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Infectious Disease [ALERT]

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

ABSTRACT & COMMENTARY

Changing Epidemiology of Bacteremia in Infants

By Hal B. Jenson, MD, FAAP

Dean, School of Medicine, Western Michigan University School of Medicine, Kalamazoo, MI., is Associate Editor for Infectious Disease Alert.

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

SOURCE: Greenhow TL, Hung YY, Herz AM: Changing epidemiology of bacteremia in infants aged 1 week to 3 months. *Pediatrics* 2012;129:e590.

A retrospective analysis was conducted of all blood cultures collected on full-term (>=37 weeks) previously healthy infants presenting for care from 1 week to 3 months of age in a large California healthcare system over 5 years (2005-2009). Of the 4,255 blood cultures collected from 4,122 infants, among a cohort of 160,818 infants born in the system during that period, 2.2% (92) were positive for pathogens and 5.8% (247) were positive for contaminants. The most common pathogen was *Escherichia coli* (52 cases; 56%), which was associated with a urinary tract infection in all but a single case (98%). The next most common pathogens were Group B Streptococcus (19 cases; 21%) and *Staphylococcus aureus* (7 cases; 8%). Other gram-negative organisms included 2 cases each of Klebsiella and Salmonella, and 1 case each of Citrobacter and Moraxella. There were 3 cases of *Streptococcus pneumoniae* (none in the first month of life), 1 case each of Enterococcus and Group A Streptococcus, and no cases of *Listeria monocytogenes* nor *Neisseria meningitidis*.

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Infectious Disease [ALERT]

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Ampicillin resistant pathogens accounted for 33 of 92 (36%) organisms. Among the *E. coli* strains, 23 of 52 (44%) were resistant to ampicillin, 3 (6%) were resistant to gentamicin, and 1 (2%) was resistant to cefazolin. There were no strains of E. coli that were resistant to ceftriaxone. All of the strains of *S. aureus* were susceptible to methicillin.

Of the 92 infants with bacteremia, 6 (7%) had no documented fevers by parental history or at presentation. Sixteen (18.6%) of the infants were described as ill-appearing. Of the 10 infants with meningitis, 7 were ill appearing, and 1 was afebrile.

Bacteremia was slightly more likely from 7-28 days of age (2.84%) compared to 29-60 days (1.92%) and 61-92 days (2.14%), though these differences were not statistically significant. There were no trends in incidence. No predictor was statistically significant by multivariate analysis.

■ COMMENTARY

Continuing the trend of other studies of the past decade on the epidemiology of bacteremia among infants, E. coli has replaced Group B Streptococcus as the leading cause of late-onset bacteremia in young infants. One limitation is that the design of this study included only full-term infants, and excluded premature newborns that are at higher risk of Group B Streptococcus infection. Despite this limitation, the results demonstrate the significant impact of recent changes in our management of perinatal maternal colonization. This healthcare system has very high rates of maternal screening for Group B Streptococcus and use of intrapartum antibiotics, which decrease vertical transmission of Group B Streptococcus. These changes in perinatal practices since recommendations were formalized in 1996 have significantly reduced the risk of neonatal Group B Streptococcus infections.

Ampicillin resistance was found in 36% of all cases, and in 44% of cases of E. coli bacteremia including the one case of E. coli meningitis. This underscores the importance of including third-generation cephalosporins as part of the empirical antibiotic regimen for management of fever and bacteremia in infants 1 week to 3 months of age. ■

ABSTRACT & COMMENTARY

Validation of Self-Swabbing for Flu Infections in the Community

By Joseph F. John, MD, FACP, FIDSA, FSHEA
Associate Chief of Staff for Education, Ralph H. Johnson Veterans Administration Medical Center; Professor of Medicine, Medical University of South Carolina, Charleston, is Co-Editor for Infectious Disease Alert.

Dr. John reports no financial relationship to this field of study.

SOURCE: Ip DKM, et al. Validation of self-swab for virologic confirmation of influenza virus infections in a community setting. *J Infect Dis* 2012;205:6314.

Hong Kong investigators conducted 2 separate community studies using careful face-to-face instructions to potentially influenza infected patients. Sterile nasal swabs

were rotated around the anterior nares. The throat culture was the sample collected by "rubbing a second sterile swab against the tonsillar fossa." Reverse-transcription polymerase chain reactions (RT-PCR) was used to find and quantitate both influenza A and influenza B particles expressed as viral particles per milliliter. There were 109 of 121 (90%) of positive patients who had detectable virus within the first 2-5 days after onset of symptoms. Virus quantity for influenza A tended to start to decline from highs of 108 particles down to 10^4–10^2 by day 8 or 9. Influenza B levels tended to be a log or 2 lower.

■ COMMENTARY

This study shows that patients are quite capable of swabbing their own nose and throat in order to find adequate RNA specific for influenza A and B viruses. In fact the viral loads were relatively huge at the outset of disease suggesting that the authors used an excellent method for transport and preservation. In the study of household transmission, in fact, the initial viral loads approached 10^{10}!

If we use www.Googlescholar.com to search self swabbing and cultures, there are 18,600 hits. So the field of self culturing is rich and getting richer. It seems that vaginal swabs have been studied most followed by throat, nasal and ultimately rectal.

The use of the swab itself for microbial culture, emerged around 1940, but a battle raged about whether a primary specimen like feces was preferable to rectal swabs. Back in the August 14, 1954, issue of the *British Medical Journal*, rectal swabs were compared to feces as a method for detecting enteric pathogens. Swabs were found to be wanting (MEM Thomas, "Disadvantages of the rectal swab in diagnosis of diarrhea").

