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Infectious Disease [ALERT]

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

SPECIAL FEATURE

Colistimethate: Risk of Serious or Fatal Medication Error

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

The National Medication Error Reporting Program (operated by the Institute for Safe Medication Practices [ISMP]) recently issued an alert on the potential risk of medication errors associated with dosing colistimethate for injection.[1] Numerous commercial preparations of colistimethate are available worldwide, and their differences have made evaluation of doses reported in clinical studies difficult to interpret when drug formulations were not fully described by investigators.[2]

Colistin (polymyxin E) was isolated from *Bacillus colistinus* 60 years ago and, during the 1960s, a new intravenous formulation (Coly-Mycin M Parenteral) became available for use in clinical practice.[3-5] Despite widespread use of colistimethate during the first two decades after its introduction, the emergence of reports of serious adverse events caused this agent to fall out of favor in the medical community.[6] At present, expansion of multi-drug resistant bacteria, including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and carbapenemase-producing *Enterobacteriaceae* has resulted in renewed interest in old antimicrobial agents such as colistimethate.[7]

The National Medication Error Reporting Program's alert highlighted a recent case in which the

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prescribing physician mistakenly ordered a dose of colistimethate approximately 2.5 times in excess of the usual recommended dose.[1] The pharmacists and nurses failed to recognize the dosing error; the patient developed acute renal failure, along with other complications, and died. DeRyke and associates reported key findings from their retrospective cohort study of adult patients who received a minimum of 48 hours of intravenous colistimethate for injection.[8] Ten of 30 patients received doses that were calculated based on actual body weight, instead of ideal body weight. The risk for developing nephrotoxicity was approximately 13 times higher in patients who received doses based on actual body weight compared with patients who received normal or low-normal doses ($P = 0.005$).

The purpose of this article is to discuss dosing formulations of commercially available colistimethate, and to provide dosing recommendations for patients with deviations in ideal body weight, along with recommending dosing in renally impaired patients.

COLISTIN FORMULATIONS

Two forms of colistin are distributed as commercially available products: colistin sulfate and colistimethate sodium (also known as colistin methanesulfate and colistin sulphomethate sodium). Because of its toxicity profile, colistin sulfate is restricted to topical use; colistimethate is used for parenteral or nebulized administration.[6]

Colistimethate, a polyanion at physiological pH, undergoes hydrolysis to yield a series of methanesulphonated derivatives and colistin, which is a polycation entity. Coly-Mycin M Parenteral is produced by JHP Pharmaceuticals LLC in the United States.[9] The current FDA-approved package insert for Coly-Mycin M Parenteral states that each vial contains 150 mg of colistin base and should be given at a dose of 2.5-5 mg/kg/day (not to exceed 300 mg/day; based on ideal body weight) in 2-4 divided doses. Given that there is 360 mg of colistimethate per 150 mg of colistin base, this translates into a 2.4-fold higher recommended dose of the colistimethate equivalent.[10]

A commonly used formulation of colistimethate in Europe is Colomycin injection, produced by Dumex-Alpharma A/S (Copenhagen, Denmark). The package insert states that each million units of the product contain 80 mg of colistimethate (12,500 units/mg). The colistin formulation distributed by Norma Pharmaceuticals (Greece) has been reported to consist of 12,500-13,300 units/mg.[10]

DOSING RECOMMENDATIONS: MINIMIZING RISK FOR ERROR

The FDA-approved package insert for Coly-Mycin states that patients with a serum creatinine of 1.3-1.5 mg/dL should be given 2.5-3.8 mg/kg of colistin base (6-9.1 mg/kg colistimethate) daily, in two divided doses. Patients with a serum creatinine of 1.6-2.5 mg/dL should be given 2.5 mg/kg of colistin base (6 mg/kg colistimethate) daily, in one or two divided doses. When serum creatinine increases to 2.6-4.0 mg/dL, the patient should receive 1.5 mg/kg of colistin base (3.6 mg/kg colistimethate) every 36 hours. The manufacturer does not provide dosing recommendations for hemodialysis patients or for peritoneal dialysis patients.[9]

A previously published article in *Infectious Disease Alert* summarized dosing recommendations in renally impaired patients.[11] Renal dose adjustments of colistimethate recommended by Marchand et al, Li et al, and Curtis et al are summarized in Table 1.[12-14] In addition, dose adjustments of colistimethate in patients with deviations in ideal body weight also can be found in Table 1.[15-17]

CONCLUSION

Based on the ambiguity of product nomenclature and the complexity of dosing colistimethate in special populations, the following guidelines should be considered by health care professionals:

- Restrict the ordering of colistimethate to Infectious Disease

Table 1. Dosing of Colistimethate for Injection.

Generic name Brand name (United States)	Colistin base Coly-Mycin®
Other names cited in literature	Colomycin (Dumex-Alpharma A/S, Copenhagen, Denmark); Colistimethate Sodium (Colistin Sulphomethate Sodium)
Differences between products	Coly-Mycin (Colistin base) contains 150 mg colistin base per vial • 150 mg colistin base = 360 mg colistimethate sodium • 1 million units Colomycin = 80 mg colistimethate sodium
Coly-Mycin dose if SCr < 1.3 mg/dL	2.5-5.0 mg/kg/day of colistin base (divided in 2-4 doses), based on ideal body weight (IBW) (see explanation below)
Calculation of IBW	Female: 45.5 kg + 2.3 (# inches above 60 inches) Male: 50 kg + 2.3 (# inches above 60 inches) Note: If a patient weighs less than IBW, use actual body weight.
Deviations in IBW[15-17]	Disability adjustment in IBW: • Subtract 5%-10% from IBW for paraplegia • Subtract 10%-15% from IBW for quadriplegia Amputee adjustment in IBW: • Entire leg and foot: Subtract 18.5% from IBW • Above the knee: Subtract 13% from IBW • Below the knee: Subtract 6% from IBW • Foot: Subtract 1.8% from IBW • Entire arm and hand: Subtract 6.5% from IBW • Forearm and hand: Subtract 3% from IBW
Coly-Mycin dose if SCr ≥ 1.3 mg/dL	SCr 1.3-1.5 mg/dL: 2.5-3.8 mg/kg/day (divided BID) SCr 1.6-2.5 mg/dL: 2.5 mg/kg/day (divided BID) SCr 2.6-4.0 mg/dL: 1.5 mg/kg Q 36 hours
Coly-Mycin dose in intermittent hemodialysis[12]	Limited data, but Marchand et al recommended: 67 mg Colistin base (equivalent to 2 million units of Colomycin) IV Q 12 hours
Coly-Mycin dose in continuous veno-venous hemodiafiltration[13]	Limited data, but Li et al recommended: 2-3 mg/kg Colistin base IV Q 12 hours based on IBW
Coly-Mycin dose in peritoneal dialysis[14]	Limited data, but Curtis et al recommended: 2-3 mg/kg colistimethate IV Q 72 hours (divide by 2.4 to obtain equivalent Colistin base dose)

