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## INSIDE



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*Infectious Disease Alert's* Physician Editor, Stan Deresinski, MD, FACP, serves does research for the National Institute of Health, is a consultant for Mrerck, and is an advisory board member Merck.
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Updates author Carol A. Kemper, MD, FACP, does research for Abbott Laboratories and Merck.

# Community Acquisition of *Clostridium difficile* – Is It What We Eat?

SPECIAL FEATURE

***By Stan Deresinski, MD, FACP***

***Synopsis:*** *Clostridium difficile often contaminates retail meat and salads, but the connection with human disease has not yet been made.*

**Source:** Gould LH, Limbago B. *Clostridium difficile* in food and domestic animals: A new foodborne pathogen? *Clin Infect Dis*. 2010;51:577-582.

A RECENT REPORT DESCRIBED A FATAL CASE OF COMMUNITY-ACQUIRED *C. DIFFICILE* diarrhea (CDAD) in a patient receiving antibiotics for a questionable diagnosis of chronic Lyme disease.[1] Community-acquired CDAD, including that caused by the putatively hypervirulent strain, NAP1/027/BI, also occurs in individuals with no prior medical contact, and its incidence appears to be increasing. Asymptomatic community carriage is reported to be in the range of 3% to 5%. The source of the acquisition of the organism in these cases has remained unknown, but among the possibilities is contact with animals, contaminated environments, and the ingestion of contaminated food.

*C. difficile* has been detected in river and seawater samples, as well as from swimming pools and even tap water.[2] Toxigenic strains have been detected in the feces of farm animals, as well as pet dogs and cats. A Canadian national survey found *C. difficile* in 6.1% of ground beef samples; most were toxin producers and were related to strains known to cause disease in human.3 *C. difficile* also has been detected in salads. Fortunately, the density of spores in meat is low — although the infectious dose for humans is unknown. Unfortunately, resistance of spores to physical eradication is significant. In fact, spores can survive standard cooking temperatures in ground beef; 20 of 20 isolates survived 71°C, the recommended temperature, for two hours.[4]


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Despite all this, no outbreaks of CDAD have been traced to food contamination, but since CDAD is ordinarily a "two-hit" disease, requiring both acquisition of the organism and exposure to antibiotics, this is, perhaps, not too surprising. Nonetheless, the role of contamination of meats and salads remains uncertain, but it seems likely that they may be the vehicle by which asymptomatic colonization occurs among community dwellers. ■

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**Leslie Hamlin,**
Managing Editor, at (404) 262-5416, or e-mail to leslie.hamlin@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.


# Antibiotic Treatment of Urinary Tract Infections in Infants

ABSTRACT & COMMENTARY


***By Hal B. Jenson, MD, FAAP***

*Professor of Pediatrics, Tufts University School of Medicine, and Chief Academic Officer, Baystate Medical Center, Springfield, MA*

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



***Synopsis:*** *A retrospective study of 12,333 infants < 6 months of age with urinary tract infections showed no difference in treatment failure between short-course (≤ 3 days) and long-course (≥ 4 days) of antibiotic therapy.*



**Source:** Brady PW, Conway PH, Goudie A. Length of intravenous antibiotic therapy and treatment failure in infants with urinary tract infections. *Pediatrics.* 2010;126:196-203.


A RETROSPECTIVE COHORT STUDY WAS CONDUCTED OF INFANTS < 6 months of age hospitalized with urinary tract infections between 1999 and 2004 at 24 children's hospitals in the United States. Of the 12,333 infants who met inclusion criteria, 240 (1.9%) experienced treatment failure, defined as readmission with urinary tract infection within 30 days. The treatment failure rate was 1.6% for children receiving short-course (≤ 3 days) intravenous treatment and 2.2% for long-course (≥ 4 days) intravenous treatment. There was not a significant association of the duration of antibiotic therapy and treatment failure comparing short- and long-course (adjusted odds ratio: 1.02; 95% CI: 0.77-1.35) or modeling antibiotic therapy as a continuous variable. The only covariates that were significantly associated with treatment failure were severity of illness and the presence of known genitourinary abnormalities.

The proportion of children receiving a long-course (≥ 4 days) of intravenous antibiotic therapy varied significantly among the 24 children's hospitals, ranging from 15% to 87% ($p < 0.001$).

## ■ COMMENTARY

In this very large cohort study, treatment failure of urinary tract infections among infants < 6 months of age was relatively uncommon — approximately 2%. Neither younger age nor short-course (≤ 3 days) duration of antibiotic treatment were risk factors for treatment failure. These results indicate that young infants with urinary tract infections may be successfully treated with short-course (three days) intravenous antibiotic treatment without a significantly increased risk of treatment failure. Severity of illness and the presence of known abnormalities of the genitourinary tract are associated with increased risk of treatment failure and,

if present, support a longer course of antibiotic treatment.

There was remarkable variation of the duration of antibiotic therapy across the 24 hospitals that was not explained by patient characteristics. This most likely represents the absence of firm, well-accepted evidence to guide clinical practices and practice guidelines. ■

# Colistin Dosing in Renally Impaired Patients

SPECIAL FEATURE

***By Jessica C. Song, MA, PharmD***

*PharmD, University of the Pacific*

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

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.[1-3] Despite widespread use of colistin 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.[4] At present, expansion of multi-drug resistant (MDR) bacteria, including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and carbapenemase-producing *Enterobacteriaceae,* has resulted in renewed interest in old antimicrobial agents such as colistin.[5]

To date, most information available about the dosing of colistin in renally impaired patients is from studies conducted four decades ago and may not apply to patients requiring treatment at the present time.[6-8] The purpose of this review is to discuss the pharmacokinetics of colistin in dialysis patients and to review dosing of this drug in renally impaired patients included in published studies.

## RENAL DOSE ADJUSTMENT OF COLISTIN

Two forms of colistin are distributed as commercially available products: colistin sulfate and colistimethate sodium (also known as colistin methanesulfonate, colistin sulphomethate sodium). Because of its toxicity profile, colistin sulfate is restricted to topical use; colistimethate is used for parenteral or nebulized administration.[4] 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.[9]

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.[10] 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 to 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.[11]

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 unit of the product contains 80 mg of colistimethate (12,500 units/milligram). The colistin formulation distributed by Norma Pharmaceuticals (Greece) has been reported to consist of 12,500 to 13,300 units per milligram.[11]

The FDA-approved package insert for Coly-Mycin states that patients with a serum creatinine of 1.3 to 1.5 mg/dL should be given 2.5 mg/kg to 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 to 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 to 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.[10] Renal dose adjustments of colistimethate reported in clinical trials are summarized in *Table 1*.

