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INSIDE

Treatment of Neurocysticercosis

ABSTRACT & COMMENTARY

Synopsis: *A 10-day treatment course of albendazole and dexamethasone for patients with seizures and neurocysticercosis with viable cysts significantly reduced the incidence of subsequent seizures.*

Source: Garcia HH, et al. A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. *N Engl J Med*. 2004;350:249-258.

GARCIA AND COLLEAGUES RANDOMIZED 120 ADULTS WITH neurocysticercosis with viable cysts and a history of seizures to receive either placebo or treatment with albendazole (400 mg twice daily) and dexamethasone (2 mg every 8 h) for 10 days. The patients were a highly selected group (*see inclusion and exclusion criteria in Table 1*). Patients with cysts with signs of inflammation as determined by the presence of edema or contrast enhancement were included only if intracystic contents had a CT density similar to that of cerebrospinal fluid with confirmation of its liquid nature by MRI. Inflamed lesions were analyzed separately.

The primary end point of the study was seizure control. All patients received adequate anticonvulsant therapy, with monitoring of serum concentrations. Anticonvulsant therapy was discontinued after a 2-month taper in patients who were seizure-free for 1 year. Study participation was discontinued after 6 seizure-free months after discontinuation of therapy.

The frequency of adverse effects did not differ between the 2 treatment arms except for abdominal pain, which was reported by 8 albendazole recipients and no placebo recipient. Two albendazole recipients and 1 placebo recipient had seizures with generalization during therapy; partial seizures occurred in 8 and 5, respectively.

Albendazole recipients had 46% fewer total seizures during the 2-30 months post-therapy follow-up period, but this difference

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was not statistically significant ($P = .30$). There was, however, a significant, 67% reduction in the rate of seizures with generalization in albendazole recipients ($P = .01$).

MRI performed 6 months after placebo administration demonstrated that 243 of 279 cysts (87%) in 54 patients persisted unchanged. In contrast, only 79 of 192 (41%) were unchanged in the 55 albendazole recipients who underwent imaging, a difference that was significant ($P < .0001$). Cysts showing signs of inflammation at study entry were also more likely to have resolved in the albendazole recipients (49% vs 21%; $P = .013$). Twenty-one (38%) in the albendazole group and 8 (15%) in the placebo group were free of active lesions ($P = .007$).

Patients with no active brain lesions 6 months after treatment had 62% fewer seizures than in those with at least one active lesion ($P = .24$).

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COMMENT BY STAN DERESINSKI, MD, FACP

Neurocysticercosis is the most common parasitic infection of the central nervous system affecting humans and the most frequent cause of post-childhood-onset seizures in most of the developing world. Cerebral cysticercosis may be the most common cause of severe burns in parts of New Guinea and Irian Jaya as a consequence of contact with fire during seizures.[1,2]

Cysticercosis is commonly encountered in the United States as well. A study involving 11 university-affiliated emergency departments in the United States found that 2.1% of patients presenting with seizures who underwent cerebral imaging had cysticercosis as the cause.[3] The infection was associated with Hispanic ethnicity, immigrant status, and exposure to areas where cysticercosis is endemic.[3] The crude mortality over 12 years attributed to cysticercosis in California is 3.9 per million population.[4]

Entry into this study required a history of seizures. Between 50% and 80% of patients with parenchymal brain cysts or calcifications have seizures,[5] but not all

Table 1
Inclusion & Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Presence of at least one well-delimited, round hypodense viable lesion on CT	Primary generalized seizures
Positive test for *T solium* infection by enzyme-linked immunoelectrotransfer blot (EITB)	History of antiparasitic treatment
History of at least 1 seizure in prior 6 months, but of less than 10 years duration	More than 20 cysts on CT
	CT evidence of disease not attributable to cysticercosis
	Moderate or severe intracranial hypertension
	Staus epilepticus
	Focal neurologic deficits
	Unstable vital signs or impending death
	Pregnancy

Table 2
Treatment Recommendations[6]

Viable parenchymal cysts	Antiparasitic treatment with steroids
Encephalitis	No antiparasitic treatment; steroids, osmotic diuretics
Calcified lesions	No antiparasitic treatment
Ventricular cysts	Endoscopic removal
Subarachnoid cysts, chronic meningitis	Antiparasitic treatment with steroids; CSF shunting for hydrocephalus
Hydrocephalus with no viable cysts	CSF shunting
Spinal cysts	Surgical removal
Ophthalmic cysts	Surgical removal

patients present with seizure. Some cases are discovered serendipitously when an individual undergoes brain imaging for unrelated reasons. In addition, neurocysticercosis may also present with headache. Some patients may have intracranial hypertension, hydrocephalus, or both due to mass effect from a cyst, from inflammation, from fibrosis, or from some combination. Rarely, a free-floating intraventricular cyst may intermittently obstruct the third ventricle.

Massive cerebral infection may lead to presentation with acute encephalitis. Approximately 1% of patients have cystic involvement of the spinal cord due to either an intramedullary or subarachnoid location. Meningitis may occur, often with an eosinophilic pleocytosis. Extraneural cysts may present in muscle and other soft tissues, as well as in ocular tissues.

The imaging diagnosis of cysticercosis is easy when multiple cysts are present and confirmed by the identification of a scolex within a cyst by MRI. Multiple calcifications are consistent with old, resolved infection. Multiple stages may be simultaneously present. Incipient death of a cyst is heralded by thickening of the cyst wall, contrast enhancement with or without surrounding edema, and increasing density of the cyst fluid.

The serological test used in this study, EITB, has been demonstrated to have very high sensitivity and specificity in patients with multiple cerebral lesions. The test, unfortunately, has significantly lower sensitivity in patients in whom the diagnosis may be most difficult—those with a single cerebral lesion.

No previous study has convincingly demonstrated benefit from anticysticercal therapy. A clear benefit appears to accrue with regard to a reduction of seizure occurrence from treatment with albendazole and dexamethasone in patients with viable cerebral cysts. This trial does not provide data by which to judge therapeutic benefit in a variety of other circumstances, such as in the patient who presents with headache alone. It also provides no evidence to support longer or shorter courses of therapy, therapy without adjunctive dexamethasone, or retreatment in cases in which patients have apparently failed previous courses of therapy. It also does not address the efficacy of praziquantel therapy or the possibility that the combination of praziquantel and albendazole may provide better results than the use of one or the other alone.

