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INSIDE

Azithromycin for Typhoid Fever

ABSTRACT & COMMENTARY

Synopsis: *Five days of oral treatment with azithromycin appeared to be at least as effective as a similar duration of treatment of treatment with ceftriaxone in children in Cairo with typhoid fever.*

Source: Frenck RW Jr, et al. Short-Course Azithromycin for the Treatment of Uncomplicated Typhoid Fever in Children and Adolescents. *Clin Infect Dis.* 2004;38:951-957.

Frenck and colleagues randomized 68 children in Cairo with typhoid fever to treatment with either orally administered azithromycin (20 mg/kg po daily) or ceftriaxone (75 mg/kg IV daily), each for 5 days. The maximum daily doses allowed were 1000 mg and 2500 mg, respectively.

Both treatments were highly effective, with 94% of azithromycin and 97% of ceftriaxone recipients achieving clinical cure by day 7. The 2 clinical failures in the azithromycin group were due to mild gastrointestinal symptoms that resolved by 7 days without further intervention, and the single clinical failure in the ceftriaxone group was due to persisting fever, which also resolved without changes in management. The mean time to defervescence was 4.5 ± 1.9 days for azithromycin recipients and 3.6 ± 1.6 days for ceftriaxone recipients, a difference that was not statistically significant.

Only 1 patient, a ceftriaxone recipient, failed to achieve microbiologic cure. None of the isolates demonstrated in vitro resistance to ceftriaxone. The azithromycin MIC90 was 6 mcg/mL, with 7 isolates having an MIC > 8 mcg/mL, and thus considered resistant. Four of these 7 were recovered from patients randomized to receive azithromyin and, despite the in vitro results, all 4 were successfully treated with this azalide antibiotic.

Blood culture after 3 days of therapy was still positive in 12 of 31 (37.5%) patients treated with azithromycin, but in none of the 36 given ceftriaxone ($P = 0.0001$). Blood isolates from all 12 of those bacteremia persisting to day 3 on azithromycin remained susceptible to this antibiotic. All 12 patients were asymptomatic by the time the

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results of the blood culture were known. The only positive blood culture at day 8 was in a ceftriaxone recipient.

Bacteremic relapse after hospital discharge was detected in 5 patients, all of whom had been treated with ceftriaxone; each isolate remained susceptible in vitro to this antibiotic. Stool cultures were negative in all patients examined at a follow-up visit at 1 month. Both treatments were well tolerated.

COMMENT BY STAN DERESINSKI, MD, FACP

It is estimated that 16 million cases of typhoid fever occur each year in the world. Unfortunately, many strains of *Salmonella enterica* serovar Typhi have acquired resistance to a number of antibiotics commonly used for treatment of this infection, resulting in the emergence of multidrug resistance (although this problem appears to be inexplicably receding in some areas).[1] Such isolates are commonly resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole. Of great concern, is the decreasing susceptibility to fluoroquinolones.

While frank in vitro resistance (the NCCLS breakpoint is 4 mcg/ml) to fluoroquinolones among *S. enterica* serovar Typhi remains uncommon, reduced susceptibility is increasingly common. In 1998, 19% of isolates had an MIC to ciprofloxacin ≥ 0.25 mcg/mL; most were from the Indian subcontinent.[2] While these would be reported as susceptible, most are resistant to nalidixic acid, providing a clue to reduced fluoroquinolone susceptibility.

Treatment of typhoid fever due to infection with such isolates as ciprofloxacin has been associated with an increase in time to defervescence and a need for prolongation of therapy and, in some cases, with frank therapeutic failure.

The Sanford guide currently recommends treatment of typhoid fever with either ciprofloxacin or ceftriaxone, listing azithromycin as an alternative choice. Ceftriaxone of course, can only be administered parenterally.

The current study confirms, previous studies that used a longer duration of antibiotic administration, that azithromycin is an excellent choice for the treatment of typhoid fever. In this study, clinical cure rates did not differ between azithromycin and ceftriaxone recipients, despite a longer duration of bacteremia in the former group. On the other hand, no bacteremic relapses were detected among the azithromycin recipients, in contrast to a 14% relapse rate in ceftriaxone recipients, a finding seen in previous evaluations of this antibiotic.

The longer duration of bacteremia in azithromycin recipients may be due to a number of factors, including the relatively low serum concentrations achieved with this drug and the presumed more rapid bactericidal activity of ceftriaxone. The absence of relapses in azithromycin recipients may be related to the extraordinarily high intracellular concentrations achieved with this drug, and the fact that *Salmonella* is an intracellular pathogen. These high intracellular concentrations may also account for the success of therapy in a number of cases, despite in vitro susceptibility test results that are interpreted by NCCLS standards as indicating resistance.

The increasing resistance of bacterial enteric pathogens to fluoroquinolones in some parts of the world, including the Indian subcontinent and southeast Asia, raises concern regarding the optimal self-treatment for travelers' diarrhea. The recent FDA approval of rifaximin provides a novel alternative, but this rifampin derivative has a more limited antibacterial spectrum and is poorly absorbed from the gastrointestinal tract.3 Azithromycin may prove a better choice in some instances, and would have the potential to abort cases of typhoid fever in travelers. ■

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The Challenge of Right-Sided Endocarditis

ABSTRACT & COMMENTARY

Synopsis: *The challenges inherent in the management of pulmonic valve endocarditis mandate a high level of awareness in the clinician.*

Source: Hamza N, et al. Isolated Pulmonic Valve Infective Endocarditis: A Persistent Challenge. *Infection.* 2004;32: 170-175.

ISOLATED PULMONIC VALVE ENDOCARDITIS IS THE TOPIC of an interesting article from the Cleveland Department of Veterans Affairs Medical Center. Hamza and colleagues reported 3 of their own cases, involving men ages 47, 64, and 76, none of whom were intravenous drug addicts (IVDA). In 2 of the patients, *Enterococcus faecalis* was the causative pathogen, and in the other patient, a coagulase-negative staphylococcus was the pathogen. Transesophageal echocardiograms (TEE) were useful in proving involvement of the pulmonic valve. The 64-year-old patient, with a history of hypertension and chronic renal insufficiency, died. Initially, this patient was treated with intravenous vancomycin and gentamicin, but fever persisted and the E. faecalis isolated remained resistant to vancomycin, ampicillin, and gentamicin. Therapy with linezolid followed for 6 weeks, and subsequent blood cultures were negative. One week after completion of linezolid therapy, while in rehabilitation, the patient developed fever, hypotension, and acute respiratory failure and subsequently died.