Dosing of colistin in hemodialysis patients has varied in published reports. Michalopoulos and colleagues used a dose of Colomycin 3 million units (240 mg colistimethate; 100 mg colistin base) IV every 36 hours in patients with serum creatinine levels of 2.6 mg/dL or higher, and administered 1 million units (80 mg colistimethate; 33.3 mg colistin base) post-dialysis.[15] Similarly, Falagas and colleagues used Colomycin 2 million units (160 mg colistimethate; 66.7 mg colistin base) IV every 36 hours in patients with serum creatinine levels of 2.6 mg/dL or higher, and used a post-dialysis dose of 1 million units of this agent in hemodialysis patients.[16] A daily dose of 1 mg/kg Coly-Mycin was administered to hemodialysis patients enrolled in a study conducted by Linden and colleagues.[18]

Recently, a case report of two patients highlighted the possibility of dosing colistin more frequently in patients receiving intermittent hemodialysis.[19] Marchand et al reported the use of more frequent dosing of colistimethate in two male patients with acute renal failure who presented with pulmonary infection caused by MDR gram-negative bacteria susceptible to this antibiotic. The patients received intermittent hemodialysis (Gambro, AK 200), with a blood flow setting of 300 mL/minute and dialysis effluent at 500 mL/minute for four hours, using a 1.6 $m^2$ B3 polymethyl-

**Table 1: Renal Dose Adjustment of Intravenous Colistin in Clinical Studies**

| Reference | Number of Patients | Pathogens | Conditions Treated | Colistin Dose |
|---|---|---|---|---|
| Trottier et al.[12] | 30 | *Acinetobacter baumannii* (100%) | Initial site of infection from BAL (70%); blood (20%) | **Product used: Coly-Mycin (colistin base)**. CrCl > 50 mL/min: 2 mg/kg IV Q12h; CrCl 10-50 mL/min: 2 mg/kg IV Q 24h; CrCl < 10 mL/min: 2 mg/kg IV Q36h; dialysis patients received 1 mg/kg post-dialysis. |
| Reina et al.[13] | 55 | *Acinetobacter baumannii* (65%); *P. aeruginosa* (35%) | Ventilator-associated pneumonia (53%); primary bacteremia (16%); urinary tract infection (18%); other infections (13%) | **Product not specified; used colistimethate sodium from Laboratory Bristol-Myers Squibb (Argentina)**. Serum creatinine (SCr) < 1.2 mg/dL: 5 mg/kg (maximum, 300 mg/day) divided in three doses; SCr 1.3-1.5 mg/dL: 2.5-3.8 mg/kg/d (divided in two doses); SCr 1.6-2.5 mg/dL: 2.5 mg/kg/d in 1-2 divided doses; SCr ≥ 2.6 mg/dl: 1.5 mg/kg every 36h; hemodialysis patients received 1 mg/kg/day |
| Levin et al.[14] | 59 | *Acinetobacter baumannii* (65%); *P. aeruginosa* (35%) | Pneumonia (33%); urinary tract infection (20%); primary bacteremia (15%); central nervous system infection (8%); peritonitis (7%); catheter-related (7%); surgical site (7%); otitis media (2%) | **Product used: Coly-Mycin or Colistimethate Sodium from Bellon (Rhone-Poulenc Rorer, France).** Dose of IV Colistin Base: SCr < 1. 3 mg/dl, 2.5-5.0 mg/kg/day divided in 2-3 doses (maximum of 300 mg/day); SCr 1.3-1.5 mg/dL, daily dose of 2.5-5.0 mg/kg; SCr 1.6-2.5 mg/dL, 2.5 mg/kg daily; SCr > 2.5 mg/dL, 1.0-1.5 mg/kg daily. |
| Michalopoulos et al.[15] | 43 | *P. aeruginosa* (81%); *Acinetobacter baumannii* (19%) | Intensive Care Unit setting. Pneumonia (72%); bacteremia (33%); urinary tract infection (5%); catheter-related (7%); surgical wound infection (5%); sinusitis (2%) | **Product used: Colomycin or Colistimethate Sodium from Norma (13,333 units/mg; Athens, Greece)**. SCr ≤ 1.2 mg/dL, 240 mg colistimethate every 8 hours; SCr 1.3-1.5 mg/dL, 240 mg colistimethate every 12 hours; SCr 1.6-2.5 mg/dL, 240 mg colistimethate every 24 hours; SCr ≥ 2.6 mg/dL, 240 mg colistimethate every 36 hours; hemodialysis patients received 80 mg colistimethate after each dialysis session. |
| Falagas et al.[16] | 17 | *P. aeruginosa* (60%); *Acinetobacter baumannii* (25%); *Klebsiella pneumonia* (10%) | Pneumonia (68%); urinary tract infection (11%); meningitis (11%); bacteremia (5%); surgical site infection (5%) | **Product used: Colomycin or Colistimethate Sodium from Norma (Athens, Greece)**. SCr 1.3-1.5 mg/dL, 160 mg colistimethate every 12 hours; SCr 1.6-2.5 mg/dL, 160 mg colistimethate every 24 hours; SCr ≥ 2.6 mg/dL, 160 mg colistimethate every 36 hours; dialysis patients received 80 mg colistimethate after each dialysis session. |
| Garnacho-Montero et al.[17] | 21 | *Acinetobacter baumannii* (100%) | Ventilator-associated pneumonia (100%) | **Product used: Colistimethate Sodium from Bellon (Rhone-Poulenc Rorer, France).** SCr < 1. 2 mg/dL, 2.5-5.0 mg/kg/day divided in three doses; SCr 1.2-1.5 mg/dL, daily dose of 2.5-3.8 mg/kg (two divided doses); SCr 1.6-2.5 mg/dL, 2.0 mg/kg daily; SCr > 2.5 mg/dl, 1.5 mg/kg every 48 hours. |
| Linden et al.[18] | 23 | *P. aeruginosa* (100%) | Pneumonia (78%); bacteremia (35%); wound infection (13%); intra-abdominal (26%) | **Product used: Coly-Mycin (colistin base)**. SCr 1.6-2.5 mg/dL, Coly-Mycin 5 mg/kg/d (2 divided doses); SCr 2.6-4.0 mg/dl, Coly-Mycin 2.5 mg/kg IV Q 24h; SCr > 4.0 mg/dL or hemodialysis patients received 1 mg/kg Coly-Mycin daily. |

methacrylate membrane (Toray Industries, Tokyo, Japan). The first patient received 1 million units of colistimethate (80 mg colistimethate, 33.3 mg colistin base) every 48 hours, with hemodialysis sessions occurring every 48 hours. The second patient received 2 million units of colistimethate (160 mg colistimethate; 66.7 mg colistin base) every 12 hours, and received hemodialysis on a daily basis.