A consensus panel has recently provided recommendations on the management of other manifestations of cysticercosis (*see Table 2*).[6] ■

References

1. Bending JJ, Catford JC. Epidemic of burns in New Guinea due to cerebral cysticercosis. *Lancet*. 1983;1:922.
2. Margono SS, et al. Cysticercosis in Indonesia: Epidemiological aspects. *Southeast Asian J Trop Med Public Health*. 2001;32(Suppl 2):79-84.
3. Ong S, et al. Neurocysticercosis in radiographically imaged seizure patients in U.S. emergency departments. *Emerg Infect Dis*. 2002;8:608-613.
4. Sorvillo FJ, et al. Cysticercosis-related deaths, California. *Emerg Infect Dis*. 2004. Online.
5. Garcia HH, et al. Taenia solium cysticercosis. *Lancet*. 2003;362:547-556.
6. Garcia HH, et al. Current consensus guidelines for treatment of neurocysticercosis. *Clin Microbiol Rev*. 2002;15:747-756.

Something in Common Between *Candida albicans* and *Staphylococcus aureus*: Coagulase Production

ABSTRACT & COMMENTARY

Synopsis: Candida albicans *and some other* Candida *species elaborate coagulase and might be confused with* Staphylococcus aureus.

Source: Rodrigues AG, et al. Expression of plasma coagulase among pathogenic *Candida* species. *J Clin Microbiol*. 2003; 41:5792-5793.

A VARIETY OF DIFFERENT CLINICAL *Candida* ISOLATES totaling 161 from blood, respiratory secretions, genital secretions, stool, and urine were tested for the coagulase reaction using the classical plasma test, as well as a commercial latex test (Pastorex Staph-Plus kit [Bio-Rad]). The identity of the different species (*C albicans* [70 isolates]; *C tropicalis* [23 isolates]; *C glabrata* [25 isolates]; *C parapsilosis* [29 isolates]; *C krusei* [11 isolates]; and *C guilliermondii* [3 isolates]) was confirmed by the germ tube test and the API 32C identification kit (BioMérieux). Coagulase production was indicated by clot formation after 4 h in rabbit plasma or, if negative, 20 h later. The latex particles in the Staph-Plus kit are sensitized with human fibrinogen and monoclonal antibodies and react with the clumping factor, protein A, and capsular polysaccharides of *Staphylococcus aureus*. Most of the *C albicans* (88.5%) and *C tropicalis* (82.6%) strains were able to induce clot formation from EDTA-rabbit plasma at 24 hours and react with the latex test (*see Figure*). The other species reacted to a much

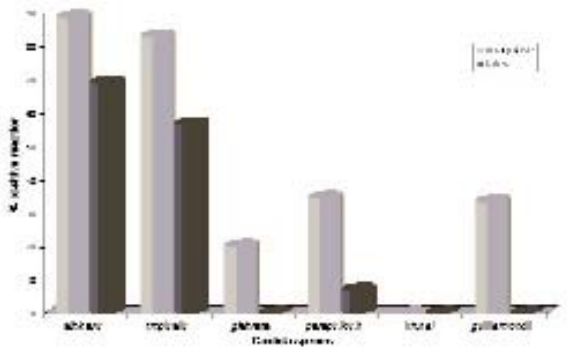
lesser extent or not at all. Rodrigues and colleagues felt that this was more than a curiosity, especially in the setting of "a large university hospital, handling a considerable number of samples daily and relying mostly on automated devices for identity confirmation" because yeasts might be taken for *S aureus* when the latex coagulase test is performed to identify white colonies appearing on agar plates after overnight incubation unless microscopic examination is done.

COMMENT BY J. PETER DONNELLY, PhD

I confess I was surprised to learn that *C albicans* and *S aureus* had something in common after all. But, then again, I was brought up on steam-age microbiology in which one would not dream of proceeding from plate to test without first carefully noting the size, shape, color, and texture of any colonies formed on petri dishes; recording the time, temperature and atmosphere of incubation; and establishing the Gram reaction and shape, and the catalase and oxidase reactions. Of course, shortcuts could, and would, be taken, but there was a safeguard that final reports would only be issued when all the results were known. This, of course, took time—too much time in many cases. Rightly so, we have come to expect rapid results, economic use of resources, and short turn-around times. However, as shown in this article, micro-organisms continue to baffle and fool us, especially when we have taken our eye off the ball. Nowadays, it is perfectly possible to pick off a colony and surrender it entirely to an electronic black box and have the result within a few hours. It is only a short step in thrift to eliminate skilled personnel altogether from this process. Many professionals' worst nightmare is that we might end up using systems beyond our control, employing techniques we don't fully understand, and releasing results we cannot rely on. How many of us have deliberately put the wrong organism in an identification kit to educate students and tease colleagues? There was also a serious side—getting the message across that elementary microbiology is and will remain our best safeguard against making mistakes. ■

Figure

Coagulase Reactions Among *Candida* Species



Mycobacterium avium Colonization and Disease Linked to Contaminated Hospital Water

ABSTRACT & COMMENTARY

Synopsis: *Both clinical disease and sputum colonization due to* Mycobacterium avium *complex were traced to the potable water system of a large public hospital.*

Source: Tobin-D'Angelo MJ, et al. Hospital water as a source of *Mycobacterium avium* complex isolates in respiratory secretions. *J Infect Dis*. 2004;189:98-104.

Investigators at Grady Memorial Hospital in Atlanta examined 161 *Mycobacterium avium* complex (MAC) isolates from respiratory specimens obtained from 131 patients and 13 MAC isolates from the hospital's hot water system. Of the 131 patients, 35% had MAC disease, based upon meeting the American Thoracic Society (ATS) criteria for MAC pulmonary infection or upon isolation of identical MAC strains from blood and sputum. Ninety-six patients (73%) had MAC colonization of sputum in the absence of disease.

Ten different MAC clusters of closely related strains were identified by pulsed-field gel electrophoresis. Of these clusters, 8 contained 1 or more isolates with MAC disease; the majority of patients were HIV-infected. Eighty-eight percent of isolates from patients with MAC colonization belonged to 1 of the 10 clusters, as did 53% of isolates from patients with MAC disease. The largest cluster contained isolates from 85 patients, 13 (15%) of which were from patients with MAC disease. The cluster also contained isolates recovered from the hospital hot water system.

Tobin-D'Angelo and associates concluded that the hospital hot water system was the source of both sputum colonization with MAC and MAC infection.

COMMENT BY ROBERT MUDER, MD

Hospital water systems can be the source of many different nosocomial bacterial pathogens, including *Legionella* species, nonfermentative Gram-negative bacilli such as *Pseudomonas aeruginosa* and *Stenotrophomonas mal-*

tophilia, and nontuberculous mycobacteria (NTM).[1] NTM can be isolated from up to 83% of municipal water supplies.[2] NTM can multiply in a variety of aquatic environments. They are resistant to many disinfectants, including chlorine in the concentrations used to treat potable water. Several species, including MAC, can grow at temperatures of 45° and above.[3]

Colonization of hospital water with NTM has several potential adverse consequences. Pseudo-outbreaks of infection can occur when medical devices, such as bronchoscopes and endoscopes, are cleaned with contaminated water. Even when no infection results, pseudo-outbreaks can impose a considerable burden on the microbiology laboratory and on the infection control program. The laboratory may be required to process many specimens for NTM; the infection control program will be required to investigate numerous cases of pseudo-infection and determine the source of the outbreak.