Hamza et al reviewed 41 other cases of isolated pulmonic endocarditis. The most common pathogens were staphylococci, both *Staphylococcus aureus* and coagulase-negative staphylococci. A potpourri of other organisms included group B *Streptococcus* and *Actinobacillus acitomycetemcomitans*. *Neisseria gonorrheae*, known to attack the right side of the heart, was the cause in only 1 patient. About 40% of reviewed patients had no detected site of entry. One fourth were IVDA patients. About 15% were related to IV or dialysis catheters. Less than half of all patients had embolic phenomena, and only a handful died.

Only 2 patients had an Enterococcus as a causative pathogen, which highlights the new cases reported by Hamza et al. The occurrence of vancomycin-resistant *E. faecalis* pushed Hamza et al to use parenteral linezolid in 1 patient with apparent sterilization of the blood, although no postmortem exam was performed. The patient who had oxacillin-resistant CNS was also treated with an oral regimen of linezolid in combination with rifampicin which produced subsequent sterile blood cultures.

COMMENT BY JOSEPH F. JOHN Jr, MD

Hamza et al, from the Cleveland VA, have uncovered 3 noteworthy cases of isolated pulmonic valve endocarditis, allowing them to produce for us a very useful review. The major points of their own cases and reviews include the uncommonness of the entity, the association with IVDA and catheter infection, the high prevalence of *Staphylococci* as the causative organisms, necessity for newer antimicrobial agents to combat multiresistant pathogens, improved diagnostic value of TEE, and finally, the emergence of *Enterococci* in 2 of the 3 reported cases in this article.

A high degree of suspicion truly helps to make this diagnosis. Basic physical examination proved useful; all 3 reported that the patients had murmurs suggestive of pulmonic valve involvement. That finding, plus positive blood cultures and a positive TEE, clinched the diagnosis. In the patient with CNS, a follow up TEE actually showed some resolution of the vegetation, suggesting the follow-up TEE may be helpful. In this patient, Hamza et al were also able to recover the CNS from a Permacath, thus suggesting a site of entry.

Hamza et al also discuss the interesting aspect of surgery. They decided against surgery in 2 of their patients, and note that medical management allowed stabilization of cardiac function. Finally, although the poorly bactericidal effect of linezolid did cause apparent failure in the 2 patients reported, other new agents now available, like daptomycin, have bactericidal mechanisms that may benefit such patients. ■

Resolution of Hepatitis C Infection

ABSTRACT & COMMENTARY

Synopsis: *Studies on HCV infection resolution show that PBMC HCV-RNA may remain, despite clearance of the virus from plasma.*

Source: Wawrzynowicz-Syczewska M, et al. Natural History of Acute Symptomatic Hepatitis Type C. *Infection.* 2004;32: 138-143.

HEPATITIS C INFECTION IS USUALLY ASYMPTOMATIC, but with insidious progression. This paper from Poland features the outcomes of a series of patients with acute hepatitis C in order to determine the resolution or progression of disease. In the 10-year period from 1988-1998, 159 patients were recognized with acute HCV, 77 of which were eventually enrolled into the study. In 46, an incubation period could be determined. Past hepatitis B infection was detected in 19. Of the 77 patients, 23 (30%) became spontaneously negative for serum HCV-RNA and had no elevation of ALT. All but 3 of these patients were still anti-HCV antibody positive. Of the 30% who were negative for routine HCV viral load analysis, 2 had positive HCV in peripheral blood mononuclear cell (PBMC) assay.

Comparison of HCV-RNA(+) and HCV-RNA(-), by univariate analysis, revealed that HCV clearance was associated with higher hepatic enzymes and a history of alcohol abuse. Multiple other analysis showed the same associations.

There were 45 liver biopsies available for review. None showed severe inflammation. Clinically silent cirrhosis was present in 19%. Mild or minimal forms of chronic hepatitis was the common finding. Factors that were associated statistically with advanced liver histologic findings included male gender, heavy alcohol consumption, increased iron stores measured as serum ferritin (particularly with levels > 115 ng/mL), and older age at time of exposure.

COMMENT BY JOSEPH F. JOHN Jr, MD

This study is unusual because Wawrzynowicz-Syczewska and colleagues found a number of patients with a history of acute HCV, the median time after acute infection being 8 years. A unique aspect of the study was the use of HCV detection in PBMCs, an approach that showed patients with negative viral loads , done by routine testing, may still have detectable HCV using PBMC analysis. This finding suggests that perhaps more rigorous searches for latent HCV infection, possibly using PBMC assays, will have implications for future antiviral chemotherapy.

Ironically, the more icteric the initial episode, the more likely the spontaneous resolution. Wawrzynowicz-Syczewska et al emphasize this finding, suggesting that early lymphocyte stimulation allows a better cell-mediated response to infection.

The issue of fibrosis/cirrhosis is more confusing. In this study, about 20% of patients had histologic evidence of cirrhosis. Recall that the findings of inflammation were so minimal that the progression of the disease to fibrosis/cirrhosis involves other factors, Wawrzynowicz- Syczewska would argue, more than the inflammatory response. ■

Diagnosis of RSV Infection: Adults Are Not Just Large Children

ABSTRACT & COMMENTARY

Synopsis: *The Binax NOW chromatographic assay was found to be the optimal method for detection of RSV in upper respiratory secretions of children, while DFA testing was optimal in adults.*

