

1999–2000 Series: Update Sessions from ACP–ASIM's 1999 Annual Session

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Update in Infectious Diseases

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An uninterrupted flow of new information and new concepts makes infectious diseases one of the fastest-changing fields of clinical medicine. The emergence of antibiotic-resistant organisms, notably gram-positive cocci, continues unabated. Foodborne disease is also a continuing problem. Among the major culprits are *Listeria* species, *Escherichia coli* O157, and *Salmonella* species, and *Cyclospora* species have made a dramatic return. The role of irradiation in preventing foodborne illness has been discussed, as have the vital issues posed by bioterrorism. A most exciting prospect is the potential role that certain treatable bacterial infections may play in coronary heart disease and resultant acute myocardial infarction. For influenza, always a hot topic, inhaled antiviral agents are proving effective. Finally, advances in understanding and managing HIV infection merit renewed attention each year.

Antimicrobial Resistance and Prescribing Practices

In addition to pneumococci, emerging resistant strains of *Staphylococcus aureus* and *Salmonella* species demand attention. Such resistance is intimately related to prevailing prescribing practices.

Broad-Spectrum Resistance of *Streptococcus pneumoniae* Continued To Increase in the United States and Canada

Doern GV, Pfaller MA, Kugler K, et al. Prevalence of antimicrobial resistance among respiratory tract isolates of *Streptococcus pneumoniae* in North America: 1997 results from the SENTRY antimicrobial surveillance program. *Clin Infect Dis*. 1998;27:764-70.

Ann Intern Med. 1999;131:273-280.

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Pneumococci are the major treatable pathogens in many of the common infections that account for an impressive share—perhaps 50% to 60%—of all antibiotic prescriptions. Otitis is the major indication in pediatric practice, whereas in adults, *Streptococcus pneumoniae* is the major pathogen identified in sinusitis, exacerbations of chronic bronchitis, and pneumonia. Doern and colleagues, in the most recent report from SENTRY, a multinational antimicrobial surveillance program, examined resistance patterns of *Streptococcus pneumoniae* in more than 1000 respiratory tract isolates from 27 centers in the United States and 7 in Canada. Resistance rates of 10% to 20% were documented for amoxicillin, cefuroxime, cefpodoxime, erythromycin and other macrolides, tetracycline, and the combination of trimethoprim and sulfamethoxazole.

Susceptibility to fluoroquinolones was not reported, but these agents seem to retain good in vitro activity against most strains, including those resistant to penicillin. Vancomycin is the only antibiotic that is universally active against *Streptococcus pneumoniae*. One precautionary note: a minimal inhibitory concentration exceeding 0.1 $\mu\text{g}/\text{mL}$ is currently recommended by the National Committee for Clinical Laboratory Standards to define intermediate- and high-level penicillin resistance. Most authorities now consider 2 $\mu\text{g}/\text{mL}$ to be the appropriate threshold for penicillin resistance in nonmeningeal pneumococcal infections. This threshold reduces the prevalence of penicillin resistance from 40% to 60% to about 10% to 20%. Also worth noting is the marked geographic variation in resistance rates, from as low as 2% to 7% in some areas, such as Chicago and Boston, to as high as 30% to 40% in others, including Charlotte, North Carolina, and Galveston, Texas.

What are the implications for prescribing practices? Fear of resistance should preclude the use of penicillin monotherapy for pneumococcal meningitis. The Centers for Disease Control and Prevention (CDC) currently recommends amoxicillin for otitis media and acute sinusitis in children and recom-

mends amoxicillin-clavulanate or an oral cephalosporin if amoxicillin alone fails. It seems likely that penicillin and cephalosporins (cefotaxime or ceftriaxone) will continue to be preferred in most cases of pneumococcal pneumonia.

Current estimates are that 70% to 80% of patients with acute bronchitis are given an antibiotic, accounting for 15% to 20% of all prescriptions in adult practice. This is viewed as antibiotic abuse because the only clear indications in bronchitis for which antibiotics have established benefit are acute exacerbations of chronic bronchitis (with varying results in clinical trials) and pertussis, for which the benefit is limitation of infection transmission. A recent attempt to reduce antibiotic use for acute bronchitis was reported by Gonzalez and colleagues, who randomly assigned patients from a large health maintenance organization into three groups: One group received no intervention, and another received "provider education instruction" with explanations for the rationale of avoiding antibiotics; for the third group, both patients and providers received the same message regarding the avoidance of antibiotics. The results showed that antibiotic prescriptions were reduced only when both patients and providers received the message; the rate of antibiotic prescribing decreased from 78% to 48% (1). The authors concluded that it is important to communicate information on antibiotic use to both providers and consumers.

