated deceleration of head growth in all 13 infants, 11 of whom developed frank microcephaly.

■ COMMENTARY

A recent study demonstrated that Zika virus preferentially infects neural stem cells (radial glial cells) as a consequence of their high expression of a surface receptor, AXL, which was expressed throughout the cortex and retina during the middle period of intrauterine neurogenesis.[1] The findings reported by van der Linden et al demonstrate that the effects of this neural stem cell infection progress post-natally.

This analysis demonstrates that the presence of microcephaly at birth is not an essential hallmark of congenital Zika syndrome. Thus, despite the presence of a normal head circumference at birth, infants may have brain and other abnormalities

associated with congenital Zika syndrome — and they subsequently may develop microcephaly. As stated by the authors, "These findings demonstrate the importance of early neuroimaging for infants exposed to Zika virus prenatally and the need for comprehensive medical and developmental follow-up." The finding by Retallack and colleagues that azithromycin blocks cellular uptake of Zika raises interesting possibilities.[1] ■

REFERENCE

1. Retallack H, Di Lullo E, Arias C, et al. Zika virus cell tropism in the developing human brain and inhibition by azithromycin. *Proc Natl Acad Sci USA* 2016;113:14408-14413.

ABSTRACT & COMMENTARY

A Short Course of Antibiotics for Acute Otitis Media in Children Leads to Worse Outcomes Compared to Standard Course Therapy

By Richard R. Watkins, MD, MS, FACP, FIDSA

Associate Professor of Internal Medicine, Northeast Ohio Medical University; Division of Infectious Diseases, Cleveland Clinic Akron General Medical Center, Akron, OH

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

SYNOPSIS: A randomized, placebo-controlled clinical trial determined that in children 6-23 months of age with acute otitis media, five days of amoxicillin-clavulanate resulted in more clinical failure compared to a 10-day course of therapy.

SOURCE: Hoberman A, Paradise JL, Rockette HE, et al. Shortened antimicrobial treatment for acute otitis media in young children. *N Engl J Med* 2016;375:2446-2456.

Results from clinical trials have shown antibiotics to be beneficial in treating acute otitis media (AOM) in children. However, controversy exists about the optimal duration of therapy because of methodological flaws in previous studies. Therefore, Hoberman et al sought to clarify whether outcomes would be similar between a standard 10-day course of antibiotics and five days of treatment.

The study enrolled children aged 6-23 months diagnosed with AOM based on three criteria: onset of symptoms in the preceding 48 hours, the presence of a middle-ear suffusion, and moderate or marked bulging of the tympanic membrane or slight bulging accompanied by otalgia or marked tympanic membrane erythema. All had received at least two doses of pneumococcal conjugate vaccine. At each research site, children were randomized to receive either a 10-day course of amoxicillin-clavulanate or a five-day course followed by five days of placebo. Children were followed for clinical failure, which was defined as worsening symptoms or worsening otologic signs of infection, or if they did not have complete resolution of signs and symptoms by the end of treatment. The primary outcome measured was the percentage of children who had clinical failure after treatment of the index infection. Secondary outcomes included symptom burden from day 6 to day 14, rates of recurrence of AOM, total days of antibiotics during the respiratory-infection season, rates of nasopharyngeal colonization, use of other healthcare services, rates of missed work by parents, and parental satisfaction with the treatment.

Of 1,569 children who were screened, 257 were randomized to the 10-day group and 258 to the five-day group. Clinical failure was higher in children treated for five days compared to 10 days (77 of 229 [34%] vs. 39 of 238 [16%], 95% confidence interval [CI], 9-25). Subgroup analysis consistently favored the 10-day group. When the two groups were combined, clinical failure rates were higher among children with exposure to ≥ three children for ≥ 10 hours per week vs. those with less exposure (P = 0.02) and in those with bilateral AOM vs. unilateral (P < 0.001). Also, the clinical failure rate was higher when there were more characteristics considered to be unfavorable based on clinical experience and/or previously published findings. The mean symptom scores from day 6 to day 14 were 1.61 in the five-day group and 1.34 in the 10-day group (P = 0.07), and at the day 12-14 assessment were 1.89 vs. 1.20,

