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Multidrug-Resistant Tuberculosis (MDR-TB)

ABSTRACT & COMMENTARY

By Lin H. Chen, MD
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Dr. Chen reports no financial relationships relevant to this field of study.

Synopsis: *The estimated number of global MDR-TB cases in 2004 was 4.3% of all TB cases, and Eastern Europe had the highest proportions of MDR-TB cases. The largest numbers of MDR-TB cases were from China, India, and the Russian Federation. Travelers with TB exposure in these countries or Eastern Europe should be assessed for the possible exposure to MDR-TB and treated accordingly.*

Source: Zignol M, et al. Global incidence of multidrug-resistant tuberculosis. *J Infect Dis*. 2006;194:479-485.

The World Health Organization/International Union Against Tuberculosis and Lung Disease Global Project on Anti-tuberculosis Drug Resistance began collecting its data in 1994 on drug resistance in 90 countries. Cases are defined as new cases when patients had received treatments for less than one month (or none at all), and previously treated cases when patients had received treatment for at least one month.

In 2004, the estimated worldwide MDR-TB cases numbered 424,203, which was 4.3% of all TB cases. About 181,408 MDR-TB cases were estimated to have occurred among previously treated TB cases, and 242,794 MDR-TB cases were estimated to have occurred among new cases. Thus, 2.7% of new cases and 18.5% of previously treated cases were MDR-TB. Eastern Europe, the Western Pacific region, Southeast Asia, and the Eastern Mediterranean region have the highest proportions of MDR-TB in new cases. Additionally, Eastern Europe, the Eastern Mediterranean region, and the Western Pacific region have the highest proportions of MDR-TB in previously treated cases.

The prevalence of MDR-TB was highest in Eastern Europe, affecting 9.9% of new cases and 39.9% of previously treated cases of TB. Southeast Asia and the Western Pacific region follow. China, India, and the Russian Federation contribute the largest numbers of MDR-TB cases, accounting for 62% of the total.

As expected, the proportion of patients who had prior TB treatment correlated with the proportion of newly diagnosed MDR-TB cases.

However, the proportion of patients with TB and HIV co-infection was negatively correlated with the proportion of MDR-TB cases among previously treated cases. The authors attributed this finding to the high mortality in patients co-infected with TB and HIV, who likely died from the initial TB infection.

Based on the assumption that the duration of disease with MDR-TB is between 2 and 3 years (although the actual duration is not known), the authors further estimate that the global prevalence of MDR-TB ranges from 850,000–1,300,000 cases.

COMMENTARY

Mycobacterium tuberculosis is an aerobic bacillus that grows slowly, but is highly contagious through airborne transmission. TB is one of the leading causes of morbidity and mortality worldwide, with an estimated incidence of 14.6 million infections and causing 1.7 million deaths in 2004.[1] The largest number of new TB cases in 2004 occurred in the south-east Asia region, but the estimated per capita incidence is highest in sub-Saharan Africa, at nearly 400 cases per 100,000 population.[1] In Eastern Europe, the per capita incidence increased during the 1990s, but has been declining since 2001. At the present, one-third of the world's population is infected with TB, and 5–10% of infected individuals become ill sometime in life.[1]

The worldwide problem of TB has been attributed to urban crowding, homelessness, and the HIV epidemic. Drug-resistance in TB appeared in the early 1990's, due to inadequate regimens, incomplete courses of treatment, and noncompliance with therapy. Even more worrisome is the emergence of extensively drug-resistant (XDR) TB. The CDC reported that during 2000-2004, 20% of worldwide TB isolates were MDR and 2% were XDR.[2]

