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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Fecal Transplant vs. Oral Vancomycin Taper for Recurrent *Clostridium difficile* Infection

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

SYNOPSIS: In a small randomized, controlled trial that compared fecal microbiota transplant (FMT) administered by enema to a six-week oral vancomycin taper, FMT was not more effective for patients with recurrent *Clostridium difficile* infection.

SOURCE: Hota SS, Sales V, Thomlinson G, et al. Oral vancomycin followed by fecal transplantation versus tapering oral vancomycin treatment for recurrent *Clostridium difficile* infection: An open-label, randomized controlled trial. *Clin Infect Dis.* First published online Nov. 9, 2016.

The management of recurrent *Clostridium difficile* infection (CDI) is challenging. The most common therapy for the past several years has been a prolonged course of oral vancomycin, frequently prescribed as a taper. Recently, fecal microbiota transplant (FMT) has become more widely available and utilized, especially in recalcitrant cases. Hota and colleagues sought to determine which of these two treatments was more effective for cases of recurrent CDI.

The study was a randomized, controlled trial from Canada that compared a 14-day course of oral vancomycin followed by an FMT vs. a six-week vancomycin taper. The inclusion criteria were patients 18 years of age and older with at least two episodes of CDI who had received at least one 10-day or more course of oral vancomycin. There were numerous exclusion criteria, including pregnancy, neutropenia, immunocompromised status, intensive care admission, severe colitis not responding to oral

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vancomycin, allergy or intolerance to oral vancomycin, chronic gastrointestinal diseases that cause chronic diarrhea, bleeding disorder, expected chemotherapy in the next 120 days, or inability to tolerate FMT. The primary outcome was recurrence of symptomatic, laboratory-confirmed CDI within 120 days of the intervention.

Of 140 patients assessed for eligibility, 12 patients in the vancomycin taper arm and 16 in the FMT arm were included in the interim analysis. Most of the patients were women (8/12 and 11/16, respectively) with a history of four to five CDI episodes (range 2-9) before starting the trial. Nine out of 16 (56.2%) patients who received FMT and five out of 12 (41.7%) in the vancomycin taper arm suffered a recurrence of CDI. This happened a median of nine days after FMT and 35 days after starting vancomycin tapering (seven days after finishing the taper). Four of the five patients who failed a vancomycin taper crossed over to FMT, and all four had another recurrence of CDI after the procedure. One of the FMT patients suffered a bowel perforation 35 days after the procedure, which was attributed to long-standing diverticulitis and not the FMT. Furthermore, there were no significant differences in fecal microbiota composition and diversity between the FMT donors and no significant differences between those associated with successful vs. unsuccessful FMT. After 30 patients were randomized, the trial was stopped due to futility.

■ COMMENTARY

Most studies of FMT for recurrent CDI have demonstrated a cure rate of about 90%. The present investigation by Hota and colleagues, which found a 44% cure rate for FMT, is notable therefore for being an outlier. There are a couple of possible explanations as to why this occurred. One is that the overall number of patients in the study was small and a larger study may have shown similar outcomes to previous ones. Another is that the methods used by Hota and colleagues were different from those employed by prior investigators. These included the delivery of FMT by enema instead of colonoscopy or nasojejunal tube, randomization of patients as soon as they experienced a recurrence of CDI and not during a symptom-free interval, only performing one FMT as opposed to multiple ones as was done in other studies, the 120-day follow-up, and no attempt to match donors and recipients (e.g., family members). Finally, pretreating patients with oral vancomycin for 14 days might have negatively affected the intestinal microbiota since oral vancomycin can be present in feces four to five days after discontinuation of therapy.

Oral vancomycin tablets have been expensive, and the cost of a six-week taper previously has cost several thousand dollars. The recent availablilty of a generic form has resulted in reduced cost. A study that compared the cost-effectiveness of different treatments found that FMT by colonoscopy was the most cost-effective initial strategy for management of recurrent CDI.[1] However, the researchers did not use vancomycin as a taper and their conclusion should be re-examined in light of the findings by Hota and colleagues.

Unfortunately, FMT may not be as effective as previous studies have shown, leading clinicians to overestimate its benefits compared to prolonged courses of vancomycin. However, one also must be aware of the economic impact that oral vancomycin can have on patients and their families, as mentioned above. Perhaps the take-away message from this study can be summarized by the old dictum "an ounce of prevention is worth a pound of cure." That is, it is far better to prevent CDI than to try to cure it with the therapies currently available. ■

REFERENCE

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ABSTRACT & COMMENTARY

No Significant Association Between Autism Risk and Maternal Influenza and Vaccination

By Hal B. Jenson, MD, FAAP

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

SYNOPSIS: A very large cohort study over 11 years failed to find an association between autism risk and maternal influenza infection or influenza vaccination during pregnancy. A low risk of autism was associated on initial analysis with first-trimester vaccination, but adjusting statistically for the multiplicity of hypotheses tested in the study showed that this association could be due to chance ($P = 0.10$).

