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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Increase in Sudden Death with ARBs or ACE Inhibitors and Co-trimoxazole

By Richard R. Watkins, MD, MS, FACP

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

SYNOPSIS: In a case-control study, older patients who received an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker along with co-trimoxazole had an increased risk of sudden death (unadjusted odds ratio 1.83, 95% confidence interval 1.50 to 2.24). Hyperkalemia is hypothesized to be the underlying mechanism.

Source: Fralick M, et al. Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system: Population-based study. *BMJ* 2014 Oct 30;349:g6196.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are commonly prescribed drugs with a number of clinical indications. One of their side effects is hyperkalemia, which occurs in approximately 10% of patients who receive them and can be life-threatening. Co-trimoxazole (trimethoprim/sulfamethoxazole) is frequently used to treat urinary tract infections (UTIs) and also increases serum potassium concentration. Fralick and colleagues sought to determine if co-prescription with an ACE inhibitor or ARB and co-trimoxazole was associated with a higher risk of sudden death compared to other antibiotics prescribed for UTIs.

The investigators conducted a case-control study of Ontario residents aged 66 years or older prescribed an ARB or ACE inhibitor between 1994 and 2012. The primary endpoint was sudden death within 7 days of an outpatient prescription for co-trimoxazole, ciprofloxacin, norfloxacin, nitrofurantoin, or amoxicillin. Patients were excluded who received any other antibiotic in the 14

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Infectious Disease [ALERT]

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days preceding the index date. For each case, the investigators randomly assigned up to 4 controls that were matched for age, sex, and the presence or absence of kidney disease and diabetes, which are known risk factors for sudden death. They adjusted for covariates associated with the risk for sudden death by creating a disease risk index derived from a multivariable regression model based on an extensive list of medical comorbidities. To approximate the absolute risk of sudden death with co-trimoxazole, the investigators conducted a supplementary analysis to determine the number of sudden deaths within 14 days of receiving either co-trimoxazole or amoxicillin.

The primary result was that co-trimoxazole was associated with a significantly increased risk of sudden death within 7 days compared to amoxicillin (unadjusted odds ratio [OR] 1.83, 95% confidence interval [CI] 1.50 to 2.24), which persisted after adjustment using the disease risk index (adjusted OR 1.38, 95% CI 1.09 to 1.76). Furthermore, ciprofloxacin was also associated with a risk of sudden death (adjusted OR 1.29, 95% CI 1.03 to 1.62), while no increased risk was found with nitrofurantoin or norfloxacin. The secondary analysis also found an increased risk of sudden death with co-trimoxazole relative to amoxicillin (adjusted OR 1.54, 95% CI 1.29 to 1.84), but no risk from the other antibiotics. This corresponded to approximately three sudden deaths with the co-trimoxazole compared to one sudden death in those prescribed amoxicillin per 1000 prescriptions dispensed. Finally, in the supplementary analysis, congestive heart failure (a known risk factor for sudden death) was removed from the disease risk index and afterward the calculated risks were no different from the primary analysis.

■ COMMENTARY

This study showed an increased risk of sudden death in patients prescribed ACE inhibitors or ARBs with co-trimoxazole and, to a lesser extent, ciprofloxacin, but not other antibiotics frequently prescribed for UTIs. The authors hypothesized that the increased risk from co-trimoxazole was due to unrecognized arrhythmic death due to hyperkalemia in a susceptible population. It is known that co-trimoxazole-induced hyperkalemia can occur quickly and produce life-threatening arrhythmias. Ciprofloxacin can prolong the QT interval, leading to torsades de pointes, and often occurs early in a course of therapy. In the current study, the risk for sudden death from ciprofloxacin was attenuated by day 14.

As mentioned in an accompanying editorial, a major strength of the study was the large sample size that allowed for adequate power to study a rare clinical outcome (sudden death).[1] However, there are important limitations to the study that deserve emphasis. First, the investigators did not have any data on serum potassium concentration or creatinine. Second, unmeasured confounders could have contributed in unclear ways to the observed association. Third, there may have been misclassification regarding the diagnosis of sudden cardiac death that led to bias. For example, the discordant results for sudden death between norfloxacin and ciprofloxacin (both quinolones) make this finding questionable. Fourth, although hyperkalemia leading to sudden death is an attractive hypothesis, the potassium-sparing drug spironolactone has been shown to decrease mortality when added to an ACE inhibitor in patients with congestive heart failure.[2] Finally, the authors did not have any information about the dosing of co-trimoxazole, which precludes a dose-response analysis.