Swab science, however, has markedly improved into the modern age, as suggested by the excellent recovery of RNA — even by self swabbing — in the current report by Ip, et al. In fact, self-collected swabs were compared for accuracy to ones obtained by health care professionals and no difference was present.

This study is the first to measure recovery of influenza virus by self swabbing. The findings are quite astounding and show that rapid sampling of the populations at large is quite feasible using self swabs, hopeful indeed that those populations can be as assiduous in sample collection as these residents of Hong Kong. Other community-based populations should be studied but this report serves as a trigger to suggest the use of a careful nose or throat swab and subsequent careful transport to the clinical virology laboratory may allow for rapid diagnosis, infection control and therapy of influenza epidemics. ■

SPECIAL FEATURE

Appropriate Dosage of Vancomycin in End-Stage Renal Disease Patients Requiring Intermittent Hemodialysis

By Kevin Singh; Sherman Lau, Pharm.D., Jessica C. Song, M.A., Pharm.D.

Jessica C. Song, M.A., Pharm.D, Clinical Supervisor of Pharmacy and Therapeutics, Ambulatory Care, and Mental Health at Santa Clara Valley Medical Center, San Jose, CA, is Associate Editor for Infectious Disease Alert.

Kevin Singh, Sherman Lau and Jessica C. Song report no financial relationships relevant to this field of study.

Infection is the second leading cause of death in hemodialysis patients, with mortality rates ranging from 12-36% in this vulnerable population.[1] Vascular-access related septicemia accounts for approximately 75% of deaths associated with infections, with *Staphylococcus aureus* causing up to 39% of all bacteremias.[1]

Moreover, hemodialysis patients have a 100-fold greater risk for experiencing invasive methicillin-resistant *S. aureus* (MRSA) infections than the general population.[1] At present, the current standard of practice is to use vancomycin, a bactericidal glycopeptide antibiotic for the treatment of hemodialysis patients with catheter-related bloodstream infections caused by MRSA.[1] Vancomycin has a complex pharmacokinetic profile in end-stage renal disease (ESRD) patients requiring intermittent hemodialysis. This agent undergoes three phases of elimination during intermittent hemodialysis: (1) a rapid extraction phase during the intradialytic phase (serum extraction rate of 30-46% with high-flux membranes); (2) administration and redistribution (lasts ~2 hours); and (3) prolonged, linear clearance during the interdialytic interval.[2] Since the half life of vancomycin in anuric patients may range from 100 to 200 hours, a very gradual reduction in concentrations occur during the interdialytic interval (typically 44-68 hours).

A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists recommended a target of a 24-hour area under the concentration curve over the minimal inhibitory concentration (AUC/MIC) of at least 400 in order to achieve clinical success in patients infected by staphylococcal species.[3] However, since multiple vancomycin levels must be drawn from patients in order to calculate AUC/MIC's, a more practical monitoring tool would be to check vancomycin trough levels, given the positive correlation between drug exposure yielded by both parameters. There has been a steady rise in the fraction of *S. aureus* strains with an MIC between 1 and 2 mg/L over the past decade. An estimated 16.2% of *S. aureus* strains in the United States exhibited MICs between 1 and 2 mg/L in 2005.[4] In addition, the emergence of vancomycin-intermediary and vancomycin resistant strains of *S. aureus* has further increased the risk of treatment failure in patients requiring vancomycin therapy.

These changing patterns in epidemiology and susceptibility to vancomycin in *S. aureus* have resulted in substantial changes in the dosing guidelines for this drug, with suggested target trough levels of 15 to 20 mg/L in patients with complicated infections caused by *S. aureus*.[3] To date, underdosing appears to be the main problem in the majority of patients undergoing dialysis.[4] The purpose of this review is to discuss newer clinical prescribing practices regarding vancomycin in patients requiring intermittent hemodialysis.

VANCOMYCIN DOSING

To date, earlier studies of vancomycin dosing in patients undergoing intermittent hemodialysis used inappropriate therapeutic ranges, thereby providing limited guidance for contemporary clinical practice.[5-7] Two investigators studied similar algorithms using a weight-based loading dose of 20 mg/kg (dry body weight), followed by fixed doses of 500 mg (timed with each dialysis session).[5,6] The only difference between the regimens involved the timing of administering vancomycin; one investigator gave the loading and maintenance doses after dialysis,[5] whereas the other investigator had patients receive vancomycin during the final hour of dialysis.[6] Twenty-eight percent of patients who received vancomycin post-dialysis achieved troughs of 15-20 mg/L and 12% of patients achieved similar levels when they received vancomycin during the last hour of dialysis. Pai and associates used a 1000 mg loading dose, with the following maintenance doses: (1) 1000 mg if trough levels fell below 8 mg/L; (2) 500 mg if trough levels ranged from 9 to 15.9 mg/L; and (3) no supplemental dose with trough levels of 16 mg/L and higher. Approximately 20% of patients achieved trough levels of 15.1-20 mg/L.[7]

Taylor et al. recently reported on the outcomes of using their vancomycin dosing protocol in 34 hospitalized hemodialysis patients (weight range, 50-118 kg).[8] Patients received a 20 mg/kg (actual body weight, dose in multiples of 250 mg) loading dose scheduled to end with the dialysis session. Patients received maintenance doses of 1000 mg during the last hour of subsequent dialysis sessions and trough vancomycin concentrations were measured immediately prior to the fourth dialysis session. Thirty-five percent of patients achieved trough vancomycin concentrations between 15 to 20 mg/L and 15% of patients displayed

trough concentrations in excess of 25 mg/L. Only 6% of patients had trough concentrations below 10 mg/L.