Antibiotics for Farm Animals Have Made a Multidrug-Resistant *Salmonella* Strain Alarmingly Prevalent in the United States

Glynn MK, Bopp C, Dewitt W, et al. Emergence of multidrug-resistant *Salmonella enterica* serotype typhimurium DT104 infections in the United States. *N Engl J Med.* 1998;338:1333-8.

This study, conducted jointly by the Food and Drug Administration and the Foodborne and Diarrheal Diseases Branch of the CDC, surveyed infections by *Salmonella enterica* serotype DT104 (definitive type 104) that occurred in the United States from 1979 through 1996. This strain, which is resistant to ampicillin, chloramphenicol, streptomycin, tetracycline, and sulfonamides and causes illness in both humans and animals, increased in prevalence from 0.6% to 34% during the period under review. The organism has also become prevalent in Europe, especially the United Kingdom. This experience suggests a possibly important cause of resistance apart from antibiotic prescription abuse in patients: the use of antibiotics in farm animals. In fact, more than 40% of antibiotics produced in the United States are given to animals to promote growth, eliminate pathogens, and treat established infection.

Another example is avoparcin, which has been used for food animals in Europe. This drug, related to vancomycin, has selected for vancomycin-resistant enterococci in animals. In addition, use of fluoroquinolones in raising poultry has led to resistant *Campylobacter* species in Europe and is now doing so in the United States (2).

Vancomycin-Resistant *Staphylococcus aureus* Began Emerging in the United States

Smith TL, Pearson ML, Wilcox KR, et al. Emergence of vancomycin resistance in *Staphylococcus aureus*. Glycopeptide-Intermediate *Staphylococcus aureus* Working Group. *N Engl J Med.* 1999;340:493-501.

Strains of *Staphylococcus aureus* bearing intermediate resistance to the glycopeptide antibiotic vancomycin were first reported from Japan in 1997 (3). Since the emergence of methicillin-resistant *Staphylococcus aureus*, vancomycin has been the only reliably effective treatment for these infections. Two cases of infection with vancomycin-resistant organisms in the United States have been described, both in older diabetic men. One of them, who was undergoing dialysis for chronic renal failure, developed *Staphylococcus aureus* peritonitis from an intermediately resistant strain after 18 weeks of vancomycin therapy. The other, who had *Staphylococcus aureus* bacteremia, developed a vancomycin-resistant strain after 18 weeks of vancomycin treatment of a methicillin-resistant strain. Both isolates had thicker extracellular matrices than did methicillin-

Table 1. Recommendation for Preventing the Spread of Glycopeptide-Resistant *Staphylococci**

Isolate the patient in a private room
Minimize the number of persons caring for the patient
Begin one-on-one care by specified personnel
Initiate epidemiologic and laboratory investigations with the assistance of the state health department and the CDC
Educate all health care personnel about the epidemiology of <i>S. aureus</i> with intermediate resistance to glycopeptides and about appropriate infection-control precautions
Monitor and strictly enforce compliance with contact precautions
Determine whether transmission has already occurred by performing baseline cultures of specimens from hands and nares of the following:
Those with physical contact with the patient
The patient's health care providers
The patient's roommates
Use contact precautions (gown, mask, gloves, and antibacterial soap for handwashing)
Assess efficacy of precautions by monitoring personnel for acquisition of the isolate
Consult with the state health department and CDC before transferring the patient (for emergencies only) or discharging him or her
Inform the following appropriate personnel about the presence of a patient with glycopeptide-intermediate <i>S. aureus</i> :
Patient's accepting physician
Admitting or emergency room personnel
Personnel admitting patients to unit

* Adapted with permission from Smith TL, Pearson ML, Wilcox KR, et al. Emergence of vancomycin resistance in *Staphylococcus aureus*. Glycopeptide-Intermediate *Staphylococcus aureus* Working Group. *N Engl J Med.* 1999;340:493-501. CDC = Centers for Disease Control and Prevention.

resistant isolates. The good news is that a survey of 177 contacts revealed no colonization by the vancomycin-resistant strain.

