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INSIDE

Financial Disclosure:

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HPV Infection in Men

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor of Medicine, Stanford University School of Medicine

Dr. Winslow serves as a consultant for Siemens Diagnostics, and is on the speaker's bureau for Boehringer-Ingelheim and GSK.

Synopsis: *Genital HPV infection is common, and is often found at multiple sites in young heterosexual men. Risk factors for HPV infection in men include number of female sex partners (FSP), condom use, and smoking. Multiple anatomic sites should be sampled in heterosexual men to optimize detection of HPV.*

Sources: Partridge JM, et al. Genital human papillomavirus infection in men: Incidence and risk factors in a cohort of university students. *J Infect Dis*. 2007;196:1128-1136; Nielson CM, et al. Risk factors for anogenital human papillomavirus infection in men. *J Infect Dis*. 2007; 196:1137-1145; Giuliano AR, et al. The optimal anatomic sites for sampling heterosexual men for human papillomavirus (HPV) detection: The HPV detection in men study. *J Infect Dis.* 2007;196:1146-1152.

THESE THREE STUDIES PUBLISHED BACK TO BACK IN JID SERVE TO better characterize HPV infection in heterosexual men. The first study from the group in Seattle followed a cohort of 240 heterosexually-active male university students from 2003 until 2006 and obtained genital samples at 4-month intervals for HPV-DNA analysis by PCR while the students maintained a web-based log of their sexual activity. By 24 months, the cumulative incidence of new infection with HPV was 62.4%. Report of a new sex partner in the preceding 8 months approximately doubled the relative risk of acquiring infection. A history of smoking increased the risk of acquiring infection with HPV by a factor of 1.6.

The second study conducted under CDC auspices recruited 463 men 18-40 years old from Tucson and Tampa and also used HPV detection by PCR and completion of a self-administered questionnaire at one time point only. Prevalence in this slightly

VOLUME 27 • NUMBER 3 • DECEMBER 2007 • PAGES 25-36

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older population of HPV infection of any type was 65.4%, 29.2% for oncogenic types, and 36.3% for non-oncogenic types. Lifetime and recent number of Femme Sex Partners (FSPs), condom use, and smoking were modifiable risk factors associated with HPV infection.

The third paper was a more in-depth analysis of technical factors associated with detection of HPV DNA derived from the dataset of the CDC study described above. Bottom line results from this study demonstrated that, at minimum, the penile shaft and glans penis/coronal sulcus should be sampled in heterosexual men, and that for optimal detection, scrotal, perianal and anal samples should be obtained as well.

COMMENTARY

Beginning in the 1970s, the association between oncogenic types of HPV infection and cervical cancer became well established. By the 1990s, increasingly sensitive molecular diagnostic techniques were available for the detection and typing of HPV in clinical samples. Appropriately, these techniques were generally initially applied in the clinical setting in young women. While genital malignancy can be associated with HPV infection in heterosexual men, HPV infection in men is mainly of importance to the extent that men provide a reservoir of infection and their sexual behavior affects women's risk of cervical cancer. Previously available information regarding penile HPV infection has been limited by the fact that it was derived from 3 sources: 1) studies of male partners of women with cervical cancer; 2) small cross-sectional studies of select populations such as men being treated for STDs or military recruits; or 3) small prospective studies.

The 3 studies described above greatly expand our knowledge of the true prevalence of HPV infection in men and our understanding of risk factors for acquisition. The high rates of HPV infection in men should be considered when developing strategies for the prevention of HPV infection in female adolescents and young women.

While not addressed in these studies, the state of knowledge regarding the natural history of anorectal HPV infection in gay/bisexual men is very limited as well. Despite the increasing acceptance of periodic performance of anorectal Pap smears in this population (especially in the San Francisco Bay Area), the utility and cost effectiveness of this practice remains unestablished, and will remain so until larger and more in depth studies of HPV infection anorectal cancer are made in gay men as well. ■

Infectious Disease Alert, ISSN 0739-7348, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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MANAGING EDITOR: Leslie Hamlin

GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.
POSTMASTER: Send address changes to *Infectious Disease Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $21.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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New Recommendations for the Prevention of Hepatitis A

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Synopsis: *Recent evidence demonstrate the efficacy of hepatitis A vaccination has let changed recommendations for its use.*

Sources: Victor JC, et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. *N Engl J Med*. 2007;357:1685-1694; CDC. Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the Advisory Committee on immunization practices (ACIP). 2007;56: 1080-1084. Available at http://cdc.gov/mmwr/preview/mmwrhtml/mm5641a3.htm/.

PREVIOUSLY, THE RECOMMENDATION IN THE UNITED States for post-exposure prophylaxis of hepatitis A virus (HAV) infection has consisted of the administration of a single dose of immune serum globulin (ISG). While some other countries recommended the use of HAV vaccine for this purpose, the evidence to support this stance had been judged to be inadequate.

New data, however, have now led to a change in recommendations in the United States.

Victor and colleagues randomized household and day-care center contacts of individuals with acute hepatitis A virus (HAV) infection who were 2 to 40 years of age to receive, within 14 days after exposure, either a single dose of HAV vaccine or of immune serum globulin. Of the 1414 subjects who were susceptible to HAV infection, 1090 were included in the final analysis of this study performed in Kazakhstan. The mean age of the subjects was 12 years and the mean interval from exposure to prophylaxis receipt was 18 days.

Laboratory-confirmed symptomatic HAV infection occurred in 25 (4.4%) of the vaccine recipients and in 17 (3.3%) of those given SIG (relative risk, 1.35; 95% CI, 0.70 to 2.67), thus meeting pre-set criteria for non-inferiority of vaccine prophylaxis. It is noted by the Victor et al, however, that at all study points examined, infection rates for vaccine recipients were higher than those observed in those given ISG. Nonetheless, "the risk of infection in the vaccine group was never more than 1.5% greater than that in the immune globulin group." These results have led to a change in the APIC and CDC recommendations for postexposure prophylaxis of HAV infection, as well as for prophylaxis in the international traveler, as discussed below.