In the United States, the 2005 TB rate was 4.8 cases per 100,000, the lowest since national reporting began in 1953.[3] However, the TB rate in foreign-born individuals was 8.7 times that of US-born individuals.[3] Hispanics, blacks, and Asians had much higher TB rates (7.3, 8.3, and 19.6, respectively) compared to caucasians.[3] Furthermore, high proportions of TB cases in Hispanics, blacks, and Asians were in foreign-born persons (75%, 27%, and 96%, respectively). [CDC trends] The states of California, Florida, Georgia, Illinois, New Jersey, New York, and Texas had the highest numbers of TB cases, accounting for about 60% of the national total.[3] The majority of foreign-born TB cases in 2005 were reported in persons from Mexico, the Philippines, Vietnam, India, and China.[3]

Within the United States, the MDR-TB rate was higher in foreign-born than US-born (1.6% vs 0.6%, respectively); Mexico, the Philippines, and Vietnam were the most common countries of origin for foreign-born individuals with MDR-TB.[3] It is unclear whether the foreign-born

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individuals acquired MDR-TB cases in their countries of previous residence or after arrival in the United States.

Because travelers may have TB exposure in highly-endemic countries, the CDC recommend that travelers who anticipate prolonged stays or frequent travel to countries with high TB prevalence have a tuberculin skin test (PPD) before travel. Assuming the reaction is negative, they should have a repeat test approximately three months after travel.[4] The two-step baseline test, which is recommended for persons with occupational exposure to TB, should also be advised for travelers who anticipate repeated prolonged travel or an extended stay.[3] Additionally, annual screening with a PPD should also be considered in expatriates.

Crowded environments may increase the risk of exposure to TB during travel, and should be discussed with the traveler. Travelers who will be working in health-care settings where TB patients may be encountered should consult infection control or occupational health experts about personal respiratory protective devices (eg, N-95 respirators), along with appropriate fitting and training.

Another concern for travelers is the transmission of TB on commercial aircraft, which has been reported.[5] The risk of TB transmission on an airplane was greater on long flights that were ≥8 hours; proximity of a passenger to an infectious person increases the risk of exposure to TB because of the possibility of inhaling small droplets containing *M. tuberculosis*.[5] WHO issued recommendations to prevent the transmission of TB in aircraft and to guide potential investigations. Persons known to have infectious TB should not travel by commercial airlines, and should limit their travel. ■

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Nitazoxanide for the Treatment of *Clostridium difficile* Colitis

ABSTRACT & COMMENTARY

By Patricia Cristofaro, MD, and Maria D. Mileno, MD

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Dr. Cristofaro reports no financial relationship relevant to this field of study, and Dr. Mileno is a consultant for GlaxoSmithKline, and does research for Merck.

Synopsis: Clostridium difficile *diarrhea and colitis have now emerged as common nosocomial infections in hospitals throughout the developed world. Alarmingly, recent epidemiological studies in ambulatory settings have documented* C. difficile *infection in both adults and children who lack the usual risk factors of prior antibiotic use or hospitalization.*[1]

Source: Musher DM, et al. Nitazoxanide for the treatment of *Clostridium difficile* colitis. *Clin Infect Dis*. 2006;43:421-427.

ORAL VANCOMYCIN ALONE OR COMBINED WITH EITHER oral or parenteral metronidazole have been workhorses during the current epidemic of nosocomial *Clostridium difficile*-associated disease. Vancomycin is actually the only drug approved by the US FDA for this purpose. However, due to vancomycin's cost and its potential ability to select for vancomycin-resistant enterococci (VRE), metronidazole has been favored for first line therapy. However, both agents are associated with a substantial rate of recurrence or treatment failures, at a combined rate of about 50%.[3] There is a considerable need for new approaches.