Marchand et al discovered that a dosing regimen of 1 million units every 48 hours resulted in sub-therapeutic pre-dialysis levels of colistimethate. The first patient had a pre-dialysis colistin plasma concentration of 0.45 mg/L, which was far below the European Committee on Antimicrobial Susceptibility Testing minimum inhibitory concentration (MIC) breakpoint of 2 mg/liter. Consequently, a higher dose of colistimethate was administered to the second patient. The second patient did exhibit pre-dialysis colistin plasma concentrations close to the MIC breakpoint of 2 mg/L. The time-averaged dialysis clearances of colistin and colistimethate were approximately 134-140 mL/minute and 90 mL/minute, respectively. Because intermittent hemodialysis removed a significant quantity of colistin and colistimethate, Marchand et al recommended a dose of colistimethate 160 mg (colistin base 66.7 mg) every 12 hours in patients receiving intermittent hemodialysis.

Li and colleagues reported a case of a 53-year-old female (ideal body weight, 61 kg) who required colistin therapy for a new MDR *Pseudomonas aeruginosa* strain isolated in endotracheal aspirate.[20] The patient received continuous venovenous hemodiafiltration (CVVHDF) with 1 L/hour of dialysate and 2 L/hour of post-dilution replacement fluid, yielding 3 L/hour of dialysis effluent; an extracorporeal circuit containing a hospital AN69HF hemofilter was used and the blood flow was set at 200 mL/minute. The patient received intravenous Coly-Mycin 2.5 mg/kg (colistin base; colistimethate equivalent, 6 mg/kg) every 48 hours. The MIC of colistin against the *P. aeruginosa* isolate from the patient was 1.0 mg/L; the concentrations of colistin in plasma were below the MIC for 42 hours of the 48-hour dosing interval. Consequently, Li et al suggested that a dose of intravenous colistin base 2-3 mg/kg (colistimethate 4.8-7.2 mg/kg) every 12 hours would have been more appropriate for their patient.

Dosing recommendations for peritoneal dialysis patients are even less clear, given that studies were conducted four decades ago in this population.[6,7] Curtis et al described the pharmacokinetics of colistin in three peritoneal dialysis patients (weight range, 50-60 kg) who received colistimethate 2-3 mg/kg during dialysis.[6] The investigators used Dialaflex solution and 2 L exchanges with 30-minute equilibration periods. The patients exhibited a mean peritoneal clearance of 9.8 mL/minute, showing poor clearance of colistin during peritoneal dialysis. Curtis et al proposed a dose of 2-3 mg/kg colistimethate (0.8-1.2 mg/kg colistin base) given intravenously every 72 hours for peritoneal dialysis patients.

## CONCLUSION

Colistin has not been studied extensively in renally impaired patients, especially those requiring hemodialysis or peritoneal dialysis. In light of these limitations, the following recommendations can be made:

- Patients with impaired renal function who do not require hemodialysis or peritoneal dialysis should be dosed according to the package insert for Coly-Mycin (colistin base).
- Because of its propensity to cause neurotoxic and nephrotoxic effects,[10] patients should be closely monitored such that appropriate dosing adjustments can be made if renal function declines.
- Clinicians should consider more frequent dosing (every 12 hours instead of every 36-48 hours) of Coly-Mycin in patients requiring intermittent hemodialysis or CVVHDF. ■

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# Airborne spread of *Pneumocystis jirovecii*

ABSTRACT & COMMENTARY

***By Dean L. Winslow, MD, FACP, FIDSA***
*Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor, Stanford University School of Medicine*
*Dr. Winslow is on the speaker's bureau for GSK and Cubist Pharmaceuticals, and is a consultant for Siemens Diagnostics.*

***Synopsis:*** *Nineteen patients admitted to the hospital with* Pneumocystis pneumonia *had air sampling performed at distances from 1 m to 8 m from patients' heads; additional samples from patient wards and outdoors were obtained. Using real-time PCR at 1 m distance,* P. jirovecii *DNA was detected in 15 (79.8%). Copy number decreased with distance from the patient, but four of 12 samples (33.3%) taken at 8 m (in the corridor) were positive.*

**Source:** Choukri F, et al. Quantification and spread of *Pneumocystis jirovecii* in the surrounding air of patients with *Pneumocystis pneumonia*. *Clin Infect Dis*. 2010;51:259-265.

USING LIQUID MEDIUM WITH A COMMERCIAL AIR SAMPLER, AIR was sampled at varying distances from 19 patients admitted to the hospital with *Pneumocystis pneumonia*. Samples were examined and DNA quantified using a real-time PCR assay targeting the large subunit ribosomal RNA gene. At 1 m distance from the patients' heads, Pnuemocystis jirovecii (PJP) DNA was detected in 15 of the 19 patients (79.8%), with fungal burdens ranging from 7.5x10e3 to 4.5x10e6 copies/me$^3$. The levels of DNA decreased proportionately to distance from the patients' heads, but four of 12 samples (33.3%), taken at 8 m in the corridor outside the patients' rooms, were positive. Forty control samples obtained from other wards in the hospital and from outside air were negative for Pneumocystis DNA.

## ■ COMMENTARY

Serologic surveys have shown that infection with PJP is almost universal by the time humans are about two years of age. It is a common cause of pneumonia in patients with advanced HIV infection, and was rarely seen prior to the AIDS era in other heavily immunosuppressed patients. The original hypothesis was that PJP pneumonia was due to reactivation of latent disease (similar to the pathogenesis of toxoplasma encephalitis in immunocompromised patients). However, host-to-host transmission of PJP has been demonstrated in rodents, and the original descriptions of PJP were reported in outbreak settings in malnourished orphans in Europe in the immediate aftermath of World War II, and strongly suggested patient-to-patient transmission. Recent studies have shown evidence of active subclinical PJP infection in immunocompetent patients, and genetic analysis of PJP obtained from these patients has supported the concept that reinfection with PJP occurs throughout life. Small studies and case reports have demonstrated human-to-human transmission of PJP in the hospital setting. Based on these case reports, the CDC recommends avoiding placing an immunocompromised patient in the same room with a patient with PJP pneumonia.