respectively (P = 0.001). Furthermore, the percentage of children whose symptom scores decreased > 50% from baseline was worse in the five-day group (181 of 227 children [80%] vs. 211 of 233 [91%], P = 0.003). Among children with recurrent AOM, the clinical failure rate was consistently higher in the five-day group (28%) than in the 10-day group (19%), and the criterion for non-inferiority of the five-day treatment course was not met. After the course of treatment, the level of nasopharyngeal colonization with penicillin-susceptible *Streptococcus pneumoniae* decreased in both groups. The mean number of days on which children received antibiotics during the respiratory-infection season was 21 in the 10-day group and 15 in the five-day group (P < 0.001), mainly due to the index infection. Adverse events were similar between both groups (primarily diarrhea and diaper rash) and there were no significant differences in the rates of use of other healthcare services, missed work by parents, or levels of parental satisfaction with the treatment.

■ COMMENTARY

AOM is the most common condition for which children are prescribed antibiotics, often for a five- to 10-day course. Shorter courses of antibiotics theoretically should lead to less disruption in the gut microbiome, fewer adverse events, less potential to spread antimicrobial resistance, and reduced costs. Indeed, the prevailing mantra about antibiotics is that "shorter is better" and that physicians should allow patients to stop antibiotics as early as possible after resolution of symptoms of infection.[1] However, concerns about the downsides of antibiotics must be balanced against the potential of undertreating an acute infection and the risk of a recurrence. The study by Hoberman et al challenges the notion that a shorter course of antibiotics is always beneficial compared to the standard duration, at least for AOM. It reminds us about being careful to avoid a "one-size-fits-all" approach when deciding about how long to prescribe antibiotics for our patients.

Despite the clear results that showed 10 days of amoxicillin-clavulanate led to less clinical failure than five days without an increase in adverse events, the study had some limitations worth mentioning. First, it was not designed to assess outcomes in older children or those with risk factors for AOM, such as a cleft palate. Second, as an accompanying editorialist noted, studies on AOM are inherently difficult due to viral coinfections, antibiotic resistance, varying age of subjects, and a high rate of spontaneous resolution.[2] How these factors affected the results of the present study is uncertain. Nonetheless, in children younger than 2 years of age with AOM, 10 days of amoxicillin-clavulanate should remain the standard of care. Researchers should be encouraged to conduct further pragmatic studies on the duration of antibiotics for other infections. ■

REFERENCES

1. Spellberg B. The new antibiotic mantra — "shorter is better." *JAMA Intern Med* 2016;176:1254-1255.
2. Kenna MA. Acute otitis media — The long and the short of it. *N Engl J Med* 2016;375:2492-2493.

ABSTRACT & COMMENTARY

Decreasing Malaria Mortality in Africa

By Philip R. Fischer, MD, DTM&H

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: Malaria mortality in Africa has decreased by approximately 57% during the past 15 years, but some areas still have low level use of bed nets, low coverage with antimalarial medication, and higher death rates due to malaria. At the same time, anti-malarial measures are still important for individuals traveling to endemic areas.

SOURCE: Gething PW, Casey DC, Weiss DJ, et al. Mapping *Plasmodium falciparum* mortality in Africa between 1990 and 2015. *N Engl J Med* 2016;375:2435-2445.

Efforts to quantitate the morbidity and mortality of malaria have been hampered by limited reporting and by geographical variations in the incidence and severity of malaria. Gething and colleagues provided careful spatiotemporal modeling to develop accurate quantitative data about the risk of death due to malaria across age spans and geography in Africa. They used material from the Malaria Atlas Project and the Global Burden of Disease Study.

The number of deaths due to malaria increased from 1990 until 2000. Then, from 2000 to 2015,

the rate of deaths due to malaria decreased 57% from 12.5 to 5.4 per 10,000 people. As populations were increasing, this led to a 37% decrease in the total number of malaria deaths each year — from 1,007,000 in 2000 to 631,000 in 2015. In areas where malaria was more common, more than 80% of malaria deaths were in preschool-aged children, while older children and adults were at greater relative risk of death in areas where malaria was less common.