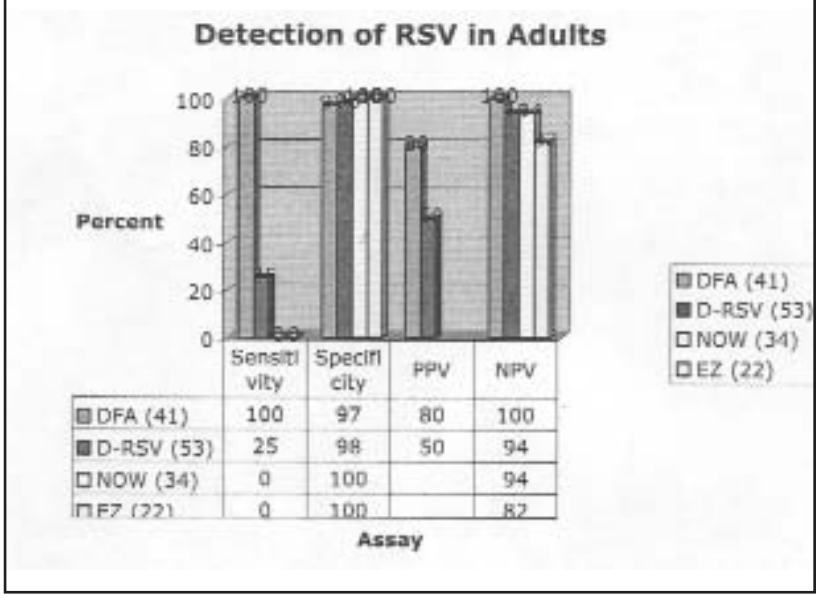
Source: Ohm-Smith MJ, et al. Evaluation of the Binax NOW, BD Directigen, and BD Directigen EZ assays for detection of respiratory syncytial virus. *J Clin Microbiol.* 2004;42: 2996-2999.

OHM-SMITH AND COLLEAGUES AT SAN FRANCISCO General Hospital evaluated 4 assays for the detection of RSV in nasal and/or nasopharyngeal wash, aspirate, or swab specimens from adults and children with suspected viral respiratory infection during the 2002-2003 respiratory illness season. The results were compared to those obtained by cell culture.

All 180 specimens were examined by direct fluorescent antibody (DFA) testing, BD Directigen RSV EIA (D-RSV), and cell culture. Eighty-eight were also tested by the BD Directigen EZ, and 118 by the Binax NOW chromatographic assays. Fifty-three (29%) of the 180 specimens were obtained from adults. Of the 180 specimens, 26% were culture positive for RSV, including 34% of those collected from children and 8% from adults.

Of 149 samples that contained an adequate number of

Figure



	Sensitivity	Specificity	PPV	NPV
DFA (41)	100	97	80	100
D-RSV (53)	25	98	50	94
NOW (34)	0	100		94
EZ (22)	0	100		82

cells, there was agreement between DFA and culture in 96%. The overall sensitivity of DFA was 93%, while those of the NOW, EZ, and D-RSV assays were 89%, 59%, and 77%, respectively. The specificities of the assays were 97%, 100%, 98%, and 96%, respectively.

The results obtained with the assays were all comparable when applied to samples obtained from children, with the NOW assay being the most sensitive and specific. With samples from adults, however, DFA was the only effective test among those evaluated (*see Figure*).

COMMENT BY STAN DERESINSKI, MD, FACP

The diagnosis of RSV infection is important for epidemiologic and clinical reasons. Hospitalized patients require adequate isolation and, although only selected high patients are candidates for antiviral therapy, a confirmed diagnosis allows the avoidance of unnecessary antibacterial therapy in others.

This study found that the rapid assays performed well in children, but that the NOW assay provided optimal results in this patient group. In stark contrast, only the DFA provided useful results in adults. Unfortunately, DFA, in contrast to the other rapid methods studied, is more labor intensive and requires highly trained technologists—individuals in short supply, especially in "off hours." Furthermore, a recent study found that DFA had a sensitivity of only 23% in adults with RSV infection.[1] That investigation differed, however, from the one reviewed here, in that the "gold standard" was either a positive culture, serology, or PCR, while the current one relied only on culture. Nonetheless, the current guidelines of the Infectious Disease Society of America, for the management of immunocompetent adults with community acquired pneumonia, state "Respiratory syncytial virus (RSV) antigen detection tests are readily available but are insensitive for detecting infections in adults and are not generally recommended for adults."[2]

Ohm-Smith and colleagues agree that while the Binax NOW assay appears to be optimal for use in children, none of the rapid kit assays other, than DFA, were useful in adults. Their data does, however, suggest that DFA, does in fact, have value in adults for whom they suggest a 2-step procedure: "Laboratories should consider performing direct immunofluorescence and/or culture testing of specimens from adults that give negative results with any of the rapid kit tests." ■

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Chrysobacterium meningosepticum

ABSTRACT & COMMENTARY

Synopsis: *Host factors are the major determinants of the outcomes of* C. meningosepticum *infections.*

Source: Lin PY, et al. Clinical and Microbiological Analysis of Bloodstream Infections Caused by *Chryseobacterium meningosepticum* in Nonneonatal Patients. *J Clin Microbiol.* 2004;42:3353-3355.

Lin and colleagues describe 9 adults (40-82 years of age) and 2 children (0.5 and 1.5 years of age) seen at 2 hospitals in Taiwan from 2001 to 2002 with bacteremia due to *Chrysobacterium meningosepticum*. Six of the infections were community acquired. The mean duration of hospitalization, prior to infection in the 5 patients with nosocomial acquisition, was 32 days (range, 13 to 99 days). All the

adults had significant underlying disease.

Each isolate represented a distinct genotype. All 11 isolates were resistant in vitro to all beta lactam antibiotics tested including piperacillin, ceftazidime, cefepime, and imipenem. The majority of the isolates produced at least 2 beta-lactamases, including an extended spectrum beta-lactamase and a metallo-beta-lactamase.

All isolates were also resistant to vancomycin, and most isolates were also resistant to gentamicin, chloramphenicol, and azithromycin. The most active antibiotics in vitro were minocycline, trimethoprim-sulfamethoxazole, and rifampin.

Fever and infection resolved in the 2 children (both without underlying disease) in the absence of any antibiotic therapy, and infection also resolved in 4 adults in the absence of appropriate antibiotic administration.

COMMENT BY STAN DERESINSKI, MD, FACP

C. meningosepticum (formerly *Flavobacterium meningosepticum*), is present in soil and water. Its ability to survive in chlorinated water allows it to colonize hospital sinks and water taps, which have served as sources for nosocomial outbreaks of infection due to this organism. Most such infections have occurred in neonates and immunocompromised adults.

A recent report from the SENTRY Antimicrobial Surveillance Program examined the in vitro susceptibility of 24 isolates of *C. meningosepticum* from throughout the world, with results largely consistent with those reported by Lin et al. Gatifloxacin and garenoxacin were each active in vitro against 100% of the isolates; levofloxacin inhibited 96% and ciprofloxacin 71%. In contrast to the current report, the SENTRY study found that 62% were susceptible to piperacillin and 71% to piperacillin-tazobactam. Fewer than 10% of isolates were susceptible to other beta-lactams tested, except for cefepime (38% susceptible). Seventy-nine percent were susceptible to trimethoprim-sulfamethoxazole and 88% were susceptible to rifampin. Fewer than 10% were susceptible to aminoglycosides, vacnomcyin, or rifampin.