The study by Fralick and colleagues calls to mind the oft-quoted dictum that association does not imply causation. This is especially true for observational studies. Nevertheless, these researchers have alerted the medical community about a potentially serious drug interaction. Co-trimoxazole is generally well-tolerated, effective, and inexpensive, and ARBs and ACE inhibitors are commonly prescribed. It seems unwarranted to restrict all patients on ARBs and ACE inhibitors from receiving co-trimoxazole. While waiting for higher quality evidence, a reasonable approach at present may be to monitor serum potassium over the course of therapy and switch the co-trimoxazole if hyperkalemia develops. ■

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ABSTRACT & COMMENTARY

The Effect of Repeated Influenza Vaccination — Not Always Good

By Joseph F. John, Jr., MD, FACP, FIDSA, FSHEA

Dr. John is Professor of Medicine, Medical University of South Carolina, Charleston.

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

Synopsis: The immunogenicity of trivalent influenza vaccine is attenuated by the administration of A(H1N1)pdm09 4 months before, an effect partially overcome by the presence of an adjuvant in the former.

Source: Roy-Ghanta S, Van der Most R, Li P, Vaughn DW. Responses to A (H1N1)pdm09 influenza vaccines in participants previously vaccinated with seasonal influenza vaccine: A randomized observer-blind, controlled study. *J Infect Dis* 2014;210:1419-1430.

There was an H1N1 influenza pandemic in 2009, which caused nearly 20,000 deaths. Several H1N1 vaccines were developed in response to the epidemic. Because of the eruptive behavior of H1N1 viruses, there is a need to understand the timing of and response to H1N1 vaccines, particularly in relation to the routine use of multivalent seasonal influenza vaccines.

These investigators from Glaxo Smith Kline (GSK) in Pennsylvania and Belgium knew that response to the H1N1pdm09 vaccine was dependent, to a degree, on the prevaccination serostatus of the population under study. In particular, there has been some evidence published that recipients of trivalent influenza vaccine (TIV) may have altered responses to subsequent H1N1 vaccine, either adjuvanted or non-adjuvanted. The observed decreased response to subsequent H1N1 vaccine alludes to the doctrine of original antigenic sin first published about 50 years ago (*J Exp Med* 1966:124:331-45): Exposure to a novel virus after exposure to a closely related strain may decrease the response to the subsequent exposure. Adjuventation of the priming vaccine may reduce the immune interference and allow a great response secondary [TO?] exposure.

This study aimed to determine the response to an adjuvanted or non-adjuvanted H1N1 vaccine when given after TIV or a placebo. The H1N1 vaccines were given 4 months after the TIV. An assortment of immune responses were determined. Vaccines were prepared at GSK in Quebec, Canada. The placebo was phosphate-buffered saline. Vaccines were mixed with either phosphate buffered saline (PBS) or the adjuvant known as AS3A. The design was to give TIV followed by adjuvanted or non-adjuvanted H1N1 (Groups A and B), or placebo followed by adjuvanted or non-adjuvanted (Groups C and D).

Of the 171 screened participants, 133 were vaccinated. Only 99 completed the study through day 507. Responses were measured in rates of a good antibody response: rates of memory B-cell responses, rates of CD4 cell responses, and rates of CD8 cell responses. There were no CD8-cell responses.

The best response — both antibody and cellular — came in the group given a placebo (fake TIV) followed by adjuvanted H1N1. That is, prior TIV produced reduced antibody and CMI responses to H1N1. Adjuvanted H1N1 tended to overcome the TIV vaccine interference. For specific CD4 response markers, the responses were stronger for IL-2 and CD40L than for TNF-alpha, interferon-gamma.

■ COMMENTARY

The data set for this study is very large and there were supplemental data. Yet the discussion, as in many excellent papers, is quite short. It emphasizes that response to a vaccine based on a pandemic H1N1 strain may be diminished by prior seasonal multivalent vaccine even though the second vaccine

is administered 122 days after the first vaccine. This diminished response includes humoral and cellular responses, both of which may be needed for protection against subsequent influenza infection through their individual responses or through assisted responses, i.e., CD4 cells may help B-cell antibody response. Adjuvants may suppress the effect of the first vaccine when the first vaccine diminishes the response to the second vaccine.

These conclusions are disquieting because they are counterintuitive. Our intuitive sense is that consecutive vaccines with similar pathogens should be additive. Indeed, we have come to accept that boosters produce augmented humoral and cellular responses. Yet the message from this study is that unless the serial vaccines use identical or very closely related strains, we cannot discount interference from the initial vaccine.