SOURCE: Zerbo O, Qian Y, Yoshida C, et al. Association between influenza infection and vaccination during pregnancy and risk of autism spectrum disorder. *JAMA Pediatr.* Published online Nov. 28, 2016.

A cohort study was performed of 196,929 singleton children born in Northern California from Jan. 1, 2000, to Dec. 31, 2010, of at least 24 weeks' gestational age and who were followed for at least the first two years of life. Data were collected on maternal influenza infection and vaccination from the date of conception to the date of delivery. Maternal influenza infection was defined by ICD-9 codes in medical records or positive influenza laboratory test results. Diagnosis of childhood autism spectrum disorder was defined by ICD-9 codes in medical records on at least two visits from birth through June 30, 2015.

Influenza was diagnosed during pregnancy in 1,400 (0.7%) mothers. There were 45,231 (23%) mothers who received influenza vaccination during pregnancy, from a low of 6% in 2002 to a high of 58% in 2010. (Beginning in 2004, influenza vaccination was recommended by the Advisory Committee on Immunization Practices and the American College of Obstetricians and Gynecologists for all women who are or would be pregnant during the influenza season, regardless of trimester of pregnancy.) Follow-up of children was from two to 15 years (median, 8.3 years).

There were 3,101 (1.6%) children diagnosed with autism spectrum disorder. Covariate analysis showed no association of autism with maternal influenza infection (adjusted hazard ratio [HR], 1.04; 95% confidence interval [CI], 0.68-1.58) or maternal influenza vaccination (adjusted HR, 1.10; 95% CI, 1.00-1.21). Trimester-specific analysis showed that first-trimester influenza vaccination was associated with increased autism risk (adjusted HR, 1.20; 95% CI, 1.04-1.39) but that this association could result from chance ($P = 0.1$) if adjusted statistically for the multiplicity of hypotheses (n = 8) tested using the Bonferroni correction.

■ COMMENTARY

Many genetic and environmental factors likely contribute to the etiology of autism spectrum disorder, and family and social factors appear to further modulate the clinical manifestations. Recent epidemiological studies report an increased risk of autism with maternal infections and fever during pregnancy, although the risk with specific infections and timing during pregnancy is not clear. Previous smaller studies of maternal influenza infection and possible association with autism have shown mixed findings.

This most recent study found no association between autism risk and influenza infection during pregnancy or influenza vaccination during the second and third trimesters of pregnancy. The initial analysis found that influenza vaccination in the first trimester was associated with a slightly increased risk of autism. However, adjusting statistically for the multiplicity of hypotheses tested in the study showed that this association could be due to chance ($P = 0.10$).

It is imperative not to over interpret the findings of a statistical association of first-trimester influenza vaccination with autism risk, especially when further statistical analysis found that the association may be due to chance. For perspective, in 1998 a small case series by Wakefield et al in *Lancet* reported a speculative association of behavioral regression and pervasive developmental disorder in children with measles, mumps, and rubella (MMR) vaccine. That uncontrolled study later was deemed fraudulent

because of scientific misrepresentation of the data, by reporting selective data as being consecutive data. There were also concerns about that study because the authors had financial conflicts of interest, and the study was conducted without appropriate ethical oversight. Ten of 12 authors subsequently retracted their interpretation of the data, and the journal subsequently completely retracted the report. Nevertheless, the time and financial costs to conduct the appropriate epidemiological studies that conclusively refuted the results were significant. More importantly, the report undermined consumer confidence in vaccines. Parents around the world did not vaccinate their children out of the unfounded fear of increased risk of autism, which exposed their children to the risks of measles and its complications and resulted in measles outbreaks in the United Kingdom, United States, and Canada.

Both young children and pregnant women are at increased risk of severe illness and complications from influenza infection. One part of the results in this most recent study, the increased risk of autism with first-trimester maternal influenza vaccination, remains a statistical association under one analysis but not under additional, more rigorous analysis. Regardless of the interpretation of the statistical analyses, the effect of influenza on pregnant mothers and their offspring, especially in the first year of life before those children themselves can receive influenza vaccination, is a reality that is seen in physician offices and hospitals every year. Infants are among the most susceptible to the complications of influenza, but are not candidates for influenza vaccination. Universal vaccination of healthy adults, especially in households with young infants, is an important step to minimize the risk of influenza in young children.

