AHC Media LLC

Vol. 30, Issue 4, January 2011
www.ahcmedia.com

Infectious Disease [ALERT]

A monthly update of developments in infectious disease, hospital epidemiology, microbiology, infection control, emporiatrics, and HIV treatment

SPECIAL FEATURE

Oral Rehydration Therapy Shows Effectiveness in Controlling Cholera in Haiti

By Stan Deresinski, MD, FACP

In 1854, London was rocked by a cholera epidemic that killed approximately 10,000 people. Using what are now considered classical epidemiological methods, Dr. John Snow traced the source of at least 500 of the infections to a single water pump at Broad Street, validating his theory that cholera was a water-borne disease 29 years before the etiologic agent was discovered by Robert Koch; removing the pump handle stopped the outbreak in that area. Although this demonstration provided all humans needed to know to prevent future cases of cholera, there have been four pandemics since that time, with the last one (the 7th pandemic) one still ongoing. A minor variant of the strain of *Vibrio cholerae,* responsible for the current pandemic, caused a Western Hemisphere outbreak that began in 1991 in Peru and spread across Central and South America. Through at least the last century, however, no cases of cholera had occurred in Haiti — until now.

A posting on a blog from the Hôpital Albert

Financial Disclosure: *Infectious Disease Alert's* Editor, Stan Deresinski, MD, FACP, does research for the National Institute of Health (NIH), and is an advisory board member and consultant for Merck, Updates author, Carol A. Kemper, MD, FACP, does research for Abbott Laboratories and Merck, and peer reviewer, Timothy Jenkins, MD, reports no financial relationship relevant to this field of study.

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Infectious Disease [ALERT]

Infectious Disease Alert, ISSN 0739-7348, is published monthly by AHC Media LLC 3525 Piedmont Road., NE Building 6, Suite 400 Atlanta, GA 30305.

POSTMASTER: Send address changes to *Infectious Disease Alert*, P.O. Box 740059, Atlanta, GA 30374.

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Schweitzer in the Artibonite valley on October 20, 2010, described the first evidence of the epidemic:[1,2]

"During the day yesterday [i.e., October 19], reports came in to us at HAS that there was a suspected outbreak of severe diarrhea and vomiting, with most of the cases in the Artibonite region. By the late afternoon, HAS began to accept an influx of such cases, all with similar symptoms, and we reviewed charts from Monday and Sunday [i.e., October 17-18] to identify possible earlier cases. A total of 30 patients had been received by the middle of the night on Wednesday [i.e., October 20], mostly adults and primarily male. The patients came from localities near the Artibonite River, and many reported that they had drunk water from the river. The regional director. . . came to HAS and reported that there were many cases in Petite Riviere (i.e., in the mid-artibonite valley, down river from Mirebalais). HAS staff, who had been to the hospital in St. Marc [i.e., coastal community near the termination of the Artibonite river], reported that there was a large crowd outside the hospital, with an estimated 60 patients there."

The outbreak in Haiti was officially confirmed on October 21, 2010, and, as of December 3, 2010, 91,770 cases were reported, with almost one-half having been hospitalized and 2,071 (2.3%) having died. Almost one-half of all cases were reported from Artibonie Department, where the epidemic started, although this aread accounts for only 16% of the population of Haiti. Almost half the deaths in that Department occurred in the community and, among these, the median interval from onset of symptoms to death was 12 hours, with one individual reported to have died only two hours after onset. Only approximately one-fourth of those who died in the community received oral rehydration therapy, which is highly effective if initiated early enough. The implicated strain is a hybrid of the El Tor biotype and the classic toxin type, with the former being associated with longer environmental persistence and the latter possibly with more severe disease. Some evidence suggests that the strain originated in Nepal.

The key to the control of cholera is largely the same as it was in the time of John Snow — provision of safe drinking water and improved hygiene. In addition, WHO and PAHO are considering the use of cholera vaccination in Haiti.[3] Two such vaccines are available — Dukoral and Shanchol —and their value in the current circumstance is being debated. ■

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ABSTRACT & COMMENTARY

Detecting Human Metapneumovirus in Young Children

By Hal B. Jenson, MD, FAAP
Professor of Pediatrics, Tufts University School of Medicine;
Chief Academic Officer, Baystate Medical Center, Springfield, MA
Dr. Jenson reports no financial relationships relevant to this field of study.

Synopsis: *Human metapneumovirus (HMPV) is an important cause of lower-respiratory tract infections among children, and is epidemiologically and clinically similar to respiratory syncytial virus (RSV). HMPV more frequently infects children older than 12-24 months of age, and is associated with a lower rate of hospitalization than RSV.*

Source: Wolf DG, et al. Association of human metapneumovirus with radiologically diagnosed community-acquired alveolar pneumonia in young children. *J Pediatr.* 2010;156:115-120.

A PROSPECTIVE STUDY FROM NOVEMBER 2001 through October 2005 in Israel collected nasopharyngeal wash specimens from children < 5 years who were diagnosed with community-acquired alveolar pneumonia. Alveolar pneumonia was defined radiographically as a dense opacity appearing as a fluffy consolidation, often containing air bronchograms and sometimes associated with pleural effusion, which is the standard of the Pneumonia Vaccine Trial Investigators' Group of the World Health Organization. Nasopharyngeal specimens were cultured for RSV, influenza A and B viruses, parainfluenza viruses, and adenoviruses by direct immunofluorescence assay. HMPV was detected by RT-PCR.