Nitazoxanide, a nitrothiazolide, used for the treatment of intestinal parasites such as cryptosporidiosis and giardiasis, has proven in vitro activity against *C. difficile*. Musher and colleagues report the first study of its use for this new indication, a noninferiority comparison with metronidazole, the mainstay of current therapy.[2]

Nitazoxanide has pharmacokinetic properties that produce high colonic concentrations. Because it is already approved for treatment of intestinal infections, it is available for off-label use. In the article under discussion, Musher et al have reported the results of a prospective, randomized, double-blind study comparing nitazoxanide to metronidazole for the treatment of hospitalized patients with *C. difficile* colitis. The study was designed to assess

non-inferiority, and they conclude that nitazoxanide is at least as effective as metronidazole.[2]

This study was divided into 3 oral treatment arms. Thirty-four patients received metronidazole at the dosage of 250 mg, 4 times per day for 10 days, a standard regimen. Forty patients received nitazoxanide at a dosage of 500 mg twice daily for 7 days. Thirty-six patients received the same nitazoxanide regimen for 10 days, thus potentially allowing for the analysis of 76 patients at 7 days and 36 at 10 days. Statistical analysis of the groups showed them to be equivalent in their patient demographics, including severity of co-morbidities.

Data for both primary response and recurrence rates were obtained. The authors concluded that there were no significant differences in the median time to resolution of symptoms, the proportion of patients who were symptom free after 7 days of therapy, or the proportion of patients who had a sustained response at 31 days. After 7 days of treatment there was a trend toward better response in those receiving nitazoxsanide. At 31 days there was a trend toward more sustained response in those who had received at least 7 days of nitazoxanide. The response was even more robust in those who had received 10 days of therapy. However, none of these differences reached statistical significance, possibly because of their small sample size. The authors did succeed in their intended goal of proving non-inferiority to metronidazole.

COMMENTARY

As pointed out by Dr. John Bartlett in the editorial commentary accompanying Musher's study, there are three distinct problems in managing *C. difficile* infections: management of acute disease, management of recurrent disease, and alternative therapies for those neither seriously ill nor experiencing recurrent disease.[4] The "gold standard" for acute disease has been oral vancomycin, and the greatest problem with this agent is ensuring delivery to the colon in the face of complications such as ileus. However, vancomycin, not metronidazole, should be the comparator drug, and Musher et al are planning such a study.

Does nitazoxanide have a role in the treatment of recurrent disease? In this article, Musher et al also report a separate open-label study in which they administered nitazoxanide to 22 patients with *C. difficile* colitis who had failed metronidazole. Their success rate was similar to that of metronidazole when it was used to treat a first bout of *C. difficile* colitis. Therefore, nitazoxanide may very well have a role in recurrent disease.

Will nitazoxanide be a niche drug, useful because of reduced cost, better tolerance, less impact on intraluminal microbial ecology or hospital environmental ecology, or lower recurrence rates? Dr. Bartlett believes its use will not be for initial therapy, but for those who do not respond to metronidazole therapy, who have repeated recurrences, or who are unable to tolerate metronidazole. The cost of a 10-day course is currently estimated to be about $240 US.

The reader is advised to await further investigation of this agent, as well as watching for other new approaches under study for this increasing problem with *C. difficile* colitis, including resins for the absorption of toxins, immune approaches such as monoclonal antibodies, and alteration of gastrointestinal flora thorough the use of probiotics. ■

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Commercial Air Travel by Prematurely Born Infants

ABSTRACT AND COMMENTARY

By Tyler Hartman, MD, Jonathan Johnson, MD, & Philip R. Fischer MD, DTM&H

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Synopsis: *Young, prematurely-born infants with neonatal lung disease are at high risk of oxygen desaturation during commercial air travel. Hypoxia testing, if possible prior to air travel, or deferral of long air trips, should be considered for young infants with neonatal lung disease, even if they are not requiring oxygen.*

Source: Udomittipong K, et al. Pre-flight testing of preterm infants with neonatal lung disease: A retrospective review. *Thorax.* 2006; 61:343-347.