Vandecasteele and associates proposed the following dosing guidelines for hemodialysis patients requiring vancomcyin therapy: (1) administer a loading dose of 20-25 mg/kg using actual dry body weight (dose not to exceed 4 grams); (2) infuse vancomycin at a rate of 15 mg/minute such that the infusion ends with the dialysis session; (3) check trough concentrations before each dialysis session; (4) aim for a target trough concentration of 15 to 20 mg/L; and (5) maintenance doses should be based on trough levels, interdialytic elapse, residual renal function, and body weight.[1]

Recently, a novel approach for dosing vancomycin in patients undergoing intermittent hemodialysis was highlighted in a report by Vandecasteele et al.[2] A vancomycin dose calculator was developed and assessed for its accuracy in achieving trough concentrations of 15-20 mg/L in 18 patients requiring intermittent hemodialysis. This multivariate model showed that predialysis vancomycin trough concentration, dry body weight, and interdialytic elapse accounted for nearly 95% of the variance observed. Patients received a fixed loading dose infusion of 20 mg/kg timed to end with the dialysis session. The median vancomycin maintenance dose was 8.05 mg/kg (given during subsequent dialysis sessions); approximately 78% of patients achieved trough target concentrations ranging from 15 to 20 mg/L.

RESISTANCE, WEIGHT-BASED DOSING

Since vancomycin is frequently used in patients undergoing intermittent hemodialysis, healthcare professionals need to monitor trough concentrations of this agent in order to prevent the occurrence of adverse events and sub-therapeutic levels. The emergence of resistance to vancomycin has resulted in a new emphasis on achieving target trough concentrations of 15-20 mg/L in patients with complicated infections caused by *S. aureus*.

Given the poor success rate of achieving trough concentrations of 15-20 mg/L with the use of fixed dosing regimens (1000 mg loading dose, followed by supplemental doses of 500 or 1000 mg), it would be prudent to use weight-based dosing regimens of vancomycin in patients undergoing intermittent hemodialysis. Areas of uncertainty in the dosing of vancomycin in this special population include selection of appropriate doses based on interdialytic elapse and the patients' residual renal function.[2,9] Some experts in the fields of nephrology and infectious disease have proposed using loading doses of 15 mg/kg, 25 mg/kg, and 35 mg/kg, respectively, for 1-day, 2-day, and 3-day interdialytic elapses.[2] Future studies are needed to determine optimal maintenance doses of vancomycin, since patient-specific factors such as weight and the extent of residual renal function may influence dosing.[9] ■

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READERS Write

Itraconazole and adrenal function

By David A. Stevens, MD, Chief, Division Infectious Disease, Santa Clara Valley Medical Center, San Jose, CA, Professor of Medicine,Stanford University

In a recent discussion of a clinical case in the *New England Journal of Medicine*[1], the authors correctly indicate itraconazole is recommended for all but the most severe cases of disseminated histoplasmosis (when amphotericin B is used). Fluconazole, though recognized as inferior, was selected for the patient's therapy, owing to concerns about itraconazole-mediated adrenal suppression (the patient had fungal adrenal involvement).

There may be unwarranted concern about adrenal suppression by itraconazole. Although another related triazole, ketoconazole, was indeed shown by us to block steroid synthesis and suppress adrenal function (the key references and the history are given in ref. 2), sufficient to actually be useful to treat Cushing's syndrome, there is, in contrast, negligible evidence of any adrenal suppression by itraconazole.[2-5].

In chronic dosing up to 200 mg itraconazole daily in volunteers and patients, plasma cortisol levels and response to ACTH were normal.[3] In doses up to 400 mg/day, the usual dose for systemic infections, responses to ACTH in patients were shown to be normal.[4] At high (>400 mg/day) doses, only one of 8 patients, receiving 600 mg/day, had a blunted response to ACTH, after a month of therapy.[5] After 6 weeks of therapy, that patient had symptoms and laboratory values consistent with depressed adrenal function. When the daily dose was then dropped to 400 mg, these findings reversed.

The superior drug for histoplasmosis therapy could have been used, with monitoring of adrenal function and hormone supplementation if necessary, in the case presented.[1] ■

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ABSTRACT & COMMENTARY

Treating VAP: The Importance of Getting Initial Antibiotic Coverage Right

By David J. Pierson, MD, Professor Emeritus, Pulmonary and Critical Care Medicine, University of Washington, Seattle.

This story ran previously in the March 2012 issue of *Critical Care Alert* and was peer reviewed by William Thompson, MD. Dr. Pierson reports no financial relationships relevant to this field of study.

SYNOPSIS: In this study in which all patients with clinically suspected ventilator-associated pneumonia were given prompt empiric antibiotic therapy, wh ether that therapy turned out to be appropriate for the organisms recovered turned out to be an important determinant of patient outcomes.

SOURCE: Muscedere JG, et al for the Canadian Critical Care Trials Group. The adequacy of timely empiric antibiotic therapy for ventilator-associated pneumonia: An important determinant of outcome. *J Crit Care* 2011;Nov 30. [Epub ahead of print.]