A few specific countries were responsible for high death rates due to malaria, and these were countries where fewer than half of households used insecticide-treated bed nets and where antimalarial medications were less available. These countries were largely in the western parts of sub-Saharan Africa and included Nigeria, Angola, Cameroon, Congo, Guinea, Equatorial Guinea, and parts of Central African Republic.

■ COMMENTARY

Malaria continues to be a major problem for children in Africa, accounting for nearly as many deaths each year as pneumonia. Fortunately, as shown by the modeling techniques of Gething and colleagues, the death rate due to malaria has dropped to less than half of what it was 15 years ago. This is encouraging, especially in view of the extensive multinational efforts to combat malaria that are estimated to have cost $2.3 billion in 2015.

Even for those of us not living in Africa, though, our care of international travelers keeps malaria relevant. Since the epidemiology of malaria is evolving in many areas of the world and since other illnesses also are more common in malaria-endemic areas, travelers can be directed to pre-travel consultation at specialized travel clinics. Geographic registries of travel clinics are available from the American Society of Tropical Medicine and Hygiene (http://www.astmh.org/education-resources/clinical-consultants-directory) and the International Society of Travel Medicine (http://www.istm.org/AF_CstmClinicDirectory.asp). Healthcare professionals who choose to care for travelers can get updated information about malaria prevention in specific regions of the world from the Centers for Disease Control and Prevention (https://www.cdc.gov/malaria/travelers/index.html) or from commercial services.

Malaria chemoprophylaxis is indicated for travelers to malaria-endemic areas.[1] Chloroquine is effective against malaria in Central America and the Caribbean, but is often unavailable in the United States. Worldwide, mefloquine may be given weekly starting one to two weeks prior to travel and continuing weekly through the trip and for four subsequent weeks; altered sleep and nausea can occur in approximately 18% of recipients of mefloquine prophylaxis. Atovaquone-proguanil is effective in daily dosing beginning one day before arrival in a malarial area and continuing through seven days after leaving the malarial area. Both mefloquine and atovaquone-proguanil may be given to children using weight-adjusted dosing. Doxycycline is effective and is generally safe in children of at least 8 years of age; it is given daily beginning one day prior to entry into a malarial area and continuing through 28 days after leaving the area of risk.

[Malaria continues to be a major problem for children in Africa, accounting for nearly as many deaths each year as pneumonia.]

Effective malaria prevention, of course, depends on more than just medication. Also, *Aedes* mosquitoes can transmit dengue, chikungunya, Zika, and yellow fever in some of the same areas where *Anopheles* mosquitoes transmit malaria. Mosquito bite prevention is effective with application on exposed skin of insect repellants containing di-ethyl-meta-toluamide (DEET) or picaridin with 20-30% preparations adequately repelling mosquitoes for approximately six hours. Clothes can be sprayed or impregnated with permethrin to provide additional protection. While *Aedes* often bite during the daytime, *Anopheles* bite more frequently from dusk to dawn; sleeping under bed nets or in air-conditioned rooms with closed/screened windows reduces the risk of nighttime bites.

Progress continues with malaria vaccine development. Lives can be saved with pediatric vaccination, but efficacy is less than 50%.[2] Follow-up vaccine studies suggest that malaria immunity wanes over time after vaccination.[3,4]

Febrile tourist travelers and immigrants who recently have been in malarial areas can benefit from rapid diagnosis (with blood smears by experienced laboratory technicians or by polymerase chain reaction testing). If test results are positive or clinical suspicion is high pending results, prompt treatment with artemisinin combination therapy (such as artemether-lumefantrine) is effective.

Even as malaria is being rolled back from some

regions of the world and even as diagnostic and therapeutic measures improve, there are increasing concerns about the development of insecticide resistance in mosquitoes and about the possibility that resistance of malaria parasites to the effects of artemisinin derivatives might spread from localized areas of Asia to Africa.[3] As evident by Gething's data, lower rates of malaria death are seen in areas with greater bed net use and more availability of antimalarial medication. Multifaceted interventions still are needed to help those most in need, the children of Africa. ■

REFERENCES

1. Freedman DO, Chen LH, Kozarsky PE. Medical considerations before international travel. *N Engl J Med* 2016;375:247-260.
2. Callaway E, Maxmen A. Malaria vaccine cautiously recommended for use in Africa. *Nature* 2015;526:617-618.
3. Maitland K. Severe malaria in African children — the need for continuing investment. *N Engl J Med* 2016;375:2416-2417.
4. Olotu A, Fegan G, Wambua J, et al. Seven-year efficacy of RTS,S/AS01 malaria vaccine among young African children. *N Engl J Med* 2016;374:2519-2529.