Of 3,507 children with community-acquired alveolar pneumonia, nasopharyngeal specimens were obtained from 1,296 (37%) children, including 997 who were hospitalized. A virus was detected in 608 (46.9%) children. RSV was the most common viral pathogen (23%), followed by HMPV (8.3%), adenovirus (3.4%), influenza A virus (2.9%), and parainfluenza viruses (2.9%). HMPV was identified in 84 children (6.5%) as a single viral pathogen and in 24 children (1.8%) as a co-pathogen, with RSV (10), adenovirus (4), RSV and adenovirus (3), RSV and influenza A virus (1), cytomegalovirus (3), influenza B virus (2), or parainfluenza virus type 3 (1).

Blood cultures were obtained in 3,160 children (90%), of which 42 (1.3%) were positive, including *Streptococcus pneumoniae* (29), *Haemophilus influenzae* (nontypable, 3; type b, 2; type a, 1), *Enterococcus* (2), *Staphylococcus aureus* (2), group A streptococcus (1), *Brucella* (1), and *Neisseria meningitidis* (1).

There was a clear seasonality with two annual peaks, a major winter peak from November through March, and a minor peak from April through June. During the winter peaks, respiratory viruses were detected in 550/1,017 specimens (54%). RSV was significantly more common than HMPV among children < 12 months of age (37% vs. 6.5%; $p < 0.001$). The predominance of RSV was still significant during the second year of life (14.7% vs. 5.4%; $p < 0.001$), with comparable proportions of RSV and HMPV during the third to fifth years of life. Children with HMPV were less likely to be hospitalized than those with RSV (76.2% vs. 93.3%; $p = 0.005$, adjusted for age).

■ COMMENTARY

HMPV was discovered in 2001, and has been increasingly recognized as an important cause of lower respiratory tract infections among young children. In this study, it was detected in 8.3% of children diagnosed with community-acquired alveolar pneumonia, including 9.3% of those evaluated during seasonal peaks from November through May. In approximately one-quarter of cases, HMPV was identified as a co-pathogen with one or more other respiratory viruses.

Although there is general overlap of HMPV and RSV epidemiologically and clinically, children with HMPV were significantly older than those with RSV alveolar pneumonia. While RSV accounts for the majority of virus-associated alveolar pneumonia among children under 12 months of age, the burden of HMPV and RSV alveolar pneumonia was approximately equal among children 2-4 years of age. Perhaps because of the older age at the time of infection, children with HMPV alveolar pneumonia were also less likely to be hospitalized than those with RSV alveolar pneumonia. ■

ABSTRACT & COMMENTARY

Endotipsitis — Difficult to Diagnose, Difficult to Treat

By Stan Deresinski, MD, FACP

Synopsis: *Infection of transjugular intrahepatic portosystemic shunts presents difficult diagnostic and therapeutic challenges.*

Sources: Mizrahi M, et al. Endotipsitis-persistent infection of transjugular intrahepatic portosystemic shunt: Pathogenesis, clinical features and management. *Liver Int.* 2010;30:175-183; Kochar N, et al. Tipsitis: Incidence and outcome at a single centre experience. *Eur J Gastroenterol Hepatol*. 2010;22:729-735.

I WAS ASKED EARLIER THIS WEEK TO SEE A PATIENT with candidemia. The patient had severe cirrhosis and had previously had placement of a transjugular intrahepatic portosystemic shunt (TIPS) for control of complications of portal hypertension. While the source of the infection has not be determined, and he appears to be responding to therapy, the possibility of infection of his TIPS is currently under investigation. This patient, in fact, brought to mind one I saw several years ago with recurrent *Enterococcus faecalis* bacteremia who relapsed after each of three prolonged (up to 8 weeks) treatment courses with ampicillin plus gentamicinfor possible endocarditis. It was finally concluded that the patient had infection of his TIPS and he was placed on suppressive therapy with orally administered amoxicillin, which was successful in preventing recurrence of his infection for the rest of his life, which ended several years later and which resulted from hepatic failure. At the time, I was not aware that his infection had a clever but kitschy name — endotipsitis (or, alternatively, just tipsitis).

Mizrahi and colleagues in Jerusalem have reviewed the literature and identified 36 reported cases of tipsitis. While a definitive diagnosis can only be made by examination and culture of the device, this is not possible except at postmortem examination or at the time of liver transplantation, since the device cannot be removed except together with the liver. A clinical diagnosis of definite infection can, however, be accepted in the presence of continuous bacteremia together with the visualization of vegetations or intraluminal thrombus in the absence of another source of the infection. TIPS infection can be considered probable with continuous bacteremia in the absence of another source, even if imaging of the device fails to demonstrate vegetation or thrombus. In addition to fever, most patients present with increasing jaundice.

In the series derived from the literature, the most frequently identified pathogens were members of the *Enterobacteriaceae*, *Enterococci*, *Staphylococci*, and *Streptococci*. Three Candida infections, including two due to *C. glabrata* and one due to *C. albicans*, were identified.

Mizrahi et al suggest that the initial evaluation should include color Doppler ultrasound examination to determine the patency of the device. Echocardiography should be performed to search for evidence of endocarditis. In some cases, endoscopy (upper and lower) and retrograde cholangiopancreatography should be performed to search for evidence of a TIPS-biliary tract fistula. Other studies should be performed as indicated.