The remarkable resistance of *C. meningosepticum* to beta-lactam antibiotics is the consequence of the frequent presence of multiple beta-lactamases, especially Ambler class A extended spectrum enzymes and chromosomal metallo-beta-lactamases. In fact, some isolates have been detected that contained multiple versions of the latter.

The Sanford guide recommends vancomycin with or without rifampin as the first choice for treatment of infections due to *C. meningosepticum*, with either levofloxacin or ciprofloxacin as alternative choices. Although there is a question regarding the therapeutic predictive value of in vitro susceptibility results with this organism, the usefulness of vancomycin has been called into question, both because of these results and because of clinical failure. To the extent that the in vitro susceptibility data is of value, it would suggest that the most active antibiotics are newer fluoroquinolones, such as gatifloxacin, desfluoroquinolone, and the investigational garenoxacin.

While the reported mortality associated with systemic *C. meningosepticum* infection has been high, that was not the case in the report from Taiwan. In fact, 2 children had "occult bacteremia" that resolved in the absence of antibiotic therapy and infection resolved in 4 adults in the absence of appropriate therapy. This is consistent with an organism of limited virulence, likely to cause death only in significantly compromised patients. ■

Candida glabrata

ABSTRACT & COMMENTARY

Synopsis: *Caspofungin and flucytosine were the active antifungals against* C. glabrata*, while fluconazole was least active. Isolates with high level resistance to fluconazole demonstrated reduced susceptibility to voriconazole.*

Source: Pfaller MA, et al. Geographic Variation in the Susceptibilities of Invasive Isolates of *Candida glabrata* to 7 Systemically Active Antifungal Agents: A Global Assessment From the ARTEMIS Antifungal Surveillance Program Conducted in 2001 and 2002. *J Clin Microbiol.* 2004;42:3142-3146.

Pfaller and colleagues at the University of Iowa evaluated the in vitro susceptibility of 601 worldwide isolates of *Candida glabrata* against 7 antifungal agents by the NCCLS broth microdilution method. North American isolates represented 55% of the total. NCCLS susceptibility criteria for fluconazole (S, < 8 mcg/mL; S-dose dependent, 16 to 32 mcg/mL; R, > 64 mcg/mL) and flucytosine (S, < 4 mcg/mL; intermediate, 8 to 16 mcg/mL; R, > 32 mcg/ml) were utilized. For the other drugs (for which no NCCLS criteria exist), < 1 mcg/mL was used as the criterion for susceptibility.

Caspofungin and flucytosine were the most active agents, with 100% and 99.2% isolates being judged susceptible (*see Table 1*). The least active agent was fluconazole, with an MIC90 of 32 mcg/mL and only 66.2% being fully susceptible. By the criteria utilized here, only 75.2% were susceptible to amphotericin B; 92.8% were susceptible to voriconazole.

Forty-six (7.7%) isolates were resistant to fluconazole (MIC ≥ 64 mcg/mL). All 46 were susceptible to caspofungin and to flucytosine, but cross-resistance to triazoles (voriconazole, itraconazole, posaconazole, and ravuconazole) was the rule. While only 78.3% of these fluconazole-resistant isolates were susceptible to < 1 mcg/mL amphotericin B, all were susceptible to < 2 mcg/mL. However, among the total of 601 isolates, both fluconazole-susceptible and fluconazole-resistant, 4.4% of European isolates had an amphotericin B MIC > 2 mcg/mL, a result found in < 1% of North American isolates.

COMMENT BY STAN DERESINSKI, MD, FACP

C. glabrata is often the second most frequently isolated Candida species isolated from bloodstream infections, surpassed only by *C. albicans*. This is true despite the fact that *C. glabrata* may be misidentified as other species of Candida.[1-2] Furthermore, its isolation may be delayed because of its slower growth in culture in the laboratory.[3] The species identification engenders further delay and antifungal susceptibility test results often take a week or more before they are available to the clinician. All of this points to the importance of the initial choice of antifungal therapy in the patient with presumed or identified candidemia. This choice must necessarily be based on presumptions regarding the potential likelihood of antifungal resistance, as well as drug toxicity.

Fluconazole is the most widely used antifungal agent. Unfortunately, *C. glabrata* is often either intermediately susceptible ("susceptible dose-dependent"—SDD) or resistant to this azole. In this study, only 66.2% were fully susceptible to fluconazole. While the reduced susceptibility of the 27.1% SDD isolates can be overcome, this requires the use of higher doses of fluconazole than are commonly used by many clinicians. The Infectious Disease Society of America recommends administration of 400-800 mg daily.[4] Pharmacokinetic analysis would suggest that the 800 mg dose is a better choice for adequate coverage of the range of MICs in this susceptibility category.

On the other hand, fluconazole at any dose is believed to be ineffective against *Candida* isolates with full resistance (MIC ≥ 64 mcg/mL). While many SDD isolates remain susceptible to newer azoles, such as voriconazole, this is not the case with the isolates with these very high MIC levels. In addition, amphotericin B appears to be less active against *C. glabrata* than against *C. albicans* and most other species of *Candida*. This has led to the recommendation that the dose of amphotericin B deoxycholate, used in the treatment of *C. glabrata* infections, be at least 1 mg/kg daily.[4] It should be noted that the susceptibility breakpoints chosen for this study for these drugs, for which there are as yet no NCCLS guidelines, tended toward the conservative.