Many different influenza vaccines are available. Unfortunately, to determine the precise response to serial administration of influenza vaccines requires intense complex laboratory methods, as demonstrated in the present study by GSK. Even when the vaccines are given as much as four months apart, there may be antagonism exerted by the first response against the second response, as was seen in this study.

In summary, caution must reign when giving advice about the use of second influenza vaccines. Depending on the similarity or dissimilarity of the influenza vaccine strains, there may be a surprise of a diminished response to the second influenza vaccine. ■

ABSTRACT & COMMENTARY

Should Lumbar Puncture Still Be Routine for Febrile Babies?

By Philip R. Fischer, MD, DTM&H

Dr. Fischer is Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

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

Synopsis: Meningitis is very unlikely in otherwise healthy-appearing febrile infants older than 21 days of age. Thus, cerebrospinal fluid analysis might not be needed as part of a "routine" evaluation of these babies.

Source: Martinez E, Mintegi S, Vilar B, Martinez MJ, Lopez A, Catediano E, Gomez B. Prevalence and predictors of bacterial meningitis in young infants with fever without a source. *Pediatr Infect Dis J* published online 12-2014, doi: 10.1097/INF.0000000000000629.

Clinical investigators in Spain prospectively evaluated all infants with fever in whom its source was not evident after initial exam and laboratory testing from 2003 to 2013 in an emergency department of a tertiary teaching hospital. A total of 2362 infants younger than 90 days of age were included in the study.

Lumbar puncture was performed in 27% of febrile infants. However, in the subset of febrile infants who did not appear to be well, lumbar puncture was done in 61%. And cerebrospinal fluid analysis was done in 70% of the study subjects younger than 21 days of age.

Meningitis was identified in only 11 of the 639 children who underwent lumbar puncture. Nine of those 11 babies were younger than three weeks old, and five did not appear well on initial exam. Meningitis was diagnosed in zero of the 1975 well-appearing febrile infants more than 21 days of age.

Group B streptococcus, *Escherichia coli*, and *Listeria monocytogenes* were each responsible for three cases of meningitis. Pneumococcus (in a 23-day-old) and meningococcus (in a 49-day-old) accounted for the other two cases of meningitis.

The authors concluded that cerebrospinal fluid analysis should be "strongly considered in not well-appearing infants and in those less than or equal to 21 days of age" who presented with fever without apparent source. They suggested that the recommendation to systematically perform spinal fluid analysis in older well-appearing febrile infants be re-evaluated.

■ COMMENTARY

None of us is accurate enough with a physical exam to reliably determine if a febrile newborn who looks well has an underlying serious bacterial infection or not. For decades, the published standard of care has been to begin antibiotic therapy while waiting for results of microbiology testing of blood, urine, and cerebrospinal fluid.

However, the vast majority of otherwise healthy-appearing febrile infants have self-limited viral infections. "Routine" testing and presumptive treatment can lead to discomfort (such as from needles to obtain samples), cost (for testing as well as for hospitalization and treatment while waiting for definitive results), and confusion (and further unnecessary testing and treatment) when initial tests show "positive" results due to contaminants.

Thus, standards of care have shifted from hospitalizing and treating all febrile babies younger than two (or three) months of age toward being a bit more selective in the management of these children. Still, however, most American pediatricians would consider it good routine care to obtain samples of blood, urine, and cerebrospinal fluid from all infants who become febrile during at least the first month of life, and to hospitalize these patients for parenteral antibiotic therapy while waiting for culture results.

The new data from Spain provide helpful evidence to suggest that cerebrospinal fluid analysis is likely not necessary in otherwise healthy-appearing babies after the 21st day of life. Removing cerebrospinal fluid sampling and analysis from the routine care of older otherwise well-appearing febrile infants could save discomfort, cost, and some complications — presumably without significantly adding risk for "missing" meningitis. But, are these results generalizable to sites outside of Spain? Perhaps not!

The Spanish investigators identified 11 younger babies who did have meningitis, and three of those were infected with *Listeria*, a germ that is decidedly uncommon among North American newborns with meningitis. (A total of 181 cases of bacteremia during the first three months of life in six U.S. hospital systems revealed no cases of *Listeria*.[1] In Kenya, an even wider variety of microorganisms is associated with neonatal and infantile meningitis.[2]) Realizing that the microbial epidemiology is different in various parts of the world, testing and care of febrile infants might also need to vary. It could be the organisms and infections that are less common in Spain are more common in the United States and might be missed by omitting lumbar puncture from routine evaluation of febrile babies. (Interestingly, though, two of the three babies with *Listeria* meningitis were born at an "outside" maternity facility during an outbreak of *Listeria* infection. There was only one case of *Listeria* meningitis in the subsequent six years at the Spanish center.)