More ominously, contaminated water can result in nosocomial infection. Outbreaks of postoperative wound infection, typically involving *M abscessus*, have affected cardiac surgery, plastic surgery, and ophthalmologic surgery patients, among others. The resulting infections are particularly problematic, as NTM tend to be resistant to many standard antituberculous medications. Surgical debridement and prolonged multidrug antimicrobial therapy are often needed.

Exposure to NTM is particularly hazardous to HIV-infected persons, as MAC is a major cause of morbidity among those with advanced immunodeficiency. MAC isolates from HIV-infected patients tend to be genetically distinct, reflecting the widespread occurrence of MAC in the environment.[4] The occurrence of multiple cases of MAC infection with closely related strains among HIV-infected patients in a single institution is unusual. In the report from Grady Memorial Hospital, the majority of isolates (53%) from patients with MAC disease belonged to a cluster of genetically related isolates, and 28% of all diseases among HIV-infected patients were caused by a strain isolated from the hospital water system.

Although it appears clear that colonization of hospital water systems by NTM poses a significant hazard to susceptible patients, the solution to the problem is unclear. There are no established methods for eradicating these organisms from potable water. As noted, chlorine in concentrations usually added to potable water is ineffective. Copper-silver ion treatment has proven effective in eliminating *Legionella* species from hospital water systems. NTM are susceptible to killing by copper and silver ions in the laboratory,[5] but actual clinical experience is lacking. Institutions whose water systems are colonized by NTM should consider providing sterile water for highly immunocompromised patients until a proven water disinfection system is available. ■

References

1. Squier C, et al. Waterborne nosocomial infections. *Curr Infect Dis Rep*. 2000;2:490-496.
2. Carson LA, et al. Prevalence of nontuberculous mycobacteria in water supplies of hemodialysis centers. *Appl Environ Microbiol*. 1988;54:3122-3125.
3. Wallace RJ, et al. Nosocomial outbreaks/pseudo outbreaks caused by nontuberculous mycobacteria. *Annu Rev Microbiol*. 1998;52:453-490.
4. Arbeit RD, et al. Genetic diversity among strains of *Mycobacterium avium* causing monoclonal and polyclonal bacteremia in patients with AIDS. *J Infect Dis*. 1993;167:1384-1390.
5. Lin YE, et al. Inactivation by *Mycobacterium avium* by copper and silver ions. *Water Research*. 1998;32: 1997-2000.

Corticosteroids for Bronchiolitis in Young Children

ABSTRACT & COMMENTARY

Synopsis: *A 3-day course of oral prednisolone for treatment of bronchiolitis in children aged 6-35 months decreased the median duration of symptoms and hospitalization and the need for additional asthma medications.*

Source: Csonka P, et al. Oral prednisolone in the acute management of children age 6 to 35 months with viral respiratory infection-induced lower airway disease: A randomized, placebo-controlled trial. *J Pediatr*. 2003;143:725-730.

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED trial of a 3-day course of oral prednisolone (2 mg/kg/d divided twice daily for 3 days) was conducted in an emergency department setting in Finland among 230 children aged 6-35 months with an apparent viral respiratory tract infection complicated by tachypnea, wheezing, or use of accessory muscles for breathing. Prednisolone did not affect the hospitalization rate but did decrease the median duration of symptoms (1 day vs 2 days) both among hospitalized (P = .001) and nonhospitalized children (P = .006), median duration of hospitalization (2 days vs 3 days; P = .06), and the

need for additional asthma medications (18.0% vs 37.1%; $P = .018$).

Adverse reactions were mild and resolved without intervention and included vomiting (4 vs 9), diarrhea (6 vs 6), rash (0 vs 2), and restlessness (2 vs 3) in the placebo and prednisolone groups, respectively. Medication was discontinued in 15 children (4 receiving placebo and 11 receiving prednisolone) because of perceived adverse effects.

COMMENT BY HAL B. JENSON, MD, FAAP

Bronchiolitis is a diagnosis that implies a viral respiratory tract infection accompanied by wheezing and is most often caused by respiratory syncytial virus. Other viruses less frequently responsible for bronchiolitis include adenovirus; parainfluenza viruses 1, 2, and 3; metapneumovirus; and influenza viruses A and B. It is extremely difficult to clinically distinguish bronchiolitis from a first episode of asthma. Furthermore, the causal relationship of bronchiolitis to asthma in children is a subject of much conjecture. There is an increased risk of asthma among children with bronchiolitis that requires hospitalization, which may reflect that children with hyper-reactive airways are more likely to require hospitalization with respiratory viral infection.

Clinical studies of the management of bronchiolitis have been plagued by difficulties in accurate virological diagnosis and inability to perform objective measurements of treatment effectiveness, such as pulmonary function tests. This study did not determine the viral etiology, which is a shortcoming, but does reflect some of the reality of clinical practice. Rapid tests for respiratory syncytial virus and influenza viruses are commonly used in the United States, but the causes of many cases of bronchiolitis still remain unidentified.

This is one of a series of studies of the value of corticosteroids for young children with bronchiolitis. Of 6 previous controlled trials, 5 showed little or no benefit, and only 1 showed accelerated improvement compared to placebo. A meta-analysis of these 6 studies concluded that there was a small but statistically significant benefit of prednisolone, reducing hospitalization by less than half a day.[1] This new study differs from the previous studies by initiation of prednisolone earlier, upon admission to the emergency department, rather than after hospitalization. This difference typically is several hours, which suggests that earlier treatment with prednisolone may prevent progression of the inflammatory response, which soon becomes irreversible.