Consult Services

- Orders for colistimethate for injection should be written as colistin in terms of base activity, with doses ranging from 2.5 to 5.0 mg/kg/day (divided in 2-4 doses) in patients with normal renal function. Ideal body weight should be used for calculating the dose of colistimethate in obese patients.
- Refer to the FDA-approved package insert for reducing doses of colistimethate in renally impaired patients.
- If the order is written as "colistimethate" or "colistimethate sodium," the ordering physician should be contacted to verify the order in terms of colistin base.
- Patients receiving colistimethate for injection should be monitored for changes in renal function and the appropriateness of dosage should be assessed periodically during treatment. ■

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ABSTRACT & COMMENTARY

Anti-staphylococcal β-lactam Antibiotics Potentiate Daptomycin Activity vs. MRSA

By Dean L. Winslow, MD, FACP, FIDSA
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Clinical Professor, Stanford University School of Medicine
Dr. Winslow is a speaker for GSK and is a consultant for Siemens Diagnostics.

SYNOPSIS: Daptomycin (DAP) plus anti-staphylococcal β-lactam antibiotics (ASBLs) were used to clear refractory MRSA bacteremia. These β-lactam antibiotics produced in vitro enhancement of DAP bactericidal activity, increased cell membrane daptomycin binding, and decreased positive surface charge in DAP-nonsusceptible MRSA.

SOURCES: Dhand A, et al. Use of antistaphylococcal β-lactams to increase daptomycin activity in eradicating persistent bacteremia due to methicillin-resistant Staphylococcus aureus: Role of enhanced daptomycin binding. Clin Infect Dis 2011;53:158-163.

Seven patients were identified when DAP-ASBL therapy was used to eradicate persistent MRSA bacteremia. Isolates from 3 patients were available for in vitro study. Standard minimum inhibitory concentrations (MICs) were determined and time-kill curves in Mueller-Hinton broth media were performed on the three isolates using DAP (10 μg/mL) alone and in combination with oxacillin 20 μg/mL. A DAP-resistant strain isolated from 1 patient was studied using fluorescein-labeled DAP.

Of the three well-characterized isolates of MRSA studied, all received initial therapy with vancomycin for 4-11 days and experienced an increase in vancomycin MICs from 1-2 to 2-4 μg/mL. Second-line therapy of these 3 patients consisted of DAP given for an additional 4-6 days and DAP MIC rose from 0.5-0.75 to 0.75-4 μg/mL with this treatment. Third-line therapy consisted of DAP + gentamicin for 3-5 days followed by DAP + nafcillin for an additional 9-55 days. With fourth-line therapy (DAP + nafcillin), all patients cleared their MRSA bacteremia within 24 hours.

Time-kill curves showed no inhibition of growth with oxacillin by itself, delayed/partial killing of the isolates by DAP alone at 10 μg/mL, and marked enhancement of bactericidal activity of DAP (approximately 6 log10 reduction in viable bacteria at 13 hours) by the addition of oxacillin 20 μg/mL to DAP 10 μg/mL.

One DAP-resistant isolate demonstrated poor binding of DAP in the absence of ASBLs. However, in the presence of nafcillin 40 μg/mL, significant DAP binding was detected, focally and on the organism's surface. This same isolate demonstrated reduction in net-positive surface charge during growth in the presence of ASBLs.

■ COMMENTARY

MRSA has emerged in many regions of the world to be the predominant isolate of *Staphylococcus aureus*. The usual treatment for life-threatening bacteremic infections due to MRSA is IV vancomycin. Unfortunately, treatment failure manifested by persistent bacteremia is seen with increasing regularity and is commonly associated with the development of increasing vancomycin MICs while on therapy. While daptomycin often is

effective in treating infections due to vancomycin-insensitive strains of MRSA, development of DAP resistance on treatment with daptomycin also is seen in some cases and treatment options are often quite limited since bacteriostatic antibiotics like clindamycin and linezolid are seldom effective in the treatment of infective endocarditis and other intravascular infections.

This paper presents preliminary data on the successful treatment of 7 patients with bacteremic infection due to DAP-resistant MRSA using DAP + ASBLs. In addition, the in vitro studies on three isolates demonstrated enhanced bactericidal activity, increased cellular binding of DAP, and reduced net-positive surface charge in the presence of ASBLs. These are important observations, which suggest a mechanism for this clinically useful antibiotic interaction. We eagerly anticipate additional studies that will shed further light on the mechanisms of DAP resistance and the useful interaction between ASBLs and DAP in these difficult-to-treat bacteremic MRSA infections. ■

ABSTRACT & COMMENTARY

Cephalosporin-resistant Gonorrhea: It's Just a Matter of Time

By Stan Deresinski, MD, FISDA

SYNOPSIS: Cephalosporin "MIC creep" in Neisseria gonorrhoeae is occurring in the United States, with full-fledged resistance to follow.