ABSTRACT & COMMENTARY

Ventilator-associated Pneumonia with Minimal Ventilatory Requirements — Discontinuing Antibiotics After Three Days

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Discontinuation of empiric antibiotic therapy given for treatment of presumed ventilator-associated pneumonia can be discontinued safely after three days in patients with minimal ventilator requirements.

SOURCE: Klompas M, Li L, Menchaca JT, Gruber S; CDC Prevention Epicenters Program. Ultra short course antibiotics for patients with suspected ventilator-associated pneumonia but minimal and stable ventilator settings. *Clin Infect Dis* 2016 Dec 29. [Epub ahead of print].

Klompas and colleagues in Boston retrospectively examined the potential usefulness of simple physiological parameters to guide early discontinuation of empiric antibiotics that had been initiated in adults for presumed ventilator-associated pneumonia (VAP). For the purposes of this analysis, the diagnosis of suspected VAP required that there had been a culture of respiratory secretions obtained more than three days after initiation of mechanical ventilation and that a new antibiotic was initiated within two days of the culture. They identified 1,290 patients receiving antibiotics for a diagnosis of VAP whose minimum PEEP was ≤ 5 cm H_2O with FiO_2 ≤ 0.40 for each of at least three days.

Of the 1,290 patients meeting these criteria, 259 had received antibiotics for three days or less, and 1,031 had received them for more than three days. Patients who received three days or less of antibiotics were significantly older, more likely to be in the medical ICU, and to initially have a higher predicted mortality, while those treated for more than three days were more likely to have *Staphylococcus aureus* or *Klebsiella pneumoniae* recovered from their respiratory secretions (endotracheal aspirate or bronchoalveolar lavage).

The two groups had a median duration of antibiotic therapy of two days (IQ range, 1-3 days) and nine days (IQ range, 6-12 days), respectively. No significant outcome differences between the short and longer duration antibiotic groups were identified with regard to time to extubation, ventilator death, or hospital death. This was true with both unadjusted analysis and with propensity matching and also was true with restricting the analysis to patients who had both > 25 neutrophils per low power field on Gram stain of respiratory secretions and positive pathogen cultures. Furthermore, the point estimates for each of these three outcomes was better for patients who received three days or less of antibiotic therapy.

■ COMMENTARY

The diagnosis of VAP is fraught with error, as indicated by a retrospective single-center study that concluded that three-fourths of patients with this diagnosis probably did not truly have VAP. Despite this post-hoc judgement, they received a mean of

almost 10 days of antibiotic therapy.[1]

Nina Singh's small but important study almost two decades ago used the clinical pulmonary infection score (CPIS) to similarly address the issue of unnecessary continuation of antibiotic administraton.[2] In that study, ICU patients with new pulmonary infiltrates and a CPIS ≤ 6, but judged by their clinicians to have pneumonia, were randomized to receive antibiotic therapy as determined by their clinician or to receive ciprofloxacin for three days with discontinuation at that time if their CPIS remained ≤ 6. There was no significant difference in mortality, but the frequency of superinfection or development of antimicrobial resistance was lower in those whose antibiotics were discontinued at three days compared to those with management by their clinicians. The latter group received antibiotics for a mean of 9.8 days. The only possible interpretations of the results of that study are that either the pneumonia was cured with three days of therapy or that they never had pneumonia — interpretations that also could be applied to the study by Klompas et al reviewed here.