This study is important since it is the first study in humans to clearly show the spread of PJP in the environment, and uses modern molecular techniques to quantify the fungal burden associated with shedding from symptomatic patients. These data, and the methods used in this study, will be important in future studies to better estimate the risk of airborne transmission of PJP. ■

# Is MRSE the Source of MRSA?

ABSTRACT & COMMENTARY

***By Dean L. Winslow, MD, FACP, FIDSA***

***Synopsis:*** *Nasal carriage of methicillin-resistant coagulase negative staphylococci (MR-CoNS) was investigated in 291 adults upon hospital admission. MR-CoNS carriage was present in 19.2% of patients. SCCmec type IV was found in 22% of the Co-NS isolated, and sequencing revealed extensive structural homology between SCCmec IV in methicillin-resistant* Staphylococcus epidermidis *(MRSE) and methicillin-resistant* Staphylococcus aureus *(MRSA).*

**Source:** Barbier F, et al. Methicillin-resistant coagulase-negative staphylococci in the community: High homology of SCCmec IVa between *Staphylococcus epidermidis* and major clones of methicillin-resistant *Staphylococcus aureus*. *J Infect Dis*. 2010; 202:270-281.

Nasal carriage of MR-CoNS was prospectively investigated in 291 adults upon hospital admission. The isolates were characterized by SCC*mec* typing, long-range PCR for SCC*mec* IV, and multiple-locus, variable-number, tandem-repeat analysis (MLVA) for MRSE strains. Three SCC*mec* IVa elements were fully sequenced.

The overall carriage rate was 19.2% (25.9% in patients with previous exposure to the health care system and 16.5% in patients without previous hospital exposure). Of the 83 MR-CoNS, nine carried SCC*mec* IVa, nine carried other SCC*mec* IV subtypes, 15 carried other SCC*mec* types, and 50 possessed nontypable SCC*mec* types. Long-range PCR analysis showed structural homology between SCCmec IV in MRSE and MRSA. Complete sequencing of SCCmec Iva from three MRSE strains revealed high homology to available sequences of CA-MRSA, including clones USA300 and USA400.

## ■ COMMENTARY

Staphylococci acquire methicillin resistance from the recombinase-mediated insertion of the staphylococcal chromosomal cassette mobile genetic element containing *mec*, a gene encoding a mutant penicillin binding protein 2 (PBP2a) with reduced affinity for virtually all beta lactam antibiotics. The most common clones of community-associated MRSA in both Europe and the United States (USA300, USA400, and ST80) all harbor SCC*mec* IVa. This SCC *mec* type also is increasing in prevalence among healthcare-associated MRSA.

Since the 1990s, CA-MRSA has, in many areas, replaced methicillin-susceptible *Staphylococcus aureus* (MSSA) as the most common isolate of *S. aureus*. At both the county hospitals in San Francisco (San Francisco General Hospital) and in San Jose (Santa Clara Valley Medical Center), more than 60% of *S. aureus* isolates from patients seeking care in the emergency departments are MRSA. In many respects, it has actually surprised me that it took so many years of use of antistaphylococcal penicillins and cephalosporins to select out MRSA, since penicillin-resistant beta lactamase-producing MSSA arose within a few years of the introduction of penicillin G in the 1940s.

Coagulase-negative staphylococci, in contrast, have been recognized for many years as being resistant to beta-lactam antibiotics, and the use of vancomycin has been recommended for their treatment for decades.

While this study does not provide definitive proof, the high prevalence of SCCmec IVa in MR-CoNS, and the high degree of homology between the SCCmec's obtained from MRSE and MRSA, strongly suggest that MRSE may have been the source of methicillin resistance in *S. aureus*. Previous evidence suggests that the original source of *mec* in Staphylococci was the animal pathogen *S. aureus*. ■

# Transmission of Yellow Fever Vaccine Virus: Blood Products and Breast-feeding

ABSTRACT & COMMENTARY

***By Mary-Louise Scully, MD***

*Dr. Scully is Director, Travel and Tropical Medicine Center, Sansum Clinic, Santa Barbara, CA.*

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

*This article originally appeared in the June 2010 issue of* Travel Medicine Advisor. *It was edited by Frank Bia, MD, MPH, and edited by Philip Fischer, MD, DTM&H. Dr. Bia is Professor (Emeritus) of Internal Medicine (Infectious Disease and Clinical Microbiology), Yale University School of Medicine, and Dr. Fischer is Professor of Pediatrics, Department of Pediatric & Adolescent Medicine, Mayo Clinic, Rochester, MN; they both report no financial relationships relevant to this field of study.*

***Synopsis:*** *Two recent reports highlight the potential risk of transmission of yellow fever vaccine virus through blood products and breast-feeding.*

**Sources:** *Centers for Disease Control. Transfusion-related transmission of yellow fever vaccine virus — California, 2009. MMWR 2010:59;34-37; Centers for Disease Control. Transmission of yellow fever vaccine virus through breast-feeding — Brazil, 2009. MMWR 2010:59;130-132.*

In March 2009, 89 active-duty U.S. trainees received yellow fever (YF) vaccination as part of standard preparation for potential travel to sub-Saharan Africa and Central and South

America. All the trainees were first-time recipients of YF vaccine. Four days later, these trainees took part in a blood drive. Standard blood bank screening procedures were followed, including questioning about recent vaccinations; however, none of the 89 trainees reported having received YF vaccine four days earlier. On April 10, 2009, a blood bank supervisor discovered the error during a routine record review in preparation for a subsequent blood drive. Despite a prompt recall, six units of blood products were transfused into five patients.

No clinical illness occurred in four blood recipients within a month of transfusion. The fifth patient was an 82-year-old male who was in hospice care for terminal prostate cancer and end-stage, transfusion-dependant, B-cell lymphoma. He died 20 days after receiving a platelet transfusion derived from one of the implicated lots. No pre-mortem blood specimens were available for testing in this patient, and no autopsy was performed. In three of the remaining four recipients, YF virus IgM antibodies were detected by plaque neutralization in serum samples taken between 26 and 37 days post-transfusion. No evidence of potential cross-reactive flavivirus infections, such as West Nile virus or St. Louis encephalitis virus antibodies, was detected. The one surviving patient who did not have serologic evidence of exposure to the YF virus was a pre-term infant who received 4 aliquots of irradiated red blood cells (30 cc in total). Two possible reasons for the lack of immune response in this case might be the immaturity of the pre-term infant's immune system and lower levels of YF vaccine virus in red blood cells as opposed to the other serum-containing products.