Bronchiolitis is an almost universal experience of childhood and accounts for a hospitalization rate of approximately 3 per 100 infants in the United States. Supportive measures of intravenous hydration and supplemental oxygen remain important. The value of bronchodilator therapy remains controversial; it may provide transient clinical improvement for some patients but does not alter the course of the disease. This study shows that oral prednisolone early in the course of bronchiolitis can have a small but discernible benefit and alters the course by reducing the duration of symptoms and subsequently the duration of hospitalization and need for additional asthma medications. ■

Reference

1. Garrison MM, et al. Systemic corticosteroids in infant bronchiolitis: A meta-analysis. *Pediatrics*. 2000;105:e44.

ICAAC/IDSA/ASTMH 2003

CONFERENCE COVERAGE

The following summary of selected abstracts from 3 meetings will be published in multiple parts. The 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) met in Chicago September 14-17, 2003. The Infectious Disease Society of America (IDSA) met in San Diego October 9-12, 2003. The American Society of Tropical Medicine and Hygiene met in Philadelphia December 3-7, 2003. — ***Stan Deresinski, MD, FACP***

Viral Infection

Viral Hepatitis

A case control study found that the risk of HCV transmission to health care workers after percutaneous exposure increases with the volume of blood injected and, probably, with higher titer of HCV in the blood of the source patient (*ICAAC V-772*).

Approximately one-fifth of 248 saliva samples from 12 HCV-infected subjects contained HCV RNA. Salivary shedding was strongly associated with serum HCV RNA concentration and may be associated with the presence of periodontal disease. Mother-to-child transmission of HCV at birth occurred at an incidence of 4.1% and was not increased in the presence of maternal coinfection with HIV (*ICAAC V-773, V-774*).

Of 209 Alaskan natives with untreated chronic HCV infection who were followed for a mean of 9.4 years, only 7 (3%) spontaneously cleared their viremia after an average of 7.4 years (0.45% per year). Patients who

experienced spontaneous resolution of viremia had significantly lower viral loads than those who did not (*IDSA 508*).

The prevalence of diabetes mellitus is increased in patients with chronic HCV infection, regardless of the presence or absence of HIV coinfection (*IDSA 594*).

The median duration of survival in 43 HIV-infected patients with HCV coinfection after the onset of ascites was only 123 days (range, 10-2355 days) (*ICAAC V-782*).

CD4 counts are reduced in HIV-seronegative patients with hepatic cirrhosis, but CD4 percentage is preserved (*IDSA 603*).

A prospective study found that serum HCV RNA decay after 4 weeks of combination therapy correlated with outcomes at 6 months, regardless of the presence or absence of HIV coinfection. None of 40 HIV/HCV-coinfected patients treated with ribavirin and interferon alpha who failed to achieve HCV RNA undetectability at 24 weeks had sustained virological responses. Fifty percent of those with such a response at 24 weeks did have a sustained response (*ICAAC V-777, V-1726*).

Only 1 of 11 HIV/HCV-coinfected patients, most with unfavorable HCV genotype, had a sustained virologic response after treatment with pegylated interferon alpha, but all 10 with initial and follow-up liver biopsies demonstrated histologic and biochemical improvement (*ICAAC V-1724*).

Renal dysfunction was observed in 3 patients undergoing treatment with interferon alpha and ribavirin for chronic HCV infection (*IDSA 593*).

Seventy percent of HIV/HCV-coinfected patients had serological evidence of prior HBV infection, and 36% of those had isolated antibody to HBc. Separately, one-half of HIV-infected patients had isolated antibody to HBc, and that was much more commonly observed in those with HCV coinfection. However, only 1 of 48 HIV-infected individuals with isolated antibody to HBc had HBV DNA detectable in plasma (*IDSA 600, 601*).

Eighty-four HIV/HBV-coinfected patients who received tenofovir as part of their antiretroviral therapy were followed for a median duration of 9 months. At baseline, although all but 4 patients were receiving lamivudine, HBV DNA was detectable in 84.5%. However, HBV DNA became undetectable in 37.1% after initiation of tenofovir. This observation was confirmed in a study of 32 HIV/HBV-coinfected patients who received tenofovir as part of an antiretroviral regimen. Administration of tenofovir in this cohort was associated with rapid decreases in plasma HBV DNA regardless of lamivudine therapy and the presence of YMDD mutations (*ICAAC V-783, V-784*).

Viral Respiratory Infection

Epidemiology

In households containing at least 1 child aged 6 months to 5 years enrolled in childcare, the use of alcohol-based gels for hand hygiene was associated with lower rates of reported secondary respiratory illness (*IDSA LB-8*). A randomized trial using a variety of commercial products, however, has failed to demonstrate benefit (*Ann Intern Med*. 2004;40:321).

Diagnosis

Nasopharyngeal washes from 90 pediatric inpatients were tested by commercial antigen detection kits for influenza A and B, RSV, and parainfluenza virus, as well as with a DNA microarray bearing the most conserved sequences of each of 934 viruses. The DNA microarray was as sensitive and specific for detection of these viruses but also detected viruses not tested for by the commercial kits, including rhinovirus, coronavirus, and metapneumovirus (*IDSA LB-3*).

Influenza

Increasing evidence demonstrates the value of vaccination against influenza in broad swaths of the population. For instance, vaccination of children against influenza was associated with a 43-67% reduction in influenza incidence in household members. A primary target group, the elderly often have impaired serological responses to vaccination. Increasing the dose of standard inactivated influenza virus vaccine was associated with enhanced antibody responses in ambulatory elderly subjects (*IDSA 497, 530*).

Another very important target of vaccination is health care workers, but a survey of nursing home health care workers in southern California found that only 34% received the influenza vaccine. Furthermore, only 54% of the workers received paid sick leave, providing incentive for the other 46% to work while ill, thus increasing the risk of influenza transmission (*IDSA 532*).

Clinical differentiation of influenza from other respiratory illness is an important, but difficult, task. Multivariate analysis of data from a prospective study of almost 40,000 patients found that temperature > 100.4° F with combined complaints of fever chills and sweating, headache, and cough were of predictive value in differentiating influenza-like illness from influenza itself. However, even many patients given a diagnosis of influenza are inappropriately prescribed antibiotics. Antibacterial

agents were prescribed to 40% of patients aged 5-49 years with a diagnosis of influenza in the United States from 1997 to 2000. This represented 2.4 million prescriptions (*ICAAC V-792, A-1367a*).

A fatal case of infection caused by avian influenza virus H7N7 in a Dutch veterinarian occurring in association with an outbreak in chickens is described (*ICAAC V-480*).

Paramyxoviruses

A prospective study of children younger than 3 years hospitalized in Quebec because of acute respiratory tract infection in the winter/spring of 2002-2003 found that 5.8% were due to human metapneumovirus, 21.6% to influenza A, and 51% to respiratory syncytial virus. Two-thirds of children with metapneumovirus infection, which tended to occur later in the season than RSV infection, had bronchiolitis, and 16.7% had pneumonia. Metapneumovirus exposure during childhood appears to be almost universal. Eighty percent of children tested in Israel had antibody to human metapneumovirus by age 2 years (*ICAAC V-478, V-479*).