INCREASINGLY, INFANTS WITH A HISTORY OF NEONATAL lung disease are traveling by air. With advancing tech-

nology, aircraft are able to fly longer distances at higher altitudes. Due to limitations in aircraft structure, planes at cruising altitude can only be pressurized to the equivalent of 6,500 ft above sea level, resulting in a lower partial pressure of cabin oxygen. In 2004 the British Thoracic Society (BTS) updated their air travel guidelines for infants and young children with a history of respiratory disease, stating that an in-flight blood oxygen saturation of < 90% was an indication for supplemental oxygen. Studies have shown that healthy, term infants drop their oxygen saturation by 4-5% during hypoxia tests with 15-16% oxygen, and more than 10% of these healthy infants have significant blood oxygen desaturations to below 80%.[1]

Udomittipong and colleagues recently conducted a retrospective chart review of 47 infants with a history of neonatal chronic lung disease (nCLD). These infants were no longer requiring supplemental oxygen, had baseline oxygen saturations > 95%, and were referred for a hypoxia test to determine fitness to fly. The hypoxia test consisted of exposure to 14-15% oxygen for approximately 20 minutes with concurrent saturation monitoring. Of the infants tested, 81%, predominantly younger than 1 year of age, desaturated to below 85%, indicating the need for in-flight supplemental oxygen. Infants that passed the hypoxia test were significantly older than those who did not, averaging a corrected (post-due date) age of 12.7 months. The authors' conclusion was that infants younger than 12 months (corrected age) with a history of nCLD are at high risk for desaturation during commercial flights. They recommended that these infants be screened with hypoxia testing prior to traveling to determine need for supplemental oxygen.

COMMENTARY

The study by Udomittipong et al considered a blood oxygen desaturation during the hypoxia test to < 85% as indicative of need for oxygen supplementation during air travel. The BTS recommends supplementation if there is a desaturation to below 90%, which is significantly more conservative. Therefore, the 81% of the infants in this study that would require in-flight supplemental oxygen is possibly an underestimation. The hypoxia test done in this study was approximately 20 minutes in length, which is considerably shorter than most commercial airline flights. Lee et al have shown a continued decrease in blood oxygen saturations occurring from 3 hours to 7 hours into air travel in population of healthy 6-month to 14-year-old children who are much less susceptible to desaturation.[2] The data suggest that Udomittipong's study may underestimate the necessity for supplemental oxygen in infants with a history of nCLD.

Several studies have shown that most people average a 4% decrease in their blood oxygen saturation during commercial airline flights. This is usually clinically insignificant for healthy children and adults. There are many reasons why former premature infants are likely to be more susceptible to in-flight desaturation, even with mild lung disease and when clinically stable on room air. High altitude pulmonary edema has been linked to an individual's tendency to respond to hypoxia with an abnormal increase in pulmonary artery pressure. Infants with a history of chronic lung disease are at risk of elevated pulmonary artery pressures with normal oxygen levels. Theoretically, these infants have a higher risk of pulmonary edema and respiratory compromise with hypoxia than infants with normal pulmonary artery pressures.[3] Premature infants have been shown to have a persistence of biphasic ventilatory response to hypoxia, resulting in a sustained decrease in respiratory frequency.[4] Unlike term infants who have been shown to have a decrease in apnea when hypoxic, infants with a history of prematurity show an increase in both the frequency and duration of apneas,[5] even after discharge from the hospital.[4] Although it seems logical that premature infants should be at a greater risk for significant desaturations when exposed to hypoxic conditions, there has been little direct evidence to support this claim.

