

## Update in Infectious Diseases

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This Update in Infectious Diseases focuses on 3 main topics: emerging and reemerging infections, public health and preventive medicine, and therapeutics. In the area of emerging and reemerging infections, important papers in 2005 shed new light on disease caused by methicillin-resistant *Staphylococcus aureus*, respiratory syncytial virus, *Clostridium difficile*-associated diarrhea, and influenza. There were new findings in the area of public health and preventive medicine regarding the treatment of recurrent sexually transmitted infections and the radiographic appearance of tuberculosis. Papers in therapeutics addressed the use of intrapleural streptokinase for pleural effusion and antibiotic prophylaxis for neutropenic patients. Changes to clinical practice emerging from these articles are shown in the Table.

### Emerging and Reemerging Infections

#### Community-Associated Methicillin-Resistant *Staphylococcus aureus* Infections Are Increasingly Common

Fridkin SK, Hageman JC, Morrison M, et al. Methicillin-resistant *Staphylococcus aureus* disease in three communities. *N Engl J Med*. 2005;352:1436-44. [PMID: 15814879]

Until this publication, the national importance of community-based methicillin-resistant *Staphylococcus aureus* (MRSA) infections was unknown. This paper conclusively demonstrated that MRSA infections are now a real problem throughout the United States, even among persons in the community who have no known risk factors.

On the basis of population-based surveillance in Baltimore, Maryland, and Atlanta, Georgia, and hospital laboratory-based sentinel surveillance of 12 hospitals in Minnesota from 2001 through 2002, the authors identified 12 553 patients with MRSA infections. They sought to distinguish community-acquired from health care-acquired MRSA infection. Health care-acquired infection was defined as infection in the following groups: people with previous MRSA isolation or those in whom MRSA was isolated at least 2 days after hospitalization; those who had surgery; those who were receiving dialysis; those who were residents of long-term care facilities; and those who had a venous catheter or a percutaneous medical device, such as a tracheotomy or a Foley catheter. Community-acquired infection was defined as infection in a person without these risk factors for health care-associated infection.

Although most infections were health care-associated,

the authors identified 1647 cases of community-associated MRSA infection, accounting for 8% to 20% of all MRSA infections in the 3 communities. Incidence was highest in individuals younger than 2 years of age (relative risk, 1.51 [95% CI, 1.19 to 1.92]). The infection led to hospitalization for 23% of patients. The community-associated infections typically presented as cellulitis or skin abscesses; 77% were skin or soft-tissue infections, and 10% were wound infections. Only 6% were invasive disease, including bacteremia, osteomyelitis, and septic arthritis, and only 2% were pneumonia. When pneumonia occurred, it tended to be severe and necrotizing. Initial treatment for 58% of the patients was a  $\beta$ -lactam antibiotic only, a drug that has no activity against MRSA. However, the outcomes in these patients were similar to those in patients who initially received an active drug because most of these infections were localized abscesses that required surgical drainage and healed with drainage alone.

The community-associated isolates had similar antimicrobial susceptibilities. All were susceptible to vancomycin. Ninety-seven percent were susceptible to trimethoprim-sulfamethoxazole, 98% were susceptible to rifampin, 96% were susceptible to linezolid, 88% were susceptible to tetracycline, 87% were susceptible to clindamycin, 65% were susceptible to ciprofloxacin, and 18% were susceptible to erythromycin. Of importance, many of the infections were quinolone-resistant, and most were macrolide-resistant.

In summary, the United States is in the midst of a national epidemic of community-associated MRSA infections. Clinicians now need to consider this organism as a potential pathogen in patients with suspected *S. aureus* infections acquired in the community. They should obtain cultures and follow up on results of susceptibility testing to be sure to prescribe the correct antimicrobial agent. Surgical drainage is recommended when feasible.