COMMENTARY

The results of this randomized trial fill in a data gap, which has allowed the CDC, upon the advice of APIC, to provide updated recommendations. It must be stressed, however, that the changes only strictly apply to the age cohort included in the study, those 2- to 40-years-old. There in no comparably reliable data that might apply to younger or older individuals, or to individuals who are immunocompromised. As a consequence, the recommendations state that "decisions to use vaccine or SIG should take into account patient characteristics associated with more severe manifestations of hepatitis A, including older age and chronic liver disease." It must also be recognized that, although vaccination efficacy was not inferior to that of ISG, according to preset criteria, the overall data did suggest that ISG "performed modestly better than vaccine." Nonetheless, the drawbacks to ISG use, including the temporary nature of the protection provided, the pain associated with injecting the large volume often required, limitations in product supply, and the concerns of some about safety, make the vaccine an attractive alternative.

Table 1

Summary of updated recommendations for prevention of hepatitis A after exposure to hepatitis A viru (HAV) and in departing international travelers

Postexposure prophylaxis

Persons who recently have been exposed to HAV and who previously have not received hepatitis A vaccine should be administered a single dose of single-antigen hepatitis A vaccine or immune globulin (IG) (0.02 mL/kg) as soon as possible.

- For healthy persons aged 12 months-40 years, single-antigen hepatitis A vaccine at the age-appropriate dose is preferred.
- For persons aged > 40 years, IG is preferred; vaccine can be used if IG cannot be obtained.
- For children aged < 12 months, immunocompromised persons, persons who have had chronic liver disease diagnosed, and persons for whom vaccine is contraindicated, IG should be used.

International travel

All susceptible persons traveling to or working in countries that have high or intermediate hepatitis A endemicity should be vaccinated or receive IG before departure. Hepatitis A vaccine at the age-appropriate dose is preferred to IG. The first dose of hepatitis A vaccine should be administered as soon as travel is considered.

- One dose of single-antigen hepatitis A vaccine administered at any time before departure can provide adequate protection for most healthy persons.
- Older adults, immunocompromised persons, and persons with chronic liver disease or other chronic medical conditions planning to depart to an area in ≤ 2 weeks should receive the initial dose of vaccine and also simultaneously can be administered IG (0.02 mL/kg) at a separate anatomic injection site.
- Travelers who elect not to receive vaccine, are aged 12 months, or are allergic to a vaccine component should receive a single dose of IG (0.02 mL/kg), which provides effective protection for up to 3 months.

NOTE: Previous recommendations remain unchanged regarding 1) settings in which postexposure prophylaxis is indicated; and 2) timing of administration of postexposure prophylaxis.

Source: http://cdc.gov/mmwr
Accessed: November 21, 2007

The bottom line is that the updated recommendations state that "Persons who recently have been exposed to HAV and who have not previously received hepatitis A vaccine should be administered a single dose of single-antigen vaccine or SIG 90.02 mL/kg) as soon as possible." Note the stress on the "single-antigen vaccine" — this is a consequence of a lack of data regarding the efficacy of the HAV-HBV combined vaccine, which contains a smaller amount

of HAV antigen. For those 12 month to 40 years of age, "single-antigen hepatitis A vaccine, at the age-appropriate dose, is preferred to IG." For those > 49 years of age, IG is preferred. IG should be used for children < 12months of age, immunocompromised persons, persons with known chronic liver disease, and in those in whom the vaccine is contraindicated. The efficacy of either vaccine or ISG, when administered more than 2 weeks after exposure, remains unknown.

The standard recommendation for travelers to countries with high or intermediate HAV endemicity has been the administration of the vaccine. However, it was also recommended that individuals traveling to an area of high endemicity less than 4 weeks after the initial vaccine dose also be considered for receipt of ISG. The updated recommendations now state that hepatitis A single-antigen vaccine alone can be recommended for travelers < 40 years of age at any time prior to departure. For optimal protection, older adults, immunocompromised individuals, and those with chronic medical conditions, including chronic liver disease, should also receive ISG (0.02 mL/kg) at a separate injection site. For those < 12 months of age, or those who refuse vaccine or are allergic to it, a single dose of SIG will provide protection for up to 3 months. If travel is to last > 2 months, the dose of SIG should be 0.06 mL/kg, and dosing should be repeated if travel time exceeds 5 months. ■

Multi-Faceted Approach to Hypervirulent *C. difficile* Control

ABSTRACT & COMMENTARY

By Robert Muder, MD
Hospital Epidemiologist, Pittsburgh VA Medical Center
Dr. Muder does research for Aventis and Pharmacia

Synopsis: *Early identification, coupled with appropriate control measures, reduces the rate of C. difficile infection and the frequency of adverse events.*

Source: Muto CA et al. Control of an outbreak of infection with the hypervirulent *Clostridium difficile* BI strain in a university hospital using a comprehensive "bundle" approach.

BEGINNING IN 2000, THE UNIVERSITY OF PITTSBURGH Medical Center (UPMC) Presbyterian experienced a marked increase in hospital-acquired *C. difficile* infection, from 2.7 infections per 1000 discharges (0.46 per 1000 patient days) in the 2 preceding years to 7.2 per 1000 discharges (1.17 per 1000 patients days). Concurrently, there was an increase of severe *C. difficile*-associated disease, defined as that resulting in colectomy or death from 0.15 cases per 1000 discharges to 0.60 per 100 discharges. REA typing of *C. difficile* isolates collected in 2001 showed that 51% were of 2 highly related types. Further testing of these isolates by the CDC showed that they were the hypervirulent BI strain.

Beginning in June 2000, the Infection Control Team, in cooperation with other relevant hospital departments, initiated a series of interventions aimed at reducing *C. difficile* transmission and use of antimicrobials associated with in increased risk of *C. difficile* disease. Interventions included institution of a standardized education module, increased case surveillance, and a *C. difficile* management team that evaluated patients for illness severity and appropriate treatment. Specific infection control measures included environmental cleaning with dilute bleach, electronic alerts, hand hygiene with soap and water, and infection control audits of isolation practices. In addition, the duration of patient isolation was extended from the previous end point of cessation of diarrhea to the duration of hospitalization.