This study was a secondary analysis of data from an earlier randomized clinical trial comparing one antibiotic vs two (meropenem alone or meropenem plus ciprofloxacin) as early empiric therapy for ventilator-associated pneumonia (VAP). In that study, once the clinical suspicion of VAP (CSVAP) had been established, lower-airway culture specimens were obtained (by endotracheal suction in half the patients and bronchoalveolar lavage in half, via a stratified design) and empiric antibiotics begun within a median of 9 hours. Here, the authors examined outcomes in that study (ICU and hospital mortality, days of mechanical ventilation, and ICU and hospital lengths of stay) among the 47% of the originally enrolled patients who were proven microbiologically to have VAP, according to whether the recovered organisms were sensitive to the antibiotics used. Bacteriologic results from the two diagnostic procedure groups were combined for the purposes of this study, and all patients determined in the earlier trial to have had VAP were adjudicated by the authors to confirm this diagnosis clinically and microbiologically.

Thus, this was a retrospective analysis of outcomes in the 350 patients with positive cultures from among 739 with CSVAP who were begun promptly on empiric broad-spectrum antibiotic therapy. The 37 patients (10.6%) with one or more organisms that were not susceptible to the initially administered antibiotics (inadequate therapy, IT) were compared to the 313 patients (89.4%) whose infecting organisms were sensitive to what they received (appropriate therapy, AT).

The IT group had statistically higher mortality, both in the ICU (35.1% vs 11.8%; $P = 0.0001$) and in the hospital (48.7% vs 19.5%; $P = 0.02$). They also spent more days on mechanical ventilation (15.8 vs 16.8 days; $P = 0.0005$), in the ICU (13.5 vs 8.4 days; $P = 0.02$), and in the hospital (42.2 vs 27.9 days; $P = 0.04$), than those in the AT group. In a separate 3:1 case-control analysis, the odds ratio of in-hospital mortality with IT was 3.00 (95% confidence interval, 1.24-7.24; $P = 0.01$).

■ COMMENTARY

In previous studies of CSVAP in which empiric broad-spectrum antibiotic treatment has been given initially and then tailored to the results of microbiologic studies among patients who prove to actually have VAP, worse outcomes have been documented in those who do not initially receive AT. However, in those studies empiric therapy in patients with initial IT has often been both microbiologically inappropriate and delayed. This is the first study to look specifically at the issue of appropriate empiric antibiotics in the context of all patients having received antibiotics promptly once CSVAP was identified. Thus, the authors were able to take the confounding variable of the timing of initial antibiotic therapy out of the equation. They demonstrate that the microbiologic appropriateness of the initial antibiotic(s) given is a significant determinant of patient outcome.

The selection of an appropriate initial empiric antibiotic regimen, once a critically ill ventilated patient is clinically suspected of having VAP, remains a complicated and controversial task. The original clinical trial from which this secondary analysis was performed found no differences in outcomes among patients who had *Pseudomonas* as the causative organism with the two antibiotic regimens used. However, the number and choice of antibiotics in patients with CSVAP cannot be approached as a "one-size-fits-all" proposition. Local practice patterns and preferences enter into it, as do the patient's immune status and recent antibiotic history, plus local VAP organism prevalence, resistance patterns, and the institution's current "antibiogram." This study's findings, though, support the concept that initial empiric antibiotic therapy for CSVAP needs to be begun promptly and be broad enough to cover the likely causative organism(s), in that context and for that patient. Once culture results are available, coverage can be narrowed appropriately. ■

ABSTRACT & COMMENTARY

Cytomegalovirus in Pregnancy

By John C. Hobbins, MD, Professor, Department of Obstetrics and Gynecology, University of Colorado Health Sciences Center, Denver

This story ran previously in the January 2012 issue of *OB/GYN Clinical Alert* and was peer reviewed by Catherine Leclair, MD. Dr. Hobbins reports no financial relationships relevant to this field of study.

SYNOPSIS: In 528 women who were infected with CMV at various times before and during pregnancy, fetal transmission was the least in the preconception and periconception period.

SOURCE: Feldman B, et al. Pregestional, perigestional, and gestational primary maternal CMV infection: Prenatal diagnosis in 508 pregnancies. *Am J Obstet Gynecol* 2011; 205:342 e1-6.

Dealing with cytomegalovirus (CMV) can be vexing for everybody involved, but a recent paper may help with the management and counseling of patients infected with this virus at different times before and during pregnancy. Feldman et al studied 580 pregnant patients who were diagnosed with seriologic evidence of CMV infection. Patients were broken up into five groups depending on when the infection occurred: preconception (before 8 weeks prior to conception), periconception (within 8 weeks prior to and 6 weeks after conception), first trimester, second trimester, and third trimester. There were 16 twin pregnancies included in the study, bringing the total number of fetuses to 524. Specifically, there were 97, 130, 152, 100, and 29 patients in the above chronological categories, respectively.

Amniocenteses were performed in all women after 21 weeks and after at least 7 weeks post sero-conversion. The amniotic fluids were tested for CMV by polymerase chain reaction (PCR). All pregnancies were monitored with ultrasound and all newborns were carefully evaluated for signs of sequelae.

There was no transmission of the virus in the pre-conception group, only 4.6% in the peri-conception group, 34.8% in the first trimester, 42% in second trimester, and 58% in the third trimester groups. There were 45 infected infants born alive, none were symptomatic at birth. In the third trimester group, there were no ultrasound signs of CNS involvement before birth, and all infants appeared normal at 18 months of age.