What is worrisome about intermediate antimicrobial resistance (for vancomycin, defined by a minimal inhibitory concentration between 4 and 32 $\mu\text{g}/\text{mL}$) is that it may be followed by the emergence of totally resistant strains. Resistance in the reported cases resulted from an accumulation of cell-wall components and increased binding of vancomycin to this material (4), processes that presumably divert the drug from its usual target. Treatment options appear to be somewhat limited but include quinolones, oxazolidinones, and some investigational agents (5). Some of the measures recently recommended by the CDC to limit the spread of *S. aureus* strains with intermediate glycopeptide resistance are listed in **Table 1**.

Infectious Diseases: General

Dental Work Was Not a Key Risk Factor for Endocarditis Even in Patients with Abnormal Cardiac Valves

Strom BL, Abrutyn E, Berlin JA, et al. Dental and cardiac risk factors for infective endocarditis. A population-based, case-control study. *Ann Intern Med.* 1998;129:761-9.

The need for antibiotic prophylaxis in patients thought to be at risk for developing endocarditis after dental procedures has largely gone unquestioned. Much of the support cited for this practice is anecdotal or is based on the reduction of bacteremia. Because neither prospective nor randomized trials are practical, Strom and colleagues monitored the occurrence of endocarditis in 54 hospitals and interviewed 273 case-patients and matched controls about recent medical and dental procedures. Nearly one fourth of each group had had dental work in the past 3 months. Fewer than 3% of case-patients received antibiotic prophylaxis within a month before dental work. The investigators conclude that antibiotic prophylaxis does not appear to significantly reduce the incidence of endocarditis and that even if prophylaxis were completely effective, few cases of infective endocarditis would be prevented.

This well-crafted study suggests that prophylaxis has limited value, if any, and that the value has to be balanced against the risk for an adverse drug reaction. David Durack, who heads the American Heart Association committee that writes the organization's guidelines, believes that prophylaxis should continue for the present, but in a restricted and more focused manner (6).

New Amphotericin Formulations Bring Good News and Bad News

Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institutes of Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med.* 1999;340:764-71.

Walsh and colleagues, representing the National Mycosis Study Group, conducted a double-blind, randomized trial comparing amphotericin in liposomal form (AmBisome, Fujisawa Healthcare, Deerfield, Illinois) and conventional amphotericin B as empirical treatment of more than 500 patients from 32 centers. Patients with cancer given chemotherapy or bone marrow transplant recipients with fever and neutropenia were enrolled after they did not benefit from 5 days of empirical antibacterial therapy. The study failed to show any substantial difference in survival at 1 week or hastening of the resolution of fever. However, three outcomes favored AmBisome. Breakthrough bacteremia, primarily with aspergillosis or candidemia, was twice as frequent with standard amphotericin (7.8% compared with 3.2% for AmBisome). Nephrotoxicity was also significantly less common in patients given the liposomal formulation, and infusion-related reactions (chills and fever) were substantially more frequent with standard treatment. As is so often the case with today's medicine, cost becomes an important consideration: The average wholesale cost of AmBisome is about \$752 per day, compared with \$38 for the standard preparation (7). At Johns Hopkins Hospital, substituting AmBisome would cost \$1.3 million a year. Thus, our hospital, like many others, is establishing guidelines for use of the more expensive but less toxic form.

Chronic Bacterial Infections Were Associated with First-Time Acute Myocardial Infarction

Meier CR, Derby LE, Jick SS, et al. Antibiotics and risk of subsequent first-time acute myocardial infarction. *JAMA.* 1999;281:427-31.