A targeted antimicrobial restriction initiative began in October 2002. The targeted antimicrobials were those that a previous investigation had shown to be associated with increased risk of *C. difficile* infection in that facility.[1] These included fluoroquinolones, ceftriaxone, and clindamycin.

There was a gradual decrease in hospital-acquired *C. difficile* infection. By 2006, the rate had declined to 3.0 per 1000 hospital discharges (0.46 per 1000 patient days). The rate of severe disease declined dramatically to 0.03 per 1000 hospital discharges. Use of targeted antimicrobials decreased by 54%. In a second survey of *C. difficile* conducted in 2005, 13.5% contained BI strain.

■ COMMENTARY

C. difficile is a common hospital-acquired pathogen that leads to significant morbidity and

occasional mortality. There is mounting evidence that the severity of *C. difficile* disease is increasing, most likely due to an increasing prevalence of a particularly virulent strain, identified as BI. This strain has a gene deletion, leading to hyperproduction of *C. difficile* toxins A and B. In addition, it produces a novel binary toxin;[2] the majority of reported isolates have been resistant to fluoroquinolones. It is likely that both the increasing frequency and severity of *C. difficile* infection at UPMC-Presbyterian was associated with the introduction of this strain into the medical center, since the majority of stains analyzed in 2001 were of this type. Dissemination of BI strains has been associated with widespread outbreaks of severe *C. difficile* disease in both the United States[2] and Canada[3].

The multi-faceted assault on *C. difficile* reported by Muto and colleagues was followed by both a significant reduction in disease incidence and disease severity. It's likely that control was the result of both the efforts to reduce transmission, such as case identification, isolation, and environmental cleaning, and the control of antimicrobial use.

As with many reports of successful programs directed against hospital-acquired infection, one is not able to assess the relative importance of individual interventions. They were introduced step-wise, and the decrease in *C. difficile* disease was gradual. However, insistence on purity of study design, during an epidemic in which major surgical procedures or death are potential outcomes, is a luxury that Infection Control programs don't have in the real world. ■

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Resolution of Chest X-ray Abnormalities for Pneumonia

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *Two hundred eighty-eight patients hospitalized with severe community-acquired pneumonia (CAP) were followed for 28 days in a prospective multicenter study. At day 7, 25% of patients had resolution of CXR abnormalities and 56% had improvement. At day 28, 53% of patients had resolution of CXR abnormalities and 78% had clinical cure. By multivariate analysis, delayed resolution of CXR abnormalities by day 7 was associated with multilobar disease, dullness to percussion by physical exam, elevated CRP (> 200 mg/L), and tachypnea (respiratory rate > 25/min.) on admission.*

Source: Bruns AHW, et al. Patterns of resolution of chest radiograph abnormalities in adults hospitalized with severe community acquired pneumonia. *Clin Infect Dis*. 2007;45: 983-991.

THIS INTERESTING STUDY FROM THE NETHERLANDS prospectively evaluated 288 consecutive patients with severe CAP (ATS pneumonia severity index > 90) admitted to the hospital on which clinical data and CXR's were available at admission, day 7, and day 28. Mean age of patients was 69.7 years and 53.5% had comorbid conditions, including CHF, underlying neoplasm, cerebrovascular diseases, and renal disease. Of these patients, 21.5% had microbiologically-documented infection with pneumococcus, 9.7% had infection with an atypical pathogen, 51.4% had pneumonia of unknown etiology, 3.8% had infection with multiple pathogens, and 17.4% had infection with other pathogens, including gram-negative enteric organisms, or Pseudomonas, *S. aureus*, *H. influenzae*, or *M. catarrhalis*. 20 (6.9%) of the patients died.

Univariate analysis for delayed resolution of CXR abnormalities at day 28 showed the following parameters to be correlated: higher PSI, *S. pneumoniae* infection, multilobar pneumonia, PCO_2 < 30 mm Hg, CRP > 200 mg/L, and BUN > 10uM on admission. By multivariate analysis, delayed resolution of CXR abnormalities by day 28 was associated only with CRP > 200 mg/L on admission.

■ COMMENTARY

My experience in several large teaching hospitals

over the last 20 years is that patients admitted with pneumonia often are subjected to routine daily CXR's during the first few days in the hospital and generally every 3 days or so until hospital discharge, despite the presence of clinical improvement. This large, prospective, multicenter study conducted in immunocompetent adult patients hospitalized with CAP shows that only one-quarter of the patients resolved their CXR abnormalities by day 7 and only approximately one-half did so by day 28. This study clearly suggests that frequent CXR's obtained prior to hospital discharge, in patients who are clinically improving, are unnecessary and unlikely to be useful. The study also suggests that one of the "old saws" many of us were taught during our Internal Medicine training (without any literature support) in the 1970s, which recommended deferring aggressive work-up of persistent radiographic abnormalities following CAP unless those abnormalities persisted beyond 6 weeks, was correct. While not specifically addressed in this study, it is likely that an interval as long as 8-12 weeks following an episode of CAP seems to be reasonable before performing follow-up radiography (including thoracic CT scans) or bronchoscopy to exclude noninfectious causes of persistent CXR abnormalities. ■

Here We Go Again! Adenovirus 14: Another Emerging Pathogen

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Synopsis: *Adenovirus 14 has emerged as a cause of severe respiratory infections in the United States.*

Source: CDC. Acute respiratory disease associated with adenovirus serotype 14 — four states, 2006-2007. MMWR 2007; 56:1181-1184.

The death of a 12-day-old infant in New York City in May of 2006 was found to have been due to adenovirus serotype 14. Almost a year later, in April of 2007, the Oregon Public Health Division was notified of the occurrence of a number of cases of severe adenovirus pneumonia at a single hospital., leading to a retrospective examination of reports from several clinical laboratories in the state. This led to the identification of a total 68 patients with a positive test for adenovirus infection from November 2006 through April 2007. Of the 50 isolates available for testing, 31 (62%) were identified as serotype 14. Medical records of 30 patients with adenovirus 14 infection were available for review; the median age of the patients was 53.4 years (range, 2 weeks to 82 years); 73% were male. Approximately one-fifth occurred in children < 5 years of age, while all the remainder occurred in individuals > 18 years of age. Three-fourths were hospitalized, and one-half of the total required intensive care. Seven patients (23%) died. No epidemiological factors linking patients was identified. A comparison with 12 patients with adenovirus infection not due to serotype 14 found their median age was only 1.1 years, and only 2 required hospitalization, none in the ICU; none died.