#### Outbreak of Community-Associated MRSA Infections among Professional Football Players

Kazakova SV, Hageman JC, Matava M, et al. A clone of methicillin-resistant *Staphylococcus aureus* among professional football players. *N Engl J Med*. 2005;352:468-75. [PMID: 15689585]

See also:

#### Web-Only

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Contact sports, such as football, lead to skin abrasions and soft-tissue injuries that put athletes at increased risk for infection. During the 2003 football season, an outbreak of MRSA infections occurred among members of the St. Louis Rams football team. The Centers for Disease Control and Prevention investigated this outbreak, conducting a retrospective cohort study of players to identify risk factors for infection and an observational study of on- and off-field activities and hygiene practices during competition and training. The investigators characterized the *Staphylococcus aureus* isolates and examined antimicrobial use.

In fall 2003, 8 MRSA infections occurred in 5 of 58 St. Louis Rams players. The infections occurred at the site of abrasions in 2 offensive linemen, 2 defensive linemen, and 1 linebacker. The infections rapidly evolved into abscesses measuring 5 to 7 cm in diameter on average; all required surgical drainage. Three of the 5 individuals developed a second abscess. Risk factors for infection included being a lineman (relative risk, 10.6 [CI, 1.3 to ∞];  $P = 0.02$ ) and having a higher body mass index. The average player received 2.6 antibiotic prescriptions per year, which is 10 times the rate for individuals of the same age and sex in the general population.

Hygiene was poor. Players shared towels on the field. Often, they did not shower before entering communal whirlpools. The weight training equipment was rarely cleaned, and when individuals with *S. aureus* skin colonization used the bench press, it was rarely cleaned before others used it. During that season, players from one of the Rams' opposing teams also developed abscesses due to the same organism.

The authors found that this community-associated MRSA infection was different in several ways from hospital-associated MRSA infections. The organism colonized the skin and almost never colonized the anterior nares. The football players' MRSA infections were all of the same clonal type—USA 300-0114—which contains a specific virulence factor (Panton–Valentine leukocidin cytotoxin) and chromosomal coding for antibiotic resistance (through staphylococcal–cassette–chromosome *mec* [SCC *mec*] type IVa resistance complex). Methicillin-sensitive *S. aureus* was present in 35 of 84 (42%) nasal swabs from players and staff, none of whom had a MRSA infection. No MRSA was found in environmental samples.

In summary, a single clone of MRSA that causes skin and soft-tissue infections appears to be transmitting infection by direct contact. Abscesses should be drained, and wounds should be covered with clean, dry dressings. Infected persons should practice good hand and personal hygiene to prevent transmission, and surfaces that are frequently touched should be cleaned appropriately.

### Health Care–Associated Endocarditis Due to *Staphylococcus aureus* Is an Increasing Problem Worldwide

Fowler VG Jr, Miro JM, Hoen B, et al. *Staphylococcus aureus* endocarditis: a consequence of medical progress. *JAMA*. 2005;293:3012-21. [PMID: 15972563]

### Table. Changes to Clinical Practice Emerging from Articles Important to Infectious Disease Specialists in 2005\*

#### Start

Including MRSA in the list of possible causes of community-acquired skin and soft-tissue infections (e.g., cellulitis and skin abscess): Send tissue cultures when appropriate, follow up on results of susceptibility testing to ensure that antibiotic coverage is adequate, and counsel patients to practice good hand and personal hygiene to prevent direct MRSA transmission

Discontinuing metronidazole therapy and beginning oral vancomycin therapy for patients with *Clostridium difficile* infection if there is no clear evidence of clinical improvement within 2 days and if the infection is acquired in hospitals with an increase in cases over baseline

Discussing with patients who have gonorrhea or chlamydia the need for treatment of their sexual partners; consider offering treatment to partners directly through the patient in states where such treatment is legal

Administering varicella zoster virus vaccine (Zostavax, Merck and Co., Inc., Whitehouse Station, New Jersey) to immunocompetent patients age  $\geq 60$  year†

#### Consider

Limiting use of antibiotics associated with *C. difficile*-related diarrhea (clindamycin, newer cephalosporins, quinolones) in hospitals with a sudden increase in case numbers or evidence of more severe disease

Routine antibiotic prophylaxis, probably with a quinolone, in patients with hematologic malignant disease who are (or are likely to be) neutropenic because of cancer chemotherapy

#### Stop

Using chest radiographic criteria to distinguish recently acquired tuberculosis infection from remotely acquired infection with reactivation  
Using intrapleural streptokinase to facilitate drainage of pleural fluid infection

\* MRSA = methicillin-resistant *Staphylococcus aureus*.