Kocahr and colleagues in Edinburgh, in a single-center study, report that probable endotipsitis occurred in 8 of 785 (1%) of patients > 14 years of age in whom a TIPS had been placed. Symptoms of the infection began at a mean of 24.7 months after device placement. None had identifiable device vegetations, but the TIPS was occluded in four. All the infections were bacterial. Patients received antibiotic therapy for a median of 3 months (range, 10 days to 3 months). Three patients, two of whom had received antibiotics for only two weeks, had recurrence of their infection. The TIPS infection

contributed to the deaths of four patients.

■ **COMMENTARY**

While apparently quite uncommon, infection of a TIPS can be difficult to manage, as are all foreign body infections. In this case, however, similar to the circumstance with infections of ventricular-assist devices, the device cannot be removed in the absence of organ transplantation. Performing organ transplantation in the face of an ongoing infection presents its own challenges, however. Thus, the optimal approach, once the diagnosis is made, is to administer the most effective bactericidal antibiotics available for a prolonged period of time and, in the cases in which relapses occur, to consider the use of suppressive antibiotic therapy for the rest of the patient's life. ■

ABSTRACT & COMMENTARY

Cranberry Juice Prophylaxis for UTIs: A Reason for Skepticism?

By Hal B. Jenson, MD, FAAP

Chief Academic Officer, Baystate Health, Springfield, MA; Professor of Pediatrics and Dean of the Western Campus of Tufts University School of Medicine

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

Synopsis: *Cranberry juice was no better than placebo in preventing recurrent urinary tract infection in young women.*

Source: Barbosa-Cesnik C, et al. Cranberry juice fails to prevent recurrent urinary tract infection: Results from a randomized placebo-controlled trial. *Clin Infect Dis*. 2011;52:23-30.

Recurrent urinary tract infections (UTI) in females is a common and distressing clinical problem. One commonly recommended intervention is attempted prophylaxis by regular ingestion of cranberry juice or other forms of cranberry, including tablets and extracts sold at health-food stores. The efficacy of this approach, however, has now been drawn into question.

Barbosa-Cesnik and colleagues at the University of Michigan randomized women 10-40 years of age with symptoms suggestive of uncomplicated UTI to receive, after treatment of their infection, cranberry juice or placebo for up to 6 months in a double-blind study. The primary endpoint of the study was the development of UTI occurring > 15 days after enrollment or, if < 15 days after enrollment, infection with an organism other than the index infection. Patients were re-evaluated at the time of recurrence or development of urinary tract symptoms and at visits 3 and 6 months after enrollment.

The cranberry juice was formulated to research standards and contained proanthocyanidin, which has been suggested to be the active component in preventing the adherence of *Escherichia coli* to uroepithelial cells, in a mean concentration of 112 mg per dose. The placebo was formulated to mimic the color and taste of cranberry juice. Both the test material and the placebo were sweetened with sucralose, and both contained ascorbic acid. Participants were to ingest 8 oz of their assigned product twice daily. Compliance was monitored by self-report. The study was designed to have an 80% power to detect a two-fold difference between groups using a two-sided test of significance and assuming a 30% incidence of UTI.

A total of 319 patients were randomized, but only 230 completed the entire protocol. All but 1% of the study subjects had a history of recurrent UTI. The rate of infection recurrence proved to be less than had been anticipated. The difference in infection incidence between groups was not statistically significant, with rates of 19.3% and 14.6% in the cranberry and placebo groups, respectively (p = .21, by log-rank test). Gastrointestinal complaints occurred twice as frequently in the cranberry juice recipients

■ COMMENTARY

Cranberry juice contains a complex array of compounds, including polyphenolic antioxidants, one of which, proanthocyanidin, may account for the ability to inhibit adherence of *E. coli* to uroepithelial cells, and whose concentration in the whole juice was regulated in this trial. While widely used for prophylaxis of recurrent UTI in women, the evidence for its efficacy in this regard may be considered less than definitive. A 2008 Cochrane meta-analysis of available trials did conclude that "There is some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12-month period, particularly for women with recurrent UTIs. Its effectiveness for other groups is less certain."[1] Of note, the analysts discarded from consideration 6 of 10 randomized trials because of methodological considerations and, of the remaining four, only one individual trial demonstrated a statistically significant benefit favoring cranberry prophylaxis. They further warned that "the large number of dropouts/withdrawals indicates that cranberry juice may not be acceptable over long periods of time. It is not clear what is the optimum dosage or method of administration (e.g. juice, tablets or capsules)."

In addition to gastrointestinal intolerance, a number of other potential downsides to cranberry juice prophylaxis must be considered, including weight gain (8 ounces of Ocean Spray cranberry juice contains 128 calories, but tablets contain minimal calories), possible increased risk of nephrolithiasis secondary to modest urinary acidification, and a potential pharmacokinetic interaction with warfarin.

In the study by Barbosa-Cesnik et al, the observed incidence of infection in the placebo group was lower than expected, a result that reduced the expected power of the analysis.

The authors also point out another potential problem in that both the cranberry juice and the placebo contained ascorbic acid (although the amount is not stated), but commercially available Ocean Spray cranberry juice is reported to contain 68 mg in an 8-ounce serving. In a small single-blind trial in which its prophylactic efficacy in pregnancy was examined, a daily dose of 100 mg of ascorbic acid was associated with a significant reduction in the incidence of UTI.[2] Reproduction of these results in a larger, better-designed study would be welcome but, until this is done, its result must be viewed with skepticism.