Interestingly, not all of the ill-appearing febrile infants and not all of the youngest febrile infants had cerebrospinal fluid analysis in the Spanish study. Despite recommendations for thorough evaluation of febrile infants, there is practice variation in other parts of the world as well.[3] In the United States, for instance, pediatric clinicians often use clinical judgment rather than guidelines to decide on testing and treatment of febrile infants; with only about 0.4% of well-appearing febrile infants older than 25 days of age having bacteremia or meningitis, following guidelines would use more medical resources without altering outcomes.[4]

The management of febrile infants will continue to evolve as microbial epidemiology changes and as diagnostic measures improve.[5] In the meantime, these new data from Spain contribute usefully to the practice of those caring for febrile newborns. First, they remind us that meningitis continues to occur, even in this era of good prenatal care and preventive treatment of mothers with known group B streptococcal colonization. Second, these data reassure us that meningitis is still uncommon but is more likely in ill-appearing babies than in otherwise well-appearing babies. Third, the Spanish report maintains our concern for possible meningitis in febrile infants younger than three weeks of age, even when those young infants do not look sick. Finally, though, these data call us to continue to seek data about risks and benefits of cerebrospinal fluid analysis in our own areas with varying illnesses and microbial epidemiology. ■

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ABSTRACT & COMMENTARY

Ethnicity and Treatment of Otitis Media

By Hal B. Jenson, MD, FAAP

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

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

Synopsis: Nationally, nonblack children with otitis media more frequently receive broad-spectrum antibiotics than black children do. The majority of children with otitis media in the United States receive inappropriate treatment with broad-spectrum antibiotics.

Source: Fleming-Dutra KE, Shapiro DJ, Hicks LA, Gerber JS, Hersh AL. Race, otitis media, and antibiotic selection. *Pediatrics* 2014;134:1059-1066.

Two large, national, publicly available databases at the Centers for Disease Control and Prevention were used to compare otitis media visits between black and nonblack children <=14 years of age during 2008 to 2010. There were 4,178 ambulatory visits for otitis media by children <=14 years of age during this period that were evaluated. Patients were excluded from analysis if there was a concomitant diagnosis also requiring antibiotic treatment.

Although otitis media visits per 1000 population were not different between black and nonblack children (253 vs 321, P = 0.12), the percentage of all visits resulting in a diagnosis of otitis media was 30% lower among black children compared with nonblack children (7% vs 10%, P = 0.004).

For children diagnosed with otitis media and for which antibiotics were prescribed, black children were less likely to receive broad-spectrum antibiotics (e.g., macrolides such as azithromycin, β-lactam/β-lactamase inhibitor combinations, quinolones, lincomycin derivatives such as clindamycin, and second- and third-generation cephalosporins) than nonblack children (42% vs 52%, P = 0.01). Multivariable analysis showed the black race/ethnicity was negatively associated with broad-spectrum antibiotic prescribing (odds ratio 0.59; 95% CI, 0.40-0.86), even after adjusting for age, sex, geographic region, insurance, setting of care, metropolitan area, and year.

■ COMMENTARY

Otitis media is the most common diagnosis that results in antibiotic prescriptions among children younger than 5 years of age. There is no evidence that treatment of otitis media with broader- versus narrower-spectrum antibiotics results in better outcomes and fewer complications. Amoxicillin-clavulanate is recommended if amoxicillin fails initially and for children with a history of amoxicillin-resistant infections. This study could not distinguish between initial and follow-up visits.

This analysis of data from large, representative databases demonstrated differences in the diagnosis and management of otitis media for black children compared to nonblack children. Even though these results found that the percentage of visits resulting in a diagnosis of otitis media was 30% lower in black children compared to nonblack children, it does not appear that the true incidence of otitis media is lower in black children. The difference in rate of otitis media across some studies appears to be confounded by differences in access to care rather than differences in racial/ethnic predisposition.