The clinical consequences of transient drops in an infant's oxygen saturation remain uncertain. In 1998 British investigators examined the administration of 15% oxygen to healthy term infants and reported an increase in irregular breathing and desaturations.[1] The authors suggested that airway hypoxia may be responsible for the anecdotal connection between commercial airline travel and Sudden Infant Death Syndrome (SIDS). The media inflated the very weak evidence supporting this claim, which resulted in public overreaction. The plausible physiologic bases for this claim have not been supported by the epidemiologic evidence. There have been no studies, prospective or retrospective, that have supported this claim. There have, however, been conflicting studies that have examined the relationship between high altitude and SIDS. Two studies in the United States[6,7] and one study in Austria[8] have indicated a significant increase in the incidence of SIDS at high altitudes; however, a study in Colorado showed high altitude is not an independent risk factor for SIDS.[9] Even though cabin oxygen content during a commercial airline flight is the equivalent being at 6,500 feet of altitude, these studies cannot be generalized to this population due to the tran-

sient nature of air travel. The UK's Confidential Inquiry into Stillbirths and Deaths in Infants (CESDI 1995–1996) found none of the 130 case of SIDS had recently flown.[10] None of these studies examined the incidence of SIDS in infants with a history of prematurity and nCLD, as these patients are at higher risk of SIDS already.

The evidence that commercial air travel is a significant risk factor for SIDS in healthy term neonates is not strong enough to recommend that this population should not fly. The present study, however, indicates that infants with a history of nCLD are more likely to have significant oxygen desaturation and require oxygen during air travel. This study likely underestimates the need for oxygen supplementation suggested by the BTS 2004 guidelines in order to maintain "adequate" oxygen saturation. The clinical significance of desaturation below 85% in this population has yet to be determined and, until further information is available, it is safer to err on the side of caution. We suggest that any infant younger than 12 months of age with a history of nCLD, regardless of current oxygen saturation, should undergo a hypoxia test equal to the duration of the upcoming flight. When this is not possible, it may be prudent to delay air travel until after 12 months of age or simply have supplemental oxygen prescribed prior to departure. ■

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High Altitude Pulmonary Edema Prevention

ABSTRACT AND COMMENTARY

By Michele Barry MD, FACP

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Dr. Barry is a consultant for the Ford Foundation, and receives funds from Johnson & Johnson.

Synopsis: *What agents are available to prevent or abort high-altitude pulmonary edema, particularly for those who are already known to be susceptible?*

Source: Maggiorini M, et al. Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema. *Ann Int Med*. 2006;145:497-506.

This is a sentinel article involving a randomized, double-blind, placebo-controlled study which took 29 adult patients with a history of high altitude pulmonary edema (HAPE) from 490 m to an ascent of 4559 m within 24 hours, treating them for 2 days with either prophylactic tadalafil 10 mg orally, twice a day, dexamethasone 8 mg orally twice a day or a placebo twice daily, starting on the morning of ascent. In these HAPE-susceptible individuals who had a 60 to 70% likelihood of again developing HAPE under study conditions, Maggiorini and colleagues performed the following tests at the summit: chest radiography to survey for infiltrates, Doppler echocardiography to measure systemic pulmonary artery pressures and cardiac output, and nasal potentials as a surrogate marker of alveolar sodium transport in order to determine if alveolar fluid re-absorption was affected by any of the study drugs.

The incidence of HAPE was 78% in the placebo-treated group but was reduced to 13% and 0% in the tadalafil and dexamethasone groups, respectively. This reduction in risk was comparable to nifedipine's efficacy (a 10% incidence of HAPE) and potentially bet-

ter than salmeterol's (a 33% incidence of HAPE), two established prophylactic drugs tested under the same conditions on the same mountain in earlier studies.[1,2]

Dexamethasone decreased the incidence of AMS, but tadalafil did not. However, patients taking dexamethasone had mild, clinically insignificant, hyperglycemia. Dexamethasone did not stimulate sodium transport via surrogate markers, nasal potentials or a decrease in expression of the alpha-1 subunit of Na+, K+, - ATPase in leukocytes. The authors conclude that although acetazolamide (Diamox®) is the standard of care for prevention of AMS, dexamethasone may be the ideal prophylaxis to reduce the risk of HAPE and AMS in HAPE-susceptible persons who must ascend rapidly, as it now has been shown to prevent both AMS and HAPE in this population.