The use of probiotics has been suggested as a potential means of preventing UTI recurrence, but a recent review concluded that there was no evidence that lactobacillus-containing products were effective in this regard.[3] Based on limited evidence, estrogens topically applied to the vagina may have a modest effect in UTI prevention in postmenopausal women, but uncertainties regarding the type of estrogen and other factors remain.[4]

The study by Barbosa-Cesnik and colleagues appears to be the largest and best designed in print. Despite the drawbacks, including the potential confounding by the presence of ascorbic acid in the placebo, it would appear to be the current standard against which other studies must be compared. In the meantime, we need to view recommendations for the use of cranberry products for prevention of UTI with an element of skepticism. ■

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ABSTRACT & COMMENTARY

Should We Adopt a Pre-exposure Prophylaxis Approach for HIV Prevention?

By Dean L. Winslow, MD, FACP, FIDSA

Professor of Pediatrics, Tufts University School of Medicine;

Chief Academic Officer, Baystate Medical Center, Springfield, MA

Dr. Winslow is a speaker for Cubist Pharmaceuticals and GSK, and is a consultant for Siemens Diagnostic.

Synopsis: *In this study, 2,499 HIV-seronegative men or transgender females who have sex with men were randomized to daily tenofovir/emtricitabine (TDF/FTC) vs. placebo. During a median period of follow-up of 1.2 years, TDF/FTC resulted in a 44% reduction in the incidence of HIV.*

Source: Grant RM, et al. Pre-exposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010 Nov. 23 (epub ahead of print).

In this study, 2,499 HIV-seronegative men or transgender females who have sex with men (MSM) were randomized to daily TDF/FTC vs. placebo in a multicenter, controlled trial with clinical sites in North America, Latin America, Thailand, and Africa. In addition to being provided TDF/FTC (or placebo), all subjects received HIV testing, risk-reduction counseling, condoms, and management of sexually transmitted infections. The study subjects were followed for 3324 person-years (median 1.2 years) and were seen every 4 weeks. One hundred subjects became infected during follow-up (36 in the TDF/FTC group and 64 in the placebo group). A subgroup of patients had serum and PBMC's examined for antiretroviral levels.

Of the 2,499 subjects, 10 were found to be infected at study enrollment, and 100 became infected during follow-up (36 in the TDF/FTC group and 64 in the placebo group), indicating a 44% reduction in the incidence of HIV. Study drug was detected in 22/43 seronegative subjects and in 3/34 HIV-infected subjects. Excess nausea was reported in the TDF/FTC treated subjects. No TDF or FTC resistance was detected in either the TDF/FTC or placebo groups who became infected with HIV during the trial.

■ COMMENTARY

Bob Grant and his team should be congratulated for completing this large international trial and conclusively demonstrating that TDF/FTC prevents many cases of HIV when given as pre-exposure prophylaxis. Several weeks ago when the news of this important study hit the lay press, a lot of enthusiasm was generated, and the press in San Francisco declared this a major breakthrough in HIV prevention. While poor adherence likely contributed to the relatively low efficacy of this intervention (based on non-human primate experiments, I would have predicted > 80% efficacy rather than observed 44% efficacy), the success of this approach will undoubtedly be significantly lower in the real world outside of the context of a clinical trial where the patients received regular monitoring and support.

I have some big issues with adopting this approach more widely for HIV prevention. These include the concern about selecting out NRTI-resistant variants of HIV in the community. While it is gratifying that this was not seen in the short term (median 1.2 years) duration of this trial, the widespread use of this non-fully suppressive regimen will surely drive resistance when many HIV-infected patients will likely get access to TDF/FTC and use it outside of a controlled clinical environment and in the absence of fully suppressive 3-drug HAART.

While I do not lose sleep over the potential renal and bone toxicity of TDF when treating patients with known HIV, I am concerned about exposing millions of HIV-uninfected people (mainly in the developing world) to ARV's for years.

The last concern is simply cost. TDF/FTC currently sells for approximately $40/tablet. Using some back-of-the-envelope calculations, the cost per patient during the 1.2 years of the study would be $16,800. The total drug supply cost for this 2500 person trial was $42 million. Therefore, the cost of preventing each of the 28 cases of HIV was $1.5 million. Is that really an effective use of limited resources? As someone who served as an Air Force physician on the front lines of many of the humanitarian crises our weary world has endured over the last 20 years, I do not think so. $42 million spent digging wells could provide enough safe water to prevent hundreds (if not thousands) of childhood deaths due to diarrheal disease. $42 million could buy permethrin-treated bed nets for just about every child in Africa and prevent thousands of deaths due to malaria. We could certainly provide routine childhood immunizations to millions of children (again preventing thousands of deaths) for that amount as well. ■

ABSTRACT & COMMENTARY

Revised Guidelines for Perinatal Group B Streptococcal Disease

By Hal B. Jenson, MD, FAAP

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

Synopsis: *The 2002 guidelines for prevention of perinatal group B streptococcal disease have been updated with expanded recommendations on laboratory methods, revised algorithms for screening and intrapartum chemoprophylaxis, a change in the recommended dose of penicillin G, updated prophylaxis regimens for women with penicillin allergy, and a revised algorithm for management of newborns.*

Source: Centers for Disease Control and Prevention: Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC, 2010. *MMWR* 2010;59(RR-10):1-32.