Further studies are needed to specifically address the possible autism risk of first-trimester influenza vaccination. In the meantime, we should continue our diligence to ensure that all individuals are appropriately vaccinated against influenza, including pregnant women, to protect both them and their offspring. ■

ABSTRACT & COMMENTARY

Antibiotic Stewardship in Outpatient Settings

By Stan Deresinski, MD, FACP, FIDSA

Professor of Clinical Medicine, Stanford University

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

SYNOPSIS: The implementation of antibiotic stewardship principles in all outpatient settings is crucial to the struggle against growing antimicrobial resistance and to optimal patient outcomes.

SOURCE: Sanchez GV, Fleming-Dutra KE, Roberts RM, Hicks LA. Core elements of outpatient antibiotic stewardship. *MMWR Recomm Rep* 2016;65:1-12.

Outpatient pharmacies in the United States in 2013 dispensed approximately 269 million antibiotic prescriptions. The entire population of the country in that year was only 316.5 million. One-fifth of pediatric and one-tenth of adult outpatient visits result in an antibiotic prescription, and 143,000 recipients of those taking an antibiotic end up with an emergency department visit because of a resultant adverse event. Approximately one-third of the estimated 453,000 cases of *Clostridium difficile* infection in the United States in 2011 were community acquired. Perhaps even more importantly, the promiscuous use of antibiotics contributes to the global public health crisis of antimicrobial resistance.

In response to these unfortunate statistics and the resultant problem of antibiotic resistance, CDC has developed Core Elements of Outpatient Antibiotic Stewardship. The intended audience for this statement is broad and includes "clinicians (e.g., physicians, dentists, nurse practitioners, and physician assistants) and clinic leaders in primary care, medical and surgical specialties, emergency departments, retail health and urgent care settings, and dentistry, as well as community pharmacists, other healthcare professionals, hospital clinics, outpatient facilities, and healthcare systems involved in outpatient care."

CDC encourages organization leaders to establish a commitment to the optimization of antibiotic prescribing and patient safety with a single responsible clinical leader but with expectations that this be a goal of all members of the organization.

Among the recommended initial steps is to identify high-priority conditions associated with inappropriate prescribing, such as upper respiratory infections, sore throats not due to *Streptococcus pyogenes*, acute uncomplicated sinusitis, and early acute otitis media. Watchful waiting with delayed prescriptions may be optimal in the last two conditions. In addition, circumstances in which antibiotic prescribing opportunities may be missed should be identified, such as sexually transmitted diseases. Barriers to appropriate prescribing, such as gaps in clinician knowledge, misperception of patient desires, and concern about patient satisfaction, as well as time pressure, must be identified. Evidence-based standards for antibiotic prescribing should be implemented within the clinical setting.

It is also recommended that at least one of the following be implemented:
- Provide communications skill training for clinicians[1];
- Require explicit written justification in the medical record for antibiotic prescribing outside the recommended norm;
- Provide clinical decision support; and
- Use call centers, nurse hotlines, or pharmacist consultation systems to prevent unnecessary visits.

Critical to altering clinician behavior is tracking and reporting (i.e., audit and feedback), preferably at the individual level — an activity that has been clearly demonstrated to improve prescribing practices.

A key element of reducing inappropriate antibiotic use in the clinic is education, not only of clinicians, but of patients as well. Effective strategies that impart knowledge to patients about when antibiotics are not needed and about the potential harm of antibiotic administration should be implemented. CDC provides a wide array of educational material for patients that are freely available online at http://www.cdc.gov/getsmart. Education of clinicians may consist of "academic detailing,"continuing education activities, and by the availability of timely access to expert input.

The implementation of stewardship principles in all outpatient settings is crucial to any hope of slowing the onslaught of antibiotic resistance. This has been recognized by many groups and is a requirement for accreditation by The Joint Commission as of Jan. 1, 2017. Many obstacles must be overcome, however, such as the increasing pressure on clinicians to generate RVUs. In addition, having to face Press Ganey reports of patient satisfaction is undoubtedly an important barrier to the reduction in antibiotic prescribing for many clinicians. ■

REFERENCE

1. "To Prescribe or Not To Prescribe? Antibiotics and Outpatient Infections." The target audience is outpatient clinicians (including the Emergency Department) who prescribe antibiotics. This 1.5 hour course is also case-based and interactive and illustrates the incorporation of stewardship principles into daily practice. It addresses the problem of dealing with societal/patient pressures to prescribe when antibiotics are indicated and, using actors, illustrates approaches to dealing with them. https://med.stanford.edu/cme/courses/online/improving-antibiotics-pcs.html.