Evidence is accumulating that *Chlamydia pneumoniae* may be a factor in atherosclerosis and its complications, including stroke and acute myocardial infarction. Serologic studies are suggestive, and the organism, or its antigen, has been demonstrated within atherosclerotic plaques. The main issues are the validity of the observations and the role of antibiotics, primarily azithromycin or doxycycline, for control. Meier and colleagues retrospectively reviewed the frequency of antibiotic use in more than 300 physician practices in the United Kingdom. Records for 3315 patients with an initial acute myocardial infarction were compared with those for

Table 2. Odds Ratios for Developing First-Time Acute Myocardial Infarction in Relation to Use of Antibiotics in the 3 Years Preceding the Date of Acute Myocardial Infarction*

Antibiotic Group	Case-Patients (n = 3315)	Controls (n = 13 139)	Odds Ratio (95% CI)†	P Value
n				
No antibiotics	1403	5318	1.0 (referent)	
Tetracyclines only	82	452	0.70 (0.55–0.90)	<0.01
Macrolides only	83	345	0.93 (0.73–1.20)	>0.2
Sulfonamides only	90	343	1.01 (0.79–1.29)	>0.2
Quinolones only	8	62	0.45 (0.21–0.95)	0.04
Penicillins only	773	3094	0.94 (0.85–1.04)	0.2
Cephalosporins only	62	253	0.90 (0.67–1.22)	>0.2
"Switchers"‡	814	3272	0.91 (0.82–1.01)	0.06

* Reproduced with permission from Meier CR, Derby LE, Jick SS, et al. Antibiotics and risk of subsequent first-time acute myocardial infarction. *JAMA*. 1999;281:427-31.

† Data are adjusted for body mass index (weight in kilograms divided by the square of height in meters) and smoking.

‡ "Switchers" are patients who used a combination of antibiotic groups.

13 000 controls. The results showed that acute myocardial infarction was significantly less common in persons who received tetracycline (odds ratio, 0.7) or quinolones (odds ratio, 0.45) (Table 2). No such association was evident for a broad range of other antibiotics, including penicillins and cephalosporins. Respiratory tract infection was the dominant indication for antibiotic treatment.

These findings certainly endorse the potential role of a bacterium such as *Chlamydia pneumoniae* in the occurrence of acute myocardial infarction, but results of other antibiotic trials have varied. Most authorities, including Aaron Fulson in a recent editorial (8), agree that it still is premature to draw firm conclusions. A seemingly anomalous finding, that macrolide antibiotics were apparently not beneficial despite their high activity against *Chlamydia pneumoniae*, may be explained by the fact that erythromycin, the macrolide most often used, was taken only briefly because many patients could not tolerate it. Tetracycline may work by exerting an anti-inflammatory effect rather than as an antibiotic per se. The National Institutes of Health has funded a large study to learn whether azithromycin is effective.

Neuraminidase Inhibitor Shortened the Course of Viral Influenza and Reduced Complications

Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. *Lancet*. 1998;352:1877-81.

Three major pandemics and experience with the Hong Kong flu ("bird flu") in 1997, as well as seasonal epidemics with an annual mortality toll of about 20 000 persons in the United States, make the

influenza virus probably the most under-rated major pathogen in the developed world. Along with HIV, it is one of the major infectious causes of death from a single microorganism. Amantadine and rimantadine, although effective, cause numerous adverse reactions and carry the potential for resistance. In addition, these drugs are not active against influenza B virus, admittedly the lesser cause of death and illness but far from harmless. Neuraminidase inhibitors are a new type of antiviral agent that exhibits good in vitro activity. Zanamivir, which is active against both influenza A and B, has been found to be clinically useful (9) and may gain Food and Drug Administration approval in time for the 1999–2000 flu season.

The MIST (Management of Influenza in the Southern Hemisphere Trialists) study was a randomized, double-blind, placebo-controlled trial that included more than 450 patients 12 years of age or older who were treated within 36 hours of symptom onset. The multicenter study was conducted in Australia, New Zealand, and South Africa at a time when influenza activity was increasing. Patients rated their symptoms four times a day. Those who inhaled 10 mg of zanamivir twice daily for 5 days remained symptomatic for a median of 5 days, compared with 6.5 days for placebo recipients. For febrile patients, the difference in duration was 2 days, and for high-risk patients (elderly persons and patients with chronic lung disease or associated illness), the difference was 2.5 days. High-risk patients given treatment had fewer complications and needed antibiotics less often. The drug had no threatening side effects.

Zanamivir substantially reduces viral shedding and holds the promise of controlling outbreaks of influenza in nursing homes. When administered, it should be given within 36 hours of symptom onset. Another problem is that the present inhalation system is awkward. An oral form that is adequately absorbed may become available, but gastrointestinal intolerance will be a problem. It would be of interest to know the prophylactic value of this agent. Amantadine and rimantadine are 70% to 90% effective in preventing influenza A, but zanamivir would protect against the B form as well. Comparative trials are under way.