Group B streptococcal (GBS) disease is the leading cause of early-onset neonatal sepsis (within the first week of life) in the United States. Since the initial recommendations for perinatal prophylaxis in the 1990s, the incidence of GBS has declined by 80%. There are approximately 1,200 cases of early-onset GBS invasive disease each year in the United States, with 70% of cases among newborns ≥ 37 weeks' gestation.

These updated guidelines from the Centers for Disease Control and Prevention (CDC) are endorsed by the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, the American College of Nurse-Midwives, the American Academy of Family Physicians, and the American Society for Microbiology.

GBS colonization is best determined by collecting both vaginal and rectal (through the anal sphincter) specimens at 35-37 weeks' gestation. Nucleic acid amplification tests (NAAT), such as PCR assays, can be used for GBS identification after an enrichment step. Enrichment increases sensitivity of detection from 54% to 92%-100%; the increased accuracy is much more important than the additional time required to obtain the result. Optical immunoassays and

enzyme immunoassays are not sufficiently sensitive to detect GBS colonization reliably. The double-disk diffusion method (D-zone test) or another validated test is recommended to identify isolates that are erythromycin-resistant and clindamycin-susceptible, which are presumed to have inducible resistance to clindamycin.

Intrapartum GBS prophylaxis is indicated for pregnant women with:

- Previous infant with invasive GBS disease;
- GBS bacteriuria during any trimester of the current pregnancy (except if cesarean delivery is performed before onset of labor with intact amniotic membranes);
- Positive GBS vaginal-rectal screening culture in late gestation (optimally at 35-37 weeks' gestation);
- Unknown GBS status at the onset of labor and any of the following:
  - Delivery at < 37 weeks' gestation;
  - Amniotic membrane ruptures ≥ 18 hours;
  - Intrapartum temperature ≥ 100.4°F (≥38.0°C); and
  - Intrapartum NAAT positive for GBS

Intrapartum GBS prophylaxis is not indicated for pregnant women with:

- Colonization with GBS during a previous pregnancy;
- GBS bacteriuria during a previous pregnancy;
- Negative GBS vaginal-rectal screening culture (optimally at 35-37 weeks' gestation), regardless of intrapartum risk factors; and
- Cesarean delivery performed before on set of labor with intact amniotic membranes, regardless of GBS colonization status or gestational age.

Penicillin G (5 million units IV initial dose, then 2.5-3.0 million units [using the dosing readily available on the hospital formulary] every four hours until delivery) remains the drug of choice for intrapartum antibiotic prophylaxis, with ampicillin (2 g IV initial dose, then 1 g IV every four hours until delivery) as an acceptable alternative. Penicillin-allergic women who do not have a history of anaphylaxis, angioedema, respiratory distress, or urticaria following administration of a penicillin or cephalosporin should receive cefazolin (2 g IV initial dose, then 1 g IV every 8 hours until delivery). Antimicrobial susceptibility testing is necessary for GBS from penicillin-allergic women at high risk for anaphylaxis. These women should receive clindamycin if the GBS isolate is susceptible to clindamycin and also erythromycin (e.g., does not have inducible resistance to clindamycin). These women should receive vancomycin if the isolate demonstrates resistance (including inducible resistance) to clindamycin, or if susceptibility to clindamycin and erythromycin is unknown. Erythromycin is no longer an acceptable alternative for intrapartum GBS prophylaxis for penicillin-allergic women.

The management of newborns has also been updated:

· Newborns with signs of sepsis should receive a full diagnostic evaluation (blood culture, CBC including white blood cell differential and platelet count, chest radiograph if abnormal respiratory signs are present, and a lumbar puncture if the newborn is stable) and antibiotic therapy;

· Newborns of mothers with signs of chorioamnionitis should receive a limited evaluation (blood culture, and CBC with differential count and platelet count) with antibiotic therapy pending culture results;

· Newborns of mothers who received intrapartum prophylaxis for ≥ 4 hours before delivery should be observed for ≥ 48 hours; and

· Newborns who are well-appearing and born to mothers who had an indication for GBS prophylaxis but received no or inadequate (incorrect regimen, < four hours before delivery) prophylaxis:

  · Newborns ≥ 37 weeks and 0 days' gestation and duration of membrane rupture < 18 hours should be observed be for ≥ 48 hours, and no laboratory evaluation is recommended unless symptoms develop; and

  · Newborns < 37 weeks gestation or duration of membrane rupture ≥ 18 hours should have a limited evaluation and ob served for ≥ 48 hours.

Antibiotic therapy for newborns should include ampicillin for GBS as well as coverage for gram-negative pathogens, pending culture results. ■

CME Questions

16. Which of the following is correct?

a. Human metapneumovirus (HMP), while causing upper respiratory tract infection, does not cause pneumonia.

b. HMP is the most common viral cause of alveolar pneumonia in children.

c. Children with alveolar pneumonia due to HMP are younger than those whose pneumonia is due to respiratory syncytial virus (RSV).

d. Children with alveolar pnuemonia due to HMP are less likely to require hospitalization than those with RSV.

17. Which of the following is correct with regard to infection of intrahepatic portosystemic shunts (TIPS)?

a. The incidence is 20% to 50% of all TIPS.

b. The initial step in evaluation should include Doppler ultrasound examination to determine TIPS patency.

c. The initial step in treatment is removal of the device followed by antibiotic therapy.

d. The majority are caused by *Staphylococcus aureus*.