† Evidence reviewed in reference 1. Recommendation discussed in full at the 2006 Update in Infectious Diseases at the Annual Session of the American College of Physicians, Philadelphia, Pennsylvania, 6–8 April 2006.

Infective endocarditis due to *S. aureus* has traditionally been viewed as a community-acquired infection associated with injection drug use. In this study, the authors used a prospective observational cohort obtained from 39 medical centers in 16 countries from June 2000 to December 2003 to assess the emerging significance of *S. aureus* as a cause of infective endocarditis, including that associated with health care contact.

According to the Duke criteria for diagnosis, 1779 patients with definite infective endocarditis were enrolled. *Staphylococcus aureus* was found to be the most common pathogen, affecting 558 patients (31.4% [range, 26% in Australia/New Zealand to 54% in Brazil]). By comparison, viridans streptococci accounted for 18% of cases.

Health care–associated infective endocarditis was defined as nosocomial (developing after more than 48 hours of hospitalization) or non-nosocomial (diagnosed within 48 hours of admission in a person with extensive health care contact, for example, home intravenous therapy, hemodialysis or intravenous chemotherapy, recent hospitalization, or residence in a nursing home). Health care–associated infective endocarditis related to *S. aureus* was seen in 218 patients (39%) and was almost twice as common as community-acquired infection associated with injection

drug use (117 patients [21%]). Patients with *S. aureus*-related infective endocarditis were more likely than those with infective endocarditis not related to *S. aureus* to have health care-associated disease ( $P < 0.001$ ); of these, 131 patients (60%) had nosocomial infection and 87 (40%) had non-nosocomial health care-associated infection. In a multivariate analysis, patients with health care-associated infective endocarditis were more likely to have infection due to MRSA (odds ratio, 3.4 [CI, 2.1 to 5.5]).

In summary, this international study points out several new features of *S. aureus*-related infective endocarditis. Worldwide, *S. aureus* is now the leading cause of infective endocarditis, and health care-associated infection is the most common form of *S. aureus*-related infective endocarditis, accounting for one quarter to half of cases depending on the geographic region. In many people, including those who are not hospitalized, a long-term intravascular device was the source of bacteremia leading to infective endocarditis. In the United States, almost one third of patients developed non-nosocomial health care-associated infective endocarditis, and a long-term central catheter was the presumed source in approximately 20%. The epidemiologic characteristics of infective endocarditis due to *S. aureus* have evolved, and the disease is now clearly a consequence of medical progress.

### The Disease Burden of Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults Is Similar to That of Nonepidemic Influenza

Falsey AR, Hennessey PA, Formica MA, et al. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med*. 2005; 352:1749-59. [PMID: 15858184]

Pediatricians know about the importance of respiratory syncytial virus (RSV), but internists do not. In 1957, RSV was identified as the cause of bronchiolitis in children, and it was recognized as a potentially serious problem in adults in the 1970s after outbreaks occurred in extended care facilities. Some subsequent small, hospital-based studies have suggested that RSV might be an important cause of illness in elderly persons, but data have been lacking. The authors conducted this prospective study over 4 consecutive winters in Rochester, New York, to examine the epidemiology and clinical effects of RSV in community-dwelling elderly persons and high-risk adults.

The authors recruited participants for the study by using advertisements and mailings from health maintenance organizations and cardiopulmonary rehabilitation programs. Participants were entered into 1 of 3 cohorts: healthy adults at least 65 years of age ( $n = 608$ ), high-risk adults at least 21 years of age with chronic heart and lung disease ( $n = 540$ ), and hospitalized patients at least 65 years of age with respiratory symptoms and underlying cardiopulmonary disease ( $n = 1388$ ). When any of the participants developed respiratory symptoms or worsening

cardiopulmonary symptoms, a health care provider evaluated them clinically, and specimens were sent for diagnosis of RSV and influenza by culture, reverse transcriptase polymerase chain reaction, and serologic tests.