The most active agents tested were caspofungin and flucytosine. The latter drug has been underutilized for fear of its toxicity, and because of the necessity to use it in combination with another antifungal to reduce the likelihood of selection of flucytosine resistant mutants. Caspofungin is safe and effective. In a randomized trial of treatment of invasive candidiasis, the response rates to caspofungin and amphotericin B deoxycholate, among the patients whose infection was due to *C. glabrata*, were 76.9% and 80%, respectively.[5] ■

Table 1

In Vitro Susceptibilities of 601 Isolates of C. glabrata

Antifungal	MIC90 (mcg/ml)	% Susceptible
Amphotericin B	2	75.2
Flucytosine	0.12	99.2
Fluconazole	32	66.2
Posaconazole	2	85.4
Ravuconazole	1	90.7
Voriconazole	1	92.8
Caspofungin	0.06	100

Table 2

In Vitro Susceptibilities of 46 Isolates of *C. glabrata* Resistant to Fluconazole

Antifungal	MIC90 (mcg/ml)	% Susceptible
Amphotericin B	2	78.3*
Flucytosine	0.12	100
Posaconazole 1	6	4
Ravuconazole	8	8.7
Voriconazole	4	13
Itraconazole	--	0
Caspofungin	0.06	100

* MIC <2 mcg/ml for 100%

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Erythromycin and the Heart

ABSTRACT & COMMENTARY

Synopsis: *Erythromycin use is associated with a 2-fold increased risk of sudden cardiac death and a 5-fold increase in those who concurrently receive other medications that significantly inhibit its metabolism by CYP3A4.*

Source: Ray WA, et al. Oral Erythromycin and the Risk of Sudden Death from Cardiac Causes. *N Engl J Med.* 2004; 351:1089-1096.

MURRAY AND COLLEAGUES EVALUATED A COHORT OF Tennessee Medicaid enrollees with 1,249,943 person-years of follow-up in order to evaluate the association with erythromycin use and the risk of sudden cardiac death. The rate of such deaths in the community was twice as high in concurrent erythromycin recipients, when compared to amoxicillin or past erythromycin recipients. Neither of the latter 2 groups evidence an increased risk of sudden cardiac death.

The adjusted incidence of sudden cardiac death was approximately 5 times higher among erythromycin recipients who concurrently received a medication known to significantly inhibit hepatic cytochrome P-450 3A (CYP3A) isoenzymes. The inhibitors considered were azole antifungals, diltiazem, verapamil, and troleandomycin, as well as clarithromycin. Patients receiving HIV protease inhibitors were excluded. In fact, however, calcium channel blockers accounted for almost all the concurrent use and all cases of sudden cardiac death in this group. No such deaths occurred in patients concurrently receiving calcium channel blockers (mostly nifedipine) that did not inhibit CYP3A. The concomitant use other drugs associated with QTc prolongation or torsades de pointes, including antiarrhyrhmics such nitazoxanide as quinidine, sotalol and the like, did not appear to increase the risk of erythromycin administration.

COMMENT BY STAN DERESINSKI, MD, FACP

Erythromycin prolongs cardiac repolarization, as reflected in an increased duration QTc interval by blocking the HERG (human ether go-go related) channel, the rapidly activating component (Ikr) of the delayed rectifier potassium channel. Erythromycin appears to be the highest blocker of this ion channel among available antibiotics. In addition to other macrolide antibacterials, some fluoroquinolones may also prolong the QTc interval. Other (non-antibacterial) antimicrobials associated with prolongation of cardiac repolarization are halofantrine and pentamidine. In individuals with polymorphisms in their HERG gene, however, other antibiotics, including trimethoprim-sulfamethoxazole, have been reported to block Ikr.[1]

Erythromycin is normally metabolized by the CYP3A isozyme. The coadministration of drugs which inhibit that metabolism results in increased erythromycin exposure, with the resultant potential for significant QTc prolongation and risk of torsades de pointes. Erythromycin may have been around for a long time, but clinicians should take a little extra time in considering its prescription.

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Pharmocology Update

Nitazoxanide Tablets for Giardiasis

By Stan Deresinski, MD, FACP

NITAZOXANIDE (ALINIA™) IS A BROAD SPECTRUM antiparasitic agent, previously approved for use as an oral suspension for the treatment of cryptosporidiosis and giardiasis in children.[1] It has now received FDA approval as a 500 tablet for the treatment of giardiasis in adolescents and adults.[2]

Clinical response rates to treatment with nitazoxanide tablets in a double-blind, controlled trial in Peru and

Egypt, with diarrhea caused by *Giardia duodenalis lamblia*, was 85% (46/54) compared to 44% (12/27) in placebo recipients. Cysts persisted in the stools of some clinical responders, however. Response rates to the oral suspension in children have been similar.[2]

Nitazoxanide, a nitrothiazolyl-salicylamide derivative, is a prodrug that is rapidly hydrolyzed to tizoxanide (desacetyl-nitazoxonide), which is then glucuronidated, with both metabolites being the active forms of the drug.[4] Tizoxanide, which is > 99% bound to plasma proteins, appears to not have an inhibitory effect on cytochrome P450 enzymes.

The tablet and oral suspensions are not bioequivalent; the latter has only 70% relative bioavailability. Administration of the tablets with food is associated with an almost 2-fold increase in AUC and approximately 50% increase in Cmax of the active metabolites; the food effect is significantly less with the oral suspension. Overall, approximatley two-thirds of an oral dose of nitazoxanide is excreted as its metabolites in feces, and one-third in urine. In adults greater than 17 years of age, the Cmax of tizoxanide and tizoxanide glucuronide after administration of a singly 500 mg table with food is 10.6 ± 2.0 mcg/mL and 10.5 ± 1.4 mcg/mL, respectively. The pharmacokinetics of nitazoxanide have not been evaluated in patients with impaired renal or hepatic function.

The active metabolites of nitazoxanide is believed to be due to interference with the pyruvate:ferredoxin oxidoreductase enzyme-dependent electron transfer reaction. Other undefined pathways may also important. Nitazoxanide appears to be well tolerated, and is a Pregnancy Category B drug.

Other drugs available for the treatment of giardiasis include metronidazole (which has never received FDA approval for this indication, paromomycin (also not FDA-approved for this infection), and furazolidone. Quinacrine is available through some compounding pharmacies. Tinidazole had recently received approval as a single 2 gram dose for treatment of giardiasis in adults. Albendazole also has activity in patients with giardiasis.[5] The most recent recommendations of *The Medical Letter* for the treatment of giardiasis in adults list 3 drugs of choice: metronidazole (250 mg tid x 5d), nitazoxanide (500 mg bid x 3d), and tinidazole (2 grams once) (ML).[6] Three alternatives are listed: paromomycin, furazolidone, and quinacrine.