In April 2009, during epidemic YF activity in Rio Grande do Sul, Brazil, a 22-year-old mother was vaccinated for YF during a routine postpartum visit. Her infant was 15 days old, and she was exclusively breast-feeding. Eight days later, her infant was hospitalized with seizures and meningoencephalitis. Yellow fever-specific IgM was detected in the infant's serum and CSF, thus confirming yellow fever vaccine-associated neurologic disease. Other causes of meningoencephalitis (dengue, herpes simplex, cytomegalovirus, varicella, and enteroviruses) were ruled out by testing of serum and CSF. The infant did recover and at 6 months was without neurologic sequelae. This is the first laboratory-confirmed case of YF vaccine-associated neurologic disease (YEL-AND) in an infant as a result of transmission of YF vaccine virus through breast milk.

## ■ COMMENTARY

These reports confirm what has always been suspected on theoretical grounds but never documented: first, that transfusion-related transmission of YF vaccine virus can occur and, second, that YF vaccine virus can be transmitted through breast milk and cause YEL-AND in infants. The infant recovered without sequelae, and in the transfusion cases, no clinical illness was noted in the four recipients who could be followed. The outcomes might have been very different if the affected blood lots had not been promptly recalled and instead transfused into many more immunocompromised or older patients. Despite its excellent track record for prevention of YF, we are increasingly aware of the potential complications including both YEL-AND and YF Vaccine-Associated Viscerotropic Disease (YEL-AVD) with the various strains of the 17D YF virus lineage. Both of these adverse events occur almost exclusively in first-time recipients of yellow fever vaccine.[1]

The documentation of YF vaccine virus transmission through breast milk has repercussions in parts of the world where epidemic YF activity occurs and breast-feeding is the predominant mode of infant feeding. The actual risk for 17 DD virus transmission through breast milk is difficult to estimate without knowing the numbers of breast-feeding women who are vaccinated without any adverse consequences for their infants. Nonetheless, it is recommended to avoid YF vaccination of nursing mothers unless travel into high-risk yellow fever-endemic areas simply cannot be avoided or postponed.2 Breast-feeding mothers who need YF vaccination should be made aware of the potential transmission issue so that an alternative mode of infant feeding could be considered during time of expected YF viremia.

Eligibility requirements for blood donation are in place to prevent inadvertent acceptance of donors with the possibility of illness or latent infections. With regard to immunizations, the American Red Cross specifically advises people to defer blood donation for two weeks after receiving either YF vaccine or oral polio vaccine, which is no longer available in the United States, and for four weeks after MMR (measles, mumps, rubella), varicella (chickenpox), and herpes zoster (shingles) vaccination. The complexities of smallpox vaccination require special considerations, but generally a minimum eight-week interval is recommended, assuming no vaccine complications have occurred. There is no deferral period after receipt of influenza, pneumococcal, tetanus (including Td or Tdap), meningitis, hepatitis A, injectable typhoid, injectable polio, or human papillomavirus (HPV) vaccination as long as the donor is in good health without any symptoms. Of note, the American Red Cross suggests a 21-day deferral after routine hepatitis B vaccination (i.e., not given for an exposure) to avoid any potential for a false-positive testing for hepatitis B carrier status.3

Although blood bank screening techniques are in place for prevention of transfusion-related illnesses, travel medicine physicians can help reinforce these recommendations at the time pre-travel vaccinations are given. Patients often ask about blood donation deferral policies after travel to malaria-endemic areas (generally one year after travel to a malaria risk area, 3 years if the person lived in a malaria area or had disease). The pre-travel visit, during which live virus vaccines such as yellow fever vaccine are administered, gives us an excellent opportunity to review with our patients the policies on blood donation deferral after immunizations.

Full eligibility requirements for blood donation are available at www.redcrossblood.org. ■

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# Schistosomiasis Treatment Failures with Single-dose Praziquantel

ABSTRACT & COMMENTARY

***By Maria D. Mileno, MD, and Paul Trowbridge, MD***

*Dr. Mileno is Director, Travel Medicine, The Miriam Hospital, Associate Professor of Medicine, Brown University, Providence, RI. Dr. Trowbridge is a resident, Internal Medicine, The Miriam Hospital, Brown University, Providence, RI.*

*Dr. Mileno and Dr. Trowbridge report no financial relationships relevant to this field of study.*

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***Synopsis:*** *Of 30 patients re-examined post-treatment with praziquantel (PZQ) for new schistosomiasis, only 10 were free of signs and symptoms, suggesting ongoing infection. Two-thirds of patients re-evaluated had an elevated blood eosinophil count or serum IgE level, increased antibody titer, or symptoms. Detectable ova were found on evaluation of urine or rectal biopsy in 20%. Re-evaluation is complicated by the lack of a diagnostic gold standard for schistosomiasis, especially for those with low parasite burdens.*

**Source:** Helleberg M, Thybo S. High rate of failure in treatment of imported schistosomiasis. *J Travel Med.* 2010;17:94-99.

A RETROSPECTIVE OBSERVATIONAL STUDY WAS CONDUCTED ON 30 individuals from a possible 49 persons who were treated for schistosomiasis between 2003 and 2008 at Copenhagen University Hospital, Denmark. All patients had traveled to endemic areas and had been previously diagnosed by detection of ova or positive serologic studies associated with symptoms. All patients had subsequently been treated appropriately with at least 1 dose of praziquantel (40-60 mg/kg) at least 12 weeks post-exposure to avoid treatment at the invasive infection phase during which PZQ has limited effectiveness. Patients were offered re-evaluation 3 to 36 months post-treatment (mean 16 months). Nineteen of the 30 patients who accepted actually required re-evaluation, as 11 had already done so. Evaluation consisted of microscopy performed on 24-hour urine samples and/or rectal biopsies for direct visualization of ova, measurement of eosinophil count, IgE levels, and schistosomiasis serology by indirect hemagglutination assay and/or immunofluorescence testing. All patients were screened by history for potential re-exposure to freshwater from schistosomiasis-endemic regions prior to re-examination.