RSV and human metapneumovirus infections are not restricted to infants and children. A PCR assay detected RSV or, at lesser frequency, human metapneumovirus, in approximately one-fifth of adults with acute exacerbations of chronic obstructive lung disease. Metapneumovirus was detected as frequently as was influenza A virus (*ICAAC L-1582*).

The relative roles of direct cytotoxicity and the immune response in causing respiratory impairment in infants with RSV infection remains incompletely defined. In one study, the RSV load in respiratory secretions was shown to correlate with disease severity in previously healthy infants (*ICAAC V-788*).

An evaluation of 3 kits for rapid detection of RSV (Directigen RSV, Directigen EZ RSV, and Now RSV) found that all gave comparable results and performed well when compared to shell vial culture results (*ICAAC V-790*).

Hantavirus

A randomized trial of intravenously administered ribavirin to patients with hantavirus cardiopulmonary syndrome was discontinued because of slow enrollment. The investigators concluded, however, that ribavirin was probably ineffective in the treatment of this infection (*ICAAC V-482*).

Follow-up of survivors of hantavirus pulmonary syndrome found that one-third had significant sequelae. These included mild-to-moderate changes in pulmonary function. Eleven of 33 had developed late-onset progressive proteinuria. IgM antibody to hantaviruses disappeared by 12 months (*IDSA 843*).

Mimivirus

Mimivirus, an intra-amoebal organism, is a giant virus that can resemble small Gram-positive cocci. Its detection in bronchoalveolar lavage fluid of a patient with pneumonia, as well as serological studies in patients with pneumonia, implicate a mimivirus as a possible pathogen (*IDSA 102*).

Picornavirus

In a prospective study, 7 of 9 upper respiratory tract infections caused by picornaviruses were associated with an exacerbation of multiple sclerosis. This was true of only 2 of 12 ($P = .01$) infections in which picornavirus was not detected (*IDSA 735*).

SARS

Prolonged duration of exposure and proximity of contact increase the risk to health care workers of developing SARS. In Toronto, 8 of 32 (25%) nurses who entered a room with a SARS patient developed SARS; none died. The probability of a nurse developing SARS was 6% per shift worked. Being present at activities related to intubation increased the risk, and the use of a mask, particularly N95, was protective. Very few infections of health care workers were asymptomatic. A serological study of a large number of exposed health care workers found asymptomatic SARS CoV infection in < 2%. In one setting, however, none of 110 health care workers with a median 3 exposures each to 1 of 6 patients with confirmed SARS in the United States had serological evidence of SARS infection, despite the fact that a large proportion of the exposures were unprotected (*ICAAC K-1314, K-1315a, K-1315c, IDSA LB-17*).

Molecular testing of respiratory specimens from 117 California patients with pneumonia of unknown etiology who met CDC criteria for SARS during the time of the 2003 outbreak with pneumonia of unknown etiology yielded evidence of a pathogen in 24%. The vast majority of pathogens identified were influenza A virus. Influenza B was detected in 1, RSV in 4, and parainfluenza virus in 1. None had evidence of infection with the SARS coronavirus (*IDSA 101*).

In an evaluation of 117 hospitalized patients with SARS in the Toronto outbreak, SARS CoV RT-PCR on specimens from multiple sites was positive in only 54%, with the result more likely to be positive on days 9-11 than earlier. Stool and lower respiratory specimens were each positive in 63-65%. Convalescent serology became positive in 35 of 39 (90%) at a mean time of 26 days. A

separate Toronto study reported that stool specimens were positive as early as 3 days after onset of illness and persisted so for up to 44 days (*ICAAC V-488a, A-1367a, V-485b*).

In the absence of the availability of rapid diagnostic testing for SARS, a strategy was frequently adopted involving rapid testing for alternative causes of respiratory infection and assuming the absence of SARS if one of those tests was negative. Two studies that found a high frequency of coinfection in SARS patients make this strategy no longer tenable. Thirty-four percent of patients with laboratory-confirmed SARS studied in Toronto had evidence of coinfection with another respiratory pathogen. In a separate report, 32 of 111 (29%) Toronto patients with laboratory-diagnosed SARS had evidence of coinfection with another respiratory pathogen. This included 19% DNA or serology positive for *C pneumoniae*, 7% for *M pneumoniae*, and 1.8% with additional viral infection (*IDSA LB-16, ICAAC K-1315d*).

Nine Toronto SARS patients treated with Interferon Alfacon-1, a consensus interferon, and corticosteroids were compared to 13 controls given steroids alone in a nonrandomized manner. The interferon recipients had a shorter time to 50% resolution of chest x-ray abnormalities (4.0 vs 11.5 days) and shorter duration of needed supplemental oxygen therapy (*ICAAC K-1315e; JAMA. 2003;290:3222*).

Postmortem examination of 19 Toronto patients with SARS dying < 60 days after onset of illness found RT-PCR evidence of SARS CoV in the lungs of all. Also virologically positive were the liver (41%), spleen (53%), bowels (73%), lymph nodes (69%), and kidney (38%). All samples were negative in 1 patient who died > 100 days after onset. There was a significant relationship between the viral load in the lungs and the presence of multiorgan dissemination. There was no correlation between viral loads and the antemortem use of ribavirin or corticosteroids (*ICAAC K-1315b*).

Post-traumatic stress disorder was frequently observed in both patients who had recovered from SARS and their caregivers (*ICAAC K-750a, V-796a*).

Varicella Virus

In the United States, an estimated average of 2.6 million to 4.3 million cases of varicella occurred annually from 1970 to 1994. The estimated annual average incidence of herpes zoster over the same period, prior to the availability of the varicella vaccine beginning in 1995, was 263,724-448,331 (*IDSA 899*).

The estimated efficacy of varicella vaccine over 10 years of follow-up was 94.4% for those who received a single injection and 98.3% after 2 injections ($P < .001$). In settings of household exposure, varicella vaccination was > 95% effective in preventing moderate and severe disease and about 80% effective in preventing all disease. Varicella introduction by a vaccinated child was only approximately one-half as likely to be transmitted as that introduced by an unvaccinated child. Similarly, a case-control study combined with active surveillance found that the overall efficacy of varicella vaccine was 87% but decreased from 97% in the first year to 72% in the sixth year after vaccination. Disease was mild in 94% of vaccines and 64% of unvaccinated children (*IDSA 895, 900, 891*).

While breakthrough infections do occur in some varicella-vaccinated individuals, they are generally mild and limited. Follow-up of 7461 children 5 years after varicella vaccination given at 12-24 months of age detected a total of 1079 cases of breakthrough varicella infection, for an average annual incidence of 2.3 per 100 person-years. The average incidence of cases with > 50 lesions was only 0.47 per 100 person-years (*IDSA 892*).