In another occurrence, four residents of the same unit of a residential care facility, 3 with chronic obstructive lung disease and one with AIDS, were hospitalized with pneumonia due to adenovirus in May 2007; all 3 isolates available for testing were found to be serotype 14. Three patients required mechanical ventilation and one (the AIDS patient) died. No cases were identified in other residents or in staff.

A large outbreak of adenovirus in basic military trainees at Lackland Air Force Base in Texas began in early 2007, resulting in 27 pneumonia hospitalizations; 5 patients required ICU care and one died. Six of 218 health care workers (3%) had laboratory evidence of adenovirus 14 infection; 5 had had direct contact with at least one of the hospitalized patients. Cases have continued to occur among trainees, with 55 having onset during the week of September 23-29.

■ COMMENTARY

Adenovirus is a non-enveloped, double-stranded DNA virus with 51 known serotypes. In addition to causing both lower and upper respiratory tract infections, it is a common cause of conjunctivitis (with most cases caused by serotypes 8, 19, and 37), gastroenteritis (types 40 and 41), and may also cause urinary tract infection (particularly in transplant patients). While cases occur throughout the year, there is a predominance of cases in the winter and spring.

While adenovirus 14 was first described in 1955, it has only been infrequently identified since an outbreak in military recruits in Spain in 1969, except for a report

of infection in children in Taiwan in 2001-2002. Restriction enzyme analysis of viral genomic DNA has demonstrated that the type 14 strains from 3 military training camps belong to a novel subtype named 14a.[1] The viral fiber protein contains cell receptor binding sites, and changes in these sites can alter adenovirus tissue tropism. In fact, when compared to a prototype type 14 strain, 14a has been found to have a deletion in the knob region of the fiber protein,[1] a change that may have contributed to the changing epidemiology and, possibly, virulence of this virus.

Evidence from a survey of adenovirus isolates from 22 medical facilities in the United States from 2004-2006 suggests a very recent change in the epidemiology of adenovirus infections.[2] In this study of 2237 isolates utilizing hexon gene sequencing, adenovirus type 14 was not among the 8 most frequently identified types. Only 3 (0.3%) cases of type 14 infection were identified among 936 nonimmunocompromised children < 7 years of age, and none were detected in 123 immunocompromised individuals of any age. There was, instead, a statistically significant increasing trend of detection of adenovirus type 21 over the time of the study. Multivariate analysis identified the following as independent risk factors for severe infection: age < 7 years, underlying chronic disease, recent transplantation, and adenovirus type 5 or type 21 infection — not type 14 infection.

Nonetheless, this report from the CDC makes it apparent that we are witnessing yet another evolutionary microbial event with the emergence of a strain of adenovirus which has caused severe disease in widespread geographic areas in the United States. This highlights the importance of the incorporation of effective viral diagnostics in the care of patients with infections, something that is sorely lacking at many health care facilities. ■

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Invasive Aspergillosis in the ICU

ABSTRACT & COMMENTARY

By David J. Pierson, MD

Professor, Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington

Dr. Pierson reports no financial relationship relevant to this field of study.

This article originally appeared in the October 2007 issue of Critical Care Alert. It was peer reviewed by William Thompson, MD. Dr. Thompson is Staff Pulmonologist, VA Medical Center; Associate Professor of Medicine, University of Washington. Dr. Thompson reports no financial relationship relevant to this field of study.

Synopsis: *With better immunosuppressive therapy and ICU care, invasive aspergillosis is being encountered more often. Making the diagnosis is challenging, especially in lower-risk patients, such as those with COPD and cirrhosis. Despite availability of effective new antifungal agents with less toxicity than amphotericin B, the effectiveness of these drugs in critically ill patients is uncertain, and the prognosis remains poor.*

Source: Meersseman W, et al. Invasive aspergillosis in the intensive care unit. *Clin Infect Dis.* 2007;45: 205-216.

MEERSSEMAN AND COLLEAGUES AT GASTHUISBERG University Hospital in Leuven, Belgium, have extensive experience in studies of invasive aspergillosis (IA) in critically ill patients, including those without the traditional risk factors.[1] In this comprehensive review, Meersseman et al summarize current knowledge of the risk factors, clinical manifestations, available diagnostic techniques, and treatment of IA, focusing on patients in the ICU.

In the general inpatient hospital population, invasive fungal infections have become more prevalent during the last 10-15 years. Much of this increase is accounted for by IA, although few data on IA, specifically in critically ill patients, have been published. Patients with neutropenia (less than 500 neutrophils/mL) are at the highest risk for IA, as are those with hematologic malignancies and allogeneic bone marrow transplants. However, categories of patients who are at lower, but still substantial risk, have increasingly been identified. These include those with prolonged treatment with corticosteroids prior to ICU admission, and patients with solid-organ cancer, HIV infection, lung and autologous

bone marrow transplantation, and systemic diseases requiring immunosuppressive therapy. Also recognized as being at increased risk for IA are patients with COPD and cirrhosis, particularly in the latter case if they have been in the ICU for more than one week. Patients at relatively lower risk for IA include those with burns, other solid-organ transplants (ie, kidney, heart, or liver), prolonged ICU stays, malnutrition, and treatment with corticosteroids for one week or less.

Because of increased awareness of the possibility of invasive fungal infections in ICU patients who are being evaluated for prolonged fever or pulmonary infiltrates, it has become commonplace to send sputum, blood, and other microbiology specimens for fungal culture, as well as for routine bacteriology. In an attempt to improve the efficiency of the microbiology services in their hospital, Bouza and colleagues evaluated 404 isolates of *Aspergillus fumigatus* in 260 patients, 37% of whom were in ICUs or special hematology wards.[2] In their study, *A. fumigatus* was isolated 2.1 times per 1,000 admissions, and one time per 1,000 microbiology samples, representing 5.6% of the total fungal isolations during the 3-year study period. Bouza et al used clinical information about the patients, as well as positive cultures to derive a predictive model for the probability of their having IA.