COMMENTARY

Rapid ascent to altitudes greater than 2500 m may cause acute mountain sickness (AMS) or high altitude pulmonary edema. In non-acclimatized mountaineers, the prevalence of AMS and HAPE at 4559 m is approximately 50% and 4%, respectively. AMS is not a prerequisite for HAPE. However, if a person has a history of HAPE, undergoing another high altitude rapid climb puts them at a 60% risk of contracting HAPE again. HAPE begins when a critical level of hypoxic pulmonary vasoconstriction causes mean pulmonary artery pressures to exceed 35 to 40 mm Hg. Reduction in hypoxic pulmonary vasoconstriction (HPV) by descent, oxygen supplementation, nitric oxide, portable hyperbaric bags or pulmonary vasodilators have all been shown to be effective therapy for HAPE.

Tadalafil, a phosphodiesterase-5 inhibitor like sildenafil (Viagra®), reduces hypoxic pulmonary vasoconstriction (HPV) and pulmonary hypertension by blocking the breakdown of cyclic GMP, the intracellular mediator of the vasodilatory efforts of nitric oxide. Dexamethasone's preventative effects had been felt to be caused by anti-inflammatory effects on both cellular and cytokine responses. As HAPE pulmonary lavage fluid does not contain inflammatory cells, the unusual finding from Maggiorini's study is that dexamethasone was 100% effective in treating HAPE, surprisingly by reducing pulmonary artery pressures. Very recent studies have shown that glucocorticoids can increase pulmonary vascular endothelial nitric oxide (NO) synthase and increase NO levels—which fits nicely with the data that HAPE-susceptible people have a lower pulmonary generation of vascular nitric oxide when exposed to hypoxia.[3]

The "elephant on the mountain" in this study—why was acetazolamide Diamox® not used in one of the arms? Animal studies have shown Diamox® to be effective in preventing HAPE as well as AMS, but no human studies have been carried out.[4] Moreover, adverse effects of high-dose dexamethasone that were not monitored beyond 48-hour treks represent unrealistic scenarios in real life. Taking dexamethasone on an extended trek could lead to hyperglycemia, hypercalciuria, protein catabolism, immunosuppression and steroid psychosis.

An accompanying editorial questions whether inhaled corticosteroids can substitute for oral dosing and whether genomic factors, sympathetic tone alterations, surfactant production or cell-to-cell tight junction strengthening may play a role in dexamethasone's preventing HAPE.[5] For now we await studies by this extremely organized and thoughtful group on whether acetazolamide is as effective as dexamethasone in preventing AMS and HAPE, and which dexamethasone regimen has the best risk-benefit profile. ■

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CME Questions

9. Complete the following with a true statement. MDR-TB:

a. has occurred most frequently in South America.
b. occurs in the highest proportion of TB cases originating from Eastern Europe.
c. is expected to affect only those travelers who are visiting friends and relatives.
d. has not been reported from southeast Asia or the Western Pacific region.
e. cannot occur through airborne transmission during commercial, regulated airline flights.

10. Which of the following statements regarding nitazoxanide for treatment of *C. difficile* colitis is true?

a. It should be considered about as efficacious as probiotics for this disease.

b. It is the equivalent of oral therapy with metronidazole for this disease.
c. It has no efficacy in the treatment of recurrent disease.
d. Its pharmacological advantages make it the agent of first choice for hospital-acquired *C.difficile* colitis.
e. It is currently an FDA approved agent for the treatment of colitis that is not responsive to vancomycin or metronidazole.

11. Long commercial air flights:
a. are associated with about a 4% decrease in blood oxygen saturation in healthy travelers.
b. pose no significant risks to prematurely born babies who are thriving on room air at home.
c. have been associated with an increased risk of SIDS (crib death).
d. are contraindicated during infancy.