Bacterial Infections

Paranasal Sinusitis

Treatment of patients with acute sinusitis with azithromycin 500 mg daily for either 3 or 6 days yielded similar rates of clinical efficacy. The end-of-treatment clinical response rates among patients with pretreatment sinus puncture cultures yielding *S pneumoniae* were 89% and 93%, respectively (*ICAAC L-1380*).

Eighty-seven percent of 71 patients with acute maxillary sinusitis or community-acquired pneumonia (CAP) from whom erythromycin-resistant *S pneumoniae* was isolated experienced clinical cure after treatment with telithromycin. The cure rate for all *S pneumoniae* infections was 93%. Similar cure rates were achieved regardless of the mechanism of macrolide resistance and included 3 of 3 patients with isolates containing *ermB* plus mefA (*ICAAC L-467*).

A pathogen was detected in sinus aspirates of 52% of 775 patients enrolled in a noncomparative open trial of treatment of acute bacterial sinusitis in adults with amoxicillin/clavulanate 2000 mg/125 mg given b.i.d. for 10 days. One-third (133 patients) of those with an identified pretherapy pathogen were infected with *S pneumoniae*, 19 of which had penicillin MICs of 2 to > 32 µg/mL. Amoxicillin MICs of 4 and 8 µg/mL were found for 4 and 2 isolates, respectively. The success rates at end of treatment and at follow-up for patients with pneumococcal infections were 93% and 96%, respectively (*IDSA 300*).

Treatment of patients compiled from 4 studies with acute sinusitis due to penicillin nonsusceptible *S pneumoniae* with amoxicillin/clavulanate 2000 mg/125 mg twice daily was associated with clinical success in 46 of 48 (96%), including 12 of 14 (86%) amoxicillin MICs of 4-8 µg/mL (*ICAAC L-1382*).

Streptococcal Pharyngitis

Fifteen of 17 (88%) children with acute uvulitis as evidenced by the presence of a beefy red swollen uvula, were found to be infected with Group A streptococci (*IDSA 783*).

Two separate meta-analyses of randomized trials found that the likelihood of bacteriologic eradication and of clinical cure was approximately twice as high in children, as well as in adults and adolescents, with Group A streptococcal tonsillopharyngitis treated with an orally administered cephalosporin compared with penicillin treatment. Nationwide, 5.4% of *S pyogenes* isolates were macrolide resistant in 2002-2003 (*ICAAC G-1546. L-1383, IDSA 210*).

Acute Exacerbations of Chronic Bronchitis/ Cystic Fibrosis

"Atypical pathogen" DNA was identified by PCR in the sputum of 14 of 161 (8.7%) patients with acute exacerbation of chronic bronchitis, including 7 with *Legionella pneumophila*, 4 with *Chlamydiophila pneumoniae*, and 2 with *Mycoplasma pneumoniae*. Separately, RSV or human meta-pneumovirus were detected in approximately one-fifth of patients with acute exacerbations of obstructive lung disease (*ICAAC L-1585, L-1582*).

In a randomized trial, amoxicillin/clavulanate 2000 mg/125 mg b.i.d. for 5 days was as effective as 875 mg/125 mg b.i.d. for 7 days in the treatment of patients with acute exacerbations of chronic bronchitis. Five-day treatment with moxifloxacin was superior to comparator agents (amoxicillin, clarithromycin, cefuroxime axetil) in patients with severe acute exacerbations of obstructive lung disease when the results of several randomized trials were combined for analysis (*ICAAC L-1592, L-1593*).

In a randomized trial, both meropenem/tobramycin and ceftazidime/tobramycin improved pulmonary status and reduced bacterial burden in patients with acute pulmonary exacerbations of cystic fibrosis. Significantly more children had improved airflow at 7 days in the meropenem/tobramycin group (*ICAAC L-1598*). ■

CME Questions

You no longer need to return a Scantron answer sheet to earn credit for the activity. Please review the text, answer the following questions, check your answers against the key, and then review the materials again regarding any questions answered incorrectly. ***To receive credit for this activity, you must return a CE/CME evaluation at the end of the testing term.***

13. The Staph-plus latex test reacts with which of the following?
a. *Candida krusei*
b. Oxidase
c. Fibrinogen
d. Clumping factor
e. Antibodies

14. A method with demonstrable efficacy for disinfecting a hospital water system colonized with *Mycobacterium avium* complex (MAC) is:
a. continuous chlorinization to 1 ppm.
b. raising the hot water temperature above 45° C.
c. copper-silver ion treatment.
d. None of the above

15. Which of the following is the principal benefit of oral corticosteroids for young children with viral respiratory infection-induced lower airway disease?
a. Decreased duration of fever
b. Decreased need for antibiotics
c. Decreased rate of hospitalization
d. Decreased need for mechanical ventilation
e. Decreased duration of symptoms

Answers: 13(d); 14(d); 15(e)

Readers are Invited

Readers are invited to submit questions or comments on material seen in or relevant to *Infectious Disease Alert*. Send your questions to: Christie Messina Petrone—Reader Questions, *Infectious Disease Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. ■

In Future Issues:

MRSA Carriage Among Hospital Employees and Their Families

UPDATES

By Carol A. Kemper, MD, FACP

Helicobacter and Your Gallbladder

Source: Silva CP, et al. *J Clin Microbiol*. 2003;41:5615-5618.

VARIOUS *Helicobacter spp.* HAVE been associated with hepatobiliary diseases in animals, including dogs, sheep, hamsters, and mice. In humans, *H pylori* has been isolated from the bile, liver, and biliary epithelium, raising questions about a possible association of *H pylori* and biliary disease. Silva and associates investigated the presence of *Helicobacter spp.*, using PCR, in the gallbladder epithelium and bile from patients (n = 46) with cholecystitis and/or cholelithiasis undergoing cholecystectomy, compared with a control group (n = 18) largely composed of liver transplant patients and patients undergoing surgery for obesity. Cholecystitis was confirmed on histopathological specimens from 28 (55%) patients. Of these, tests for *Helicobacter* DNA were positive in 15 (50%) gallbladder tissue samples and 7 (23%) bile specimens. Inflammation of gallbladder mucosa was visualized in 94% vs 37% of *Helicobacter* DNA-positive vs DNA-negative specimens, respectively. However, despite attempts to culture *Helicobacter* organisms for up to 3 weeks, none was isolated, although 80% of patients had received preoperative antimicrobacterials.