Intravenous Doxycycline Was an Effective and Low-Cost Empirical Treatment for Hospitalized Patients with Community-Acquired Pneumonia

Ailani RK, Agastya G, Ailani RK, et al. Doxycycline is a cost-effective therapy for hospitalized patients with community-acquired pneumonia. *Arch Intern Med*. 1999;159:266-70.

Few diseases have been studied more and with less consensus on appropriate management than community-acquired pneumonia. The problem is compounded by increasing resistance of *Streptococcus pneumoniae* to numerous antibiotics, including penicillins and cephalosporins, and also by “atypical” organisms such as *Mycobacterium pneumoniae* and *Chlamydia pneumoniae*. The result: diverse guidelines recommending different strategies for diagnosing pneumonia and treating it empirically.

The randomized trial conducted by Ailani and colleagues compared intravenous doxycycline with the “doctor’s choice” of treatment for 87 adult patients presenting with community-acquired pneumonia. The patients received 100 mg of doxycycline intravenously at 12-hour intervals. About 40% of patients in each group had underlying lung disease. Doxycycline recipients had statistically significantly better outcomes in three categories: time to clinical improvement (mean, 2.2 days compared with 3.8 days); average length of stay (4 days compared with 6 days); and mean hospital costs. Only 3 of the 43 patients assigned to doxycycline required alternative treatment to achieve a response.

This study, although not a large-scale effort, does suggest that doxycycline—which certainly would not be preferred by most experts for empirical use in hospitalized patients with pneumonia—is in fact an effective and comparatively inexpensive choice. Two qualifications: Severely ill patients were excluded from this trial, and it is possible that *any* fixed regimen would prove superior to the “doctor’s choice.”

Cyclospora Returns: Voluntary Control Efforts Proved Ineffective

Herwaldt BL, Beach MJ. The return of *Cyclospora* in 1997: another outbreak of cyclosporiasis in North America associated with imported raspberries. *Cyclospora* Working Group. *Ann Intern Med*. 1999;130:210-20.

Outbreaks of foodborne infection by *E. coli* or *Listeria* species or reports of food recalls are now an almost daily occurrence; this was not the case two decades ago. The difference is attributed to major changes in the food industry. Many more food products are available in grocery stores, and many more of these products travel some distance to get there. The dimensions of the problem may be appreciated by comparing a typical hen house in 1950, which held perhaps 500 birds, and a modern one, which houses an average of 100 000. Similarly, a hamburger used to come from a single cow, not 100 or more animals, as is now the case. Innovations in food processing and distribution ensure that a “little” contamination can go a long way.

The report by Herwaldt and Beach for the *Cyclospora* Working Group is a reprise of a 1996 outbreak of cyclosporiasis caused by contaminated raspberries from Guatemala (10). More than 1000 persons in 20 states were reported to have *Cyclospora* infection in 1996. An investigation of farms in the source country disclosed low food-quality standards but no clear single source of infection. The Guatemalan Berry Commission voluntarily took measures to improve sanitation, employee hygiene, and the quality of the water used in farming. Imports were halted but were reopened for low-risk farms in 1997, and a new epidemic promptly emerged; 41 clusters totalling 762 cases of cyclosporiasis were identified in 17 states from April through June of that year. (A cluster consisted of two or more patients who developed gastrointestinal symptoms within 2 weeks of eating at some event.) The only common food was raspberries, which, as in the previous outbreak, were likely to have come from Guatemala. The diarrhea experienced by these patients is not a trivial form but rather persists for some time and has proved difficult to treat effectively. In an editorial, Osterholm (11), from the Minnesota Department of Health, concluded from the high attack rate among persons eating raspberries (92%) that the infectious dose of *Cyclospora cayetanensis* is low and that affected berry lots probably were uniformly contaminated. Trace-back studies suggested that one farm was the source of about two thirds of the contaminated fruit, although just how the fruit became contaminated remains unclear. The outbreak ceased when Guatemala stopped exporting fresh raspberries at the end of May 1997.