Viable schistosome ova were detected in 6 of 30 (20%) patients during re-examination following initial treatment, and these cases were considered treatment failures. This level of treatment failure is largely congruent with previous studies of schistosomiasis treatment among travelers. Notably, all of these patients had initially been diagnosed by detection of viable ova, not by a positive serology alone, potentially indicating higher initial parasite load. In addition, these patients were all tourists, expatriates, or immigrants from endemic areas. Treatment of schistosomiasis with praziquantel in patients from endemic areas has produced lower treatment failure rates. It has been hypothesized that this occurs because praziquantel only exposes parasitic antigens and requires host immunity in order to clear the adult organisms and obtain a cure. The latter would be more likely to occur in sensitized individuals from endemic areas than in travelers who were previously uninfected with the parasite.

In addition to known treatment failures, additional treatment failures were suspected in patients who did not have detectable schistosome ova, but were symptomatic two years after treatment and showed a rise in antibody titer of at least eightfold with an elevated serum IgE level. Only one-third of the study population (10 patients) had no confirmed ova or signs/symptoms suggesting potential ongoing schistosomiasis.

Other than direct detection of schistosome ova, no other parameters such as eosinophil count, serum IgE levels, or clinical symptoms could be shown to be a reliable indicator of infection, as none of them were found to show significant differences between patients in whom ova were detected and those in whom ova were not detected. Antibody titer, notably, was actually decreased in one patient who was subsequently found to have ova present on rectal biopsy. The diagnosis of schistosomiasis among individuals who do not have a heavy parasitic burden, and thus have limited excretion of ova, can be difficult; detection of ova, by any means, is fairly insensitive, elevations in serum IgE levels or eosinophil counts are nonspecific, and serologic markers can remain elevated long after effective therapy. Although polymerase chain reaction (PCR) testing for parasite DNA may aid diagnosis in the future, empiric repeat treatment of travelers with schistosomiasis may be the best strategy, given the general safety of PZQ use.

■ **COMMENTARY**

There are several interesting aspects to this study. First of all, the high rate of treatment failure with PZQ is somewhat disturbing. With at least a 20% treatment failure rate in this study and the possibility that up to two of every three patients treated failed to clear the parasite, the drug of choice for schistosomiasis may require some new guidelines for its effective use, or it even may need to be replaced.

What may be of more interest than the results from this study is what we learn about what we simply do not know. Interestingly, even though this study points out that PZQ may be failing to treat some cases of schistosomiasis, we do not even understand how this medication works, much less how or why it fails. One of the hypothesized mechanisms of action is disruption of the parasitic surface membrane, allowing antigen exposure to the host's immune mechanisms. This hypothesized mechanism potentially could explain why there seems to be a higher rate of treatment failure among people exposed while traveling, including children, than among adults from endemic areas. However, this is not yet clear. Additional research on a larger scale than performed in this study would be useful for detailing the range of risk factors for treatment failure.

In addition to highlighting our lack of knowledge about treatment, this study also indicates that we currently lack a reliable method for choosing whom to treat or even retreat. Our gold standard for detection of infection is quite insensitive, and our serologic methods often are not helpful during re-evaluation. PCR tests looking for parasitic DNA may be helpful in the future, but have not yet been studied sufficiently. ■

## *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. ■

## *CME Questions*

**4. Which of the following is correct?**

A. Colistin is a polymyxin antibiotic.

B. Colistin dosing does not require adjustment in patients undergoing hemodialysis.

C. Colistin dosing does not require adjustment in pateints undergoing peritoneal dialysis.

D. Colistin is not renally cleared.

**5. Which of the following is correct with regard to Pneumocystis jirovecii?**

A. There is evidence that infection occurs during infancy or childhood.

B. Its DNA can be detected in the air at a distance of 1 meter, but not at 8 meters from a patient with active infection.

C. Its DNA cannot be detected in the air within 1 meter of a patient with active infection.

D. Patient-to-patient transmission has never been reported.

**6. Recent vaccination with which one of the following is a contraindication to blood donation?**

A. Injectable typhoid vaccine.

B. Injectable polio vaccine.

C. Injectable yellow fever vaccine.

D. Injectable human papillomavirus vaccine.

Answers: 4. (a); 5. (a); 6. (c)

**In Future Issues:** **Ventilator-associated Tracheobronchitis and Pneumonia**

# UPDATES

By Carol Kemper, MD, FACP

## HAART and Ribavirin: Mitochondrial Toxicity

**Source:** Reiberger T, et al. Mitochondrial toxicity is associated with virologic response in patients with HIV and hepatitis C virus coinfection treated with ribavirin and highly active antiretroviral therapy. *J Infect Dis*. 2010;202:156-160.

This subset analysis from a larger prospective, multicenter HIV-HCV coinfection treatment trial found that patients receiving highly active antiretroviral therapy (HAART) in combination with pegylated interferon alfa and ribavirin for HCV were at greater risk for lactic acidosis and hyperlactatemia than those receiving HCV treatment alone. Patients received PEG-IFN 180 micrograms weekly and ribavirin 800 mg/day (for genotypes 1 and 4) or 1000-1200 mg/day (for genotypes 2 and 3), with their usual HAART regimen or with no HIV treatment. The use of d4T, ddI, or AZT was not allowed during study. Venous lactate levels were measured at baseline and at regular intervals during the study.

The subgroup of 64 HIV-HCV coinfected patients was followed for up to 12 months during HCV therapy. Forty-eight of these were also receiving HAART. Lactate levels were increased in both HAART and non-HAART users during HCV treatment, compared with baseline, although mean lactate levels were significantly higher at weeks 4 and 12 in HAART users than those receiving HCV therapy alone. By six months of HCV therapy, lactate levels appeared to stabilize and were similar between HAART and non-HAART users.

Thirteen of 14 patients with significant elevations in lactic acid (> 2 mmol/L) were receiving HAART, as was the single patient who developed lactic acidosis with lactate levels (> 5 mmol/L). Nine patients also had severe weight loss (> 10% body weight), all of whom were receiving higher-dose RBV and seven of whom were receiving concurrent HAART. Elevations in pancreatic enzymes were significantly more frequent in patients receiving HAART vs. those who were not (32% vs. 12%). Six patients developed symptomatic pancreatitis, necessitating discontinuation of therapy. A trend toward reduction of hepatic steatosis was observed in patients receiving HAART and lower-dose RBV (possibly because many of these patients were infected with genotype 3).

A trend toward improved response to HCV therapy was observed in patients with evidence of hyperlactatemia and mitochondrial toxicity (a sustained response occurred in 56% of patients receiving HAART vs. 31% non-HAART users, $p = .088$). The authors suggest this may be the result of higher intracellular ribavirin levels, with greater anti-HCV suppression but a consequent increased risk of mitochondrial toxicity.