ABSTRACT & COMMENTARY

Cryptosporidiosis in India — and in Your Community Swimming Pool?

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Almost all children in some parts of India have at least one Cryptosporidium infection during the first three years of life.

SOURCE: Kattula D, Jeyavelu N, Prabhakaran AD, et al. Natural history of cryptosporidiosis in a birth cohort in Southern India. *Clin Infect Dis*, published online Nov. 9, 2016.

Cryptosporidiosis is common (about 5 million episodes per year) and deadly (about 10,000 deaths per year) during the first two years of life in India. Affected children who survive are at risk of poor nutritional status and altered cognition. However, the natural history of this infection is not well known. Thus, Kattula and colleagues prospectively evaluated diarrheal illnesses and stool pathogens in a cohort of 410 children in India from birth until 3 years of age. In the study area, HIV is rare (< 0.3% of pregnant women), and premature babies were excluded from the study. Stool was tested every two weeks and

whenever diarrhea occurred. Anti-cryptosporidial serology was tested every six months.

Of the 497 children who were recruited, 410 completed the study. (Migration out of the area was the most common reason not to complete the study). During the three years of the study, 97% of children had at least one cryptosporidial infection. *Cryptosporidium hominis* was identified more commonly than *Cryptosporidium parvum* (73% vs. 17%). The overall incidence was 0.86 infections per year, with the first infection being identified at a median of 9 months of age. Two-thirds of infections were asymptomatic, but 9.4% of all diarrheal episodes were associated with Cryptosporidium in the stool. Most diarrheal episodes lasted two to four days. There was partial protection against subsequent infections, but only at a level of 69% protection after four infections.

The authors point out that the incidence of Cryptosporidium infection was higher in their study than has been found in other developing countries such as Peru, Guinea Bissau, Brazil, and Bangladesh. Some of the difference could have been due to the frequent monitoring of the Indian study subjects.

■ COMMENTARY

Cryptosporidiosis should not be considered uncommon or inconsequential. In many areas of the world, the infection occurs early, repeatedly, and symptomatically in many young children. Even immunocompetent children can suffer adverse consequences. Interestingly, and unlike in North America, *C. parvum* is less common than other Clostridium species among infected children in India.

Are Americans risk-free? Of course not. Human infection with Cryptosporidium was first documented in 1976, and many of us remember the Milwaukee outbreak of 1993 when municipal water supplies were contaminated and nearly half a million people were sickened.[1]

Investigators in Arizona recently evaluated recreational swimming habits of children and adults who frequented treated pools.[2] Based on frequencies and durations of swimming times and based on reported water ingestion behaviors (splashing, drinking, spitting/spraying) and coupled with presumed levels of water contamination by Cryptosporidium, they calculated that children risk 2.9 Cryptosporidium infections per 100 swimmers per year, while adults risk 2.2 infections per 100 swimmers per year. The typical duration of chlorine exposure used to prevent contamination by pathogenic bacteria in swimming pools is inadequate to kill Cryptosporidium. Improved water purification combined with reminders to avoid getting pool water in the mouth should help reduce the risk of cryptosporidial infections. ■

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ABSTRACT & COMMENTARY

Diabetes and Vitamin C Deficiency May Be Common

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: Low levels of vitamin C were noted in seven of 11 patients with diabetes, including six of seven with lower extremity ulcers. Vitamin C repletion appeared to help heal these ulcers.

SOURCE: Christie-David DJ, Gunton JE. Vitamin C deficiency and diabetes mellitus — easily missed? *Diabet Med* 2016 Nov 18. [Epub ahead of print].

In this retrospective study, 11 patients with diabetes from a clinic in Sydney, Australia, with either nonhealing foot ulcers or patients who were suspected by history to have a poor diet were studied. Seven had nonhealing ulcers of their lower extremities, and four other patients without ulcers

were suspected of having vitamin deficiency.

In the group of 11 patients tested, the median vitamin C level was 19 umol/L (normal > 40 umol/L). Six of seven patients with lower extremity ulcers had low vitamin C levels compared to only one of four who did not have an ulcer and had low levels. All of these patients were treated with vitamin C 500-1,000 mg daily. Five of six patients with ulcers who were vitamin C-deficient healed their ulcers, and the remaining ulcer patient who was found to be zinc-deficient (but not vitamin C-deficient) healed after zinc repletion.