This particular foodborne infection undoubtedly is vastly underreported because many (or most) laboratories cannot identify *Cyclospora* species. Osterholm pointed out that this and many other forms of foodborne illness, including listeriosis, can be prevented by irradiating the food, a totally safe method (1). Irradiating meat would probably add 1 to 2 cents a pound to its cost, and the food tastes no different. In some ways, resistance to irradiating food products is reminiscent of the situation with fluoride 40 years ago. The wholesale and retail food service industries strongly support irradiation, but activists are strongly opposed to it and the U.S. government has been slow in promoting this as an important public health measure (11). Recent legislation mandating that certain forms of meat be irradiated will probably not be implemented for several years.

Thoughts on Bioterrorism

The key aspects of bioterrorism as a clear and present danger in the United States have been dis-

cussed by Henderson (12). The first question is whether it is likely to occur in this country, and most of those concerned now seem to believe that it is. Nevertheless, it is proving difficult to get the attention of U.S. physicians, despite the manifest importance of doing so. Many probably would acknowledge that an act of bioterrorism is going to happen somewhere in the United States, "but not in Cincinnati." In fact, the likelihood of an attack in some city is high, but in any particular city, low. Certainly, logic would dictate that New York City and Washington, D.C., are the most tempting targets, but terrorist acts of all kinds have occurred at unpredictable places and times. The next question about bioterrorism is which agents will be launched. The consensus is that the "big two" are smallpox and anthrax.

The key question is whether we in the United States are ready to deal effectively with bioterrorism. The tendency has been to approach the problem in the manner used for chemical warfare, which in fact is a different challenge. Chemical exposures occur in a matter of minutes and affect those near the point of release, and the site of origin is readily detected. Biological assault, in contrast, takes place over a period of days and affects a widespread population. Its point of origin is difficult to detect. The rules and regulations for dealing with chemical exposure are intended largely for fire fighters, police officers, and paramedics as the first responders. But in the event of a bioterrorism attack, the initial responders will include physicians, other care providers, and emergency department staff. Physicians will administer antibiotic prophylaxis to many thousands of people if an anthrax attack is launched, and it is physicians as well who will have to deal with smallpox or other biological agents.

Just how likely is a bioterrorism attack in the United States? It is estimated that at least 10 nations and possibly 17 possess biological warfare agents. In 1991, Iraq produced large amounts of anthrax, botulinum toxin, and other agents, deliverable by SCUD missiles or drones. The facility itself was destroyed in 1996, but it seems likely that the biological materials reside elsewhere. The Japanese man who led the sarin gas attack in 1995 is to be released from prison and, with thousands of followers and abundant assets, remains a substantial threat. The same group attempted an anthrax attack in Tokyo that was foiled only by climatic conditions. The former Soviet Union's highly sophisticated biological weapons program employed 60 000 workers in eight cities before its political demise. Today, Russian experts in bioterrorism are being recruited by many nations that wish to develop a biological warfare capacity. These include Iraq, Iran, Libya, Syria, and North Korea. Organized efforts by some

nations aside, the FBI reports that, at least once a day, a politician, school, abortion clinic, or other controversial person or institution receives an envelope from a dissident containing a powder and a note announcing exposure to a lethal dose of, say, anthrax. That they have so far been hoaxes does not mean that dissidents in the future will not be sending the real thing.

The U.S. Congress has allocated more than \$130 million to deal with bioterrorism, but the all-important element of an effective response—the civilian response—has not been adequately funded. Limited hospital facilities, a consequence of the downsizing that accompanies managed care, are also a potential problem. Antibiotics can probably be readily stockpiled regionally so that several million doses will be on hand if needed, but vaccines are a problem. Industry estimates are that, if we start now, a smallpox vaccine probably would not be available to civilians until about 2002.

HIV Infection

The Department of Health and Human Services (DHHS) Guidelines on Antiretroviral Agents in Adults and Adolescents are the product of a committee of scientists, federal agencies, consumers, and pharmacists who meet monthly by telephone conference. All published versions of current guidelines are outdated by the time they are published, so the best source of the latest version is always the World Wide Web (<http://www.hivatis.org>). The guidelines address the issues of when to treat, what to treat with, when to change therapy, and what regimen to change to. Treatment recommendations for HIV change rapidly, and this document represents an important consensus statement regarding HIV management.