18. Which of the following is correct with regard to prevention of urinary tract infection (UTI)?

a. Cranberry juice has been unequivocalloy confirmed to be effective.

b. Cranberry juice prevents UTI by causing marked acidification of the urine.

c. One or more components of cranberry juice inhibit adherence of *E. coli* to uroepithelial cells

d. There is strong evidence that adminsitration of probiotics is effective in the prevention of UTI.

Answers: 16. (d); 17. (b); 18. (c)

CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis and treatment 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.

[IN FUTURE ISSUES]

The Hospital Enviornment as a Source of MRSA

UPDATES By Carol Kemper, MD, FACP

Opportunity for Antimicrobial Stewardship

Source: Jenkins TC, et al. Skin and soft tissue infections requiring hospitalization at an academic medical center: Opportunities for antimicrobial stewardship. *Clin Infect Dis*. 2010;51:895-903.

These authors examined the use of antimicrobials for skin and soft tissue infection (SSTI), comparing the presentation, complications, microbial results and outcomes of adults hospitalized at Denver Health Medical Center. Cases were identified based on discharge diagnosis and ICD-9 codes. Organisms found in culture from a deep-tissue specimen, aspirate or blood were considered pathogens.

A total of 404 patients with SSTI were identified; 81 were excluded for various reasons (refusal of care, odontogenic infection, etc.), leaving a total of 332 evaluable patients. Of these 66 (20%) had cellulitis, 103 (32%) had cutaneous abscess and 153 (48%) had complicated SSTI (which included deeper infection at or below the fascial plane, bacteremia, sepsis, diabetic ulcer or chronic ulcer, human or animal bite, recent hospitalization, or surgical-wound infection). Diabetes, alcohol use, and injection drug use was common.

Staphylococcus aureus and *Streptococcus spp*. were present in 97% of cutaneous abscess and in 96% of complicated SSTI. Additional bacteria were present in some of these, including anaerobes in 17% of cutaneous abscesses and 22% of complicated SSTI, and aerobic gram-negative rods in 13% of cutaneous abscesses and 14% of complicated SSTI. Therefore, only *S. aureus* and/or *Streptococcus spp*. were isolated in 77% and 71% of cases, respectively. Approximately two-thirds of the *S. aureus* in culture were methicillin-resistant.

All of the patients received parenteral therapy. Broad-spectrum antimicrobials were employed for most of the cases, especially during the first 3 days. Vancomycin was the most frequently used agent (73% of cutaneous abscesses and 79% of complicated SSTI infection); the median duration of use was 3 days. Agents with broad gram-negative activity were used in 61% and 80% of cutaneous abscess and complicated SSTI, respectively, for a median of 3 days. And, agents with anaerobic activity were used in 73% and 83%, respectively, for a median of 3 and 4 days. Three or more antibiotics were used in 40% and 48% of these cases, respectively. The average duration of therapy for cellulitis, cutaneous abscess, and complicated SSTI was 13, 13, and 14 days, respectively.

Radiographic studies were performed in 20% of patients, with a resulting low yield. Only 2% of cases undergoing CT and 1% of cases undergoing MRI, yielding meaningful information.

Based on the culture results, the authors concluded that most of the antibacterial therapy used for SSTI was unwarranted, especially considering that 52% of the cases in this study were uncomplicated cellulitis and cutaneous abscess, providing a perfect target for education and antimicrobial stewardship. Several studies suggest that the duration of total antibacterial therapy can also be safely reduced in most of these patients.

Antimicrobial Effects of Citrus in Food

Source: Herrara A, et al. The effect of preparation of cebiche on the survival of enterotoxigenic *Escherichia coli*, *Aeromonas hydrophila*, and *Vibrio parahaemolyticus*. *J Travel Med*. 2010;17: 395-399.

Cebiche is a common Latin American dish made of raw fish and vegetables, marinated with lime juice. It is a commonly held belief, not especially evidenced-based, that the acidic nature of the citrus destroys any bacteria present in the raw food, rendering it safe to eat. In fact, the opposite may be true. One Mexican study found that 16% of cebiche samples surveyed contained Salmonella spp.

The United States Naval Medical Research Department examined the bacteriocidal effect of lime juice on bacterial colony counts in cebiche, inoculated with infectious doses of either enterotoxigenic *Escherichia coli* (ETEC), *Aeromonas hydrophila*, or *Vibrio parahaemolyticus*. First, the Naval researchers whipped up a batch of a familiar Peruvian cebiche recipe containing cilantro, garlic, hot peppers, sweet potato, corn, and fresh lime juice. They next took a local coastal fish, called Toyo, purchased fresh from the supermarket, and marinated it with 50 mL bacterial suspensions containing 1 x 10^8 CFU/mL of the three bacteria, and let stand for 10

minutes. The fish medley was then combined with the vegetables, and the pH and bacterial colony counts were tracked for 30 minutes.

The baseline pH of the fish without the lime juice was 6.5. Immediately after combining with the lime juice-vegetable medley, the pH fell to 5.0, but rose to 5.2 and 5.4 over the next 10 to 30 minutes. Homogenates of the mixture yielded lower bacterial colony counts within the first 10 minutes (with an approximate half log drop from baseline), but bacterial counts remained well above the infectious dose of bacteria. After 10 minutes, bacterial growth for both *A. hydrophila* and ETEC appeared to recover and, by 30 minutes, approached the baseline inocula.