Unfortunately, the CPIS score has been found to have many shortcomings and appears to be little used currently. Another approach is the use of procalcitonin measurements to assist the clinician in making decisions regarding antibiotic discontinuation, and evidence clearly indicates that this is an effective and efficient means of achieving this.[3]

While clinical judgement remains important, the very evidence contained in studies such as the one reviewed here clearly indicate that, in practice, such judgement frequently is inaccurate. The recently published IDSA/ATS guideline recommends a treatment course of only seven days for VAP[4] — and this appears to be appropriate for patients who truly have VAP and should be included in clinical pathways. In addition, consideration may be given to incorporating the results of the study by Klompas et al. Thus, patients initiated on empiric antibiotic therapy for VAP but who meet their criteria of minimal ventilator settings for three days may be considered for antibiotic discontinuation. In borderline cases, the use of procalcitonin measurement may assist in this decision. ■

REFERENCES

1. Nussenblatt V, Avdic E, Berenholtz S, et al. Ventilator-associated pneumonia: Overdiagnosis and treatment are common in medical and surgical intensive care units. *Infect Control Hosp Epidemiol* 2014;35: 278-284.
2. Singh N, Rogers P, Atwood CW, et al. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 2000;162(2 Pt 1):505-511.
3. de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: A randomised, controlled, open-label trial. *Lancet Infect Dis* 2016;16:819-827.
4. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016;63:e61-e111.

ABSTRACT & COMMENTARY

Flu in Pregnancy: Increased Inflammation Demonstrated

By Dean L. Winslow, MD, FACP, FIDSA

Professor of Medicine, Division of Hospital Medicine, 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: In pregnant women, monocytes and plasmacytoid dendritic cells (pDCs) exhibit an exaggerated proinflammatory immune response to influenza A virus compared to nonpregnant women.

SOURCE: Le Gars M, Kay AW, Bayless NL, et al. Increased proinflammatory responses of monocytes and plasmacytoid dendritic cells to Influenza A virus infection during pregnancy. *J Infect Dis* 2016;214:1666-1671.

Twenty-one healthy pregnant women and 21 nonpregnant control subjects were recruited. PBMCs were isolated from whole blood by Ficoll-Hypaque, cryopreserved, thawed, washed, and then infected with either a pH1N1 or H3N2 strain at an MOI of 3. Cells then were stained and analyzed by CyTOF-1 for markers of activation and cytokine production.

[It has been known for at least a century that pregnant women often develop severe influenza and suffer greater morbidity and mortality than other young people do.]

Increased expression of CD69+, HLA-DR, IP-10, and MIP-1B was seen following infection of monocytes and pDCs in culture with both strains of flu. Compared to cells from nonpregnant women, cells from pregnant women showed statistically significantly greater expression of these activation markers.

■ COMMENTARY

In pregnancy, the immune system is challenged to strike a balance between protecting the mother from infection, yet not rejecting the growing fetus. It has been known for at least a century that pregnant women often develop severe influenza and suffer greater morbidity and mortality than other young people do. This study demonstrated both elevation of activation markers and increased cytokine production in cells from pregnant women compared to nonpregnant women when infected with two different strains of influenza A. This study at least partially elucidates the mechanism of innate immune system activation in response to influenza A virus infection in pregnancy and suggests potential avenues for research on therapeutic interventions.

Another paper published earlier in 2016 showed that the intense pro-inflammatory response of the innate immune system may even be severe enough to induce hemophagocytic lymphohistiocytosis (HLH), which often was found at autopsy in fatal cases of influenza virus infection.[1] It would be interesting to see if cells obtained from certain subjects in the current study had pro-inflammatory responses that correlated with genetic markers that were seen in 36% of the cases of HLH seen at autopsy in fatal influenza virus infection. ■

REFERENCE

1. Schulert GS, Zhang M, Fall N, et al. Whole-exome sequencing reveals mutations in genes linked to hemophagocytic lymphohistiocytosis and macrophage activation syndrome in fatal cases of H1N1 influenza. *J Infect Dis* 2016;213:1180-1188.

PHARMACOLOGY UPDATE

Bezlotoxumab Injection (Zinplava)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Medical Director, Pharmacy, Northern California Kaiser Permanente, and Assistant Clinical Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a selective, fully human monoclonal antibody directed at *Clostridium difficile* toxin B. Binding of toxin B neutralizes its toxic effect. Bezlotoxumab is marketed as Zinplava.