■ COMMENTARY

While this is a very small, non-randomized, observational study, I found the results intriguing. We all learned in medical school how important vitamin C is for wound healing and maintaining tissue integrity, but most of us practicing in the developed world probably do not even think of some of the more subtle manifestations of scurvy. Although this small study does not describe well the presence or absence of traditional risk factors for lower extremity ulcers in these 11 patients with diabetes (vascular disease and neuropathy), the prevalence of vitamin C deficiency in this small cohort of patients is striking. I confess to not even considering vitamin C (or other micronutrient) deficiency in most of the generally obese diabetic patients I see in the hospital and clinic for diabetic ulcers and foot infections, but I will definitely do so in the future. Clearly a larger prospective, randomized study of assessment and repletion of vitamin C (and other micronutrients) in diabetic patients with foot ulcers would be welcome. ■

Cefpodoxime proxetil (Vantin®)

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

INTRODUCTION[1,2]

Cefpodoxime is an oral third-generation cephalosporin antibiotic that was FDA-approved in 1998 for the treatment of various mild to moderate susceptible infections. There is now growing interest in the use of cefpodoxime, given the emphasis on early IV to oral conversion in patients hospitalized for community-acquired pneumonia (CAP) as well as the increasing resistance of antibiotics used for urinary tract infections (UTIs). This review focuses specifically on the use of cefpodoxime for community-acquired pneumonia caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* (including beta-lactamase-producing strains) and uncomplicated urinary tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Staphylococcus saprophyticus*.

GUIDELINES[3,4]

The Infectious Diseases Society of America (IDSA)/ American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults mention cefpodoxime as an alternative to high-dose amoxicillin or amoxicillin/clavulanate, although oral cephalosporins were found to be less effective in vitro.

The International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women suggest that cefpodoxime, as well as other β-lactam agents, are appropriate when other recommended UTI antimicrobials cannot be used. Caution is advised given the inferior efficacy and adverse effects of the β-lactam agents.

CLINICAL TRIALS[5-11]

Pneumonia

Combined Phase II and Phase III prospective, comparative, randomized studies in adult patients with lower and upper respiratory tract infections included 1,477 cefpodoxime-treated patients from July 1988 to December 1989. For lower respiratory tract infections, cefpodoxime was found to be as effective as amoxicillin, ceftriaxone in community-acquired bronchopneumonias, and amoxicillin/clavulanate in acute exacerbations of bronchitis.

A 1994 randomized, double-blind, double-dummy multicenter trial compared cefpodoxime and cefaclor for the outpatient treatment of culture-proven acute CAP. Of the 198 isolates recovered, *S. pneumoniae* and *H. influenzae* were the most common organisms. Of 178 isolates, 94% were susceptible to cefpodoxime compared to 82% of 181 isolates that were susceptible to cefaclor ($P = 0.001$). At the end-of-therapy visit, 100% of pathogens were eradicated in the cefpodoxime group and 92% of pathogens were eradicated in the

cefaclor group (P = 0.06). For patients with culture-proven pneumonia, both groups had similar clinical cure rates, with 77% of cefpodoxime patients and 71% of cefaclor patients cured.

A more recent study in 2002 compared linezolid with a standard ceftriaxone step-down to cefpodoxime regimen for the treatment of hospitalized patients with CAP. This randomized, comparator-controlled, multicenter, open-label trial compared linezolid IV switch to oral therapy compared to ceftriaxone 1 g IV every 12 hours switch to cefopdoxime oral therapy. Bacterial pathogens were isolated in 33.6% (128/381) of the linezolid group and 34.4% (126/366) of the ceftriaxone/cefpodoxime group, with *S. pneumoniae* as the most common organism identified in both groups. In the patients who had confirmed *S. pneumoniae* pneumonia and received ≥ 80% of study drug, there was no difference in clinical cure between cefpodoxime (62/69; 89.9%) and linezolid groups (63/71; 88.7%) (P = 0.830).

Urinary Tract Infection (UTI)
In the early studies, cefpodoxime was evaluated in two prospective, randomized, parallel, double-blind trials that included about 570 patients in each trial. The studies showed that cefpodoxime did not differ in clinical and bacteriological efficacy to that of amoxicillin and cefaclor for uncomplicated UTIs.