Black children diagnosed with otitis media were more likely to receive narrow-spectrum antibiotics (e.g., amoxicillin) than nonblack children. The observed difference more likely represents overtreatment of otitis media among nonblack children rather than undertreatment of otitis media among black children. Parent expectations for antibiotics vary by race/ethnicity, and physician perceptions of parental expectations can influence physician antimicrobial prescribing. Such factors likely contribute to the differences found in this study. Whatever the root cause, overuse of antibiotics among children with respiratory tract infections and otitis media is costly and also a significant contributing factor to the increased prevalence of antimicrobial resistance generally. ■

ABSTRACT & COMMENTARY

Spherusol® — Testing for Dermal Delayed Hypersensitivity to Coccidioides

By Stan Deresinski, MD, FACP, FIDSA

Dr. Deresinski is Clinical Professor of Medicine, Stanford University; Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center.

In the fifth and sixth decades of the 20th century, Charles Smith reported the results of skin testing with coccidioidin, a culture filtrate of the mycelial phase of *Coccidioides*. This preparation became widely used in the detection of delayed hypersensitivity (DH) to this regionally acquired fungus, but became unavailable in the United States after 1997. In the meantime, beginning in the 1960s, a spherule-derived reagent was evaluated and, after coccidioidin became unavailable, was commercialized as Spherulin®.[1] Studies indicated that Spherulin® had modestly greater sensitivity compared to coccidioidin in the detection of DH to *Coccidioides*, and modestly improved specificity as evidenced, e.g., by less cross-reactivity in patients with histoplasmosis. In 2000, however, this product suffered the same commercial fate as coccidioidin so that, once again, no skin test reagent for detection of DH to *Coccidioides* was commercially available.

This has since been rectified by the availability of Spherusol®, which contains spherulin but has phenol added as a preservative together with a reduction in the concentration of thimerosal to 1:1,000,000 by volume. The FDA states that "Spherusol® is a skin test antigen indicated for the detection of delayed-type hypersensitivity to *Coccidioides immitis* in individuals with a history of pulmonary coccidioidomycosis. Spherusol is approved for use in individuals 18-64 years of age."[2]

In the absence of prior knowledge of a recent negative test result, DH skin testing is not useful in the diagnosis of acute coccidioidomycosis, and a negative test does not rule out infection, especially in patients with disseminated and/or progressive disease. In circumstances in which individuals are at continued high risk of infection, such as some microbiology personnel, surveillance skin testing or testing after exposures may prove useful. It also may provide information regarding the patient's cellular immune status as reflected by delayed hypersensitivity and has been used in this way in the serial monitoring of patients with severe coccidioidomycosis who may be initially anergic but subsequently, with effective antifungal therapy, regain reactivity. Furthermore, the presence of absence of DH to coccidioidal antigens in infected patients has prognostic significance.

An oddity of this history of skin testing is the fact that one of the places chosen to examine the specificity of spherulin was Spokane, Washington — chosen because it was believed to be an area non-endemic for coccidioidomycosis and where it, in fact, performed well, with a specificity of 98.2%. Recently, however, *Coccidioides immitis* was recovered from soil in south central Washington state during an investigation following the occurrence of 3 cases of coccidioidomycosis in that area that appeared to have been autochthonously acquired.[3] The lesson: Do not assume non-endemicity of *Coccidioides* or other "endemic" fungi. ■

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Letter: Coccidioidal Exposure in the Laboratory

By David A. Stevens, MD

Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Stanford, CA; California Institute for Medical Research, San Jose, CA

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

Dear Editor:

Accidental laboratory exposure to *Coccidioides* species is the major cause of clinical laboratory-acquired fungal infection,[1] and coccidiodomycosis is thought to be the least responsive deep mycosis to treatment.[2] This letter is written for the benefit of the microbiologist or infectious disease practitioner who is confronted by an accidental exposure, by self or staff, to *Coccidioides* in the clinical laboratory and, searching for advice from the literature on how to approach the problem, finds our article on the subject.[3] We can now update the article, and a literature search could now also locate this update.

We advised that serum be taken at the time of exposure from exposed personnel, for antibody testing, for two purposes. One, to determine whether there had been a prior infection by the fungus, because such prior exposure would extremely lessen the risks of developing an infection from the laboratory exposure. Second, as a baseline to compare to a second serum drawn at a later time, to diagnose infection as a result of the exposure, particularly in the presence of a confusing set of symptoms, or a subclinical infection, almost always in a worker without the prior coccidioidal experience. At the time of publication of our article, there was not a licensed skin test reagent available on the market to assess immunity. However, there now is available a commercial spherule (parasitic phase)-derived reagent to assess delayed-type hypersensitivity, Spherusol (Nielsen Biosciences, San Diego, CA). Spherule-derived antigens have proven sensitive in detection of prior coccidioidal infection in epidemiological studies, with minimal cross-reactivity and no perturbation of the serology.[4] Skin testing would be expected to be a better detector of infection because of problems with lessened sensitivity, and possible transience of positivity, with serology.