12. High altitude pulmonary edema (HAPE) has been proven to be prevented by:
a. rapid ascent and slow descent to prevent leaky capillary syndrome.
b. exercise fitness prior to ascent and a small dose of a diuretic such as acetazolamide prior to ascent.
c. high dose dexamethasone at 8 mg po BID as treatment once symptoms begin.
d. prophylactic dexamethasone 8 mg po BID prior to ascent.

Answers: 9. (b); 10. (b); 11. (a); 12. (d)

CME Objectives

The objectives of *Travel Medicine Advisor* are:

• To present the latest data regarding the diagnosis and treatment of various travel-related diseases;

• To present new data concerning recommended precautions and prophylaxis for patients traveling to specific areas of the world; and

• To alert the readers to recent disease outbreaks and epidemics. ■

ISTM Travel Medicine Courses

The International Society of Travel Medicine is pleased to sponsor and run 2 preparatory courses for the ISTM Certificate of Knowledge Examination (CTH® Program). The courses will be held on February 9-10, 2007, in Liverpool, United Kingdom, and on February 9-11, 2007, in Dallas-Fort Worth, TX.

The courses will review the Body of Knowledge for the Practice of Travel Medicine, as well as updates on recent advances in Travel Medicine.

Registration for the Certificate of Knowledge Exam is not a pre-requisite for taking the course. For further information, please visit www.istm.org.

The UK course is co-sponsored by the National Travel Health Network and Center (NaTHNaC, www.nathnac.org/pro/index.htm), United Kingdom. The US course is co-sponsored by the Mount Auburn Hospital, a community teaching hospital of Harvard Medical School. ■

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Sweeping Changes Needed for US Drug Safety System

In response to several high-profile drug misadventures including the rofecoxib (Vioxx®) withdrawal from the market, the FDA's Center for Drug Evaluation and Research (CDER) asked the Institute of Medicine (IOM) to assess the drug safety system in the United States. The recommendations, published in the October 26 *New England Journal of Medicine*, call for sweeping changes, especially in the post-marketing surveillance of new drugs.

The report suggests that the FDA has acted to accelerate drug approvals without ensuring the safety of these drugs once they are approved and on the market. Direct-to-consumer advertising is also partially to blame, especially when aggressive marketing campaigns lead to sudden widespread use of a new drug. Chronic under funding and a poor work environment at the FDA are also partially to blame. But the biggest culprit is the lack of an effective mechanism of continued evaluation of new drugs once they're on the market, which currently amounts to little more than reports of adverse events from practitioners. The IOM's report recommends changes in the FDA's committee structure, which strengthens conflict-of-interest restrictions and recommends that the FDA commissioner be appointed for a fixed term of 6 years. They also recommend labeling new drugs with a symbol such as a black triangle for up to 2 years to signify "the uncertainty associated with new drugs" and a moratorium on direct to consumer advertising during that period. Five years after a drug's launch, the FDA should perform a review of the risk/benefit status of all approved drugs (*N Engl J Med*. 2006;355:1753–1755).

An accompanying editorial points out that much of the money provided to the CDER is for drug approval, and much of it derives from industry, whereas little funding is earmarked for monitoring of the safety of drugs after they've been approved and introduced onto the marketplace. The editorialists recommend that all clinical trials beyond phase I must be registered in the public database, as has been recommended previously. The editorial also endorses the black triangle indication in the first 2 years after the drug's approval in a moratorium on direct-to-consumer advertising during that time. Most importantly, the editorialists ask for better funding and more transparency in the FDA, and urges Congress to implement the recommendations (*N Engl J Med.* 2006;355:1821).

Antiaging Supplements Proven Ineffective

Dehydroepiandrosterone (DHEA) and testosterone are not effective antiaging supplements, according to 2 new studies. Both compounds have been widely marketed as antiaging supplements. The first study from the *New England*

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Journal of Medicine was a 2-year, placebo-controlled, randomized, double-blind study involving both women and men.