The 1998 experience with HIV outcomes continues to show great benefits with highly active antiretroviral therapy (HAART). One of the most important recent reports concerns the Swiss Cohort Study (13) of 2674 patients receiving protease inhibitors from 1995 through the end of 1998. This study showed that about 80% of patients had undetectable viral load (threshold of 400 copies/mL) after 12 months and that patients who were treatment naive had the best virologic outcome. The previously untreated patients were also less likely to have a virologic rebound within 2 years of the start of treatment. Monitoring of clinical events showed that the frequency of an AIDS-defining diagnosis was 7% in patients without detectable virus, 9% in those who rebounded from a virus-undetectable status, and 20% in patients who never had a substantial virologic response. One important lesson learned in

this and earlier studies is that even patients in whom HAART is considered to be a virologic failure may derive considerable—sometimes very impressive—clinical benefit from antiretroviral treatment.

The Health Cost and Service Utilization Study (HCSUS) is an important national prospective study of HIV care in the United States. Bozette and colleagues published a report from the HCSUS study, the first of at least 30 papers (14). They wanted to learn who is getting care, how much care they are getting, what it costs, and who is paying for it. The investigators in effect took a “snapshot” of the United States to randomly select metropolitan areas and certain rural areas, physicians within them, and HIV-infected patients from those practices. The conclusion: Roughly 335 000 patients are currently receiving care in the United States, and 49% of them have a CD4 count less than 200 cells/mm³, an indicator of relatively late-stage disease. About half of patients currently receiving care are homosexual men, who predominate in the western part of the country. Another one fourth, many of them in the northeastern United States, have used injection drugs, and 18% acquired HIV infection through heterosexual contact. Patients with HIV are disproportionately male and poor. Nearly half of all patients have a yearly income less than \$10 000. One in five have no insurance, and very few have private insurance. Patients who meet criteria for poverty and are enrolled in Medicaid predominate in the northeastern United States. In all, it is estimated that only 36% to 63% of HIV-infected patients are under care. Total costs for patients in care, based on estimates from the CDC for the number of persons living with HIV, are approximately \$6.7 billion, or about \$20 000/person per year. This sounds like a lot but is only about 1% of the health care budget (14).

Recent reports show that cesarean delivery can prevent the vertical transmission of HIV infection. One of these studies (16), from centers in Spain, France, Italy, Sweden, and the United Kingdom, distinguished between elective and emergency cesarean section and took maternal risk into account; these factors were omitted in previous reports. This randomized study, conducted from 1993 through 1998, determined the rate of perinatal transmission with HIV serology at 18 months. The risk for infant infection after elective cesarean section was 1.8% compared with 10.5% after vaginal delivery. It was even lower (less than 1%) when patients having cesarean section also received zidovudine. Postpartum complications were slightly more frequent after vaginal delivery (6.7% compared with 1.1%), but none were major (15). This report and others on the topic did not analyze data by the frequency of

transmission in women receiving HAART and the impact of viral load on transmission rates with cesarean section. Many authorities now believe that the risks associated with cesarean section outweigh the benefits among women who have a good virologic response (16).

Brosgart and colleagues (17) addressed the question of who should be caring for patients with AIDS. This study was prompted by the realization that HIV was previously considered a “primary care disease” but that the situation became complicated when complex treatment strategies began evolving in 1996 with the widespread use of protease inhibitors. Strong evidence suggests that patients do better if their physicians are experienced, but this does not necessarily mean that the physician should be a specialist in infectious diseases. Brosgart and colleagues used a mail survey in mid-1996 that asked care providers about their choice of treatment for a hypothetical patient and their knowledge of prophylaxis against *Mycobacterium avium* complex. Correct answers, according to DHHS guidelines, increased with the number of HIV-infected patients in the physician’s practice (17). “Expert” status in this area is uncredentialed, but most authors agree that 25 to 50 or more patients and possibly continuing medical education work are the most relevant qualifications. The HCSUS investigators (14) found that 75% of newly HIV-infected patients now see physicians who have a case load of at least 50 HIV-infected patients, whereas fewer than 3% see physicians who have fewer than 5 such patients. The community of physicians seems to have reached a consensus on who should be treating HIV disease, suggesting that legislation of expertise may not be necessary.

Emergence of HIV Resistant to Multiple Antiretroviral Drugs Is a Disturbing Trend

Hecht FM, Grant RM, Petropoulos CJ, et al. Sexual transmission of an HIV-1 variant resistant to multiple reverse-transcriptase and protease inhibitors. *N Engl J Med.* 1998;339:307-11.