INDICATIONS

Bezlotoxumab is indicated to reduce recurrence of *C. difficile* infection (CDI) in patients ≥ 18 years of age who are receiving antibacterial treatment of CDI and are at high risk for CDI recurrence.[1]

DOSAGE

The recommended dose is a single dose of 10 mg/kg administered intravenously over 60 minutes during antibacterial treatment.[1] Bezlotoxumab is available as a single-dose vial containing 1 g of bezlotoxumab or 25 mg/mL.

POTENTIAL ADVANTAGES

Bezlotoxumab neutralizes the effect of toxin B and reduces the rate of recurrence of CDI.

POTENTIAL DISADVANTAGES

In subjects with underlying congestive heart failure, the frequency of heart failure was 12.7% in those randomized to bezlotoxumab compared to 4.8% in the placebo group.[1] More deaths were associated with this population (19.5% vs. 12.5%). Bezlotoxumab was associated with infusion-specific adverse reactions in 10% of subjects compared to 8% for placebo. Other adverse events vs. placebo include nausea (7% vs. 5%), pyrexia (5% vs. 3%),

and headache (4% vs. 3%).

COMMENTS

The efficacy and safety of bezlotoxumab was assessed in two similar randomized, double-blind, placebo-controlled studies in subjects receiving standard of care (SoC) antibacterial treatment (metronidazole, vancomycin, or fidaxomicin) for a confirmed diagnosis of CDI.[1] Subjects were randomized to a single-dose of bezlotoxumab or placebo. In study one, 403 patients were randomized to bezlotoxumab and 404 to placebo. Study two randomized 407 and 399, respectively. The median time for the single-dose bezlotoxumab infusion was three days after the start of SoC (range -1 to 14). The efficacy endpoint was clinical cure, and those who achieved cure were assessed for recurrence through 12 weeks after infusion. Clinical cure was defined as no diarrhea for two consecutive days following the completion of ≤ 14 days of treatment. Recurrence was defined as development of a new episode of diarrhea and positive stool test of toxigenic *C. difficile*. Sustained clinical response was defined as clinical cure and no recurrence through 12 weeks after infusion. Sustained clinical response was 60.1% for bezlotoxumab vs. 55.2% for placebo in study one, and 66.8% vs. 52.1%, respectively, for study two. Statistical significance was achieved in study two only. Recurrence was significantly lower with bezlotoxumab (17.4% vs. 27.6% and 15.7% vs. 25.7%, respectively).

CLINICAL IMPLICATIONS

C. difficile is the leading cause of antibiotic-associated diarrhea. Two endotoxins (A and B) are secreted by the disease-causing strains.[2] The original Phase III studies included bezlotoxumab, actoxumab (antibody to toxin A), or the combination. Treatment with actoxumab or the combination provided no benefit; therefore, only bezlotoxumab was marketed.[3] Toxin B is thought to be primarily responsible for disease symptoms.[2] The drug appears to have marginal effect in producing sustained clinical effect but appears to reduce recurrence. The effect may be greater in those with high risk of CDI recurrence. These include ≥ 65 years of age, history of CDI in the past six months, immunocompromised state, severe CDI at presentation, or *C. difficile* ribotype 027. In patients with a history of congestive heart failure, risk vs. benefit must be assessed before treatment.[1] The cost for bezlotoxumab was not available at the time of this review. It is expected to be available in the first quarter of 2017. ■

REFERENCES

1. Zinplava Prescribing Information. Merck & Co., Inc. October 2016.
2. Carter GP, Chakravorty A, Pham Nguyen TA, et al. Defining the roles of TcdA and TcdB in localized gastrointestinal disease, systemic organ damage, and the host response during *Clostridium difficile* infections. *M Bio* 2015 Jun 2;6:e00551. doi: 10.1128/mBio.00551-15.
3. Merck. Pivotal Phase 3 Studies of Bezlotoxumab, Merck's Investigational Antitoxin to Prevent *Clostridium difficile* Infection Recurrence, Met Primary Endpoint. Available at: http://bit.ly/1F9lrXv. Accessed Nov. 21, 2016.

ABSTRACT & COMMENTARY

Discharge Antibiotic Prescriptions Often Are Inappropriate with Regard to Choice, Dose, Duration

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Seventy percent of discharge antibiotic prescriptions are inappropriate.