I would recommend, therefore, at this time that assessment of skin test reactivity be a part of the baseline and followup assessment of exposed individuals, along with serology. ■

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ABSTRACT & COMMENTARY

Prior Authorization versus Prospective Audit with Provider Feedback: Does the Effectiveness of the Core Antimicrobial Stewardship Strategies Differ?

By Timothy C. Jenkins, MD

Assistant Professor of Medicine, Denver Health and University of Colorado School of Medicine

Dr. Jenkins reports no financial relationships in this field of study.

SYNOPSIS: In a single academic medical center, changing from a strategy of prior authorization to prospective audit with feedback led to significantly increased total antibiotic use and use of agents with a broad spectrum of gram-negative activity.

SOURCE: Mehta JM, et al. Comparison of prior authorization and prospective audit with feedback for antimicrobial stewardship. *Infect Control Hosp Epidemiol* 2014;35(9):1092-1099.

Infectious Diseases Society of America (IDSA) guidelines for developing antimicrobial stewardship programs refer to two core antimicrobial stewardship strategies: prior authorization and prospective audit with provider feedback.[1] With prior authorization, use of selected antibiotics requires approval from a stewardship team member; whereas prospective audit with feedback involves post-prescription review of antibiotic regimens by a stewardship team member with real-time recommendations to providers regarding antibiotic choice, dose, and duration of therapy. Both strategies have been shown to reduce antibiotic use in hospitals; however, the most effective approach has not been established.

In this study by Mehta and colleagues at the Hospital of the University of Pennsylvania, these two stewardship strategies were compared using a pre-intervention post-intervention study design. During the pre-intervention period, prior authorization was required for commonly used broad-spectrum antibiotics including cefepime, piperacillin/tazobactam, vancomycin, and antifungals. In June 2009, the prior authorization requirement for cefepime, piperacillin/tazobactam, and vancomycin was removed. Instead, prospective audit with provider feedback for all patients receiving these three antibiotics was performed each weekday. Importantly, the prior authorization requirement for other broad-spectrum antibiotics and antifungals was continued during the post-intervention period; these agents thus served as control groups. The authors evaluated changes in the trends of total antibiotic use, use of agents with broad gram-negative activity, antifungals, and length of hospital stay during 24-month periods before and after the change in the stewardship strategy.

Over 55,000 inpatients received antimicrobial therapy over the entire study; severity of illness was similar in both time periods. Use of antibiotics with broad gram-negative activity declined at a rate of -4.00 days of therapy (DOT) per 1000 patient days (PD) per month during the pre-intervention period. During the post-intervention period, use of these agents increased by 0.80 DOT/1000PD per month, for a slope increase of 4.80 DOT/1000PD per month after the change in the stewardship strategy ($p < .001$). Specifically, use of cefepime and piperacillin/tazobactam was declining during the pre-intervention period but increased by 3.21 DOT/1000PD per month ($p = .003$) after the transition to prospective audit with feedback. For the other antibiotics with broad-spectrum gram-negative activity for which prior authorization was required in both time periods, there was no significant change between the periods.

Use of vancomycin declined during the pre-intervention period but significantly increased after the transition to prospective audit with feedback (0.89 DOT/1000PD per month, $p = .005$). Interestingly, use of antifungal agents (one of the control groups) declined during the pre-intervention period but also increased during the post-intervention period (2.42 DOT/1000PD per month, $p = .001$). Total length of hospital stay and length of stay after the first dose of antibiotics were declining during the pre-intervention period but increased significantly after the change in stewardship strategy.

■ COMMENTARY

Both prior authorization and prospective audit with feedback have been shown to be effective strategies to reduce unnecessary antibiotic use in hospitals.[1] In this academic medical center, changing from prior authorization to prospective audit with provider feedback for cefepime, piperacillin-tazobactam, and vancomycin was associated with increased use of these agents as well as increased overall antimicrobial use.

This study is novel in that it is the first to directly compare these two core antimicrobial stewardship interventions. The conclusions that can be drawn are somewhat limited given the single-center, pre-intervention/post-intervention study design. In addition, use of antifungals (a control group in which prior authorization was required in both periods) increased during the post-intervention period, raising the possibility that factors other than the change in the stewardship strategy may have impacted prescribing patterns. Nevertheless, the findings are intriguing and suggest that there could be important

differences in the effectiveness of the two core stewardship strategies currently recommended by the IDSA.