In their study of 102 patients with positive cultures for aspergillus in their medical ICU,[1] Meersseman et al found that almost all of them had required mechanical ventilation. Of the 56 patients with IA (26 with underlying hematological malignancy and 30 without malignancy), more than half had evidence of IA at the time of ICU admission. Individual case reports suggest that some patients acquire the infection while in the ICU, although available evidence indicates that most cases involve activation or progression of previously acquired infection in the context of critical illness.

Clinical presentations of IA most often encountered in the ICU include a) the aggressive, angio-invasive form typically seen in neutropenic patients, b) cavitating pulmonary infiltrates most often observed in patients on corticosteroids, those with COPD or cirrhosis, or in solid-organ transplant recipients, c) anastomotic infections in lung transplant recipients, and rarely, d) miscellaneous presentations, such as wound infections, mediastinitis (in cardiac surgery patients), and endocarditis.

The diagnosis of IA, in ICU patients who are not in the classic high-risk category, is challenging because the presentation tends to be clinically nonspecific and the sensitivity and specificity of most commonly-used tests vary. Angio-invasive IA typically produces multiple small nodules, with characteristic halos on chest CT, but these signs are seldom present in patients in the lower-risk categories. Most patients in these categories are in the ICU because of processes, such as pneumonia or acute lung injury, whose clinical and radiographic signs obscure or mimic those of IA. Cultures of respiratory specimens in such patients are both insensitive and nonspecific, and fungal stains of such specimens are negative in at least half of patients subsequently proven to have IA. Serologic tests, such as galactomannan and b-1,[3] D-glucan, and PCR techniques for detection of fungal DNA, are increasingly available, although very few published data on the effectiveness of these tests are from ICU patients. In one study of IA in a general medical ICU population, serum galactomannan was positive in only 53% of patients with documented IA.[1] Although there has been the suggestion that this test is more sensitive in bronchoalveolar lavage fluid (BALF) than in serum, this is yet to be confirmed, and making the diagnosis continues to be challenging.

For ICU patients in all risk categories, IA carries a very unfavorable prognosis and responds poorly to available antifungal therapies. Voriconazole has recently become the standard of care for treating IA, replacing the more toxic amphotericin B.[3] Other antifungal agents of potential future value in this condition include posaconazole and the echinocandins caspofungin and anidulafungin. Lipid-based formulations of amphotericin B, which are touted as being less toxic than the traditional version, have also seen increasing use. However, for all these antifungals, data on treating IA in ICU patients are exceedingly sparse, and for multiple reasons, the response rates in such patients would be expected to be less favorable than in most of those included in clinical trials to date.

COMMENTARY

With ever-increasing availability of new immunosuppressive drugs, along with improvements in life support and other aspects of ICU care, clinicians can expect to encounter IA more and more frequently in critically ill patients. As this thorough review by Meersseman et al demonstrates, diagnosis and treatment of IA in patients who are not in the classic high-risk groups are especially challenging.

The relative likelihood of this infection is much greater in certain patient categories than others, and fortunately, the diagnosis is often easier to confirm in them than in the larger numbers of patients at lower, yet still important, risk. Neither positive nor negative findings on chest imaging, stains, and cultures of respirato-

ry tract specimens, and serum tests can be considered definitive, and the clinician is faced with synthesizing complex, and sometimes contradictory, results in attempting to diagnose IA. In most instances, definitive diagnosis continues to require histologic demonstration of tissue invasion. ■

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Yogurt for Diarrhea

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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Dr. Wilke reports no financial relationship to this field of study.

This article originally appeared in the September 15, 2007, issue of Internal Medicine Alert. It was edited by Stephen Brunton, MD, and peer reviewed by Gerald Roberts, MD. Dr. Brunton is Clinical Professor, University of California, Irvine, and Dr. Roberts is Clinical Professor of Medicine, Albert Einstein College of Medicine. Dr. Brunton is a consultant for Sanofi-Aventis, Ortho-McNeil, McNeil, Abbott, Novo Nordisk, Eli Lilly, Eno, EXACT Sciences, and AstraZeneca, and serves on the speaker's bureau for McNeil, Sanofi-Aventis and Ortho McNeil. Dr. Roberts reports no financial relationships relevant to this field of study.

Synopsis: *Patients receiving a probiotic yogurt drink were protected from antibiotic associated bacteria.*

Source: Hickson M, et al. Use of probiotic *Lactobacillus* preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial. *BMJ.* 2007;335:80-84.

In this randomized, double-blind, placebo-controlled study, Hickson and colleagues hypothesized that they could reduce the occurrence of antibiotic-associated diarrhea (AAD) and *Clostridium difficile*-associated diarrhea (CDAD) among older hospitalized patients taking antibiotics by feeding them a commercially-available probiotic yogurt drink. They screened 1760 patients and, after exclusion, enrolled 135 (54% female, 89% white, average age 74 years). Exclusion criteria included diarrhea within a week of admission, antibiotic use up to 4 weeks before admission, conditions that might predispose to infection from the bacteria in the probiotic (eg, immunosuppression), probiotic use before admission, and lactose intolerance. The two groups were balanced with regards to the usual demographic data, the number of antibiotics taken during hospitalization, the number of high-risk antibiotics (aminopenicillins and cephalosporins) taken, and the conditions requiring antibiotics (respiratory tract infections, surgical prophylaxis, and urinary tract infections accounting for almost all). The primary end point was the development of diarrhea (> 2 liquid stools daily for ≥ 3 days). The secondary end point was *C. difficile* infection (diarrhea plus detection of toxins A and/or B). The intervention group received 100 mL (3 ounces) of a yogurt drink containing *Lactobacillus casei*, *Streptococcus thermophilus*, and *Lactobacillus bulgaricus* twice daily. Controls similarly received a sterile milkshake. Subjects were enrolled within 48 hours of receiving an antibiotic, at which time, baseline data and a stool sample to rule out *C. difficile* were obtained and the randomized drink prescribed. The drinks were continued for one week after finishing the course of antibiotics, including those patients who were discharged home on antibiotics. No adverse effects were noted for either drink. Analysis was by intention-to-treat.