A 2002 study compared a three-day regimen of cefopdoxime to an established short-course three-day regimen of oral trimethoprim-sulfamethoxazole (TMP-SMX) for the treatment of women with acute uncomplicated cystitis. *E. coli* was the most common pathogen isolated in both groups. The results showed no statistically significant difference in clinical or bacteriological cure rates between both groups. All patients in both treatment groups who failed bacteriologically had histories of ≥ 3 episodes of UTI per year (P < 0.001).

A more recent study in 2012 compared a three-day course of cefpodoxime to a standard three-day course of ciprofloxacin for the treatment of acute uncomplicated cystitis. Both groups had similar baseline characteristics except more women had a previous UTI, especially within the past year, in the cefpodoxime group. Of the uropathogens isolated, 75% were *E. coli*. Overall clinical cure at 30 days was 93% (139/150) for the ciprofloxacin group and 82% (123/150) for the cefpodoxime group (11%; 95% confidence interval [CI], 3%-18%). Cefpodoxime failed to demonstrate clinical non-inferiority to ciprofloxacin given the 11% difference in 95% confidence interval was greater than the pre-specified non-inferiority margin of 10%.

Table 1. Dosing Regimen for Adults/Adolescents (≥ 12 years old)

Indication	Dose/Frequency	Duration
Acute CAP	200 mg every 12 hours	14 days
Uncomplicated UTI	100 mg every 12 hours	7 days

DOSAGE AND ADMINISTRATION[1]

See Table 1 for dosing regimen.

Cefpodoxime Film-coated Tablets
- Tablets should be administered orally with food to enhance absorption.

Cefpodoxime Oral Suspension
- Oral solution may be given without regard to food.

Renal Dose Adjustment
- Creatinine clearance < 30 mL/min: Reduce dosing interval to every 24 hours.
- Hemodialysis: Reduce dosing frequency to three times per week after hemodialysis.

PHARMACOLOGY[1]

Cefpodoxime proxetil is a prodrug that is converted to cefpodoxime. Cefpodoxime is an extended-spectrum, semi-synthetic bactericidal cephalosporin antibiotic that inhibits bacterial cell wall synthesis. Cefpodoxime has activity against some beta-lactamases, both penicillinases, and cephalosporinases.

Pharmacokinetics[1]

Absorption	• Peak concentration ~ 2-3 hours T_{max} prolonged for 200 mg suspension taken with food • Absolute bioavailability 50% 200 mg tablet: AUC 21-33% higher with food 200 mg suspension: AUC unchanged with food
Distribution	• Protein binding ~ 21-29% • Penetrates lung, skin, and tonsil tissue. Data on CSF levels not available.
Metabolism	• De-esterified to active metabolite, cefpodoxime • Minimal metabolism of cefpodoxime in vivo
Elimination	• Half-life ~ 2-3 hours • 29-33% excreted unchanged in urine in 12 hours

MICROBIOLOGY[1]

Cefpodoxime has been shown to be active against most isolates of the following bacteria in vivo and in clinical infections.

Gram-positive bacteria	Gram-negative bacteria
• *Staphylococcus aureus* (methicillin-susceptible strains, including those producing penicillinases) • *Staphylococcus saprophyticus* • *Streptococcus pneumoniae* (excluding penicillin-resistant isolates) • *Streptococcus pyogenes*	• *Escherichia coli* • *Klebsiella pneumoniae* • *Proteus mirabilis* • *Haemophilus influenzae* (including beta-lactamase producing isolates) • *Moraxella catarrhalis* • *Neisseria gonorrhoeae* (including penicillinase-producing isolates)

Cefpodoxime resistance occurs primarily through hydrolysis by beta-lactamase, alteration of penicillin-binding proteins, and decreased permeability.

ADVERSE EFFECTS[1]

Cefpodoxime Film-coated Tablets

• No deaths or permanent disabilities related to drug toxicity.

• Twenty-nine (2.7%) patients discontinued medication due to adverse events possibly related to drug toxicity. Significantly more patients discontinued medication at a total daily dose of 800 mg than 400 mg and 200 mg.

• Adverse events possibly or probably related to multiple doses of cefpodoxime in clinical trials (N = 4,696 cefpodoxime-treated patients)

Adverse Effect > 1%	Incidence
Diarrhea	7.0%
Nausea	3.3%
Vulvovaginal infections	1.3%
Abdominal pain	1.2%
Vaginal fungal infections	1.0%
Headache	1.0%

Cefpodoxime Oral Suspension

• No deaths or permanent disabilities related to drug toxicity.

• Twenty-four (1.1%) patients discontinued medication due to adverse events possibly related to drug toxicity.