SOURCE: Scarpato SJ, Timko DR, Cluzet VC, et al; CDC Prevention Epicenters Program. An evaluation of antibiotic prescribing practices upon hospital discharge. *Infect Control Hosp Epidemiol* 2016 Nov 28:1-3. [Epub ahead of print] PubMed PMID: 27890038.

Scarpato and colleagues retrospectively examined the appropriateness of antibiotics prescribed at discharge from their large, quaternary care, urban teaching hospital that has a robust antimicrobial stewardship program. During 2014, 7,313 patients received 9,750 discharge antibiotic prescriptions, 86% for oral administration and the remainder to be given parenterally.

Both seven-day and 30-day readmission rates were higher in those with a discharge antibiotic prescription than in the general discharge population: 6.4% and 19.4% vs. 3.7% and 13.8%, respectively. Those patients discharged on a parenteral (intravenous or intramuscular) antibiotic had readmission rates that were similar to those of patients prescribed oral antibiotics.

Analysis of a randomly selected subset found that as inpatients, a median of 3.5 days (IQ range, 2-5 days) of antibiotics was received, followed by 8 days (IQ range, 6-14 days) as outpatients. Seventy percent of prescribed outpatient antibiotics were judged to be inappropriate, regarding choice, dose, or duration and this was true for 87.7% of surgical patients and 57.6% of medical patients. Thus, among those with a documented infection, the prescribed antibiotic was either too broad spectrum or considered to have an insufficiently broad spectrum in 13.7%, and 17% of this group received an incorrect dose. The duration of prescribed administration was too short in 7.3% but was excessive in 55%, and the mean duration of unnecessary antibiotic administration was 3.8 days.

■ COMMENTARY

My colleague, Marisa Holubar, recently developed a new clinical pathway for management of community-acquired pneumonia at Stanford, and as part of the process, examined the baseline duration of antibiotic treatment, which was, as we expected, longer than recommended in national guidelines. A large portion of that excessive duration resulted from the length of continued antibiotics prescribed at discharge. Although we did not investigate it, our assumption was that a major reason was a lack of taking into consideration the days of therapy received before discharge. Thus, the person writing the discharge prescription may be aware that at least five days are currently recommended and proceed to write a prescription for this duration despite the fact that the patient had already received, e.g., four days of antibiotic therapy as an inpatient. As suggested by Scarpato et al, additional reasons may be lack of knowledge of recommended durations, lack of familiarity with the patient as a result of "hand-offs," and a delay in discharge beyond the anticipated date at the time the prescription was written.

[The problem of inappropriate discharge antibiotic prescribing is clearly one that requires attention and intervention.]

The number of days of unnecessary antibiotic administration has some direct cost consequence, but the more important undesirable effects include increased risk of complications, such as allergic reactions and the development of *Clostridium difficile* infection, as well as the selective pressure exerted on the bacterial ecology with resultant antibiotic resistance.

The problem of inappropriate discharge antibiotic prescribing is clearly one that requires attention and intervention. At the institution where this study was performed, all patients discharged to receive outpatient parenteral antibiotic therapy are followed by a team of infectious disease specialists and pharmacists, but this does not apply to those receiving orally administered antibiotics in the outpatient setting. Interventions suggested by Scarpato et al include medication reconciliation at the time of discharge, prescriber education, and prospective audit and feedback. All will require further engagement for antimicrobial stewardship. ■

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. Which of the following is true regarding malaria?

a. It rarely kills children in Africa.

b. It continues to kill millions of Africans each year.

c. It is spreading rapidly due to both mosquito resistance to insecticides and parasite resistance to mefloquine.

d. It has been nearly eliminated from western regions of sub-Saharan Africa.

2. Which of the following is correct regarding Zika virus-infected infants?

a. If microcephaly is absent, the neurological examination is always normal.

b. If microcephaly is absent at birth, the infection did not affect the infant's brain.

c. The brain is the only target of infection.

d. Neural stem cells are infected during fetal development.

3. Which of the following is correct regarding the duration of treatment of acute otitis media in infants 6-23 months of age?

a. Treatment for five days was superior to treatment for 10 days.

b. Treatment for 10 days was superior to treatment for five days.

c. Treatment for five days and treatment for 10 days were equally effective.

d. Treatment for five days was superior to treatment for three days.

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.