The authors concluded that CMV infection prior to 8 weeks of conception does not result in transmission of the virus and that peri-conception infection up until 6 weeks of gestation had less than a 5% chance of fetal transmission. First and second trimester exposure could have an effect on the 30-40% of fetuses in whom the virus was found. However, although there was a high transmission rate in the third trimester, none of the infants appeared to be affected by the CMV.

■ COMMENTARY

The emergence of this paper coincided with a counseling dilemma we had regarding a patient who appeared in the second trimester with an elevated sequential screen for Down syndrome. At 21 weeks, the fetus was noted to be small for dates and had a few soft markers for Down syndrome, including echogenic bowel. When the amniocentesis was productive of normal chromosomes, we screened her for cystic fibrosis—which was negative. At the time of her follow-up ultrasound examination, the fetus showed adequate growth, but the bowel remained weakly echogenic. Reaching a bit, we did an infectious workup. The CMV IgG was strongly positive and the IgM was at the laboratory's threshold of normal. We repeated the titer and the IgM was then solidly negative. We resurrected the frozen amniotic fluid sample and tested the supernatant for CMV with PCR. This was negative. We also did avidity testing on the patient's blood, which returned as "high," suggesting a non-recent infection.

The above paper helped us to counsel this couple that the likelihood of their baby being affected by CMV was remote based on the premise that the time of exposure was pre- or, at worst, peri-conception.

The finding that triggered this diagnostic saga was echogenic bowel. In the vast majority of cases, this is a normal variant and commonly occurs when fetuses swallow particulate material in the amniotic fluid that light up the bowel. Sometimes they are heme pigments which can be linked to an episode of first or second trimester vaginal bleeding. However, it can be a marker for aneuploidy, cystic fibrosis, or even early IUGR (especially when coupled with high hCG or inhibin-A). A lesser possibility is CMV, and, in this case, I think the finding was unassociated with this condition. In fact, isolated echogenic bowel is so common and, in our experience, so rarely associated with CMV, that we often will not test for it. ■

Updates

By Carol A. Kemper, MD, FACP

Barriers to Preventing Infant HIV

Whitmore SK, et al. Correlates of mother-to-child transmission of HIV in the United States and Puerto Rico. *Pediatrics* 2012; 129 (1):e74-81

The number of infants born with HIV-infection in the United States reached its peak in 1991 with about 1650 HIV-infected infants, at which point the implementation of prevention guidelines resulted in a rapid reduction in neonatal infection. By 2004 and 2005, the number of cases of maternal-to-child-transmission (MTCT) resulted in 138 and 247 HIV+ infants, respectively, with an estimated transmission rate of 2.8%. Despite this improvement, barriers to elimination of MTCT remain, and approximately 250 infant HIV infections continue to occur annually in the United States. Most MTCT occurs as the result of a lack of prenatal care or failure to receive antiretroviral therapy (ART) during pregnancy. Newer guidelines published in 2006, and updated in 2011, attempted to address this problem, with recommendations for routine screening of all pregnant women, as early as possible in pregnancy; with additional testing for those at increased risk for HIV in the 3rd trimester (e.g., injectable drug users or partners of injectable drug users)[1]. Rapid HIV testing was recommended for mothers presenting for delivery who had not been screened during pregnancy, so that appropriate peri-partum ART could be administered (recognizing that a certain number of mothers and babies may receive inappropriate ART for a falsely-positive rapid test). Nonetheless, MTCT is still occurring, largely as result of "missed opportunities" for intervention.

Using the Enhanced Perinatal Suveillance System, these authors examined the data for live births to HIV+ mothers within 15 U.S. jurisdictions and Puerto Rico from 2005-2008, characterized those "missed opportunities". Missed opportunities were defined as a lack of prenatal care; lack of HIV testing during pregnancy; lack of prenatal HIV medication; lack of intrapartum HIV medication; lack of ART for the exposed infant; failure to perform cesarean section for women with detectable HIV viral loads > 1000 copies/mL; and breastfeeding.

Among 8054 live births to HIV+ mothers during the period of observation, 179 (2.2%) infants were diagnosed with HIV-infection. Overall, 52.6% of the 8,054 mother-infant pairs experienced at least one missed opportunity and all interventions were done in 32.3% (there was insufficient data available for 15.1%). Among HIV+ infants, 64.3% were attributed to at least one missed opportunity, for an overall transmission rate of 3.1%, compared with 1.1% for those receiving all of the interventions. The transmission rate was greatest for infants born to moms who did not get testing during their pregnancy (15.5%) compared with those who did (1.6%). A lack of ART during pregnancy resulted in a MTCT rate of 9.3% compared with 1.2% for those who were treated. A lack of prenatal care was associated with a MTCT rate of 8.5% compared with those who did receive prenatal care (1.6%). In addition, other factors significantly increased the risk of MTCT including the younger age of the mom (13-19 years), women with injectable drug use, and woman with CD4 counts < 200 cells/mL. For example, the transmission rate among HIV+ mother-infant pairs where the risk factor for HIV infection was injection drug use (22%) was 5.8% compared with those whose risk factor was listed as heterosexual exposure (45%) (2.1%).

Summarizing this data, MTCT could be attributed to a lack of maternal testing (either because of a lack of prenatal care or a lack of early testing during pregnancy) (26%), a lack of ART during pregnancy (45%), and breastfeeding (10%). These data indicate that 90% of maternal child HIV transmission can be prevented by getting women into prenatal care, prompt HIV testing during pregnancy, and appropriate treatment.