• Adverse events possibly, probably, or of unknown relationship to multiple doses of cefpodoxime oral solution in clinical trials (N = 2,128 cefpodoxime-treated patients)

Adverse Effect > 1%	Incidence
Diarrhea	6.0%
Vomiting	2.3%
Diaper rash/fungal skin rash	2.0%
Other skin rashes	1.8%

CONCLUSION[1,2]

Cefpodoxime is an oral third-generation cephalosporin antibiotic that received FDA approval many years ago. It has activity against certain Gram-positive pathogens, including *S. aureus* (methicillin-susceptible strains), *S. saprophyticus*, *S. pneumoniae* (excluding penicillin-resistant strains), and *S. pyogenes*, as well as Gram-negative pathogens, including *E. coli*, *K. pneumoniae*, *P. mirabilis*, *H. influenzae*, *M. catarrhalis*, and *N. gonorrhoeae*. As healthcare costs and resistance rates rise, cefpodoxime may have a more significant role as an oral treatment option for CAP and UTI compared to established therapies. Cefpodoxime is fairly well-tolerated, with diarrhea as the most common adverse event reported for both the tablet and oral suspension formulations. ■

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Updates

By Carol A. Kemper, MD, FACP

Dental Care May Reduce Risk of Pneumonia

SOURCE: Doll M, Kelly K, Ratliff S, et al. Access to dental care and the risk of pneumonia: The importance of healthy teeth. IDWeek Thursday afternoon poster session, Oct. 27, 2016; New Orleans.

Dentists have seized on this data presented at IDWeek in New Orleans in October, and for good reason. It is generally believed that dental care is important to overall good health, nutritional status, and a reduction in certain kinds of infection. Indeed, data derived from the 2013 Medical Expenditure Panel Survey (MEPS) found that a lack of routine dental care may be associated with an increased risk of pneumonia.

MEPS is administered by the Agency for Healthcare Research and Quality, and evaluates national data on healthcare utilization and cost, with data garnered from individual households. Data from the 2013 survey included questions regarding the number of annual dental visits, the frequency of dental check-ups, and the presence of dental insurance during the previous two years. In addition, the survey identified 441 individuals diagnosed with at least one episode of pneumonia in 2013 (1.68% of the sample).

In simple and bivariate logistical analyses, Caucasian race, older age, a perception of general poor health, a lack of dental insurance, and a lower frequency of dental visits were each significantly associated with an increased risk of pneumonia. Individuals with no routine dental check-ups in the previous two years had an 86% increased risk of pneumonia compared to those with two or more routine annual dental check-ups (confidence interval [CI] 1.30-1.65, $P = 0.0008$). In a complex multivariate model, an increased frequency of routine dental check-ups remained significantly associated with a lower risk of pneumonia. Interestingly, while the presence of dental insurance was strongly associated with the frequency of dental check-ups, dental insurance did not appear to affect the risk of pneumonia in the final statistical model.

Stop Kissing Your Chickens

SOURCE: *MMWR*. Eight multistate outbreaks of human Salmonella infections linked to live poultry in backyard flocks (final update). Oct. 6, 2016. Centers for Disease Control and Prevention. Available at: www.cdc.gov/salmonella/live-poultry-05-16/index.html. Accessed Dec. 12, 2016.

The year 2016 has shaped up to be a banner year for *Salmonella* infections in the United States. Beginning Jan. 4 through Sept. 10, 2016, eight large multistate outbreaks of *Salmonella* were investigated by the CDC, multiple states, and the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (USDA-APHIS), each of which has been linked to backyard chicken flocks and purchases of chicks and ducklings. This is the largest number of outbreaks in a single year (from 2005 to 2014 there were only about four outbreaks per year).

In 2016, a total of 895 individuals were affected by these eight multistate outbreaks, which were caused by eight different strains of *Salmonella* (two strains of *S. infantis*, and one strain each of *S. enteritidis*, *S. muenster*, *S. hadar*, *S. mbandaka*, and *S. braenderup*). The ill people ranged in age from 1 to 106 years, with a median age of 27 years. A total of 209 individuals were hospitalized, and three died. Children aged 5 years or younger represented 28% of the total number affected.

Epidemiologic tracking and laboratory analysis linked the eight outbreaks to contact with live backyard poultry, including chicks and ducks purchased from multiple hatcheries.

Of 745 individuals who provided information, 552 (74%) reported contact with live poultry (including chickens, chicks, ducks, and ducklings). Exposures occurred at home, at other people's homes, at schools, and at work. Nearly 60% of exposures were to baby poultry — and most of these occurred in the home. Cultures obtained from individual homes, hatcheries, and work locations confirmed the presence of five of the strains.