SOURCES: Centers for Disease Control and Prevention (CDC). Cephalosporin susceptibility among Neisseria gonorrhoeae isolates — United States, 2000 —2010. MMWR Morb Mortal Wkly Rep 2011;60:873-877.

By 2007, the prevalence of fluoroquinolone resistance among *N. gonorrhoeae* had become so widespread in the United States that the CDC recommended against use of drugs of that class in the treatment of gonorrhea. When the CDC updated its guidelines for the treatment of sexually transmitted diseases in 2010, they noted that, at that time, the only class of antibiotics acceptable for empiric treatment of gonorrhea were cephalosporins. However, they also noted that approximately 50 cases of failure of oral cephalosporins (cefixime is recommended for oral therapy in the United States) had been reported worldwide, with most having occurred in Asia. One possible case of failure of cefixime therapy in Hawaii had, however, been reported. While cephalosporins still generally remain effective for treatment of gonorrhea in the United States, CDC has now documented "MIC creep" of *N. gonorrhoeae*, a harbinger of worse to come.

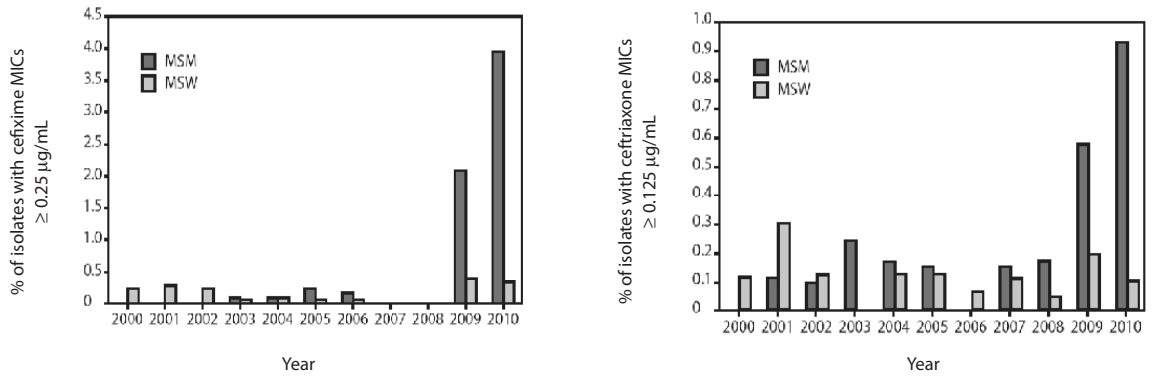
An average of almost 6,000 isolates from male urethras recovered at U.S. sentinel sites were tested against each year from 2000-2010 and the proportion of isolates with cefixime MIC ≥ 0.25 µg/mL and ceftriaxone with MIC ≥ 0.125 µg/mL was examined. Reduced susceptibility to these antibiotics is defined by CLSI as an MIC > 0.5 µg/mL; there are no defined breakpoints for resistance defined for *N. gonorrhoeae*.

The percentage of isolates with cefixime MIC ≥ 0.25 µg/mL increased from 0.2% to 1.4% during 2000-2010 ($P < 0.001$), while those with ceftriaxone MIC ≥ 0.125 µg/mL increased from 0.1% to 0.3% during 2000-2010 ($P = 0.047$). In the Western region of the United States, the proportion of isolates with cefixime MIC ≥ 0.25 µg/mL increased from 0% to 3.3% ($P < 0.001$), and the percentage of isolates with ceftriaxone MICs ≥ 0.125 µg/mL increased from 0% to 0.5% ($P < 0.001$). This reduced susceptibility was most marked in Honolulu, with cefixime MICs ≥ 0.25 µg/mL, increasing from 0% in 2000 to 7.7% of isolates in 2010 ($P < 0.001$). In California, the comparable results were 0% in 2000 and 4.5% in 2010 ($P < 0.001$). An increase in ceftriaxone MICs also was observed in California (0% in 2000 and 0.6% in 2010; $P = 0.001$). Overall in the United States, reduced susceptibility was more marked among men who have sex with men (MSM) than in others *(see Figure 1)*. Although azithromycin resistance has been previously reported, isolates in this study remained susceptible to this azalide.

■ COMMENTARY

The pattern of reduced susceptibility to cephalosporins noted by CDC is eerily reminiscent of the pattern observed with fluoroquinolones before full resistance emerged in *N. gonorrhoeae*. Thus, these data are almost certainly a harbinger

Figure 1. Percentage of gonorrhea isolates with cefixime MICs ≥ 0.25 µg/mL and ceftriaxone MICs ≥ 0.125 µg/mL, by sex of sex partner — Gonococcal Isolate Surveillance Project, United States, 2000-2010.



of continuing evolutionary change in this organism in the face of β-lactam exposure that will eventually lead to a high prevalence of full-fledged resistance to cephalosporins. The emergence of reduced susceptibility to cefixime surely predicts that ceftriaxone will follow. This is problematic, since agents from this class are currently critical to effective therapy of gonorrhea and no other effective antibiotic treatment options that have been well-studied are currently available.

CDC now recommends treating uncomplicated gonorrhea with ceftriaxone 250 mg intramuscularly and azithromycin 1 g by mouth. Patients should undergo test-of-cure and cultures, rather than just nucleic acid amplification tests, obtained from those with possible treatment failure so that antibiotic susceptibility can be determined. Patients with cefixime treatment failure should be re-treated with 250 mg ceftriaxone intramuscularly and 2 g azithromycin orally. ■

ABSTRACT & COMMENTARY

Plasma β-glucan for the Diagnosis of Pneumocystis Pneumonia in AIDS Patients

By Brian G. Blackburn, MD

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

SYNOPSIS: Among a cohort of AIDS patients with opportunistic infections, the sensitivity of plasma β-glucan for the diagnosis of Pneumocystis jirovecii pneumonia (PCP) was 92% and the specificity was 65%. Although an intriguing alternative, β-glucan did not perform well enough in this study to supplant sputum/BAL examination as the primary laboratory means of diagnosing PCP.