It seems intuitive that an optimal stewardship approach might be to combine prior authorization and prospective audit with feedback, given their complementary nature. Initial prior authorization helps to ensure an appropriate indication exists for broad-spectrum, toxic, or expensive antibiotics and that these agents are optimally dosed, while prospective audit with feedback 48 to 72 hours later and beyond promotes de-escalation of therapy and shorter treatment courses. However, since not all stewardship programs may have the capacity to perform both interventions, the question of whether prior authorization or prospective audit with feedback is more effective remains relevant. Although the answer to this question may depend on a number of factors specific to the individual institution or stewardship program, the present study demonstrates that multicenter studies comparing these two strategies are warranted. ■

Reference

1. Dellit TH, Owens RC, McGowan JE, Jr., et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007;44(2):159-177.

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Ebola and Pregnancy

Jamieson D, et al. What obstetrician-gynecologists should know about Ebola: A perspective from the Centers for Disease Control and Prevention. *Obstet Gyn* 2014;124 (5):1005-1010.

Hospital infection control policies for the management of suspect or documented Ebola Virus disease (EVD) should give consideration to appropriate triage procedures for their labor and delivery units. Only 4 cases of EVD have thus far been diagnosed within the United States, 2 of which were imported, and 2 of which were health care worker (HCW)-acquired. The chances of a pregnant woman with EVD presenting for care are relatively small. If it does occur, it is unlikely the patient would coincidentally presenting in term labor. It is more likely that a pregnant woman with EVD would present with vaginal and uterine bleeding or hemorrhage, spontaneous miscarriage, or fetal distress.

No data on pregnancy outcomes are available for the current outbreak ongoing in Liberia, Guinea, and Sierra Leone, which has, by conservative estimates, affected 17,527 people, resulting in 6,187 deaths. Limited data from earlier and much smaller outbreaks indicate that pregnant woman may be at increased risk for pregnancy complications and death. And neonates born to mothers with EVD have not survived.

For example, during an outbreak in Kikwit, Democratic Republic of Congo, in 1996, which affected 105 women, 14 of 15 pregnancies ended in maternal death within 10 days (93%). In contrast, 70% of non-pregnant persons requiring hospitalization died. All 10 first- and second-trimester pregnancies ended in spontaneous miscarriage, and all 5 term deliveries ended in fetal or neonatal death. Young pregnant women were disproportionately affected in one of the original outbreaks in Zaire in 1976, perhaps because young women more frequently act as caregivers. Of 177 women infected with EVD, 82 (44%) were pregnant and their mortality was high (89%). Nearly one-fourth had spontaneous abortions during their first or second trimester, and all 11 neonates born to mothers with EVD died.

With this in mind, procedures should be developed for screening patients presenting to labor and delivery for recent travel and signs and symptoms of EVD. Emergency department triage protocols should include questions about pregnancy. In addition, Ob-Gyns should be counseled about potential complications of pregnancy in EVD, as well as the likelihood of other travel-related diseases, including influenza, malaria, and typhoid fever. The medical care of a pregnant woman with EVD is similar to that for non-pregnant persons, with an emphasis on aggressive treatment of coagulopathy and hemorrhage. EVD precautions should automatically extend to any live or dead infants born to affected women.

There's an ESBL in My Soup!

Seiffert SN, et al. High prevalence of extended-spectrum beta-lactamase, plasmid-mediated AmpC, and Carbapenemase genes in pet food. *Antimicrob Agents Chemother* 2014;58(10);6320-6323.

Investigations into resistance factors present in human foodstuffs prompted these authors to turn their attention to the presence of similar genetic footprints in pet food. Thirty different cat and dog food products (both wet and dry) were purchased from 3 stores in Bern, Switzerland. All of the products were manufactured in the European Union, and nearly three-fourths provided a list of ingredients on the packaging, including the presence of meat products (duck, chicken, turkey) in proportions ranging from 4% to 18%. The rest of the ingredients were listed as various grains, organic products, fruits and vegetables, and fish byproducts.

The different samples were diluted in an enriched media plus ampicillin and held overnight at 37°F. DNA was extracted, looking for various beta-lactamases, including ESBL (CFT-M and VEB), plasmid-mediated AmpC (pCMY), and carbapenemases (KPC, OXA-48-like, and NDM).