The authors evaluated 2514 illnesses, roughly half of which occurred in the hospitalized patients. They diagnosed RSV infection and influenza A in 102 and 44 participants in the outpatient cohorts and 142 and 154 of the hospitalized patients, respectively. The signs and symptoms of infection due to RSV and influenza were virtually identical.

In the healthy elderly patients, RSV infection developed in 3% to 7% annually and generated fewer office visits than influenza. In the high-risk adults, RSV infection developed in 4% to 10% annually and caused 23% to call their physicians, 29% to visit their physicians, and 9% to visit an emergency department; 16% were hospitalized. In these individuals, RSV infection was responsible for 11% of all hospitalizations for pneumonia, 11% of all hospitalizations for exacerbations of chronic obstructive pulmonary disease, 5% of all hospitalizations for congestive heart failure, and 7% of all hospitalizations for asthma. In the hospitalized adults, RSV infection and influenza produced similar lengths of stay, similar use of the intensive care unit (15% for RSV and 12% for influenza), and similar mortality rates (8% for RSV and 7% for influenza).

In summary, this study demonstrated that RSV is an important cause of serious illness in elderly persons and in high-risk adults. The disease burden is similar to that of nonepidemic influenza, causing an estimated 175 000 hospitalizations and approximately 14 000 deaths in U.S. adults annually. These findings indicate the need for an RSV vaccine for adults as well as for children.

### Dangerous *Clostridium difficile* Illness Is Growing More Common

Pepin J, Valiquette L, Alary ME, et al. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. *CMAJ*. 2004;171:466-72. [PMID: 15337727]

Pepin J, Alary ME, Valiquette L, et al. Increasing risk of relapse after treatment of *Clostridium difficile* colitis in Quebec, Canada. *Clin Infect Dis*. 2005;40:1591-7. [PMID: 15889355]

Warny M, Pepin J, Fang A, et al. Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. *Lancet*. 2005;366:1079-84. [PMID: 16182895]

McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med*. 2005;353: 2433-41. [PMID: 16322603]

Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-

institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med*. 2005;353:2442-9. [PMID: 16322602]

An epidemic of severe, antibiotic-related colitis caused by an emerging strain of *Clostridium difficile* is occurring in North America. The strain is less responsive to treatment, and it causes more complications and relapses. Five recently published papers described important factors related to this emerging new strain.

The first 2 papers described an increase in the incidence of *C. difficile*-associated diarrhea in Québec, Canada. Incidence grew from 36 per 100 000 people in 1991 to 153 per 100 000 people in 2003. Among people at least 65 years of age, incidence of *C. difficile*-associated diarrhea increased from 102 per 100 000 patients in 1991 to 867 per 100 000 patients in 2003. The number of cases with complications (megacolon, perforation, colectomy, shock requiring vasopressor therapy, and rates of death within 30 days after diagnosis) also increased from 7% (12 of 169 patients) in 1991 to 18% (71 of 390 patients) in 2003 ( $P < 0.001$ ). Rates of deaths within 30 days of diagnosis increased from 5% (8 of 169 patients) to 14% (54 of 390 patients) ( $P < 0.001$ ).

The strain responsible for the epidemic was more common in health care-associated disease (67% of cases) than in community-associated disease (37% of cases). The reasons behind the virulence of this emerging strain of *C. difficile* appear to be related to its molecular makeup. Investigators studied 2 genes—*tcdA* (toxin A) and *tcdB* (toxin B)—that are responsible for production of the cytotoxin and enterotoxin in *C. difficile*. The peak median concentrations of these toxins were 16 and 23 times higher, respectively, in the emerging strain of *C. difficile* than in 12 different existing strains of *C. difficile* ( $P < 0.001$  for both toxins).

The fourth paper was a U.S. study of 187 *C. difficile* isolates collected from 8 health care facilities in 6 states (Georgia, Illinois, Maine, New Jersey, Oregon, and Pennsylvania) in which outbreaks of *C. difficile*-associated disease had occurred between 2000 and 2003. The study also detected a deletion in a feedback gene that controls toxin production—*tcdC*—and might result in increased production of toxins A and B.