In the yogurt group, 12% of patients developed AAD vs 34% in the milkshake group (number-needed-to-treat [NNT] 5). None of the yogurt group developed CDAD; 17% in the milkshake group did (NNT 6). Interestingly, one patient in both groups tested positive for *C. difficile* toxin before antibiotics were administered, but neither developed diarrhea. Length of stay did not differ significantly.

■ COMMENTARY

Previous studies have found a beneficial effect of *Saccharomyces boulardii* on diarrhea in children taking antibiotics.[1] A more recent Cochrane review of pediatric probiotic use concluded, "The current data are promising, but it is premature to routinely recommend probiotics for the prevention of pediatric AAD."[2] A meta-analysis written by one of the co-authors of this study found support for the use of *S. boulardii* and lactobacilli, but suggested that "a further large trial in

which probiotics are used as preventive agents should look at the costs of and need for routine use of these agents."[3] Another meta-analysis found that "3 types of probiotics (*Saccharomyces boulardii*, *Lactobacillus rhamnosus GG*, and probiotic mixtures) significantly reduced the development of antibiotic-associated diarrhea. Only *S. boulardii* was effective for [*C. difficile* disease]."[4]

The yogurt product in question was Actimel®, marketed in the United States as DanActive®. The manufacturer helped fund the study. At my local supermarket, it is sold in a 4-pack at $2.49. That's $1.25 per day if given as it was in this study. Some physicians might bristle at its marketing, which emphasizes that it [DanActive®] "helps strengthen your body's defenses" (http://www.danactive.com/). What applies to sick patients taking antibiotics does not necessarily translate into a panacea for the whole population.

A few questions: would a different probiotic product work as well? Do we need all 3 bacterial strains or would one or 2 be enough? What is the role of *S. boulardii*? Are there differences between adults and children in the prevention of ADD? Despite its limitations (huge exclusion rate, difficulty in blinding, predominantly elderly white population), this is an important study. If its results are confirmed in other studies, it could save the health system a lot of money. Unlike some other interventions, the savings would not come from shorter lengths of stay, but from the costs of treating AAD-vancomycin, which isn't cheap. A 10-day oral course runs about $2,000. If, on the other hand, it was shown that the yogurt drink reduced hospitalizations for AAD when given to outpatients starting a course of antibiotics, then we'd be talking real money. Three ounces of prevention is worth a pound of cure. ■

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CME Questions

7. Isolates of the hypervirulent BI strain of *Clostridium difficile* have the following characteristics EXCEPT:
a. hyperproduction of toxins A and B.
b. production of binary toxin.
c. fluoroquinolone resistance.
d. metronidazole resistance.

8. Which of the following is correct with regard to a recommendation for the administration of hepatitis A vaccine to exposed individuals to prevent acute infection?
a. Its efficacy has been demonstrated when administered as late as 6 weeks after exposure.
b. Its efficacy has been demonstrated in individuals as old as 65 years of age.
c. It may be given for this purpose as a component of the commercially available combined hepatitis A and B vaccine.
d. Its efficacy for this purpose in children less than 12 months of age has not been demonstrated.

9. Which of the following is correct?
a. Adenovirus is an RNA virus.
b. Adenovirus serotype 14 may cause fatal infection in adults.
c. There are only 3 serotypes of adenovirus.
d. Adenovirus most commonly causes a "summer flu."

Answers: 7. (d); 8. (d); 9. (b)

CME Objectives

The objectives of Infectious Disease Alert are to:

• discuss the diagnosis and treatment of infectious diseases;

• present current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• present the latest information regarding the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy. ■

In Future Issues:

Antiretroviral Agents on Lipid Profiles of HIV Patients

UPDATES

By Carol A. Kemper, MD, FACP

Non-gonococcal urethritis

Source: Yokoi S, et al. The role of *Mycoplasma genitalium* and *Ureaplasma urealyticum biovar* 2 in postgonococcal urethritis. *Clin Infect Dis*. 2007;45:866-871.

The possible causative infectious agents of non-gonococcal urethritis (NGU) in men remain somewhat controversial. Studies point to a role for genital mycoplasmas and genital ureaplasmas, although some men with evidence of colonization or infection with these organisms remain asymptomatic, while others without evidence of infection have persisting symptoms.

Yokoi and colleagues examined the prevalence of infection due to genital mycoplasmas and ureaplasmas in men diagnosed with acute gonococcal urethritis and their association with persistent inflammation and clinical symptoms. A total of 390 men were treated for acute GU with cefixime, ceftriaxone, or spectinomycin. They were told to refrain from sex and return to the clinic 7 days later; at which time, cultures for GC were obtained and urethral smears were examined for the presence of PMNs. Using molecular techniques, first voided urines at both the initial and second visit were tested for non-GC organisms. NGU was defined as the presence of PMNs 7-14 days post-treatment for GC in the absence of a positive gram stain or culture for GC.

At the initial visit, chlamydia trachomatis, genital mycoplasma, and/or ureaplasmas were detected in 34%. Twenty-two percent had positive specimens for *C. trachomatis*, and 3.8% had both *C. trachomatis* and one or two species of genital mycoplasmas and ureaplasmas. Twelve percent had one or more species of genital Mycoplasma and/or ureaplasmas without chlamydia co-infection.

A total of 327 (84%) men returned to the clinic for a second visit, of which 11% were still positive for GC. Of the remaining patients, 36% had detection of urethral PMNs detected, nearly two-thirds of whom were symptomatic, and one-third were asymptomatic. NGU (as defined by the presence of urethral PMNs) was found in 51 of 66 men with positive *C. trachomatis* specimens (or co-infection with Chlamydia and one or more of the other species); 15 of 30 men without *C. trachomatis* but with positive specimens for one or more species of genital mycoplasmas and ureaplasmas; and 38 of 195 men who had negative urine studies. In other words, no bacterial etiology was identified in 38/104 (36%) of men with evidence of persisting inflammation 7-14 days post-treatment for GC.