Reference

1. Department of Health and Human Services Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States, September 14, 2011: http://1.usa.gov/xj7Qo8 ■

The problem with C difficile Infection

Centers for Disease Control and Prevention. Vital Signs: Preventing Clostridium difficile infection. *MMWR* 2012;61(9): 157-162.

This report attempts to catalogue the ballooning number of cases of C difficile infection (CDI) in the United States using available resources, including data collected from the IDSA Emerging Infections Program (which has a catchment area of 111 acute-care hospitals and 310 nursing homes); the 2010 National Health and Safety Network data, which covers 711 acute care hospitals in 28 States; and data derived from 3 CDI prevention programs in 3 different states. A case of CDI was defined a positive test for CD in persons without a positive test within the previous 8 weeks. Enzyme immunoassay for toxin A and/or B was used to diagnose 51% of cases, while nucleic acid amplification test was used in 33% (other tests, not clarified, were used in 12%).

Based on the Emerging Infection Program data, 10,342 cases of CDI occurred in 2010, 44% of which occurred in people < 65 years of age. Based on available data, 94% of these had some kind of health care exposure within the preceeding 12 weeks. A total of 75% occurred outside of the hospital (44% were attributed to community-onset and 25% to nursing home onset), while 24% were hospital onset. The authors argue this data may, on the surface, be misleading and that deeper analysis reveals that 21% of hospital-onset cases occurred in nursing home residents and 67% of nursing home cases occurred in patients who had recently been hospitalized.

According to the 2010 NHSN data from acute care hospitals in 28 states, 42,157 laboratory-incidents of CDI were identified, 52% of which were present on admission to hospital (pooled hospital-onset CDI rate = 7.4/10,000 hospital days).

A collection of 71 hospitals in 3 different States participating in CDI prevention programs served as a third source. Using a variety of measures, these programs demonstrated a 20% reduction in CDI rates during a 21-month period of observation (from 9.3 to 7.5 per 10,000 hospital days). The specific measures were not detailed, but involved prompt testing of suspect cases, isolation of suspect and confirmed cases, improved environmental measures, and antibacterial stewardship.

The authors acknowledge problems with this data, including the definition of CDI — while some cases are defined based on laboratory test results alone, the NHSN data requires concurrent symptoms with 3 or more loose stools per day. Test assays with varying sensitivity also differ between facilities, yielding potentially different results (hospitals using the newer nucleic acid testing may get unfairly dinged for enhanced case detection). In addition, adherence to the case definition of hospital-onset if > 72 post-admission obviously biases the results towards implicating hospitals as the "source" for infection — since the inherent time delay in the recognition of symptoms, ordering the test, and submitting a sample all serve to push forward the time of diagnosis — at least based on a lab report and not symptom-onset.

While the effort to enhance reporting of CDI is laudable (CDI is not even listed as a "reportable" pathogen in our country) does anyone truly believe the problem begins with hospitals or that hospitals are to blame? The plan for Medicare and Medicaid Services Inpatient Prospective Payment System Quality Reporting Program to tie reimbursement to CDI hospital rates is preposterous — and only serves to take much needed dollars away from hospital efforts to prevent this infection.

These punitive efforts are missing the point: Every patient should feel comfortable their life is not in danger when receiving appropriate and necessary antibiotics — which is presently not the case. I recently saw a patient nearly die from CDI following receipt of a single dose of peri-operative cefazolin for a routine hip procedure. What we really need is a focus on how people acquire this organism, limiting exposure in long-term care facilities (where isolation and environmental hygiene is often lacking), eliminating CD from food sources, methods to quickly identify patients at risk before they receive antibacterials, and improving methods to prevent infection in patients at risk. ■

ID drug shortages threaten patient safety

Griffith MM, et al. The impact of anti-infective drug shortages on hospitals in the United States: Trends and causes. *CID* 2012: 54: 684-691

Recent efforts to treat a patient in hospital with acute pneumocystis pneumonia (PCP) were hampered by a lack of available injectable trimethoprim-sulfamethoxazole. The hospital pharmacy staff begged a few doses from the county and from the veteran's hospital in

Palo Alto, but eventually I was forced to switch this patient to oral atovaquone, a second-line agent. At least the patient got through the more critical period of treatment, and gradually improved. Unfortunately, this scenario is becoming all too familiar to infectious disease specialists. Hardly a month goes by where I am not faced with a difficult therapeutic decision precipitated by a drug shortage of some kind. Coupled with the rise in antibacterial resistance, drug shortages can have a significant impact on medical care.

This salient article examines the clinical dilemmas created by the increasing frequency of critical drug shortages, and summarizes the current anti-infective drug shortages in the United States. Were you aware there is an entity called the Center for Drug Evaluation and Research (CDER) Drug Shortage Program of the FDA, which tracks the availability (or non-availability) of pharmaceuticals and anti-infectives in use? The CDER defines a drug shortage as "a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand…"

Such shortages often lead to clinical dilemmas, result in delays in initiation of treatment (while staff attempt to clarify availability of drug and hunt for a supply); often require an alternate and possibly less effective therapy, with the potential for worse outcome.

As of February 2011, a total of 193 agents were officially listed on the CDER's drug shortage list, 13% of which were anti-infectives. Some of these agents have been on the CDER list for months or years. In 2008, 5 anti-infective agents were listed on the CDER drug shortage list, one of which had not been resolved as of February 2011. Shortages of 6 of 11 agents listed in 2009 and 12 of 17 listed in 2011 had not been resolved and remain in short supply or are unavailable.