Nearly half of the individuals said they allowed poultry in the house, including the living room (22%), the kitchen (12%), the bathroom (10%), and the bedroom (10%). (As a poultry owner, I can personally add the dining room and the garage, where we have kept a sick bird on occasion, and even raised hatchlings.) Of those who owned baby poultry, 49% snuggled the birds, and 13% kissed chicks.

Keeping backyard poultry is increasingly popular (and the eggs are fantastic). In addition to ourselves, at least three immediate neighbors keep chickens and one neighbor kept a small flock of ducks until they were killed one afternoon (we live six miles from Stanford University, in a semi-rural area bordering open space, so deer, coyote, and an occasional mountain lion are not unfamiliar). It is not unusual to see kids holding their chickens or petting them — and for many of us, they have become pets, with special places in our families. But many people may not know that chickens and ducks can harbor *Salmonella* and *Campylobacter*, even if they look perfectly healthy. While the authors of this report were adamant that "poultry should never be allowed in the house," it seems doubtful this practice will stop.

Recommendations for backyard poultry owners include the following basics:

- Always wash your hands thoroughly with soap and water after handling live poultry or chicks, and after cleaning cages or water dispensers.
- Do not eat or drink while handling the birds or while cleaning cages.
- Do not bring live poultry in the house.
- Do not let children younger than the age of 5 years handle birds or chicks without supervision, and make sure they wash their hands well afterward.

Blood Safety and Global Infections

SOURCE: Bloch EM, Simon MS, Shaz BH. Emerging infections and blood safety in the 21st century. *Ann Intern Med* 2016;165:57-58.

With globalization, increased international travel, and emerging infections around the globe, never has the potential infectious threat to the safety of blood products been greater — and directly colliding with cost-containment efforts and healthcare utilization reforms. This interesting editorial focuses the problem. Mergers of blood centers and increased transport of blood products (to save cost) increases the risk of unexpected pathogens in non-endemic areas. I realized that although I have been focusing my histories on recent travel and potential international exposures, I seldom focus on receipt of blood products as a potential risk for non-locally active infections.

At present, United States blood screening tests for HIV, hepatitis B virus, hepatitis C virus, human T-lymphotropic virus, syphilis, Chagas disease, and West Nile virus — and the potential for transmission of these organisms has been virtually eliminated in our blood supply. Testing varies for each organism. For example, since 2003, screening for West Nile virus employs a complex algorithm based on local West Nile virus activity and NAT testing, using both testing of batched blood samples and specific testing of suspect specimens. As a result, transfusion-associated West Nile virus has virtually been eliminated from the U.S. blood supply.

But what about other infections, such as *Babesia microti*, dengue, hepatitis E, Anaplasma, and Zika? A major problem is that there is little incentive for industry development of screening tests for certain organisms, e.g., Babesia, given its limited regional occurrence. Although molecular screening for Babesia has been developed, FDA approval for such assays requires years of testing, which is quite expensive. And yet, 13% of the 162 reported transfusion-associated Babesia cases within the United States occurred outside of endemic areas due to donor travel or traveling blood products.

Other parts of the world may have a greater issue with blood product safety. For example, 2.8% of blood donations during a recent outbreak in French Polynesia tested PCR positive for Zika virus. And 4 of 2,149 (0.2%) donated blood samples in Martinique were NAT+ for dengue virus.

It is hoped that newer multiplex screening techniques can be developed that can save on cost and efficiency of screening. In the meantime, consider that blood products may pose a risk for unusual pathogens not necessarily endemic to your area. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. In the United States, playing in treated recreational swimming pools:

a. is not associated with a risk of Cryptosporidium infection.

b. can lead to more Cryptosporidium infections in adults than in children.

c. has not been associated with acute gastroenteritis.

d. risks Cryptosporidium infection, especially for children who splash and get water in their mouths.

2. Which of the following is correct regarding implementation of the core elements of outpatient antibiotic stewardship as proposed by CDC?

a. Urgent care centers are excluded.

b. Retail health settings are excluded.

c. Surgical specialty clinics are excluded.

d. None of the above are excluded.

3. Which of the following is correct regarding cefpodoxime proxetil?

a. It is considered a first-generation cephalosporin.

b. It is a prodrug.

c. It is active against *Enterococcus*.

d. It is ineffective as step-down therapy in the treatment of community-acquired pneumonia.

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.