Multivariate logistic regression analysis demonstrated that several species were associated with an increased risk of NGU, including Chlamydia (an 11-fold increase), *M. genitalium* (a 14-fold increase), and *U. urealyticum* biovar 2 (a 3.6-fold increase). *M. hominis* and *U. parvum* did not appear to be causative factors in this study.

In conclusion, one-third of the men receiving treatment for GC had evidence of one or more NGU species, data which support the current PHS guidelines recommending concurrent empiric treatment for NGC organisms in men being treated for GC. Treatment with a 7-day course of doxycycline is effective in > 90% of cases due to *C. trachomatis*, although there is controversy how best to treat *M. genitalium*. However, at least one-third of men with NGU post-treatment for GC have no bacterial etiology found in this study. It would have been interesting to see if any of those men were symptomatically improved or had resolution of urethral inflammation with empiric treatment.

Abnormalities Common on Routine Brain MRI

Source: Vernooij MW, et al. Incidental findings on brain MRI in the general population. *N Engl J Med*. 2007;357;1821-1828.

As part of a broader population-based survey, Vernooij and colleagues determined the prevalence of incidental asymptomatic brain findings (infarcts, tumors, white matter lesions) in 2000 people undergoing non-contract brain MRI. Volumetric techniques were used to quantify white matter lesions. The films were initially reviewed by a resident in radiology and a resident in neurology. Two experienced neuroradiologists, blinded to clinical history, reviewed any film with abnormalities and reached a consensus reading.

The mean age was 63 years (range, 46 -97 years), and 52% were

woman. Asymptomatic brain infarcts were the most common findings, present in 145 persons (7.2%), more-than two-thirds of which were lacunar infarcts. The next most common finding was asymptomatic aneurysms in 1.8% of people, all but 2 of which were located in the anterior circulation, and all but 3 of which were 7 mm in diameter or smaller. (Other data found the risk of rupture of aneurysms of this size present in the anterior circulation was 0% over 4 years of observation). Benign tumors were detected in 31 (1.6%) people, more than half of which appeared to be benign meningiomas (overall prevalence, 0.9%), but also included a few vestibular (0.2%) and trigeminal schwannomas (< 0.1%), pituitary adenomas (0.3%), and intracranial lipomas (0.1%).

White matter lesions proved to be the norm in almost every patient scanned, and increased in volume and distribution with older age. Only 5% of persons 45 to 59 years of age had no evidence of white matter lesions, and this figure dropped to 2% in persons 75 years or older. The prevalence of meningiomas also increased with increasing age.

Only 3 patients had findings of urgent clinical significance, including one person each with multiple metastatic lesions (he confirmed an earlier history of lung cancer); a probable primary brain tumor; and a large chronic subdural hematoma (with a recent history of minor head trauma 4 weeks earlier). A weakness to this study is the lack of confirmatory histological data, since none of these findings required surgical intervention. However, the prevalence of asymptomatic findings on brain MRI is fairly common, and higher than reported in earlier studies. While the identification of some of these findings may result in an increase in unnecessary referrals to specialists and follow-up scans, some, such as meningiomas actually probably do require long-term follow-up.

The Immune System's Response to *M. Leprae*

Source: De Messias-Reason IJ, et al. The association between mannin-binding lectin gene polymorphism and clinical leprosy: new insight into an old paradigm. *J Infect Dis*. 2007;196: 1379-1385.

Only a minority of people infected or exposed to *M. leprae* develop clinical disease, probably as the result of host genetic factors and immunity. At the same, those same host factors play a significant role in the progression of disease and spectrum of disease manifestations. For instance, we know that *M. leprae*-specific Th1 activation leads to a vigorous immune system response, with limited numbers of lesions and few organisms (tuberculoid leprosy), whereas the lack of Th1 responsiveness leads to proliferation of bacteria, extensive clinical lesions, and a resulting strong humoral response (Lepromatous leprosy).

Other factors may also play a role in the immune system response to *M. leprae*. Mannin-binding lectin (MBL) is a soluble protein which binds to organisms, such as mycobacteria, and facilitates their attachment to, and enhanced opsonization by, macrophages. MBL deficiency is known to protect against leishmania, and it is theorized that similar deficiency may protect against lepromatous leprosy.

De Messias and colleagues examined 264 patients with leprosy in southern Brazil, comparing them with 214 unrelated healthy adults, matched by ethnic background. The frequency of MBL genotypes and haplotypes were assessed and divided into those with low or high expression of MBL. Haplotypes associated with low production of MBL were significantly less frequent in patients with lepromatous leprosy than those with tuberculoid leprosy. For example, the LYPB/LYQC haplotypes were more frequent in patients with multibacillary disease, although their presence was nonetheless found to increase the risk of tuberculoid leprosy as well. The LYPA haplotype, which is also associated with a low expression of MBL, also conferred a 2-fold increase in susceptibility to leprosy, as well as to progression to the lepromatous and borderline forms of the disease.

In other words, the inability to express MBL not only failed to protect against infection with *M. leprae*, but actually increased the risk of infection, although it protected against the most severe multibacillary form of disease. De Messias et al theorize that the selective pressure of leprosy has actually shaped and defined MBL genotypes and haplotypes in populations at higher risk for leprosy. MBL2 haplotypes/genotypes associated with low expression of MBL are more common in places such as Africa and South American and, on the other hand, older (more ancient) haplotypes associated with a high amount of MBL are commonly found in populations with little selective pressure. Australian aboriginal population, which had no exposure to leprosy until the 19th century, is currently experiencing a significant problem with leprosy infection, as well as tuberculosis. ■

PHARMACOLOGY WATCH

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

Adult Immunization Guidelines from CDC Released

In this issue: *Updated Immunization Guidelines from the CDC; Do antivirals have a role in the treatment of Bell's palsy? Topiramate is a promising treatment for alcohol dependence; and FDA Actions.*

The *Annals of Internal Medicine* has published updated Adult Immunization Guidelines from the CDC as an early release article on their website dated October 18. Full guideline will be available in the November 20 print edition. The guideline has several important changes and updates.