In univariate analysis, cholelithiasis was significantly associated with older age, female gender, and the presence of *Helicobacter* DNA in the gallbladder epithelium (no association was found with the presence of *Helicobacter* in bile). After adjusting for age, there was a strong statistically significant relationship between *Helicobacter* DNA found in gallbladder tissue and histological evidence of cholecystitis (P = .002). This data convincingly suggest that *H pylori* may play a significant role in the pathogenesis of gallbladder disease. It remains to be explained why women are at greater risk for cholecystitis, although I'm unaware of data suggesting a gender difference in the frequency of infection with *H pylori*. ■

Warning: Can Gardening be Hazardous to Your Health?

Source: ProMED-Mail Post. December 29, 2003; December 30, 2003; and January 3, 2004. www.promedmail.org.

ADDITIONAL CASES OF AN UNUSUAL species of legionellosis related to exposure to contaminated potting soil continue to be reported in Australia and New Zealand. Five new cases of pneumonia due to *Legionella longbeachae* occurred in December in Australia; 4 of the victims had recently used potting mixes made in that country. At least 49 cases of this type of pneumonia were reported to health authorities in Australia last year, including 2 deaths, plus additional cases in New Zealand. *L longbeachae* can be found in potting mixes, mulches, composts, and soils and has been previously linked to human disease in California, Oregon, and Washington, as well as in Japan. Symptoms occur within 2-10 days of exposure and range from mild cough, headache, muscle aches, and diarrhea to potentially fatal pneumonia.

Gardeners are advised to use caution when using potting mixes. Open bags outdoors or in a well-ventilated room, wear a mask and gloves, moisten the contents of the bag to limit dust before use, and wash hands thoroughly when done. ■

Sylvester Shares His *Salmonella*

Source: ProMED-Mail Post. February 2, 2004. www.promedmail.org.

A FEW YEARS AGO, WE REPORTED in this column the occurrence of human infection from *E coli* 0157 from exposure to a pet dog fed undercooked hamburger meat.

The Idaho Humane Society in Boise has similarly been linked to 10 cases of human *Salmonella* infection, which has been traced back to cats and kittens housed at the facility. The health epidemiologist tracking the cases was quoted as saying that "18% of the cat population has *Salmonella* at any given time." Although this figure seems alarmingly high (especially to a cat owner), it is probably dependent on a number of factors, especially living circumstances and diet. Stray cats (and by extension, cats that spend a good deal of time outdoors) are more likely to be infected with *Salmonella*, where their diets may consist of birds, small snakes, and lizards, compared with their indoor counterparts. Dogs and cats fed raw or undercooked eggs or chicken may also be at risk for *Salmonella*, which spreads to their owners. ■

Combination Therapy for Bacterial Endocarditis

Source: Le T, Bayer AS. *Clin Infect Dis*. 2003;36:615-621.

THIS SUCCINCT ARTICLE NICELY summarizes the evidenced-based recommendations for combination antimicrobial therapy for infective endocarditis (IE) due to common pathogens, including newer data and recommendations. Le and Bayer make the point that, despite advances in echocardiography, surgical techniques, and newer antimicrobials, mortality rates due to IE from viridans streptococci, staphylococci, and enterococci are still in the range of 4-16%, 25-47%, and 15-25%, respectively. Mortality rates for prosthetic valve IE (PVE) may be higher. These figures are likely to worsen with the increasing frequency of penicillin-, aminoglycoside-, and vancomycin-resistant enterococci, and methicillin-resistant staphylococci. Most available synergy data are limited, except for EI due to *Enterococcus*, although there is still no universally accepted methodology for demonstrating in vitro synergy.

Enterococcus

For aminoglycoside-sensitive strains, clinical data suggest that shorter courses of aminoglycoside (2 weeks) may preserve clinical efficacy (~81%) and limit toxicity, especially in older patients. Reducing the time interval between each aminoglycoside dose reduces in vivo efficacy. Maintaining sustained penicillin (or ampicillin) concentrations plus the use of either 3 µg/mL or 5 µg/mL of gentamicin was synergistic, thereby limiting nephrotoxicity. For aminoglycoside-resistant strains, several in vitro and in vivo studies have demonstrated an enhanced bactericidal synergistic effect with combinations of ampicillin and third-generation cephalosporins. Using a combination of ampicillin and cefotaxime, MICs for 48 of 50 strains of high-level aminoglycoside-resistant enterococci were reduced from 0.25-1.0 to 0.01-0.25. Similar results using this combination were obtained in a rabbit aortic valve model, although only when lower levels of amoxicillin were used. Combined imipenem-imipenem was bactericidal in vivo against vancomycin-aminoglycoside-resistant strains. Ampicillin-ceftriaxone combinations were synergistically effective but again only at lower levels of ampicillin. However, the dose of ceftriaxone used was quite high (4 gm/d), in order to ensure sustained high levels.

Staphylococcus

Combination of cell wall active agents with either rifampin and/or aminoglycoside may be synergistic, although the mechanism is poorly defined, the data are somewhat conflicting, and, in some circumstances, the addition of rifampin may be antagonistic. However, clinical data in PVE (most of which was due to CNS) suggest that the addition of rifampin and/or aminoglycoside to either vancomycin or a cell wall active agent improves efficacy. Using vancomycin alone, clinical cures were ~81% but increased to 90% with the addition of rifampin and/or an aminoglycoside. In PVE due to high-level aminoglycoside-oxacillin-resistant isolates of CNS, a combination of vancomycin, gentamicin, and rifampin was synergistic against 7 of 10 isolates.

Viridans Group *Streptococcus*

For penicillin-susceptible isolates, the addition of streptomycin was not found to be better than PCN G or ceftriaxone alone. A number of studies have confirmed that short courses of aminoglycosides (2 weeks) allows the reduction in total therapy from 4-6 weeks to 2 weeks. A recent study found that a 2-week course of ceftriaxone plus once-daily gentamicin was similar to a 4-week course of ceftriaxone alone (clinical cures ~96%). The dose of gentamicin (~3 mg/kg) needed for synergy is less than that required for Gram-negative infection. The recommendations for penicillin-resistant VGS strains (MIC to PCN > 0.1 to < 0.5 µg/mL) remain 2 weeks of combined gentamicin plus PCN G or ampicillin, followed by 2 weeks of PCN G or ampicillin alone. For those strains with an MIC to PCN > 0.5 µg/mL, > 4 weeks of combined PCN G or ampicillin plus gentamicin should be used, similar to that recommended for *Enterococcus*. However, clinicians should be aware that there are no good clinical trial data to support these recommendations. ■