Overall, nitazoxanide is an useful, albeit expensive, addition to our therapeutic options in the management of patients with giardiasis. ■

Table

Nitazoxonide Treatment of Giardiasis

Age	Dosage	Duration
1-3 yrs.	5 ml (100 mg) oral suspension* 12 hourly with food	3 days
4-11 yrs.	10 ml (200 mg) oral suspension* 12 hourly with food	3 days
> 12 yrs.	One 500 mg tablet 12 hourly with food	3 days

*The oral suspension contains 1.48 grams of sucrose per 5 ml

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Pharmacology Update

Rifaximin: Another Choice for Treatment of Travelers' Diarrhea

By Stan Deresinski, MD, FACP

RIFAXIMIN (XIFAXAN™) HAS RRECEIVED US FDA approval on May 25, 2004, for the treatment of travelers' diarrhea caused by enteropathogenic (non-invasive) *Eschericiha coli* in individuals at least 12 years of age. Rifaximin is a rifamycin that is poorly absorbed (< 0.4%) from the gastrointestinal tract, and thus achieves very high concentrations in the feces. It is active in vitro against enterotoxigenic and enteroaggregative *E. coli*, *Shigella* spp., and *Salmonella* spp., as well as against *Vibrio cholerae*.[1-2] Its activity against *Campylobacter jejuni* is limited.

In a randomized, double-blind placebo-controlled trial in patients with travelers' diarrhea, rifaximin administration was associated with a reduction of the median time to the last unformed stool, from 60 hours to 32.5 hours.[4] Rifaximin shortened the duration of travelers' diarrhea due to enteroaggregative *E. coli* from 72 hours in placebo recipients to 22 hours.[3] In a blinded, randomized comparison to ciprofloxacin therapy, the median time to resolution of diarrhea was 25.7 hours in the rifaximin group and 25

hours in the ciprofloxacin group.[5] Clinical trial data, however, suggest that rifaximin is ineffective in the treatment of shigellosis and campylobacteriosis, both of which are invasive infections.

Rifaximin appears to be well tolerated, although hypersensitivity reactions may occur. Adminstered in high doses, it is teratogenic in animals. Pharmacokinetic drug interactions have not been identified.

The recommended dose is one 200 mg tablet 3 times daily for 3 days. It should not be used in individuals with fever or blood in their stools. The cost is comparable to other recommended antibacterial regimens for treatment of travelers' diarrhea. ■

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CME Questions

10. What is the most common microbial cause of isolated pulmonic valve endocarditis?
a. *Enterococcus faecalis*
b. *Hemophilus parainfluenzae*
c. *Neisseria gonorrhoeae*
d. *Staphylococcus aureus* and coagulase-negative *Staphylococci*

11. In patients who have had acute hepatitis C infection, what is not a good predictor of progression?
a. heavy alcohol use
b. high ferritins
c. severe early icterus
d. late age of disease acquisition

12. The optimal non-culture test for diagnosis of RSV infection in children is:
a. DFA
b. BD Directigen RSV EIA
c. BD Directigen EZ
d. Binax NOW

13. *Chryseobacterium meningosepticum* is most frequently susceptible in vitro to:
a. Vancomycin.
b. Gatifloxacin.
c. Gentamicin.
d. Cefepime.

14. Which of the following is most likely to be an effective treatment for an invasive infection due to an isolate of *C. glabrata* with an MIC to fluconazole > 64 µ/ml in an adult?
a. Fluconazole 800 mg IV daily.
b. Voriconazole 6 mg/kg IV for 2 doses, then 4 mg/kg IV 12 hourly.
c. Caspofungin 70 mg IV, then 50 mg IV daily.
d. Amphotericin B deoxycholate 0.5 mg/kg daily.

15. Which of the following is correct?
a. Erythromycin is metabolized by the CYP3A isozyme.
b. Medications that induce CYP3A isozyme increase exposure to erythromycin.
c. The QTc interval is a reflection of cardiac depolarization.
d. Torsade de pointes is associated with shortening of the QTc interval.

Answers: 10. (d); 11. (c); 12. (d); 13. (c); 14. (c); 15. (a)

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In Future Issues:

Lassa Fever—It's Back!

UPDATES

By Carol A. Kemper, MD, FACP

The High Cost of MRSA

Source: Rubin RJ, et al. *Emerg Infect Dis*. 1999;5:9-17.

ALTHOUGH THIS ARTICLE IS older, its message is timely, and for this reason, I elected to include it. The increasing prevalence of MRSA in both community-acquired and nosocomial staphylococcal infections is placing a greater burden on an already over-burdened, costly medical system. The proposed United States' Public Health Service guidelines for MRSA advocate more aggressive screening, identification, and isolation of MRSA cases in hospitals. Shouldering the cost of these measures will, however, largely fall to hospitals.

Rubin and colleagues modeled estimates of the incidence, duration of hospital stay, death rates, and medical cost of *Staphylococcal aureus* infection, and the relative impact of methicillin-resistance in the New York metropolitan area in 1995. At that time, Rubin et estimated that, of the total number of *S. aureus* infections, 54% were community-acquired and 46% were nosocomial, of which 10% and 29% were methicillin-resistant, respectively. Death rates were significantly higher for MRSA compared with MSSA (21 vs 8%). The duration of hospital stay varied, with surgical site infections requiring the least number of days and endocarditis requiring the most, with an average hospital stay of ~20 days. The direct average cost was about $32,100 per case of *S. aureus* infection (in 1995 dollars). Overall, costs for MRSA infection were 6% to 10% higher than those associated with MSSA, largely due to the higher cost of vancomycin and the cost of isolation procedures, not because of any difference in the severity of infection or duration of hospitalization.

Based on today's estimates in our area, where one-third of community-acquired staphylococcal infections and more than half of nosocomial staphylococcal infections are MRSA, the number of MRSA cases has easily tripled those 1995 estimates. In addition, Rubin et al were not factoring in the additional costs of the most recent recommendations, which include screening high risk patients on admission to hospital (or possibly all admissions) for MRSA, performing susceptibility tests and E-tests on all *S. aureus* isolates, the use of more costly agents, such as linezolid, plus the increased bed space needed for isolation all of these people. And, to what end? MRSA is quickly becoming the new norm, not the exception in most hospitals. Can hospitals bear the burden of these recommendations without some kind of additional compensation? ■

Treatment of Latent TB: A High Priority

Source: Horsburgh CR Jr. *N Engl J Med.* 2004;350:2060-2067.