SOURCE: Sax PE, et al. Blood (1->3)-β-D-glucan as a diagnostic test for HIV-related Pneumocystis jirovecii pneumonia. Clin Infect Dis 2011;53:197-202.

Pneumocystis jirovecii pneumonia (PCP) is a common opportunistic infection (OI) in AIDS patients. Laboratory diagnosis of this life-threatening infection is based primarily upon identifying *P. jirovecii* cysts in respiratory secretions, a technique that is variably sensitive and requires adequate patient effort (for induced sputum examination) or an invasive test (bronchoscopy); both are quite operator dependent.[1]

β-glucan is a component of the cell wall of many fungi, including *P. jirovecii*. Earlier studies have suggested that measurement of β-glucan in the blood may have utility in the diagnosis of PCP.[2,3] The authors therefore undertook a study to evaluate the usefulness of this assay for diagnosing PCP in a cohort of AIDS patients with various OIs.

HIV-infected patients were recruited on the basis of having a suspected acute OI; patients with tuberculosis and some other OIs were excluded. Plasma samples from each patient were tested by the Fungitell® β-glucan assay (Associates of Cape Cod). The "gold standard" for the

diagnosis of PCP in the study was a combination of clinical, radiologic, and laboratory parameters, as adjudicated by the study investigators. Both probable and confirmed cases were included in the study, and for confirmed cases, the case definition included direct observation of *Pneumocystis* in respiratory secretions.

Two hundred fifty-two persons with a valid β-glucan result were included in the study. Their median CD4+ count was 26 cells/μL; 69% had PCP, 14% had cryptococcosis, 9% had bacterial pneumonia, 6% had a Mycobacterial infection, and 3% had histoplasmosis. Although by itself not an inclusionary criterion, 44% had oral/esophageal candidiasis in addition to another OI.

Median β-glucan levels were significantly higher in patients with PCP than in those without PCP (408 vs. 37 pg/mL; $P < 0.001$). Using a cutoff of 80 pg/mL, significantly more patients with PCP had a positive β-glucan result than those without PCP (92% vs. 35%; $P < 0.001$). Conversely, significantly fewer patients with PCP had a negative β-glucan result than those without PCP (8% vs. 65%; $P < 0.001$). Detection of β-glucan was not affected by antimicrobial treatment and did not correlate with disease severity (as measured by use of concomitant corticosteroids). The sensitivity of the test was 92%, specificity 65%, positive predictive value (PPV) 85%, and negative predictive value (NPV) 80%. β-glucan is not specific for *Pneumocystis*, and many patients with oral/esophageal candidiasis and histoplasmosis had positive β-glucan results.

■ COMMENTARY

At first glance, this report of the association between high β-glucan levels and AIDS-related PCP might seem a major step forward in the diagnosis of this infectious disease, particularly given the limitations of the induced sputum examination. Indeed, having a standardized, reliable serologic test would greatly simplify the diagnosis of PCP. However, several methodological problems hinder the interpretation of the study results. Given that only HIV-infected patients were enrolled, the results of this study are not generalizable to other immunocompromised populations. In addition, the lack of a true gold standard for the diagnosis of PCP means that interpretation of the sensitivity and specificity data in this study are subject to uncertainty. Data are not provided regarding the relative proportion of probable vs. confirmed cases, and the performance of β-glucan was assessed based upon a case definition that included only clinical and radiologic criteria for probable cases. Even among laboratory-confirmed cases (for which a positive direct examination of respiratory secretions was required), use of the very test against which β-glucan will be considered in the clinical setting as part of the gold standard definition is problematic.

Because β-glucan is a component of the cell wall of many fungi, it is inherently nonspecific for PCP. As the authors note, other fungi, hemodialysis, intravenous immunoglobulin, and even certain antimicrobials can cause false-positive results. Many patients in the study who had PCP also had candidiasis, further confounding interpretation of the results. Despite a specificity of only 65%, the PPV was a surprisingly high 85% (in part because of the high prevalence of PCP in the study population). Unfortunately, this PPV is still suboptimal for clinical practice, and may actually be lower in many real-world settings. Therefore, the true value of β-glucan testing may be instead to rule out PCP when negative, analogous to the use of other nonspecific (but highly sensitive) tests such as the D-dimer for pulmonary embolism, or the sedimentation rate and C-reactive protein for bone and joint infections.[4,5] Unfortunately, even with the relatively high sensitivity of 92%, the NPV of β-glucan was only 80% in this study, insufficiently low for this purpose. Perhaps adjusting the positive/negative cutoff to a lower β-glucan value, which would increase sensitivity (and thus NPV) at the expense of specificity, would maximize the use of β-glucan in this manner, rendering the diagnosis unlikely when negative, but leaving a positive result to be of less certain value.

At this point, PCP remains largely a clinical diagnosis, supported by direct visualization of respiratory secretions. β-glucan may have an emerging, supportive role, but at this point does not appear to be the Holy Grail we might have hoped for in the diagnosis of PCP. ■

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ABSTRACT & COMMENTARY

How Many Days of Ceftriaxone Is Enough for Meningitis?

By Alan D. Tice, MD, FACP
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Dr. Tice reports no financial relationship to this field of study.

SYNOPSIS: Standard therapy for bacterial meningitis in children is probably overkill but it is risky to cut back in resource-rich countries.

SOURCES: Molyneux E, et al; CSF 5 Study Group. 5 versus 10 days of treatment with ceftriaxone for bacterial meningitis in children: A double blind randomized equivalence study. Lancet 2011;377:1837-1845.