Quinolones appeared to be a new risk factor for *C. difficile*-associated diarrhea. Researchers in the Québec studies determined that this emerging strain was almost universally resistant to quinolones, a quality occurring only approximately 40% of the time in the other strains of *C. difficile*. Clindamycin resistance was similar to that of earlier strains. The authors determined that taking quinolone antibiotics was a risk factor for *C. difficile* infections.

For initial treatment of this new strain, vancomycin was found to be superior to metronidazole. In the second paper from Québec, the proportion of *C. difficile*-infected

patients who were switched from metronidazole to vancomycin or who had vancomycin added to metronidazole stayed at approximately 10% between 1991 and 2002; in 2003, it increased to 26%. Patients initially treated with vancomycin had a 79% lower risk for progressing to complications compared with those who were initially treated with metronidazole (adjusted odds ratio, 0.2 [CI, 0.06 to 0.8];  $P = 0.02$ ). The recurrence rate in individuals treated initially with metronidazole increased from 21% from 1991 to 2002 to 47% in 2003.

In summary, a new strain of *C. difficile* has appeared in several North American communities and is likely to spread more widely. Compared with the “old” *C. difficile* to which we are accustomed, this isolate causes more severe and life-threatening illness, particularly in elderly persons. Patients being treated initially with metronidazole who do not have a clear clinical response within 2 days should be switched to oral vancomycin. Prevention efforts in hospitals should include hand washing with soap and water as a supplement to alcohol-based sanitizers and rigorous use of barrier precautions and isolation. Hospitals noting an increase in case numbers over time or evidence of more severe disease should institute antibiotic stewardship programs to limit use of implicated agents, including clindamycin, second- and third-generation cephalosporins, and fluoroquinolones.

#### The 1918 Influenza Pandemic Was Caused by a Remarkably Virulent Strain

Tumpey TM, Basler CF, Aguilar PV, et al. Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science*. 2005; 310:77-80. [PMID: 16210530]

The 1918–1919 influenza pandemic killed approximately 50 million people around the world, including 675 000 people in the United States. In some communities in the United States, 10% of the population died in a 2-week period. This epidemic, unlike earlier epidemics, produced an unusually high mortality rate in healthy individuals between the ages of 15 and 34 years and lowered the life expectancy in 1 year by 10 years. A similarly high mortality rate has not been seen in any other influenza outbreak.

In this investigation, the authors studied the virulence properties of the 1918 influenza virus. Using a sample of the virus recovered from the body of an Alaskan flu victim preserved in permafrost since the epidemic, they used reverse genetics to develop the complete virus coding sequence bearing all 8 gene segments. They then compared the reconstructed virus with control viruses, including contemporary human influenza viruses and the avian flu virus; they also made various recombinant viruses, including one that had 7 of the 8, but not all 8, of the 1918 genes.

The authors found that, compared with the control viruses, the 1918 virus replicated in the absence of the pathogenesis factor trypsin and, 4 days after intranasal inoculation into mice, produced lung titers of virus as much

as 39 000 times greater than those of any of the other viruses. This caused severe lung injury. The virus was 100 times more lethal in mice than any other virus.

Of note, all 8 of the 1918 genes were more closely related to those of today's bird flu viruses than any mammalian virus. This suggests that the 1918 virus did not originate through a reassortment of bird and human viruses but rather jumped directly from birds to humans and adapted to them. The study of this virus might enable recognition of the potential public health threat of new viruses and may help to control pandemic influenza.

### Documentation of Person-to-Person Transmission of Avian Influenza Virus

Ungchusak K, Auewarakul P, Dowell SF, et al. Probable person-to-person transmission of avian influenza A (H5N1). *N Engl J Med*. 2005;352:333-40. [PMID: 15668219]

Scientists have identified 3 main subtypes of influenza that circulate in humans: H1N1, H1N2, and H3N2. In late 2003 and early 2004, they also identified the avian subtype H5N1 in humans after it crossed the species barrier. Large outbreaks of H5N1 infection occurred in poultry in Southeast Asia, and the virus infected 44 humans, killing 32.