REDUCTION IN THE NUMBER OF cases of TB in the United States is one of the United States Public Health Department's highest priorities. In order to achieve this goal, the numbers of patients who undergo testing and treatment for latent TB must be increased. I've always encouraged patients to accept treatment by providing a rough estimate of their lifetime risk of reactivation (~5-10%), but specifically encourage 3 groups of patients, irrespective of age, to accept treatment: those with 1) recent skin test conversion, 2) evidence of old healed disease on chest radiograph, or 3) those with immunosuppression, corticosteroid use, or HIV. Of course, any infant or child < 5 years of age with household exposure should be presumptively treated with INH; such patients are at high risk for primary progressive disease, and it is too late to wait for skin test conversion.

It has always been assumed that the risk of reactivation is generally greatest in the 2-3 years following conversion, then begins to decrease over the next decade, and remains fairly stable at low levels thereafter. Recent data suggests that ~10% of patients lose their tuberculin reactivity each decade; these individuals do not contribute to the overall risk of reactivation TB. Therefore, estimates of the risk of reactivation may actually be lower than previously assumed especially in younger persons, but the effect of this statistical finding on risk diminishes as patients age.

Believing that more precise information on the risk of reactivation can allow clinicians to target groups at highest risk, Dr. Horsburg constructed a risk model based on age, degree of induration on tuberculin skin test, and whether there was recent conversion, evidence of old healed TB, immunosuppressive therapy, or HIV. Five groups at significant lifetime risk for reactivation TB were identified: 1) children ≤5 years of age with ≥10 mm of induration have a 10-20% risk; 2) younger persons ≤35 years of age with ≥15 mm of induration and recent conversion have a 10-20% risk; 3) younger per-

sons ≤35 years of age with ≥15 mm of induration receiving immunosuppressive therapy have a 10-20% risk; 4) persons with ≥10 mm of induration and evidence of old healed TB have ≥20% risk; and 5) persons with HIV and ≥5 mm of induration have ≥20% risk.

Interestingly, in Horsburg's model, persons >66 years of age have <10% risk of reactivation under any circumstance (except HIV infection); this suggests that it may be reasonable to defer treatment in persons over the age of 65.

I suspect the reason that too few patients are treated for latent TB is because clinicians still have 3 bad rules stuck in their heads: these include patients with a history of a positive test for many years do not need treatment, a history of BCG means you don't need treatment, you have a false-positive PPD, and anyone older than 35 is at higher risk for side effects and should not be treated. This backwards approach ensures that immigrants from a country endemic for TB (especially one where BCG is common), and anyone over the age of 35, is less likely to receive treatment for latent TB, even if they have risk factors. Confronting these fallacies, convincing clinicians that the benefits of INH prophylaxis outweigh the risks, disregarding a history of BCG, and keeping the rules of who should be treated as simple as possible may ensure that more patients receive treatment for latent TB. ■

The APRICOT HCV/HIV Co-infection Study

Source: Torriani FJ, et al. *N Engl J Med.* 2004:351(5):438-450.

While treatment with pegylated-interferon plus ribavirin has been shown to successfully suppress HCV infection in ~56-63% of mono-infected patients, virologic responses have been poorer in patients with HCV/HIV co-infection. In this multicenter study, conducted at major HIV centers around the world, 868 patients with HCV/HIV co-infection were randomized to receive 1 of 3 different HCV treatment regimens for 48 weeks [peginterferon alfa-2a (180 μ/week) plus ribavirin (800 mg daily) vs peginterferon alfa-2a plus placebo, or interferon alfa-2a (3 million IU 3 times weekly) plus ribavirin]. The primary endpoint was sustained virologic response (SVR) at 72 weeks. Eligible patients had detectable HCV RNA, CD4 counts >100, stable HIV disease, with or without antiretroviral therapy, and no prior HCV therapy. The study was conducted at 95 centers in 19 different countries and took 3 years. Patients were stratified based on HCV genotype, liver histology, HIV treatment, and CD4 count (< or >200 cells/mm^3). The groups were remarkably balanced with regard to HCV RNA, degree of abnormal liver histology, HIV viral load, CD4 count, and use of antiretroviral therapy.

Treatment responses were poor but better than expected: the overall rate of SVR was significantly higher in patients receiving peginterferon with RBV (40%) compared with patients receiving peginterferon alone (20%), or interferon plus RBV (12%) (P < .001, both comparisons). Patients infected with HCV genotype 1 (GT-1) had significantly lower rates of response than those with other genotypes (GT). Among patients with GT-1, SVR occurred in 29% of those receiving peginterferon plus RBV, compared with peginterferon alone (14%), or interferon plus RBV (7%). In patients with GT-2 or GT-3, responses were much better (62%, 36%, and 20%, respectively).

Treatment was associated with the usual toxicities: neutropenia (~27%) and thrombocytopenia (6-7%) were more common in patients receiving peginterferon, and anemia was more common in patients receiving ribavirin (11-16%). Notably, these patients were receiving a lower dose of RBV than used in other studies. One percent or fewer in each arm developed pancreatitis and lactic acidosis, and about 1% in each arm developed hepatitic decompensation.

While 75% of patients receiving peginterferon with RBV completed 48 weeks of therapy, only 69% of those receiving peginterferon alone, and 61% of the interferon plus RBVgroup did. This was due to both treatment toxicity and a lack of treatment response and early withdrawal. Patients with a ≥ 2 log drop in HCV viral load by week 12 were much more likely to have SVR (56% in the pegasys plus RBV group). This negative predictive response was not improved if responses at week 24 were examined. Only 2 patients without an early virologic response at week 12 went on to have a SVR (only 1 of whom had GT-1). Thus, consideration should be given to stopping treatment at week 12 in those who fail to achieve a good virologic response by 12 weeks of therapy. In addition, although earlier data suggests that patients with non-GT-1 virus may respond favorably to only 24 weeks of therapy, these data suggest there may be additional benefit in continuing treatment in these patients for 48 weeks. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Linking COX-2 Inhibitors and Cardiovascular Event Risk