A consortium of 10 pediatric hospitals in Bangladesh, Egypt, Malawi, Pakistan, and Vietnam was assembled by the World Health Organization CSF5 study group with funding from the U.S. Agency for International Development to compare 5 days vs. 10 days of therapy with ceftriaxone. All patients received 5 days of antibiotic, then, if stable, were randomized to receive another 5 days or nothing more. The study started a decade ago and replaced usual therapy, which consisted of chloramphenicol — often combined with penicillin — that had a 40% fatality rate. The situation is a sad one in many of the resource-poor regions where there is a high incidence of meningitis, with estimates of 173,000 cases due to *Hemophilus influenza* type b and 103,000 cases of *Streptococcus pneumoniae* worldwide — in sharp contrast to incidence rates in the United States. Ceftriaxone was not commonly used due to the expense, which has been reduced because it is now generic. However, the cost of hospital care and resources for intravenous administration remain significant in these hospitals.

A total of 2,000 cases of children between ages 2 and 12 years was evaluated with 1,004 qualifying after exclusion factors were applied, which included death before randomization (269) or a positive culture on a repeat lumbar puncture at 48 hours. Bacteria were recovered in 67% of cases, with 27% being *H. influenza* b, 33% *S. pneumoniae*, and 7% *Neisseria meningitidis*.

There were no bacteriological failures after 5 days, but there was a clinical relapse in two children in the 5-day group (one with HIV) and none in the 10-day group. Complications were equivalent between the groups with hearing loss in 211, visual loss in 14, and other neurologic loss in 51. Dexamethasone was given to 437 children, but there was no apparent benefit by statistical analysis.

The obvious limitations of the study relate to the resources available despite the good laboratory methodology and protocols for the study. The time from the onset of symptoms until ceftriaxone initiation averaged 4 days, a major problem for outcomes.

The authors conclude that children with bacterial meningitis who are stable on therapy after 5 days of therapy with ceftriaxone can safely have the antibiotic stopped.

■ COMMENTARY

Bacterial meningitis in resource-poor countries accounts for a high loss of life and neurologic function among children. Vaccine programs have had some benefit, but far more is needed.

This study is a tremendous advance given the limited resources in funding, facilities, and medical staff. Ceftriaxone has had a dramatic effect in dealing with the common bacterial causes of meningitis, with studies reported as early as 1982 in Niger. In that study, patients were treated for 4-7 days with a good response. Another study of children in Ghana had a case fatality rate of 22%, although nearly half of the children had been ill for 4 days. In that group, ceftriaxone alone appeared as good as penicillin and chloramphenicol together. Since then, resistance appears to be evolving with both *Streptococcus* and *Hemophilus*.

This study provides a useful update on bacterial meningitis with good microbiology and statistical analysis of outcomes of mortality and complications.

The situation outside pediatric hospitals remains a desperate one, particularly in rural areas. Much of this is due to limited access to care, sometimes with days of travel required to get to a hospital,

in addition to the cost of parenteral antibiotics. With the limitations and apparent activity of ceftriaxone, it has been postulated that a single injection for 10 children with meningitis would save more lives than 10 daily injections for just one child. The first dose of an antibiotic is likely the most important factor in a good outcome, but how long therapy is necessary after that is unknown. This study does not suggest single-dose therapy, but it is a step in the right direction in determining how many days are really needed.

This study was conducted with good quality control and outcomes measurements and with as informed consent as able. The results confirm the safety of a shorter course of therapy, but this will be difficult to implement in most developed countries where cost is not as relevant to care. The risk of shorter courses of therapy includes malpractice and the threat of legal action if there is anything less than a perfect outcome with full and traditional therapy. With the high complication rate, it would be difficult to convince a jury that 5 days is as good as 10 days if the outcome is less than perfect.

How long do we really need to treat meningitis? How many other infections could be treated with shorter courses of therapy? It seems we must turn to the disadvantaged to learn about appropriate care and antibiotic use. Let us hope there will be more studies such as this and that the antibiotic stewards will be able to help with the information systems available. ■

NEWS BRIEF

The AMA and the Infectious Diseases Specialist: House of Delegates Update

By Alan D. Tice, MD, FACP

The American Medical Association convened the biannual House of Delegates meeting in Chicago in June with more than 500 delegates from a variety of societies and organizations. The focus was on health care reform with concerns about practical issues of fee-for-service medical care, scope of practice, conflicts of interest, electronic health records, accountable care organizations, tort reform, and care of minorities and the disadvantaged. There also were discussions about quality of care, payment for performance, and the methods to be used with the help of the Physician Consortium for Performance Improvement.

There were a number of resolutions proposed that are relevant to our specialty. These included vaccine programs, which the AMA recommended be universal for children; the AMA also advocates adequate reward for doctors to provide them.

The IDSA submitted a resolution regarding antibiotic stewardship. It was noted that requirements are likely coming for implementing a program to stave off antimicrobial resistance, limit overuse, and provide optimal and specific therapy. An effective program must incorporate input from physicians, pharmacy, microbiology, and infection control, among others. The IDSA asked that a physician be the leader of this team and that this individual be familiar with the use of antibiotics, such as an infectious diseases specialist, if available. Comments from the delegates usually were supportive, but many were concerned with the possible added expense, even though it was suggested that the funding be taken from Medicare funds to be taken back because of hospital-associated infections. There also was some concern about the resolution being self-serving, although it did not specify that the leader be an infectious diseases specialist. The resolution was not approved in the voting, but was referred to the AMA Board for review and recommendations for the next House of Delegates meeting.

The IDSA also brought up the issue of notes in the electronic medical record, as the work of infectious disease specialists is often in the hospital doing consultations and follow-up visits. Noted were the problems of copy-and-paste notes that satisfy the reimbursement criteria but may be essentially identical from one day to the next as "clones." Concerns surround how to identify daily notes and the criteria for reimbursement, including:

- What should the minimum note include?
- How much needs to be new and different each day?
- How important is it to note changes from day to day and to repeat findings that are the same?