## ED Drugs and Unsafe Sex

**Source:** Jena AB, et al. Sexually transmitted diseases among users of erectile dysfunction drugs: Analysis of claims data. *Ann Intern Med.* 2010;153:1-7.

This large-scale population study, sponsored by the BING Center for Health Economics and the RAND Roybal Center for Health Policy, examined whether rates of STDs and HIV infection were affected by the use of drugs for erectile dysfunction. A large database of users was created from pharmacy and medical claims between 1997 and 2006 for 44 states. Men over the age of 40 years (who were more likely to have ED) who had filled at least one or more prescriptions for an ED drug for any quarter were identified, and all claims for STDs, HIV, or other comorbid conditions likely associated with ED were reviewed.

From 1997 to 2006, 33,968 men filled at least one prescription for an ED drug, while 1,376,838 remained non-ED drug users. In the year before the first ED drug was filled, rates of all newly diagnosed STDs were significantly higher in ED drug-users compared with non-users (adjusted OR 2.80, $p < .001$), including higher rates of HIV, Chlamydia, syphilis, and gonorrhea (although only those figures for HIV and Chlamydia were statistically significant). In the year after the first ED drug was filled, the risk of STD was also significantly higher in ED drug-users compared with non-users (adjusted OR 2.65, $p < .001$), although these figures were largely driven by cases of new HIV infection.

A surprising finding from this data was the rates of HIV infection and STDs in ED-drug users were similar both in the year before and in the year after the first prescription for an ED drug was filled. Thus, there was no apparent change in the rates of HIV and STDs in men who began using sildenafil or another similar agent — but the use of an ED agent appears to be a marker for riskier sexual behavior, at least in some men. The authors suggest that earlier studies fo-

cusing on the use of these agents did not adequately capture baseline STD rates, resulting in the impression that increased rates of STDs were the result of (or facilitated by) the use of an ED agent.

Requests for an ED agent should prompt discussion regarding safer sex behavior and STDs — even in those over the age of 40.

## Update on Brucellosis: The Latest STD?

BRUCELLOSIS IS THE MOST COMMON zoonosis world-wide, resulting in an estimated half million cases annually. Infection usually occurs from ingestion of contaminated dairy, aerosolization, or mucocutaneous contact with conjunctiva, abraded skin, or open infected tissues. Sexual transmission has seldom been documented in humans, although it is common in farm animals, and the organism has been found in both semen and vaginal fluids. One can imagine that disseminated infection could result in infection in genital secretions, which is indirectly supported by the fact that genital infection does occur, and infection within families is common (up to 50%).

The first article describes the apparent sexual transmission of Brucella spp. between two married couples.[1] The first patient was a 55-year-old man who had traveled to Israel, where he consumed unpasteurized goat milk. About two weeks later, he developed fever and rigors, and blood cultures yielded *B. melitensis* biovar 1. He received a combination of rifampin and doxycycline for two weeks and quickly recovered. Four weeks following the man's diagnosis, his wife, who had not traveled, presented with fever and rigors, and blood cultures yielded the same organism. Semen samples, obtained from the husband at that time (towards the end of his treatment course), failed to yield an organism, but PCR was positive for Brucella spp. Despite the same treatment regimen, and initial response, the wife relapsed with recurrent infection four weeks later. Culture of semen was negative, but PCR remained positive.

The second case described a 65-year-old man who presented with fever, chills, cervical discitis and osteomyelitis, and epididymo-orchitis. Blood cultures grew B. melitensis. He responded well to treatment. He recalled eating unpasteurized cheese purchased in a small village in Israel. About four weeks later, his wife, who had not traveled with him and had no history of exposure to unpasteurized dairy, developed fever and chills. Blood cultures grew *B. melitensis*.

Both cases are highly suggestive of sexual transmission from husband to wife. The persistence of the organism in semen in the first case, at least as demonstrated by persistently positive PCR, raises concern that persistence of the organism in genital secretions may present an ongoing risk to sexual partners, despite apparent response to treatment. Persistence of infection is, in part, what makes certain species of brucella particularly difficult to treat.

At least 10 different species of Brucella have been identified, each with apparent differences in host specificity, virulence, and in the ability to cause persistent infection, including more commonly *B. melitensis* (in goats), *B. abortus* (in cattle), and *B. suis* (in pigs). Increasing number of cases are being reported from Israel, Iraq, Iran, Kyrgyzstan, and Mongolia, as well as the U.S.-Mexican border. Two newer species have been identified within the past decade, including B. microti, which was first described in an outbreak in the Czech Republic in 2001. The reservoir for this organism in the wild appears to be the common vole.

Laboratory work with *B. microti* indicates that it may be more virulent than other species of Brucella, but may lack the ability to persist in tissues as other species.[2] Jimenez de Bagues and colleagues infected human and murine macrophages with both *B. microti* and *B. suis*. At 24 hours of cell culture, *B. microti* demonstrated a significantly increased capacity for intracellular replication compared with *B. suis*. In vivo inoculation of different mice strains showed that the bacterial load in liver and spleen peaked at day 3 for *B. microti*, compared with day 7 for *B. suis*. Intraperitoneal inoculation of $10^5$ *B. microti* resulted in death in 82% of Babl/c mice within 4-7 days. However, sublethal doses of *B. microti* resulted in total protection from subsequent lethal doses of organism — suggesting that naturally occurring immunity in the wild may be important in preventing spread of the organism. Furthermore, *B. microti* had a lower residual capacity for persistence of infection in spleen tissue.

Interestingly, genetic sequencing studies suggest that all of the brucella species share a high degree of homology and, specifically, *B. microti* appears to be nearly identical to *B. suis* — enough so that it has been proposed that all of these organisms should be grouped into one species (tentatively named *B. melitensis*). However, genetic analyses do not seem to adequately explain the observed differences in host specificity and possibly virulence between the various organisms. ■

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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.*

# Weight-loss Drug Effective Without Cardiac Side Effects?

***In this issue:*** Lorcaserin submitted for FDA review, FDA advisory panel votes against phentermine/topiramate, mixed vote on rosiglitazone, advisory panel votes to remove breast cancer indication from bevacizumab labeling, no increase in seizures found with DTaP vaccine, new REMS for quinine.