A new, and as of yet unpublished study, has raised increased concern about the relationship between rofecoxib (Vioxx), Merck's blockbuster COX-2 inhibitor, and cardiovascular events. The study, which was presented at a meeting in Bordeaux France, was financed by the FDA in collaboration with California's HMO giant Kaiser Permanente. The study was designed to determine if celecoxib, rofecoxib, ibuprofen, naproxen, or other NSAIDs increase the risk of acute myocardial infarction (AMI) or sudden cardiac death (SCD). Utilizing the 6-million member California database for Kaiser Permanente, all patients ages 18-84 who had taken a COX-2 inhibitor or nonselective NSAIDs between January 1999 and December 2001 were entered into the cohort. Controls were a risk-set match 4:1 on event date, birth year, gender, and health plan region. There were 8199 acute cardiac events within the study cohort (6675 AMI, 1524 SCD). The data revealed that rofecoxib use at > 25 mg per day increased the risk of acute cardiac events 3.15 fold (OR, 3.15 [1.14-8.75]). Rofecoxib at a dose < 25 mg resulted in an odds ratio of 1.29 (0.93-1.79), which was not statistically significant. When comparing low-dose rofecoxib to celecoxib (Celebrex), the risk of AMI and SCD was higher with rofecoxib (P= 0.04). Other NSAIDs, including naproxen, indomethacin, and possibly diclofenac, also increased the risk of AMI and SCD. These data will be presented in this country in October at the American College of Rheumatology. Concern about the relationship between rofecoxib and cardiac events was first raised with the publication of the VIGOR trial (*N Engl J Med.* 2000;343:1520-1528) which showed a relative risk of cardiac events associated with rofecoxib of 2.38 (95% CI, 1.39-4.00; P= .002). Dr. Eric Topol and colleagues from the Cleveland clinic subsequently reevaluated these data along with data from other studies and raised the concern of prothrombotic potential of COX-2 inhibitors, especially rofecoxib (*JAMA.* 2001;286:954-959). Their concern centered on the tendency for COX-2 inhibitors to block production of prostacyclin—thus blocking antiaggregatory and vasodilatory effects, while having no effect on thromboxane, which is responsible for platelet aggregation. Blockage of thomboxane is a COX-1 effect and accounts for the majority of the cardioprotective effects of aspirin and other NSAIDs. Rofecoxib, the most COX-2 specific of the drugs tested, may unbalance thromboxane and prostacycline accounting for the cardiovascular risk.

Some have considered a strategy of adding aspirin to a COX-2 inhibitor, but a new study suggests that aspirin negates the GI benefits of the COX-2 inhibitor, the primary benefit of COX-2 inhibitors over nonselective NSAIDs.

Researchers from USC performed a double-blind trial of rofecoxib, rofecoxib plus low-dose

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. Telephone: (404) 262-5416. E-mail: leslie.hamlin@ thomson.com. 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.

aspirin, ibuprofen, or placebo in patients without ulcers or erosive esophagitis. Endoscopies were performed at baseline, 6 weeks, and 12 weeks. At 12 weeks, the cumulative index of ulcers was placebo 5.8%, aspirin 7.3%, rofecoxib plus aspirin 16.1%, and ibuprofen 17.1% ($P < 0.001$ for rofecoxib plus aspirin and for ibuprofen vs each of placebo and aspirin). Over the same time, rofecoxib plus aspirin and ibuprofen both significantly increased the number of erosions (both $P < 0.001$ vs aspirin and placebo). The authors conclude that low-dose aspirin does not significantly increase ulcer recurrence, but that the addition of a COX-2 inhibitor with aspirin increases the rate of ulceration to a rate that is similar to a nonselective NSAIDs (*Gastroenterology.* 2004;127:395-402).

Viagra: Maximum Capacity at High-Altitudes?

High-altitude hikers may soon be requesting sildenafil (Viagra) prescriptions based on the results of a new study. The drug, which is a phosphodiesterase-5 inhibitor, is known to cause pulmonary vasodilation. German researchers postulated that such an effect may increase exercise capacity during induced hypoxemia at low altitudes and at Mount Everest base camp. Fourteen healthy mountaineers and trekkers were assessed with measurements of systolic pulmonary artery pressure, cardiac output, and peripheral arterial oxygen saturation at rest and during assessment of maximal exercise capacity on cycle ergometry while breathing a hypoxic gas mixture at low altitude, and retested at high-altitude at the Mount Everest base camp. Sildenafil 50 mg significantly increased arterial oxygen saturation during exercise ($P = 0.005$), reduced systolic pulmonary artery pressure at rest ($P < 0.001$), and during exercise ($P = 0.031$). Sildenafil also increased maximum workload and maximum cardiac output compared with placebo. At high-altitude, the drug had no effect on arterial oxygen saturation at rest nor during exercise compared with placebo, however, the sildenafil reduced systolic pulmonary artery pressure at rest ($P = 0.003$), during exercise ($P = 0.021$), increased maximum workload ($P = 0.002$), and cardiac output ($P= 0.015$). Two patients noted worsening headache at high-altitude with the drug. The authors conclude that sildenafil is the first drug to increase exercise capacity during severe hypoxia both at sea level and at high-altitude (*Ann Intern Med.* 2004;141:169-177). An accompanying editorial suggests that sildenafil is not a substitute for acclimatization to high-altitude and suggests that the findings of the study are compelling and that further research into a phosphodiesterase inhibitors in the treatment of pulmonary vascular disease is needed (*Ann Intern Med.* 2004;141:233-235).

FDA Actions

Eli Lilly has received FDA approval to market duloxetine (Cymbalta) for the treatment of major depression. The drug is a serotonin and norepinephrine reuptake inhibitor (SNRI), similar to venlafaxine (Effexor-Wyeth). The drug is also being studied for the treatment of stress urinary incontinence and diabetic neuropathic pain. Lilly, and the drug approval process for duloxetine, came under scrutiny earlier this year when a 19-year-old female volunteer committed suicide after discontinuing the drug during clinical trials. The patient had no history of depression prior to the study.

Shire Pharmaceuticals has received expanded indication for its mixed amphetamine product Adderall XR for the treatment of adults with attention deficit hyperactivity disorder (ADHD). The drug is a one-a-day preparation that has been widely used in children since 2001.

The FDA and Genentech have issued a warning to physicians regarding the risk of serious arterial thromboembolic events associated with bevacizumab (Avastin). The drug is an angiogenesis inhibitor, a novel antineoplastic used to treat metastatic colon cancer and other solid tumors. Reports of cerebral infarctions, myocardial infarctions, transient ischemic attacks, and angina have all been associated with use of the drug.

The FDA has approved an orally disintegrating form of carbidopa/levodopa for the treatment of Parkinson's disease. The preparation dissolves rapidly in the mouth without the need for water, allowing for dosing even when patients are rigid or suffering from "off periods," when producing can be problematic. It will be marketed under the trade name Parcopa and will be available in 10/100 tabs, 25/100 tabs, and 25/250 tabs, similar to brand name Sinemet levodopa/carbadopa.