The addition of lime juice to this common Peruvian cebiche dish, spiked with pathogenic bacteria, did not appreciably reduce bacterial colony counts.

Alcohol Hand Gel in Schools

Source: Prazuck T, et al. Reducing gastroenteritis occurrence and their consequences in elementary schools with alcohol-based hand sanitizers. *Pediatr Infect Dis J.* 2010;29:994-998.

AT OUR NEW HOSPITAL IN MOUNTAIN View, California, rates of hand cleansing have improved to > 95% with the installation of a hand-gel dispenser at the doorway of every patient room (Gel in! Gel out!). Coupled with an employee contest to promote hand cleansing among hospital staff (win a videocam!), hand cleansing has finally become habit. Alcohol-based hand gels have now made it into other areas of our lives, including schools, homes, and I've even seen bridge players (mostly ladies) pull tiny Purell bottles out of their purses during tournaments, when duplicate boards are passed around to multiple tables (those dirty cards).

These authors examined whether the use of alcohol-based hand gels in primary school reduces the risk of gastrointestinal illness in children during the epidemic season. Children at one school were schooled in the use of hand gel throughout the day for 17 weeks; children at a second school did not use hand gel and served as controls. The authors state that use of hand sanitizers was "under strict teacher supervision" (spare the rod, but not the hand gel). Weekly surveys of the children assessed rates of reported illness, absenteeism, doctor visits, and missed days of work by parents.

A total of 476 children participated in the project, returning 4,654 weekly surveys. One-hundred and fifty-five children (36%) developed at least one episode of gastroenteritis. Children in the intervention group were significantly less likely than control children to develop gastroenteritis (24.7% vs. 41.9%, $c^2 = 16.4$, $p < .0001$). A 41% reduction in the average number of gastroenteritis episodes was observed in the school using alcohol-based hand gel compared with the control school ($p < .001$).

Alcohol-based hand gel appears to be a simple and inexpensive intervention in reducing rates of infectious gastroenteritis children in elementary schools.

Reality TV Uncovers the Dirt

Source: Hintikka A, et al. The reality of hand hygiene compliance in two Finnish hospitals based on watching and analyzing two hospital reality televion series. J Infect (letter); 2010 (e- release, avail. at www.sciencedirect.com).

TWO HOSPITAL-BASED REALITY TV shows from Finland provided an opportunity to watch hospital employees in action and observe their compliance with hand hygiene and other infection control practices. The two prime-time TV shows aired in 2008, totaling 60 thirty-minute segments, and tracked the day-to-day activities of hospital staff at two Helsinki hospitals. One investigator watched all 60 episodes (hopefully he TiVo'ed).

A total of 142 hand hygiene opportunities were observed (approximately 2.3 patient care contacts per 30 minute segment). Despite the fact that hospital employees knew they were being filmed, alcohol-based hand gel was used appropriately for only 19% of these. In one scene, a hospital employee dried his hands on patient bedding.

Gloves were used 206 times – but nearly half of this (46%) was inappropriate overuse, and not once were hands cleansed before or after donning gloves, as per hospital policy. Gloves were also commonly used for multiple tasks without being removed. The investigators report that it was common for employees to scratch their head with a gloved hand. Mostly, gloves were used for patient transport, patient contact not requiring gloves, and during radiographic procedures, suggesting that employees used gloves when they perceived there was a risk to themselves, and not to protect patients. In addition, the investigators observed numerous other violations of hospital IC policies, including frequent food at the nursing stations, placing charts on patient beds, and artificial nails.

Hospital Infection Control staff at the two hospitals were understandably dismayed by these findings. In a final episode, a special segment devoted to improved hand hygiene and other infection control measures was aired. Now if only life was a bit like reality TV! ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Rivaroxaban: Another Warfarin Replacement

In this issue: Rivaroxaban may be dabigatran's first competitor; a new way to measure non-adherence to medication therapy; FDA Actions.

Another Warfarin Replacement on Horizon

Just as Boehringer Ingelheim begins marketing dabigatran (Pradaxa®) as a replacement for warfarin, a competitor drug may be on the horizon. As reported at the American Heart Association (AHA) meetings in November, rivaroxaban, an oral drug factor Xa inhibitor, is as effective as warfarin at preventing stroke and blood clots in patients with nonvalvular atrial fibrillation.

The ROCKET AF study (Stroke Prevention Using the Oral Direct Factor Xa Inhibitor Rivaroxaban Compared With Warfarin in Patients with Nonvalvular Atrial Fibrillation) looked at more than 14,000 patients with atrial fibrillation. Patients were randomized to warfarin or rivaroxaban (20 mg/day). The time in therapeutic range for warfarin was 57.8%. With a primary endpoint of stroke and non-CNS systemic embolism, rivaroxaban was associated with a rate of 1.71 events per 100 patient-years vs 2.16 for warfarin (P = 0.015 for superiority and P < 0.001 for non-inferiority). On an intention to treat (ITT) basis, event rates were 2.12 for rivaroxaban vs 2.42 for warfarin (P = 0.117). There were 55 intracranial bleeds with rivaroxaban compared with 84 with warfarin (P = 0.019). Rivaroxiban also showed numerically fewer MIs (0.91 vs 1.12 per 100 person-years; P = 0.12). All-cause mortality was 1.87 in the rivaroxaban group vs 2.21 in the warfarin group (P = 0.073). In the ITT analysis, mortality was 4.52 vs 4.91 (P = 0.152), respectively.