Discussions indicated continued on page 132

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Vertical HIV Transmission in the United States

Source: MMWR. Enhanced perinatal surveillance — 15 areas, 2005-2008. Available at: www.cdc.gov/hiv/surveillance/resources/reports/2010supp_vol16no2/index.htm.

The United States Perinatal HIV Surveillance Project tracks HIV-infected pregnant women in care in 15 locations throughout the United States and Puerto Rico. Data for the period of 2005-2008 provides insight into the epidemic's effects on HIV+ women, and the risk of maternal-child HIV transmission. During this 4-year period, data for 8,054 mother-baby pairs were collected. About half (54%) of the identified pregnant woman with HIV infection were U.S.-born, one-third were unknown, and the remainder were from a variety of other countries, generally in Central America and Africa. Six percent were < age 20, 21% were age 20-24, 49% were age 25-34, and 24% were ≥ age 35 at the time of delivery.

From 2005 to 2008, the majority of HIV+ pregnant women were African-American (65%) or Latina (23%). Nearly half were heterosexually exposed to HIV. At the time of delivery, 55% were unmarried, 15% were married, and the marital status of 28% was unknown.

Two-thirds of the women were aware of their HIV status at the time of their pregnancy; only a minority learned of their positive HIV status during pregnancy screening (26%) or at the time of delivery (3%). Of those whose HIV status was recognized before their pregnancy, 84% were in care and on antiretroviral therapy (ART). During pregnancy, 90% of HIV+ women were receiving perinatal care (7% were not and 3% were unknown) and 85% were receiving ART.

A total of 179 infants (2%) were confirmed HIV+; a significant number of infants (27%) were either lost to follow-up, or the results of the HIV tests were pending or indeterminate (as of December 2009). Only 71% were known to be HIV-negative. These figures were similar regardless of ethnicity. The number of birth defects was lowest for Asians (2%) and highest for African Americans (6%) and Latinos (7%).

Screening of pregnant woman for HIV remains a priority for every Ob-Gyn and pregnancy clinic, regardless of perceived risk for HIV. More than half of the women in this survey had no identifiable risk factor other than a sexual partner, which is pretty much true for every pregnant woman. Identifying these women early in their pregnancy and getting them on ART is essential to preventing maternal-child HIV transmission. The French Perinatal Cohort Study, a comparable program in France, recently published data on 7,425 mother-infant pairs.[1] The overall rate of HIV transmission to infants was 1.5% — somewhat better than the U.S. data. And the rate of mother-baby HIV transmission for women who were virologically suppressed at the time of delivery (< 20 copies per mL) was only 0.4%. If the United States could come close to achieving these results, more than 100 children in this study could have been successfully protected from HIV infection. ■

Reference

1. Tubiana R, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load < 500 copies/mL at delivery: A case-control study nested in the French Perinatal Cohort (EPF-ANRS C01). Clin Infect Dis 2010;50:585-596.

The Appendix as Protector

Source: Im GY, et al. The appendix may protect against Clostridium difficile recurrence. Clin Gastroenterol Hepatol 2011 June 13; Epub ahead of print.

Although the appendix has been much maligned as a vestigial organ of uncertain value, these authors theorized that the lymphoid tissue and biofilm produced by the intact appendix may protect against intestinal infection with *Clostridium difficile* (CDI). They examined the medical records of 396 patients admitted to a tertiary care center between January 2005 and January 2007 with a diagnosis of CDI. A total of 254 patients with CDI and known appendix status were included in the analysis (76% with a first episode of CDI and 24% with a recurrent episode of CDI). The median age of the group was 79 years. The rate of colectomy was 2.5% and mortality was 5.6%.

Multivariate analysis of 11 different variables suggested that patients older than 60 years were at greatest risk for relapse (P = 0.028, adjusted relative risk [ARR] 2.44). In addition, the presence of an appendix appeared to be highly protective of CDI relapse (P < 0.0001, ARR 0.398). The CDI recurrence rate was 45% for those without an appendix and only 18% for those with an appendix. Further study is needed to confirm these results prospectively. ■

Tdap for Health Care Workers

Source: ACIP Provisional recommendations for health care personnel on use of tetanus toxoid,reduceddiptheriatoxoid,andacellular pertussis vaccine (Tdap) and use of post-exposureanitmicrobialprophylaxis.Available at:www.cdc.gov/vaccines/recs/provisional/default/htm.

Add Tdap to the growing list of recommended (and often required) vaccinations for health care workers (HCWs) in hospital, including MMR, hepatitis B, influenza, and possibly varicella. In April, the American College of Immunization Practices (ACIP) issued provisional recommendations for pertussis vaccination (Tdap) of all hospital HCWs, regardless of age and prior vaccine history (i.e., regardless of the time since last Td dose). Current hospital employees (and future hires) should receive a single dose of vaccine now, in one broad sweep to provide blanketed coverage of every hospital, and then continue to receive the usual booster vaccine recommended for adults.

Pertussis appears to be cycling up in our communities, especially in California, where 8,383 cases were reported in 2010, including 10 deaths in infants. Neonates and infants < 12 months of age are at the greatest risk for severe infection. For this reason, initial ACIP recommendations were to provide vaccination to all caregivers of small children, thus providing a protective "cocoon" of immunogenic individuals. The current recommendations expand on this philosophy, especially to physicians and nurses who provide care for infants and small children.