The government's role is mostly passive in this process, and can provide only oversight and monitoring, although they are charged with monitoring good manufacturing practice (GMP), and can help to precipitate a drug shortage by halting production of a drug or vaccine if a company fails to meet GMP standards. Drug shortages occur for a variety of reasons, including the lack of raw materials; a company can shut down manufacturing because of problems in a facility, or the FDA can interrupt production (as has been the case with Influenza vaccine and PCN G). For example, manufacturing issues hampered the production of injectable acyclovir, the only agent recommended for the treatment of HSV and VZV encephalitis. The shortage of PCN G in 2007, which is manufactured by a single company, created a serious problem for physicians attempting to treat neurosyphilis (inferior agents such as tetracycline and ceftriaxone had to be used). Manufacturing issues hampered production of injectable TMP-SMZ in May 2010, a problem that has still not been fully resolved; creating difficult decisions when attempting to treat PCP and infections due to Stenotrophomas maltophilia.

Occasionally, the demand for certain anti-infectives may outstrip production (as has occurred with Polymixin B, isoniazid, and mupirocin nasal ointment). Changes in clinical guidelines may also create an increased demand for certain agents, which existing production can not meet. Shortages of vaccines have also posed problems, including vaccines for Influenza, varicella, herpes zoster, yellow fever, and Hepatitis B.

In addition, a company can choose to halt or stop production of any agent for any reason, and they are not legally required to provide an explanation, nor are they required to provide status updates regarding any particular drug. Some drugs just disappear from the market, presumably as a marketing decision. Companies are required to provide 6 months notice to the FDA before ending production of a "medically necessary" drug. If they are the only manufacturer, the definition of medically necessary may be open for debate. For example, when Wyeth began marketing tigecycline in 2005, their other product, parenteral minocycline, was dropped from the market. It turns out that IV minocycline may prove to be one of the most useful agents against some strains of multidrug resistant Acinetobacter baumannii.

A panel of experts from several national associations has proposed changes to the FDAs current role, and a current U.S. Senate bill seeks to amend the law regarding manufacturer notification before halting production of any agent that could potentially lead to a shortage, as well as other recommendations made by a U.S House of Representatives Bill (Preserving Access to Life-Saving Medications Act). Those with opinions regarding this subject should contact their U.S. congressman or senator. ■

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. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.

3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.

5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. Which of the following is correct with regard to bacteremia in full term infants in California presenting from 1 week to 3 months of age?

A. The most frequently isolated pathogen is *Escherichia coli*.
B. The most frequently isolated pathogen is Group B Streptococcus.
C. The most frequently isolated pathogen is *Staphylococcus aureus*.
D. The most frequently isolated pathogen is *Listeria monocytogenes*.

2. Which of the following is correct with regard to the effect of itraconazole on adrenal function?

A. A blunted response to ACTH was first detected at a chronic dose of 200 mg daily.
B. A blunted response to ACTH was first detected at a chronic dose of 400 mg daily.
C. A blunted response to ACTH was first detected at a chronic dose of 600 mg daily.
D. A blunted response to ACTH was first detected at a chronic dose of 800 mg daily.

3. Which of the following is correct with regard to cytomegalovirus infection in pregnancy?

A. Transmission to the infant was most likely to occur when infection occurred after maternal infection during the preconception (before 8 weeks prior to conception) phase.
B. Transmission to the infant was most likely to occur when infection occurred after maternal infection during the periconception (before 8 weeks prior to conception) phase.
C. Transmission to the infant was most likely to occur when infection occurred after maternal infection during the first trimester.
D. Transmission to the infant was most likely to occur when infection occurred after maternal infection during the third trimester.

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]

Human rhinoviruses in severe respiratory disease in very low birth weight infants

Epstein-barr virus co-infection in cerebrospinal fluid

Listeria in Prosthetic joints

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.*

Statins and the Risk of Diabetes

In this issue: Statins and diabetes risk; new treatment guideline for diabetes; new pertussis vaccine recommendation; antibiotics and rhinosinusitis; fluoroquinolones and cystitis; and FDA actions.

Do statins increase the risk of diabetes?

Studies have suggested that statins may increase the risk of diabetes in the elderly, women, and Asians. A new study reviews data from the 162,000 postmenopausal women enrolled in the Women's Health Initiative to investigate whether the incidence of new onset diabetes mellitus (DM) is associated with statin use among these women. This study reviewed records from women who were enrolled between 1993 and 1998 through 2005. More than 7% of the women in the study reported taking statins. Statin use at baseline was associated with an increased risk of DM (hazard ratio, 1.71; 95% confidence interval, 1.61-1.81). This association remained after adjusting for other potential confounders, including obesity, and was observed for all types of statin medications. The authors conclude that statin medication use in postmenopausal woman is associated with an increased risk for DM and that this may be a medication class effect (*Arch Intern Med* 2012;172:144-152). As pointed out in a brief comment in the same issue, observational data are potentially susceptible to "bias (confounding) by indication." In other words, women who would be prescribed statins may be inherently at risk for DM. This study did a good job of evaluating women with and without a history of cardiovascular disease and found that there was still an increased risk of DM. This finding "may have important implications for the balance of risk and benefit of statins in the setting of primary prevention in which previous meta-analyses show no benefit on all-cause mortality." The FDA has issued a new warning about statins and the risk of diabetes (see FDA actions). ■