Resistance has been documented with every antiviral compound developed to date, and antiretroviral drugs for HIV are no exception. This report describes a single patient with acute HIV infection caused by a strain shown by genotypic assays to be resistant to numerous antiretroviral drugs, including nucleoside reverse-transcriptase inhibitors and protease inhibitors. The source patient, who had a viral load of 28 000 copies/mL, had been exposed to multiple antiviral drugs. Resistance mutations in the index case matched those identified in the study patient.

Antiretroviral drugs are delivered over the long term, which favors the emergence of resistance. Un-

Table 3. Incidence of Sexually Transmitted Disease and HIV per 100 Person-Years among Royal Thai Army and Air Force Conscripts, Northern Thailand, 1991–1993 and 1993–1995*

Variable	1991–1993		1993–1995	
	Events	Incidence per 100 Person-Years (95% CI)	Events	Incidence per 100 Person-Years (95% CI)
	<i>n</i>	<i>n</i>	<i>n</i>	<i>n</i>
Gonorrhea	313	8.8 (7.8–9.8)	20	0.9 (0.6–1.4)
Syphilis	66	1.8 (1.4–2.4)	4	0.2 (0.06–0.48)
Nongonococcal urethritis	139	3.9 (3.3–4.6)	15	0.7 (0.4–1.1)
Chancroid	290	8.1 (7.2–9.1)	10	0.5 (0.24–0.84)
Any sexually transmitted disease	609	17.0 (15.7–18.4)	39	1.79 (1.3–2.4)
HIV	85	2.48 (2.00–3.07)	11	0.55 (0.30–0.99)

* A total of 2191 and 1549 participants contributed to the calculation of sexually transmitted disease incidence in 1991–1993 (3575 person years) and 1993–1995 (2183 person years), respectively; 1935 and 1371 participants contributed to the calculation of HIV incidence in 1991–1993 (3429 person years) and 1993–1995 (2007 person years), respectively. Reproduced with permission from Celentano DD, Nelson KE, Lyles CM, et al. Decreasing incidence of HIV and sexually transmitted diseases in young Thai men: evidence for success of the HIV/AIDS control and prevention program. *AIDS*. 1998;12:F29-36.

like with antibiotics, the ratio of toxic dose to therapeutic dose is low, often bringing exposure just to the edge of what is needed to inhibit HIV. Problems with adherence to treatment magnify the problem. Finally, HIV mutates more than any other known virus, including influenza virus. Hecht and colleagues' case confirms that resistant variants of HIV are transmissible. The implication is that wild-type strains will develop resistance as extensive community exposure to HIV in treated patients continues. It is obviously important to optimize resistance testing, use these drugs judiciously, and develop new drugs. Detection of resistant variants is currently advocated during primary infection or in the chronic phase when antiretroviral therapy has failed.

Program Encouraging Condom Use Reduced Rates of HIV and other Sexually Transmitted Diseases in Young Thai Men

Celentano DD, Nelson KE, Lyles CM, et al. Decreasing incidence of HIV and sexually transmitted diseases in young Thai men: evidence for success of the HIV/AIDS control and prevention program. *AIDS*. 1998;12:F29-36.

At the same time that HIV infection has become "endemic" rather than epidemic in the United States, with up to 50 000 new infections each year, the infection continues to explode epidemically in developing nations. An estimated 8% of adults in sub-Saharan Africa are infected, and, in the developing world as a whole, nearly 5 million new infections occur annually. Celentano and colleagues

describe one of the few successful government-sponsored efforts to control heterosexually transmitted HIV infection in a developing nation.

The Thai government, faced with an HIV epidemic that clearly was threatening the country's future, introduced a "100% Condom Program" in 1991 that was endorsed by all elements of society, including, most importantly, the brothels. In addition, messages on minimizing sexual risk were periodically reinforced during training. A prospective cohort of more than 4000 military conscripts, tested serologically every 6 months, experienced a greater than fourfold decline in HIV incidence. The rates of other sexually transmitted diseases, including syphilis, gonorrhea, and chancroid, were reduced even more (Table 3). Similar programs could prove effective in other countries, in Asia and elsewhere, that are subject to major epidemics of sexually transmitted HIV infection.

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