HCWs are at risk for pertussis exposure — both from their patients and fellow colleagues. Outbreaks of pertussis in the hospital setting can rapidly evolve, resulting in significant hours and effort to provide post-exposure prophylaxis to everyone exposed. Those who develop symptoms of pertussis are required to receive antibacterial therapy and are furloughed for a minimum of 5 days. In two separate outbreaks in Minnesota, 12% and 52% of cases occurred in HCWs who were exposed to either an ill index case or to each other. At our county hospital in the 1990s, an outbreak of a pertussis-like illness (pre-PCR test availability) necessitated the administration of chemoprophylaxis to more than 400 HCWs; a supreme effort over a Memorial day weekend, with significant cost to the hospital.[1]

HCWs who have received Tdap vaccine nonetheless require close monitoring for signs and symptoms for 21 days after pertussis exposure. Post-exposure prophylaxis is still recommended for vaccinated HCWs with documented exposure. Even mild respiratory symptoms (e.g., runny nose, sneezing, low grade fever, or cough) should prompt PCR testing for pertussis, receipt of antibiotics, and furlough from work for 5 days. The paroxysmal stage of pertussis, with the characteristic cough, generally only begins 1-2 weeks into the illness. ■

Reference

1. Martinez SM, et al. Azithromycin prophylaxisduringahospitalwideoutbreak ofapertussis-likeillness.InfectControl Hosp Epidemiol 2001;22:781-783.

The Buzz on TB

Source: Suckling DM, Sagar RL. Honeybees Apismelliferacandetectthescentof Mycobacteriumtuberculosis.Tuberculosis201191:327-328.

First there were lab techs, peering through microscopes to identify acid-fast organisms, and then there were Gambian rats, who could sniff out tuberculosis (MTb), like small incendiary devices in sputa. Now, there are trained honeybees…

Recent work has focused on the aromatic compounds characteristic to MTb that allow Gambian rats to "sniff out" the organism in sputa, and may allow other more sensitive means for identification of active pulmonary tuberculosis infection. Three such compounds have been identified, which are considered aromatic "signatures" of both *Mycobacterium tuberculosis* and *M. bovis*. The compounds include methyl phenylacetate, methyl-p-anisate, and methyl nicotinate.

These authors cleverly manipulated honeybees to recognize these compounds using their proboscis extension reflex. Once "trained," 20-25 honeybees were exposed to filter paper inoculated with one of the three compounds in varying amounts, blown with small puffs of air, alternating with clean air every 10 seconds. The number of bees exhibiting a response to the presence of varying dilutions of each of the compounds compared with a neutral control was determined. Methyl-p-anisate provided the best response, followed by methyl phenylacetate (which has a jasmine-like odor), with as little as 10 picograms eliciting a response. Response to methyl nicotinate was less robust, and required a threshold concentration of 1 ng. The honeybees were able to detect these compounds over 8 orders of magnitude!

So, how do you train a honeybee? First, you collect some fresh foragers from the garden in the late afternoon… Then you chill them to -4° C for 2 minutes, insert them in a plastic tube, so only their head and tongue can move, then feed them a 50% sucrose solution till they are full. Then starve them overnight at 28° C, careful to keep them warmer when not eating. In the morning, chill them down to 23° C for 10 minutes, and then begin the conditioning. Every time they correctly elicit a proboscis extension reflex to one of the signature compounds, reward them with sugar solution for 5 seconds. Those bees that fail training are given a pink slip. They were probably not great foragers anyway. ■

continued from page 129 Medicare and private insurance companies are looking into this issue and are expected to propose suggestions for guidelines soon. The resolution was voted down, but will likely resurface when more information has been received from payers.

Although the infectious diseases specialist may have little interest in issues that are beyond their specialty, it should be noted that the AMA is the only real organization that can speak for physicians. While their membership is primarily doctors in fee-for-service medical care, their influence and interests are far greater than that and also apply to physicians in academics and government service. The AMA has more influence with Congress and payers than any other organization and remains financially comfortable despite limited membership. It is an organization that can and does speak with knowledge of infectious diseases, especially as two Board members are infectious diseases specialists.

Keep your eyes open to payers' concerns and contact the IDSA for their input and with any thoughts you have to contribute to better health care as health care reform unfolds. ■

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 colistimethate?

a. It commonly causes bone marrow toxicity.

b. Its dose for obese patients should be calculated on the basis of actual body weight.

c. Its use should be accompanied by monitoring of renal function.

d. It is interchangeable with colistin sulfate.

2. Which of the following is *correct* with regard to *Neisseria gonorrhoeae* in the United States?

a. Ciprofloxacin is recommended for treatment of infection with this organism.

b. The amount of cefixime required to inhibit its growth in vitro has been increasing.

c. Cefixime is more potent than ceftriaxone against it in vitro.

d. Reduced susceptibility to cephalosporins arose in the eastern United States and has been spreading westward.

3. Which of the following is *true* regarding β-glucan?

a. Plasma β-glucan levels are elevated only in patients with PCP.

b. Plasma β-glucan levels may be elevated in patients with many different fungal infections (including PCP), as well as in patients receiving hemodialysis, intravenous immunoglobulin, and certain antimicrobials

c. β-glucan should immediately replace all other diagnostic modalities for PCP.

d. Cross-reactivity between multiple fungal species is not an issue for β-glucan.

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]

Revolution in the micro lab: MALDI-TOF MS and PCR ESI-MS

Fidaxomicin: Formulary concerns with this advance in clinical therapeutics

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.*

FDA issues Multiple Drug Warnings

In this issue: FDA issues multiple drug safety alerts; ARBs and cancer risk; and FDA actions.

Avoid high-dose simvastatin

The FDA is advising physicians to avoid high-dose simvastatin (Zocor) because of the risk of myopathy and rhabdomyolysis. The agency is advising that patients should not be started on the 80 mg dose and patients who already are on 80 mg should be continued only if they have been on that dose for 1 year or longer. The recommendations are based on results of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocystine (SEARCH) trial — a 7-year randomized, controlled trial comparing the efficacy and safety of simvastatin 80 mg vs simvastatin 20 mg with or without vitamin B12 and folate in survivors of myocardial infarction. There was no significant difference in the incidence of major vascular events between the two doses; however, 52 patients (0.9%) in the 80-mg group developed myopathy vs one patient (0.02%) in the 20-mg group. Of the high-dose group, 22 patients (0.4%) developed rhabdomyolysis vs no patients in the 20-mg group. The risk for myopathy and rhabdomyolysis with simvastatin 80 mg was highest in the first 12 months of treatment. Of concern, the risk of myopathy was approximately doubled in patients taking a calcium channel blocker, particularly diltiazem. The majority of patients who developed myopathy also had a genetic variant that affects coding of the transporter responsible for simvastatin uptake in the liver, resulting in higher serum simvastatin levels. The FDA not only recommends against using simvastatin 80 mg, but also suggests that the drug is contraindicated for use in patients taking itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, and danazol. The maximum dose of simvastatin should be only 10 mg in patients taking amiodarone, verapamil, and diltiazem while the maximum dose is 20 mg in patients taking amlodipine and ranolazine. The new guidance recommends using a different statin if the patient's LDL targets aren't met with the 40-mg simvastatin dose. The loss of high-dose simvastatin comes as a blow to cost-concious consumers who now likely will be prescribed brand name atorvastatin (Lipitor) or rosuvastatin (Crestor). Generic atorvastatin is likely to be available in late 2011. ■