This study (presented at the American Heart Association Scientific Sessions; Chicago, IL; Nov. 15, 2010) was the seventh Phase III trial in the development of rivaroxaban, with other studies evaluating the drug for prevention and treatment of venous thromboembolism, indications that Bayer and Johnson & Johnson have already filed with the FDA. It is also expected that a new drug application will be filed soon for the prevention of stroke in patients with nonvalvular atrial fibrillation. Like dabigatran, rivaroxaban requires no monitoring and has few drug interactions. Rivaroxaban has the advantage of being dosed once a day compared to twice-daily dosing for dabigatran. ■

Non-adherence: A New Way to Measure

A new study examines drug adherence in an interesting way — by looking at the rate of prescriptions abandoned at the pharmacy. Traditional non-adherence studies have looked at refill rates, pill counting, and patient reports of medication use. But prescriptions abandoned at the pharmacy represent a potential opportunity to intervene and improve adherence at the very onset of the prescribing process.

Researchers used the CVS pharmacy database to evaluate more than 10 million prescriptions

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filled by more than 5 million patients. The overall abandonment rate was 3.27%, although nearly half of those were eventually filled by the same drug or a similar drug within 30 days. Not surprisingly, patients were least likely to abandon opiate prescriptions, and were most likely to abandon expensive prescriptions. Prescriptions with a copayment of $40-$50 and those with a copayment of more than $50 were 3.4 times and 4.68 times more likely to be abandoned, respectively, than prescriptions with no copayment ($P <$ 0.001 for both comparisons). New users of medications were more likely to abandon prescriptions than prevalent users, and prescriptions that were delivered to the pharmacy electronically were 1.64 times more likely to be abandoned than those that were not electronic ($P < 0.001$); however, they were unable to determine whether written prescriptions were never delivered to the pharmacy by patients.

The authors concluded that prescription abandonment represents an important opportunity to intervene and improve adherence (*Ann Intern Med* 2010;153:633-640). An accompanying editorial points out that the rate of abandonment in this study was actually quite low. Others studies have suggested that 17%-20% of patients do not pick up new prescriptions, and 8% of patients' prescriptions are denied by health plans. Physicians and pharmacists are urged to remain mindful that costs are an important barrier to adherence and that lower cost alternatives should be prescribed "whenever feasible" (*Ann Intern Med* 2010;153:680-681). ■

FDA Actions

The FDA has asked the manufacturers of propoxyphene-containing pain medications (Darvon®, Darvocet®, and generics) to withdraw them from the market. The withdrawal is based on new data showing the drugs are associated with serious and fatal heart arrhythmias. Health care professionals are advised to stop prescribing propoxyphene and patients are asked to contact their health care providers to discuss switching to other pain medications. Propoxyphene has been the target of consumer groups for more than 30 years because of evidence of poor efficacy in treating pain and a high level of side effects including falls. ■

The FDA has approved duloxetine (Cymbalta®) for the treatment of chronic musculoskeletal pain. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, was previously approved for treating depression, generalized anxiety disorder, diabetic neuropathy, and fibromyalgia. The new indication for musculoskeletal pain includes low back pain and osteoarthritis. The expanded indication was based on the results of four double-blind, placebo-controlled trials, which showed that patients treated with duloxetine had significantly greater pain reduction than those patients treated with placebo. Duloxetine is marketed by Eli Lilly and Company. ■

The FDA has approved lurasidone for the treatment of schizophrenia in adults. The drug is classified as an atypical antipsychotic, and like other drugs in this class, carries a boxed warning regarding an increased risk of death associated with off-label use to treat behavioral problems in older adults with dementia. Common adverse reactions include drowsiness, feelings of restlessness, nausea, agitation, and Parkinsonian symptoms such as bradykinesia, tremor, and muscle stiffness. Lurasidone will be marketed by Sunovion Pharmaceuticals as Latuda™. ■

The FDA has approved a new injectable cephalosporin, ceftaroline, to treat community-acquired bacterial pneumonia (CABP) and bacterial skin infections, including those caused by methicillin-resistant *Staphylococcus aureus*. Ceftaroline was approved based on data from four studies that showed the drug to be as effective as ceftriaxone for the treatment of CABP and as effective as vancomycin plus aztreonam for the treatment of acute bacterial skin and skin structure infections. The recommended dose for patients with normal renal function is 600 mg given as a one-hour IV infusion every 12 hours. Ceftaroline is marketed by Forest Laboratories as Telflaro™. ■

The FDA's Vaccines and Related Biological Products Advisory Committee has recommended an expanded indication for Gardasil®, Merck's quadravalent human papillomavirus vaccine to prevent anal intraepithelial neoplasia and anal cancer in males and females ages 9-26. The approval was based on a phase III double-blind, placebo-controlled trial in which more than 4000 males were randomized to receive the three-dose vaccine or placebo. There was a significant reduction in the rate of anal intraepithelial neoplasia or anal cancer, especially in men who have sex with men. The vaccine is already approved for prevention of genital warts and cervical, vulvar, and vaginal cancer in females ages 9-26 and prevention of genital warts in males ages 9-26. ■