Exposure to sick or dying poultry was documented in most of these recent human cases of avian influenza. No evidence of efficient person-to-person transmission was reported until this case study of an 11-year-old girl in a village in Thailand who became ill with fever, cough, sore throat, and dyspnea 3 to 4 days after exposure to dying household chickens. She was hospitalized and died 6 days after the onset of illness. Both her 26-year-old mother, who had no bird exposure and came from another city to care for her, and her 32-year-old aunt, with whom the girl lived and who also cared for her, caught the virus. The mother died of pneumonia after providing 16 to 18 hours of unprotected nursing care to her daughter, and the aunt also developed pneumonia but lived.

Field teams isolated and treated the aunt, instituted active surveillance for the disease, provided prophylaxis to exposed contacts, and removed the remaining poultry in the affected village. They tested specimens from family members by viral culture, serologic analysis, immunohistochemical assay, reverse transcriptase polymerase chain reaction, and genetic sequencing. Autopsy tissue from the mother and throat swabs from the aunt were positive for H5N1 influenza by reverse transcriptase polymerase chain reaction, and the gene sequences clustered closely with other bird influenza isolates. Influenza is typically a tracheobronchitis, and most people with influenza have normal chest radiographs. In these 3 cases of avian influenza, however, the radiographs showed severe pulmonary infiltrates.

This small family cluster—with infection of the mother who lived in a distant city but then provided direct in-

hospital care to the index case-patient—strongly supports the occurrence of person-to-person transmission. So far—fortunately, considering the highly lethal nature of this influenza—such transmission has been extraordinarily rare.

## Public Health and Preventive Medicine

### Expedited Treatment of Sex Partners Reduced Persistent and Recurrent Gonorrhea and Chlamydial Infection

Golden MR, Whittington WL, Handsfield HH, et al. Effect of expedited treatment of sex partners on recurrent or persistent gonorrhea or chlamydial infection. *N Engl J Med*. 2005;352:676-85. [PMID: 15716561]

Public health resources for the control of sexually transmitted infections (STIs) are limited, with funds being diverted to bioterrorism preparedness and HIV management. Partner notification is the central approach to STI control; however, in the areas of the United States where STI rates are the highest, health departments provide partner notification for fewer than 20% of patients with gonorrhea or chlamydial infection. Not surprisingly, as a result, re-infection and further transmission are common. New approaches are needed.

In this randomized trial, the authors compared the effectiveness of expedited treatment for sex partners of patients with gonorrhea or chlamydial infection with that of standard partner referral for treatment to see whether the former approach might reduce rates of persistent or recurrent infection. They studied 1860 women and heterosexual men with gonorrhea or chlamydial infection who had at least 1 untreated partner with contact information. Patients in the expedited treatment group were offered treatment packets to give to their sex partners; partners were also able to obtain packets at STI clinics, at pharmacies, or by direct mail. The packet for partners of patients with gonorrhea contained a single 400-mg dose of cefixime and a 1-g sachet of azithromycin; partners of patients with chlamydia received azithromycin alone. Packets also included condoms, information about medicines, warnings about side effects, information to contact study staff, and a booklet about preventing STIs. Patients assigned to standard partner referral were told to ask their partners to seek care and to tell them that they could receive free care at the STI clinic. The primary outcome was persistent or recurrent gonorrhea or chlamydial infection in patients 3 to 19 weeks after treatment.

On follow-up evaluation, the authors found that the presence of infection was statistically significantly less common in the expedited treatment group. Persistent or recurrent gonorrhea or chlamydial infection occurred in 92 of 929 (10%) patients in the expedited treatment group compared with 121 of 931 patients (13%) in the standard partner referral group (relative risk, 0.76 [CI, 0.59 to

0.98]). In particular, expedited treatment reduced the rate of persistent or recurrent infection among patients with gonorrhea by 73% (11% in the standard referral group vs. 3% in the expedited treatment group;  $P = 0.01$ ) and reduced the rate of persistent or recurrent infection among patients with chlamydia by 15% (13% in the standard referral group vs. 11% in the expedited treatment group;  $P = 0.17$ ). The  $P$  value was 0.05 for the comparison of treatment effects. Patients in the expedited treatment group more often reported that their partners had been treated and less often reported having sex with untreated partners. There were no adverse drug effects.