Among the men, 29 received DHEA, 27 received testosterone, and 31 received placebo. Among women, 27 received DHEA and 30 received placebo. After 24 months the men showed no significant effect of DHEA on body-composition measurements. Neither DHEA nor testosterone affected oxygen consumed per minute, muscle strength, or insulin sensitivity. Testosterone resulted in a slight increase in fat-free mass, and both DHEA and testosterone resulted in an increase in bone mineral density at the femoral neck. Women who received DHEA had an increase in bone mineral density at the ultradistal radius. There was no difference in quality-of-life issues in either group with any intervention. The authors conclude that neither DHEA nor low-dose testosterone replacement in elderly people has physiologically relevant beneficial effects on body composition, physical performance, insulin sensitivity, or quality of life (*N Engl J Med*. 2006; 355:1647–1659).

The second study was also a double-blind, randomized, controlled trial that included a hundred men age 70 and over. Subjects were randomized to receive DHEA 50 mg/d, the anti-estrogen atamestane 100 mg/d, the combination of the 2, or placebo for 36 weeks. No differences were found in either treatment arm compared with placebo on a battery of tests, which included isometric grip strength, leg extensor power, and physical performance (*J Clin Endocrinol Metab*. 2006;91:3988–3991).

The Three Most Common Culprits of ADE

Three drugs are responsible for a third of the estimated 700,000 outpatient adverse drug events per year in this country, according to a new study. A collaborative effort of the FDA, CDC, and US Consumer Chronic Safety Commission developed the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project several years ago to assess the risk of adverse drug events (ADEs) in the outpatient setting. During the 2-year study period, 21,298 ADEs were reported that resulted in patients presenting to the emergency departments of the 63 reporting hospitals. This extrapolates to over 700,000 cases annually in this country. Individuals age 65 or older were more likely than younger individuals to suffer an ADE. Drugs for which regular outpatient monitoring is used to prevent toxicity accounted for 41.5% of hospitalizations, and 50% of hospitalizations were in people age 65 and older. Of those drugs, insulin, warfarin, and digoxin were responsible for one in 3 estimated ADEs treated in emergency departments. The authors conclude that adverse drug events are an important cause of morbidity in the United States, especially among the elderly, and that ongoing population-based surveillance may help target prevention strategies (*JAMA*. 2006; 296:1858–1866).

New Guidelines for Lyme Disease Prevention

The Infectious Disease Society of America has issued new guidelines for Lyme disease (LD) prevention. Of note, guidelines state that routine use of antimicrobial prophylaxis or serologic testing is not recommended after a recognized tick bite; however, a single dose of doxycycline 200 mg may be given to adults and children over the age of 8 if 1) the attached tick is recognized as a potential carrier of LD and has been attached for least 36 hours; 2) the dose can be given within 72 hours of tick removal; 3) the patient is in an endemic area; 4) doxycycline is not contraindicated. Testing of ticks is not recommended. Even if patients have been prophylaxed, they should be monitored for signs and symptoms of tick-borne illness for up to one month (*Clin Infect Dis*. 2006:43—published online October 2, 2006).

FDA Actions

The FDA has approved a new agent for the treatment of hepatitis B infections. Telbivudine (Tyzeka™), from Novartis, has been approved for the treatment of adults with chronic hepatitis B infections. In clinical trials, the drug was shown to suppress replication of hepatitis B virus and reduce liver inflammation.

The FDA has approved Merck's sitagliptin (Januvia™), a new oral antidiabetic for the treatment of type 2 diabetes. The drug is a DPP-4 inhibitor, a new class of medications that prolongs the action of incretin hormones, resulting in improved glycemic control. The drug is approved for monotherapy or as add-on with metformin or a thiazoldinedione. Sitagliptin has the theoretical advantages of not causing weight gain or increasing the risk of hypoglycemia. It is supplied as a 100 mg tablet that is given once a day. ■