Sixteen of the samples (53%) were positive for blaESBL genes. Fourteen (47%) of these were positive for blaCTX-M-1 group DNA, one was positive for blaCTX-M-1 and blaVEB DNA, and one had blaVEB DNA alone. Six samples (14%) were positive for blaCMY-4 genes and two (6.7%) had blaVEB genes. Most concerning, OXA-48-like genes were found in 4 of the specimens (13%) — which could result in potential transmission of these extra-drug resistance genes to pets.

Because of the food processing and sterilization procedures, which cause denaturation and fragmentation of the larger pieces of DNA, it was not possible to determine the genetic source for the genes. In other words, whether certain bacteria harboring resistance genes were present in the food could not be determined. But the lack of other specific bacterial genes suggested that the resistance genes identified were unlikely to be due to bacterial flora in the animals — but rather to extrinsic contamination from environmental or even human sources.

Indian Neonatal Deaths from MDR Bacteria

Pro-MED-mail post. Antimicrobial resistance — India. December 3, 2014. www.promedmail.org.

The increase in ESBL- and NDM1 (New Delhi metallo-beta-lactamase 1)-containing bacteria in India has triggered an unexpected national health crisis. Just as in-roads were being made in decreasing the neonatal death rate in India, multidrug-resistant bacterial infections are claiming the lives of thousands of infants. In just 5 years, an unprecedented increase in neonatal deaths from NDM and other multi-drug resistant bacteria has been occurring. Last year (2013), it is estimated that 58,000 neonates (7.3% of all infant deaths) died from multidrug-resistant infection. Pediatricians and neonatal intensive wards struggle to provide care to these infants, many of whom have infections that are untreatable.

Many of these infections are due to NDM1-containing Klebsiella or multi-drug resistant Acinetobacter, which are commonly found in untreated sewage and waste water. While indiscriminate antibacterial use for decades may have triggered the problem, the spread of these multidrug-resistant organisms (MDRO) has been magnified by the lack of adequate sewage treatment, contaminated water supplies, and crowded living conditions.

This means that otherwise healthy Asian Indians have become colonized with these organisms as part of their normal fecal flora — which has implications for the management of these individuals when they present for care in other parts of the world. Rectal swab screening for CRE/NDM is recommended for high-risk persons recently hospitalized in India or Pakistan. However, even apparently young healthy people may be affected by these organisms. At our medical facilities in Mountain View, CA, which services the large Indian population in Silicon Valley, many first-time UTIs in young healthy Indian women are ESBL-*E. coli*, presumably from intestinal and perineal colonization with these organisms. One neonate born to a young Indian mother quickly succumbed to sepsis and meningitis from ESBL-*E. coli* within hours of birth, presumably from vaginal and skin colonization from intestinal flora. ■

Correction
In the December 2014 issue of IDA (page 26, left column) an error occurred in a sentence explaining how VAP was confirmed. Superscripted numbers 6 and 4 were inadvertently published in normal size. The sentence should have read:
"VAP was confirmed by quantitative bacterial culture of > 10^6 CFU/mL from an endotracheal specimen of > 10^4 CFU/mL from bronchoalveolar lavage fluid."

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following is correct?

A. Angiotensin-converting enzyme inhibitors may often cause hypokalemia.

B. Angiotensin receptor blocking drugs may often cause hypokalemia.

C. Trimethoprim-sulfamethoxazole may often cause hypokalemia.

D. Co-administration of an angiotensin-converting enzyme inhibitor together with trimethoprim-sulfamethoxazole is associated with an increased risk of sudden death.

2. Which of the following sentences is most accurate?

A. All febrile infants younger than 3 months of age should undergo spinal fluid analysis.

B. Only febrile infants younger than 3 weeks of age should undergo spinal fluid analysis.

C. *Listeria* is a common cause of neonatal fever in many areas of the world.

D. Ill-appearing febrile infants younger than 3 weeks of age are most likely to have meningitis.

3. Which of the following is correct, according to the study?

A. Black children receive a diagnosis of otitis media less frequently than do nonblack children.

B. Black children receive a diagnosis of otitis media twice as frequently as do nonblack children.

C. Black children who are prescribed an antibiotic for otitis media are more likely than nonblack children to receive a narrow-spectrum antibiotic.

D. Black children who are prescribed an antibiotic for otitis media are more likely than nonblack children to receive a broad-spectrum antibiotic.

CME OBJECTIVES

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

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies

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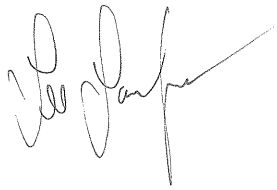

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