In summary, expedited treatment of sex partners provided an effective approach for reducing rates of persistent or recurrent gonorrhea or chlamydial infection. Of note, the expedited treatment program did not provide opportunities to test partners for other STIs, such as HIV infection, or to offer risk reduction counseling, cervical cancer screening, hepatitis vaccination, or advice about contraception. The legality of patient-delivered partner therapy is not straightforward: In some states it is legal, in some it is illegal, and in some the law is unclear. Nevertheless, this is a new and effective model of partner care that circumvents traditional evaluation by a clinician but increases the likelihood that an exposed partner will get proper therapy and reduces the original patient's risk for re-infection.

#### **Radiographic Appearance of Tuberculosis Was Not Predicted by the Time from Acquisition of Infection to Development of Clinical Disease**

**Geng E, Kreiswirth B, Burzynski J, et al.** Clinical and radiographic correlates of primary and reactivation tuberculosis: a molecular epidemiology study. *JAMA*. 2005;293:2740-5. [PMID: 15941803]

Traditional teaching about active tuberculosis holds that certain features on a chest radiograph (mid-lung infiltrates, adenopathy, and pleural effusion) reflect acute primary disease from recent infection while others (upper-lobe infiltrates and cavities) reflect reactivation of disease acquired earlier in life. This teaching is not based on well-established clinical evidence. It is possible that chest radiograph features may depend not on characteristics of the tuberculosis infection itself, such as the time since acquisition, but on the host's immune response to the infection. Atypical chest radiograph features (lower-lobe infiltrates, adenopathy, and effusions) are commonly seen with HIV-associated tuberculosis.

In this retrospective study in New York City, the authors examined the clinical and radiographic correlates of primary and reactivation tuberculosis in 456 patients with pulmonary tuberculosis who were treated between 1990 and 1999 and had at least 1 positive respiratory culture for *Mycobacterium tuberculosis* and available radiographic data. Primary and reactivation infection were defined by using DNA fingerprinting. The authors assumed that similar DNA fingerprints in isolates from different patients repre-

sented clustering of infection caused by recent transmission and that a unique DNA pattern represented reactivation of infection acquired somewhere else or at a more remote time. The authors sought to correlate these DNA patterns with radiographic appearance using 6 radiographic features: upper-lobe infiltrate, cavitory lesion, adenopathy, effusions, lower- or mid-lung zone infiltrate, and miliary pattern. They considered radiographs typical if the films displayed an upper-lobe infiltrate or cavity, regardless of whether other features were present, and atypical if they had adenopathy, effusion, or lower- or mid-lung zone infiltrates or had none of the described features.

The authors found that HIV infection was the most statistically significant predictor of radiographic appearance and that DNA cluster status did not predict appearance. Infection with HIV was associated with atypical patterns regardless of whether the fingerprinting indicated recent infection or reactivation (odds ratio for the association between HIV infection and typical radiographic appearance, 0.20 [CI, 0.13 to 0.31]). A clustered fingerprint, representing recently acquired disease, was associated with an atypical radiograph in univariate analysis (odds ratio for the association between clustering and typical radiographic appearance, 0.68 [CI, 0.47 to 0.99]). However, the association became insignificant when adjusted for HIV status.

In summary, traditional teaching about the relationship between radiographic appearance and the time of tuberculosis infection (recent vs. past with reactivation) turns out to be wrong. The time from acquisition of tuberculosis infection to development of clinical disease does not reliably predict radiographic appearance. Radiographic appearance in tuberculosis says more about the host immune status than about the timing of disease acquisition.

#### **Therapeutics**

##### **Intrapleural Administration of Streptokinase Did Not Benefit Patients with Empyema**

**Maskell NA, Davies CW, Nunn AJ, et al.** U.K. controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med*. 2005; 352:865-74. [PMID: 15745977]

Published guidelines recommend intrapleural fibrinolytic agents to aid chest tube drainage of empyemas. These recommendations, however, are based on small trials and case series with very few patients. In this multicenter, randomized, double-blind trial from the United Kingdom, the authors assessed the therapeutic role of intrapleural streptokinase in patients with infected pleural fluid. They enrolled patients with pleural infection (defined by the presence of purulent pleural fluid or pleural fluid with a pH <7.2 with signs of infection or by proven bacterial invasion of the pleural space) to receive intrapleural streptokinase (250 000 IU twice daily for 3 days) or placebo. Patients also received routine care, including antibiotics, chest tube drainage, and

surgery. The average duration of symptoms before entering the study was approximately 2 weeks; 80% of the empyemas were secondary to community-acquired pneumonia, and 7% were secondary to nosocomial pneumonia.