Increased risk of prostate cancer

The FDA has issued a somewhat controversial warning regarding an increased risk for high-grade prostate cancer associated with the 5-alfa reductase inhibitors finasteride (Proscar, Propecia) and dutasteride (Avodart, Jalyn). Ironically, the new warning stems from studies designed to evaluate whether the drugs offer protection *against* prostate cancer. Both drugs are marketed to treat benign prostate hypertrophy and both are known to significantly decrease the prostate-specific antigen levels. In separate studies, both drugs were investigated to see if they reduce the incidence of prostate cancer. FDA experts reviewed the results of the Prostate Cancer Prevention Trial (PCPT), which evalu-

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ated finasteride vs placebo for 7 years, and the Reduction by Dutasteride of Prostate Cancer Events trial (REDUCE), which compared dutasteride to placebo for 4 years. Prostate cancers were significantly reduced in both trials; however, the reduction was limited to low-grade prostate cancers with a Gleason score of 6 or lower. The rate of cancers with a Gleason score of 8-10 was increased in both studies. Previous analyses of these data have suggested that finasteride did not increase the risk of high-grade prostate cancers, but rather made them easier to diagnose by decreasing the volume of the prostate (*Clin Cancer Res* 2009;15:4694-4699; *J Natl Cancer Inst* 2007;99:1366-1374). The FDA panel, however, disagrees and feels it prudent to add a warning to labeling of both medications regarding increased risk of high-grade prostate cancer associated with use of the drugs. The guidance further recommends that prior to initiating therapy patients should be evaluated to rule out other urologic conditions, including prostate cancer, that might mimic benign prostatic hypertrophy. ■

Actos and bladder cancer risk

The diabetes drug pioglitazone (Actos) is the subject of a new warning from the FDA regarding possible bladder cancer risk associated with use of the drug. The FDA ongoing safety review suggests that use of pioglitazone for more than 1 year may be associated with increased risk of bladder cancer based on review of a 5-year interim analysis of an ongoing 10-year epidemiologic study. Patients who had been on pioglitazone the longest and who had the highest cumulative dose of the drug had a slightly increased risk of bladder cancer. This warning falls on the heels of a French study that also showed increased risk of bladder cancer. Based on these findings, France's drug regulatory agency has suspended use of the drug. While the FDA is not recommending withdrawing the drug from the market, it does recommend avoiding pioglitazone in patients with active bladder cancer and using it with caution in patients with prior history of bladder cancer. Thiazolidinediones — including pioglitazone — have also come under scrutiny in recent years because of increased risk of congestive heart failure and bone fractures in females. ■

Chantix and cardiovascular events

The FDA has issued an alert regarding varenicline (Chantix) regarding a small increased risk of certain cardiovascular adverse events in patients who have cardiovascular disease. The warning regarding the smoking cessation drug was the result of review of a randomized, double-blind, placebo-controlled trial of 700 smokers with cardiovascular disease who were treated with varenicline or placebo. The overall rate of adverse effects was low but cardiovascular events, including heart attack, were reported more frequently in the treatment group. The warning will result in a change in labeling for the drug and the FDA is also requiring Pfizer, the drug manufacturer, to conduct an analysis of other trials to further assess the risk. Varenicline already carries a box warning regarding neuropsychiatric symptoms including suicidality. ■

ARBs and cancer risk

Finally some good news from the FDA. After a 2010 meta-analysis showed a possible link between angiotensin receptor blockers (ARBs) and cancer, the agency has completed its own review and has found no evidence of increased risk of "cancer events" including new cancers, cancer-related deaths, breast cancer, lung cancer, or prostate cancer associated with the drugs. The agency conducted a much larger meta-analysis than the original study, including more than 150,000 patients in 31 long-term, randomized, controlled clinical trials. The rate of cancer events in the ARB group was 1.82 per 100 patient years while the rate in the non-ARB group was 1.84 per 100 patient years (relative risk of incident cancer in patients taking ARBs 0.99, 95% confidence interval, 0.92 to 1.06) There was no statistically significant difference in cancer death rates or incidence of individual cancer types. The agency continues to monitor this issue but currently states that the benefits of ARBs continue to outweigh the potential risks (summary available at FDA.gov/drugs/drugsafety/). ■

FDA actions

The FDA has approved the first generic version of levofloxacin (Levaquin). The popular fluoroquinolone is commonly used for treatment of respiratory infections, sinusitis, prostatitis, pyelonephritis and skin infections. Generic forms will include tablets, oral solutions, and injectable solutions.

The FDA has approved an abuse-resistant short-acting oxycodone tablet. Pfizer Pharmaceuticals has licensed the "AVERSION Technology" from Acura Pharmaceuticals. The technology prevents dissolving and injecting tablets by creating a gel when mixed with water or other solvents that prevents snorting crushed tablets by burning nasal passages, and also prevents intentional swallowing of excess quantities by adding niacin which causes intense flushing, itching, and sweating. Long-acting oxycodone (OxyContin) was similarly reformulated in 2010 to prevent misuse and abuse. ■