## Weight loss without cardiac side effects

A new weight-loss medication may soon be available in the United States. Arena pharmaceuticals has filed a new drug application with the FDA for lorcaserin, a selective serotonin 2C-receptor agonist, and will likely get a formal review this fall. Unlike previous nonselective serotonergic agonists such as fenfluramine and dexfenfluramine, which were effective at causing weight loss, but also inhibited serotonin 2B receptors in the heart and were associated with valvulopathy, lorcaserin is specific for the serotonin 2C receptor in the brain.

Results from a company-sponsored study were published in the in *New England Journal of Medicine* and validate the effectiveness of the drug. The phase III trial was conducted at 98 academic and private trial sites, where 3180 patients were randomly assigned to receive lorcaserin 10 mg or placebo twice daily. After 1 year, patients receiving the active drug were randomly reassigned in a 2:1 ratio to continue to receive lorcaserin or change to placebo. All patients were age 18-65 years with a BMI of 30-45 or 27-45 kg/m$^2$ with one coexisting condition, including hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, or sleep apnea. Patients were also counseled on lifestyle modification. Echocardiography was done at baseline and every 6 months thereafter.

At the end of 1 year, 47.5% of patients receiving lorcaserin lost 5% or more of their baseline body weight as compared with 20.3% of patients receiving placebo ($P < 0.001$). The average patient in the lorcaserin group lost 5.8% of their body weight compared with 2.2% in the placebo group ($P < 0.001$), and more patients in the active treatment group lost 10% or more of their baseline body weight than in the placebo group (22.6% vs 7.7%; $P < 0.001$). In those who lost weight with the active drug, the loss was maintained in a greater proportion of patients who continued to receive lorcaserin in year 2 compared to those who were reassigned to placebo (67.9% vs 50.3%; $P < 0.001$). Markers of cardiovascular risk were improved in the active treatment group including C-reactive protein, fibrinogen levels, lipid levels, and insulin resistance. Systolic and diastolic blood pressures also decreased slightly in the lorcaserin group. Significantly, there was no evidence of cardiac valvulopathy found with use of lorcaserin and the rate of serious side effects was similar in the two groups.

The authors conclude that lorcaserin was associated with significant weight loss and improved maintenance of weight loss as compared to placebo (*N Engl J Med* 2010;363:245-256). Already being tagged the new, safe "diet drug," it is a sure bet that approval of lorcaserin will be associated with tremendous interest from our patients. ■

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

## Advisory panel votes against Qnexa

An FDA advisory panel recommended against approving (10-7 vote) the combination weight-loss drug Qnexa® (phentermine/topiramate) because of concerns about safety. The drug appears to be effective at inducing weight loss, but is associated with significant side effects including depression, anxiety, sleep disorders, attention, memory, and language and other cognitive disorders, as well as metabolic acidosis, increased heart rate, and teratogenicity. Qnexa is a combination of two available drugs and both remain on the market individually. Phentermine was approved in 1959 and is currently indicated as short-term treatment for weight reduction. It was part of the infamous Fen/Phen combination along with fenfluramine (later dexfenfluramine; both fenfluramine and dexfenfluramine were eventually removed from the market when they were found to cause pulmonary hypertension and cardiac valvulopathy). Topiramate is approved for the treatment of seizures and migraine prophylaxis. The FDA generally follows the recommendations of its expert panels. ■

## Mixed vote on rosiglitazone

The same FDA committee also recently ruled on the embattled diabetes drug rosiglitazone (Avandia®), and the vote was decidedly mixed. GlaxoSmithKline's rosiglitazone has been under intense scrutiny since 2007 when a study from the Cleveland Clinic linked the drug to an increased rate of heart attacks (*N Engl J Med* 2007;356:2457-2471). Recently, the FDA has evaluated reports from the *New York Times* and others that the company suppressed crucial safety information about the drug for years. At the July meeting of the Endocrinologic and Metabolic Advisory Committee, 12 members voted to withdraw rosiglitazone from the market, 10 voted to keep the drug on the market with additional warnings and restrictions, 7 wanted additional warnings only, and 3 members voted for no label changes. The FDA is not required to follow the advice of its advisory panels, and it is unclear what course they will take when they finally make a decision later this year. ■

## Breast cancer indication for bevacizumab

The Oncologic Drugs Advisory committee of the FDA has recommended removing the indication for breast cancer treatment for bevacizumab (Avastin®). The 12-1 vote was made after data were presented that the drug provided no survival benefit when used in combination with docetaxel, while contributing significant adverse effects. Bevacizumab, a humanized monoclonal antibody, which blocks new blood vessel formation (angiogenesis inhibitor), also carries indications for treatment of colon, lung, kidney, and brain cancers. ■

## No increase in seizures with DTaP vaccine

The diphtheria-tetanus-acellular pertussis vaccine (DTaP) does not increase the risk of seizures in children, according to a recent article published on-line in *Pediatrics*. The previously used diphtheria-tetanus-whole-cell pertussis vaccine (DTP) is associated with seizures, but there were limited data on DTaP. Using data from the CDC's Vaccine Safety Data linked project, a retrospective study from 1997 through 2006 at 7 managed-care organizations was performed. Eligible children were age 6 weeks to 23 months and had not previously received DTP. Of the more than 433,000 children who were vaccinated, there were 7191 seizure events. The adjusted incident rate for seizures across all doses was 0.87 in the cohort analysis and 0.91 in the comparison group with the same patients during unexposed periods. The authors conclude that they did not observe an increased risk for seizures after DTaP among children age 6 weeks to 23 months. ■

## New REMS for quinine

The FDA banned the OTC use of quinine sulfate for the treatment of nocturnal leg cramps in 1994 after receiving more than 150 reports of adverse reactions, including 23 deaths. Quinine sulfate (brand name Qualaquin®) remains the only quinine product on the market, but is approved only for the treatment of uncomplicated malaria caused by *Plasmodium falciparum*. Qualaquin, however, is much more commonly used off-label for nighttime leg cramps. The FDA continues to get reports of life-threatening hematologic reactions associated with quinine sulfate including thrombocytopenia, hemolytic-uremic syndrome/TTP, hearing loss, and cardiovascular problems. Between 2005 and 2008 there were 38 cases of serious side effects including 2 deaths. The FDA has announced a new Risk Evaluation and Medication Strategy (REMS) for Qualaquin that will include a Medication Guide explaining what the medication is and is not approved for, as well as the potential side effects of the drug. The medication guide specifically states that "Qualaquin should not be used for nighttime leg cramps," and those using it for this indication are at risk of serious side effects (FDA Drug Safety Communication, July 8, 2010). ■