The primary end point was the number of people who died or required surgical drainage during the first 3 months after randomization. Secondary end points were the rate of death from surgical drainage after 1 year, the duration of hospital stay, residual radiographic changes, dynamic lung volumes, and antistreptokinase antibody levels compared with baseline.

Sixty-four of 206 patients (31%) in the streptokinase group died or needed surgical drainage compared with 60 of 221 (27%) in the placebo group, a nonsignificant difference (relative risk, 1.14 [CI, 0.85 to 1.54];  $P = 0.43$ ). Streptokinase had no beneficial effect on postsurgical mortality rates at 1 year, residual radiographic changes, or length of hospital stay. Streptokinase seemed likely to be associated with a higher rate of serious adverse events (chest pain, fever, or allergy): 7% versus 3% (relative risk, 2.49 [CI, 0.98 to 6.36];  $P = 0.08$ ). Of note, levels of antistreptokinase antibodies increased in the patients who received streptokinase, an event that might be important if these people later presented with myocardial infarction and were given streptokinase.

In summary, intrapleural administration of streptokinase did not benefit patients with pleural infection and may have caused some harm. Streptokinase is therefore no longer recommended.

### Antibiotic Prophylaxis Reduced Mortality Rates among Neutropenic Patients Undergoing Cytotoxic Therapy

Gafter-Gvili A, Fraser A, Paul M, et al. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. *Ann Intern Med.* 2005;142:979-95. [PMID: 15968013]

Bacterial infections are a well-known cause of morbidity and death in patients who are neutropenic because of chemotherapy for cancer. Because clinical trials have shown that prophylactic antibiotics decrease infections but not mortality rates, the current Infectious Diseases Society of America guidelines do not recommend prophylactic antibiotics for patients with cancer and neutropenia.

The authors of this meta-analysis examined 95 randomized, controlled trials published between 1973 and 2004 that investigated the effects of prophylactic antibiotics in more than 9000 afebrile neutropenic patients receiving chemotherapy for cancer. Fifty-two of the 95 trials addressed quinolone prophylaxis. Controls used in the trials included placebo, no intervention, or prophylaxis with

another antibiotic. Two reviewers independently reviewed the quality of the trials and extracted data. There was no pharmaceutical industry support for the study.

The authors found that antibiotic prophylaxis statistically significantly decreased all-cause risk for death compared with placebo or no treatment (relative risk, 0.67 [CI, 0.55 to 0.81]). It also reduced infection-related death (relative risk, 0.58 [CI, 0.55 to 0.81]). Fluoroquinolones in particular reduced the risk for all-cause mortality (relative risk, 0.52 [CI, 0.35 to 0.77]) and for infection-related death, fever, clinically documented infections, and microbiologically documented infections.

Prophylactic antibiotics were associated with an increased risk for adverse events, such as allergic reactions (relative risk, 1.69 [CI, 1.14 to 2.50]). There was no evidence in these studies of an increased risk for fungal infections, a concern when antibiotic prophylaxis is administered to neutropenic individuals.

The meta-analysis had some limitations. It might not have accounted for all negative results, which tend to be underreported in the literature. Most of the studies occurred in the setting of hematologic malignant disease, not solid-tumor chemotherapy settings. Ten of the 50 trials comparing prophylaxis with no prophylaxis lacked data on all-cause mortality. The benefit of prophylaxis appeared to be less in higher-quality studies, although there was still demonstrable benefit. Also, in 78 of the 95 trials, antibiotics were started when the patient began chemotherapy, not when the patient became neutropenic.

In summary, the benefits of antibiotic prophylaxis probably outweigh the harms in most patients with hematologic cancer and neutropenia. The data suggest that fluoroquinolones are the preferred antibiotic class. On the basis of this study, guidelines that recommend against antibiotic prophylaxis in these patients, or that make no recommendations, should probably be reconsidered.

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