PHARMACOLOGY WATCH

Estrogen Found to Not Affect Heart Disease, Breast Cancer

The NIH has halted the estrogen-alone wing of the Women's Health Initiative (WHI) a year before its scheduled end. The 11,000 postmenopausal women who have had a hysterectomy and were enrolled in the estrogen-alone trial recently received a letter informing them of the preliminary results of the study and asking them to stop their study medication. After nearly 7 years of follow-up it appears that estrogen alone does not affect the rates of heart disease or breast cancer (either positively or negatively), both key findings of the estrogen/progesterone wing of the study, which was halted in July 2002. The researchers did find, however, that estrogen alone led to a slightly higher incidence of stroke (8 per 10,000), similar to the rate found in the estrogen/progesterone wing. Estrogen alone was also found, however, to decrease the risk of hip fracture. The NIH statement also says that older women (65 and older) showed a trend toward increase risk of probable dementia or mild cognitive impairment with estrogen-alone treatment. All of the women in the study were taking Wyeth & Co.'s conjugated estrogen product, Premarin. The full results of the trial will be published in a major peer-reviewed journal in the next 2 months. The NIH statement concurs with the guidance from the FDA, which states that hormone use should be limited to treatment of moderate-to-severe menopausal symptoms, vulvovaginal atrophy, and prevention of osteoporosis (as a second-line drug). The NIH statement is available on its web site at www.nih.gov/news.

Antibiotics Associated With Cancer Risk

Is antibiotics use associated with an increased risk of breast cancer in women? The question, which was first raised decades ago, has been the subject of much debate, but now a new study suggests that the answer may be yes. Researchers looked at data from more than 10,000 female members of the Group Health Cooperative in Washington state and identified 2266 women with invasive breast cancer and 7953 randomly selected controls without breast cancer. The variable evaluated was cumulative days of antibiotic use over the study period from January 1993 to June 2001. Increasing cumulative days of antibiotic use was associated with increased risk of breast cancer. The categories were 0 days, 1-50, 51-100, 101-500, 501-1000, and > 1001 days. The odds ratios (95% CI) for breast cancer were, respectively, 1.00 (reference), 1.45 (1.24-1.69), 1.53 (1.28-1.83), 1.68 (1.42-2.00), 2.14 (1.60-2.88), and 2.07 (1.48-2.89) ($P < .001$ for trend). Increased risk was seen in all antibiotic classes, including women taking tetracycline or macrolides for treatment of acne or rosacea. After adjusting for age, length of enrollment, and use of postmenopausal hormones, the death rate from breast cancer also increased with cumulative days of antibiotic use. The authors conclude that use of antibiotics was associated with an increased risk of incidence of breast cancer and death from breast cancer; however, it cannot be determined

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from the study whether antibiotic use is causally related or whether the indication for use of antibiotics was the primary factor (*JAMA*. 2004; 291:827-835). The link between antibiotics for breast cancer is plausible since antibiotics affect intestinal microflora, thus affecting phytochemical metabolism in the gut. Phytochemicals are thought to play an inhibitory role in the carcinogenesis pathway. Antibiotics also affect immune and inflammatory responses, which may lead to mammary carcinogenesis. An accompanying editorial reviews the possible mechanisms of the antibiotic/breast cancer connection and suggests that this study provides more questions and answers but that further research is needed. In the mean time, antibiotic use in women should be scrutinized, especially when other treatment options are available (*JAMA*. 2004;291:880-881).

Topiramate Effective Against Migraine

Topiramate is an effective agent for migraine prevention, according to a new double-blind study of 483 migraine patients. The drug, which is approved for prevention of seizures, was used in maximal doses of 50, 100, or 200 mg for 18 weeks in patients aged 12-65, who had at least a 6-month history of migraine and averaged 3-12 migraines per month. Mean monthly migraine frequency decreased significantly in the 100-mg ($P = .008$) and 200-mg ($P \leq .001$) doses, and the benefit was seen within the first month of therapy. Migraine days and use of rescue medication were also significantly reduced in the 100-mg and 200-mg groups. Adverse events included paresthesia, fatigue, and nausea (*JAMA*. 2004;291:965-973). Johnson & Johnson has already received conditional approval from the FDA for topiramate for the indication of migraine prevention pending additional safety information.

Statin Therapy For Heart Failure

Statin therapy has been found to be beneficial for a number of chronic illnesses; now add 2 more to the list. Statins have been found to benefit patients with advanced ischemic and non-ischemic heart failure. Researchers from UCLA reviewed the records of 551 patients with systolic heart failure with ejection fractions of 40% or less. After risk adjustment, statin use was associated with improved survival without the necessity of urgent transplantation in both non-ischemic and ischemic heart failure patients (91% vs 72% [$P < .001$] and 81% vs 63% [$P < .001$], at 1-year follow-up, respectively) (*J Am Coll Cardiol*. 2004;43:642-648). A new, large, randomized trial shows statins may also reduce the risk of stroke. As part of the Heart Protection Study in the United Kingdom, 3280 adults with cerebrovascular disease and an additional 17,256 patients with other occlusive arterial disease or diabetes were randomized to simvastatin 40 mg per day or placebo. Over the 5-year treatment period, there was a significant 25% proportional reduction in the rate of first stroke (4.3% simvastatin vs 5.7% placebo; $P < .0001$). The entire benefit was found in reduction in ischemic stroke. There was no difference found in the rate of hemorrhagic stroke, either increase or decrease. Simvastatin also reduced the number of TIAs ($P = .02$) and requirement for carotid endarterectomy or angioplasty ($P = .0003$). Among patients with pre-existing cerebrovascular disease, there is no apparent reduction in the stroke rate, but there was a highly significant 20% reduction in the rate of any vascular event ($P = .001$). Interestingly, benefit was seen in all levels of LDL, even in patients with LDL levels less than 116 mg/dL. The authors conclude that statin therapy reduces the risk of ischemic stroke by one-quarter to one-third in these at-risk patients (*Lancet*. 2004;363:757-767).

FDA Actions

The consumer watchdog group Public Citizen is calling for the FDA to ban AstraZeneca's new statin, rosuvastatin (Crestor), because of the risk of myositis and rhabdomyolysis. The drug, which was introduced to the American market in September, has been associated with 7 cases of rhabdomyolysis, 9 cases of renal failure, and 1 death. Myositis is a class affect of statins, especially the high-potency statins like Crestor. AstraZeneca states that the drug has been used in more than 1 million patients and that its benefits outweigh the risks. The FDA banned Bayer's cerivastatin (Baycol) in 2001 because of more than 100 deaths associated with the drug due to rhabdomyolysis.

Drug Approved to Target Angiogenesis

The FDA has approved the first monoclonal antibody that targets tumor angiogenesis. Genentech's bevacizumab (Avastin) is approved for the treatment of metastatic colorectal cancer. The drug works by binding vascular endothelia growth factor, thus inhibiting the formation of new blood vessels in tumors. In clinical trials the drug was found to extend survival time in patients with metastatic colorectal cancer by several months. ■