The new herpes zoster vaccine is added to the guideline this year. The vaccine should be given routinely to all immunocompetent adults age 60 and older. It is not recommended for immunocompromised adults as it is a live attenuated virus. The vaccine is given once in a lifetime, and does not require a booster.

The new human papilloma virus has also been added. The vaccine protects against 4 types of HPV, which causes 90% of genital warts and 70% of cervical cancers. It is recommended for women aged 11 to 26 years. It requires three doses given at zero, 2 and 6 months. It should not be given to pregnant women.

The new pertussis vaccine is coupled with diphtheria and tetanus to form Tdap (Adacel- Sanofi Pasteur). This is a 1-time, 1-dose vaccine that should be given to all adults age 64 or younger when they are scheduled for their next tetanus (Td) booster. Tetanus boosters should be given every 10 years, but the interval may be shortened to as little as two years for high-risk patients including postpartum women, close contact of infants younger than 12 months of age, and all healthcare workers with direct patient contact. It has not been tested in adults age 65 or older. This vaccine is different from the previously approved Tdap for adolescents aged 10 to 19 (Boostrix-GlaxoSmithKline).

There are now 15 indications for influenza vaccine. New indications include those who have difficultly handling respiratory secretions or have increased risk of aspiration. All women who are pregnant or will be pregnant during the flu season should be vaccinated. All healthcare workers should be vaccinated unless they have strong contraindications.

Hepatitis B vaccine recommendations have changed, and the vaccine is now recommended for all sexually active adults who are not in a long-term mutually monogamous relationship.

Because of several recent large-scale mumps outbreaks in this country, a mumps vaccine booster is now recommended for specific age groups, especially adults who work in healthcare settings. The standard is to give MMR, even if immunity exists for one or more of the components of MMR.

The pneumococcal vaccine recommendations remain the same. The vaccine should be given at age 65 unless the patient has specific risk factors, in which case it should be given to those younger than 65. A small subgroup of patients should be given a second booster. If the vaccine was initi-

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ated under age 65 for high-risk patients, a booster should be given at age 65 or five years after the initial vaccine. If the vaccine was initiated over age 65, a booster should only be given to immunocompromised patients after five years. The vaccine should not be given every five years (a common misconception). In fact, no one should receive more than two doses under any circumstances. There is even some evidence that more than two doses may be harmful and could potentially attenuate the immune response.

Antivirals and Bell's Palsy?

Do antivirals have a role in the treatment of Bell's palsy? This question has been debated for decades, with several small studies indicating a relationship between herpes simplex infections and facial paralysis. Despite this, treatment with acyclovir or valacyclovir has not been proven to be effective in treating Bell's palsy. Regardless, antivirals are frequently prescribed along with oral steroids. A new study confirms that steroids are useful, but antivirals are not. Nearly 500 patients with new onset of Bell's palsy were randomized to 10 days of treatment with prednisolone, acyclovir, both agents, or placebo. The primary outcome was recovery of facial function. At three months, the proportion to patients who had recovered facial function were 83.0% in the prednisolone group compared with 63.6% among patients who did not receive prednisolone ($P < 0.001$) and 71.2% in the acyclovir group as compared to 75.7% among patients who did not receive acyclovir (adjusted $P = 0.50$). After nine months, recovery was 94.4% for prednisolone and 81.6% for no prednisolone ($P < 0.001$) and 85.4% for acyclovir and 90.8% for no acyclovir (adjusted P = 0.10). For patients treated with both drugs, recovery was 79.7% at 3 months ($P < 0.001$) and 92.7% at nine months ($P < 0.001$). There were no serious adverse effects in either group. The authors conclude that early treatment with prednisolone significantly improves the chance of complete recovery, while there's no evidence of benefit with acyclovir alone or in combination with the steroid (*NEJM*. 2007; 357:1598-1607).

Topiramate Promising for Alcohol Treatment

Topiramate is a promising treatment for alcohol dependence according to a new study. The drug was shown to be effective in this role in a small study published in 2003. This new, larger multisite 14 week double-blind, randomized, placebo controlled trial enrolled 371 men and women age 18 to 65 years who were diagnosed with alcohol dependence. Up to 300 mg per day of topiramate was given to 183 participants while 188 were treated with placebo. Both groups were enrolled in a weekly compliance enhancement intervention program. The primary end point was self-reported percentage of heavy drinking days, while secondary outcomes included other self-reported drinking measures along with laboratory measures of alcohol consumption. Topiramate was more efficacious than placebo at reducing percentage of heavy drinking days from baseline to 14 weeks (mean difference 8.44%; 95% CI, 3.07%-13 .80%; $P = .002$). Topiramate also reduced all of the drinking outcomes ($P <.001$ for all comparisons). Adverse events were more common with topiramate, including paresthesia (which occurred in over 50% of those on the drug), taste perversion, anorexia and difficulty with concentration. In general, however, the drug was safe and consistently efficacious for treating alcohol dependence (*JAMA*. 2007;298:1641-1651). An accompanying editorial points out that the benefits of topiramate were still increasing at the end of the study, indicating the longer treatment may be more effective (*JAMA*. 2007;298:1691-1692).

FDA Actions

The FDA has announced new warnings on phosphodiesterase type 5 inhibitors regarding hearing loss. The drugs include sildenafil (Viagra, Revatio), tadalafil (Cialis) and vardenafil (Levitra). The agency has received 29 cases of sudden hearing loss associated with use of the drugs dating back to 1996. Most cases were unilateral and temporary.

Modafinil (Provigil) has also been the subject of new warnings including serous rashes and psychiatric symptoms. The drug, which is used for narcolepsy, obstructive sleep apnea, shiftwork disorder, and multiple sclerosis, has been associated with severe rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis. The FDA suggested caution should be exercised when modafinil is given to patients with a history of psychosis, depression, or mania.

An FDA advisory panel has recommended restricting childhood cold medications to children over the age of six years. They also recommend strong limits on marketing these products for younger children. This follows a voluntary withdrawal from the market of infant cough and cold medications by most manufacturers of these products. Voluntary withdrawal involves medications used in children younger than two years. The drugs that contain decongestants and antihistamines have been associated with more than one hundred deaths since 1969. ■