Oral medications for diabetes

The American College of Physicians has published a new guideline for the "Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus" in the February 21 issue of the *Annals of Internal Medicine*. The guideline suggests that if diet, exercise, and weight loss fail to improve hyperglycemia, oral drug therapy should be initiated. Most diabetes medicines lower HbA_{1c} levels to a similar degree, and none of the medications have compelling outcomes data to suggest one class is superior to another class with regard to cardiovascular or all-cause mortality. But metformin "was more effective than other medications as monotherapy as well as when used in combination therapy with another agent for reducing HbA_{1c} levels, body weight, and plasma lipid levels (in most cases)." Therefore, the guideline recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy for most patients with type 2 diabetes. Metformin is effective at reducing glycemic levels and is not associated with weight gain. Additionally, the drug helps reduce LDL cholesterol and triglyceride levels. Metformin is contraindicated in patients with impaired kidney function, decreased tissue perfusion or hemodynamic instability, liver disease, alcohol abuse, heart

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failure, and any conditions that might lead to lactic acidosis. For patients with persistent hyperglycemia despite metformin, a second drug should be added. No good evidence supports one combination over another. Sulfonylureas have a higher risk for hypoglycemia and thiazolidinediones are associated with an increased risk for heart failure. There are no specific recommendations for the use of the glinides (nateglinide or repaglinide) or the DPP-4 inhibitors (linagliptin, saxagliptin, or sitgliptin). The guideline does not make a recommendation for combinations of more than two oral agents. Injectables, such as the various insulins and GLP-1 analogs, were not addressed in the guideline. (*Ann Intern Med* 2012; 156:218-231). ■

New recommendation for Tdap vaccine

The Advisory Committee on Immunization Practices, a division of the Centers for Disease Control and Prevention, is recommending that all adults get immunized against pertussis (whooping cough). Previously the committee had recommended that only adults who spend time around infants or young children should be immunized. The goal of the expanded recommendation is to prevent teenagers and adults from spreading the disease to infants. In 2010, California experienced a pertussis outbreak that infected 9000 people and resulted in 10 infant fatalities. The adult vaccine combines tetanus, diphtheria, and acellular pertussis (Tdap). ■

Antibiotics not needed for rhinosinusitis

Physicians now have more ammunition for not treating patients with acute rhinosinusitis with antibiotics, based on the results of a new study that shows amoxicillin is of no benefit in these patients. Researchers at Washington University in St. Louis randomized 166 adults with uncomplicated, acute rhinosinusitis to a 10-day course of amoxicillin 500 mg three times a day or matching placebo. The main outcome (change in the Sinonasal Outcome Test) was not significantly different between the two groups at day 3 or day 10. There was a slight improvement in the antibiotic group at day 7. The authors conclude that "treatment with amoxicillin for 10 days offers little clinical benefit for patients clinically diagnosed with uncomplicated acute rhinosinusitis." Patients with symptoms indicative of serious complications were excluded from the trial (*JAMA* 2012;307:685-692). ■

Fluoroquinolones for cystitis

Cefpodoxime is inferior to ciprofloxacin for short-course treatment of acute uncomplicated cystitis in women, according to new study. In a randomized, double-blind trial, 300 women ages 18-55 with uncomplicated cystitis were randomized to ciprofloxacin 250 mg orally twice daily for 3 days or cefpodoxime 100 mg twice daily for 3 days. The overall clinical cure rate with the intent-to-treat approach in which patients lost to follow-up were considered as having a clinical cure was 93% for ciprofloxacin compared to 82% for cefpodoxime. For the intent-to-treat approach in which patients lost to follow-up were considered as not having responded to treatment, the clinical cure rate was 83% for ciprofloxacin compared to 71% for cefpodoxime. The microbiological cure rate was 96% for ciprofloxacin compared with 81% for cefpodoxime. At follow-up, 16% of women in the ciprofloxacin group had vaginal *Escherichia coli* colonization compared with 40% in the cefpodoxime group. The authors conclude that cefpodoxime did not meet criteria for non-inferiority to ciprofloxacin for treating uncomplicated cystitis in women (*JAMA* 2012;307:583-589). The study is somewhat disappointing given the increasing rates of fluoroquinolone resistance in the community and the need for effective alternatives. ■

FDA actions

The FDA has issued a new warning and is requiring label changes to all statins regarding the risk of elevated blood sugar and reversible cognitive changes. The agency is making these changes after a comprehensive review of multiple studies that show increases in blood sugar associated with the drugs. A separate labeling change warns that cognitive effects have been reported with statin use, including transient memory loss and confusion — symptoms that are reversible with stopping the medication. There is no evidence that statins are associated with long-term cognitive changes or dementia. Statins affected by these warnings include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. In a separate warning, lovastatin is now contraindicated with strong CYP3A4 inhibitors, such as itraconazole and erythromycin. This is a similar warning to that issued for simvastatin in 2011.

In one of the strangest stories of the year, the FDA is warning oncologists that a counterfeit version of bevacizumab (Avastin) may have been purchased and used by some medical practices in the United States. The counterfeit version does not contain any active drug and may have resulted in patients not receiving needed therapy. Counterfeit bevacizumab was purchased from a foreign supplier known as Quality Specialty Products or Montana Health Care Solutions. The FDA is recommending that physicians stop using bevacizumab purchased from the suppliers and call the FDA immediately. ■