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This Update in Infectious Diseases reviews important literature from 2004 related to infectious diseases. The year had significant achievements, including substantial progress in the area of antiviral therapy for hepatitis B and C. The severe acute respiratory syndrome (SARS) was defeated; although we may not be able to fully attribute its disappearance to the public health efforts of the World Health Organization, the agency showed great leadership during a period of crisis. Intensive intervention also prevented a major public health crisis from materializing after the Asian tsunami. Within 48 hours, 60 major organizations established a presence in the area to provide antibiotics and to vaccinate disaster victims against measles. The year also introduced several new challenges; perhaps the greatest was the threat of avian influenza, which loomed large as yet another example of nature's mockery of man. The following papers represent the medical reports that guided research in the field in 2004.

Haemophilus influenzae Infection

Sputum Cultures Underestimated the Frequency of Colonization of the Respiratory Tract by Haemophilus influenzae in Chronic Obstructive Pulmonary Disease

Murphy JF, Brauer AL, Schiffmacher AT, et al. Persistent colonization by Haemophilus influenzae in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2004;170:266-72. [PMID: 15117742]

In this study, the authors investigated the role played by Haemophilus influenzae in chronic obstructive pulmonary disease (COPD), particularly in exacerbations of chronic bronchitis. The researchers performed monthly sputum cultures on 104 patients with COPD between 1994 and 2000 during 3009 monthly clinic visits.

In 17 instances involving 10 patients, initial sputum cultures grew Haemophilus influenzae, but repeated cultures obtained for 6 months or longer showed no growth. In every case, the negative cultures were then followed by cultures that again showed growth of the same strain. The investigators studied these episodes in detail to test the

hypothesis that the interim periods represented continuous colonization by the same strain of *Haemophilus influenzae* despite an inability to detect it.

The researchers used 3 methods of molecular typing to learn if the strain observed after the period of negative cultures was new or identical to the preceding strain. Molecular analysis showed that the later strain was identical to the earlier strain, suggesting persistence. Although the researchers were concerned that cultures may have been negative because saliva was analyzed instead of sputum, they later dismissed this possibility because fibrinogen was present in the samples. A review of clinical records also allayed the concern that antibiotics interfered with culture results. These results suggest that some patients with COPD have persistent colonization of *Haemophilus influenzae*, and sputum cultures may underestimate the frequency of colonization. Failure to detect *Haemophilus influenzae* from sputum cultures did not necessarily mean that it was not present; the organism may have just been undetectable with the standard culturing methods that were performed.

The same research group reported in a previous study that one third of patients with exacerbations of COPD are found to have a new microbial strain of *Haemophilus influenzae* (1). A subsequent report showed that these new strains generated an immune response in 22 of 36 episodes (61%) (2). This information, coupled with the newest research findings, suggests that the presence of the persistent strains may play an important role in understanding the host response in exacerbations. Earlier reports from the same research group also suggested that *Moraxella catarrhalis* is the second most common bacterial pathogen after *Haemophilus influenzae* and that *Streptococcus pneumoniae* is the third most common. If these findings are true, and if bacteria are responsible for some exacerbations, the American College of Physicians' current recommendations for antibiotic selection-amoxicillin, trimethoprim-sulfamethoxazole, or doxycycline (3)-would need to be reconsidered because amoxicillin is inactive against 40% of *Haemophilus influenzae* strains and 95% of *Moraxella catarrhalis* strains. Although physicians should not automatically dismiss a bacterial cause for disease exacerbations merely because sputum cultures show no growth, many exacerbations probably are related to viral infection, environmental factors, or other noninfectious conditions. The roles of bacteria and antibiotics are still unclear, and clinicians do not have good tools to distinguish exacerbations caused by bacterial infection from those caused by viral infection or other factors, such as environmental pollution or smoking.

Pneumonia

Antibiotic Administration within 4 Hours Prevented Deaths in the Medicare Population

Houck PM, Bratzler DW, Nsa W, et al. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med.* 2004;164:637-44. [PMID: 15037492]

Each year, 600 000 or more Medicare patients require hospitalization for pneumonia. A previous analysis of charts from more than 12 000 Medicare patients revealed that mortality rates increased significantly if antibiotics were not administered within 8 hours after the patient entered the emergency department (4). This study updates that

research by asking if rapid administration of antibiotics after arrival at the hospital affects outcomes in Medicare patients with community-acquired pneumonia.

The investigators studied 18 209 medical records, a random sample from a national database of Medicare patients 65 years of age and older who were hospitalized with community-acquired pneumonia from July 1998 through March 1999. They tracked the following outcomes: severity-adjusted mortality rates, readmission within 30 days of discharge, and length of stay.

After a careful analysis of multiple variables, the investigators found that antibiotic administration within 4 hours after arrival was associated with a statistically significant reduction in mortality rates and length of stay. Among the 13 771 (75.6%) patients who had not received outpatient antibiotic agents, mortality rates were 6.8% for those who received treatment within 4 hours after arriving at the emergency department compared with 7.4% for those who did not receive treatment until later (adjusted odds ratio, 0.85 [95% CI, 0.74 to 0.98]). Early treatment was also associated with fewer deaths within 30 days of admission (11.6% vs. 12.7%; adjusted odds ratio, 0.85 [CI, 0.76 to 0.95]); these differences were statistically significant ($P = 0.005$). Rapid therapy was also associated with a reduced length of stay.

Physicians often deliberate about which antibiotic to use in patients with community-acquired pneumonia (5), but this study demonstrates that prompt administration of antibiotics is also extremely important. These findings led the Center for Medicare & Medicaid Services to reevaluate the "8-hour rule" when it established the criteria for its quality assurance program. This initiative, which seeks to refine and standardize management guidelines for common conditions by analyzing hospital performance data, will probably play a role in Medicare's anticipated "pay for performance" plan.

Gastroenteritis

Better Outbreak Surveillance and Data Collection Would Help Identify Common Sources of Gastroenteritis

Widdowson MA, Cramer EH, Hadley L, et al. Outbreaks of acute gastroenteritis on cruise ships and on land: identification of a predominant circulating strain of norovirus-United States, 2002. *J Infect Dis.* 2004;190:27-36. [PMID: 15195240]

Norovirus, first described in 1982 after outbreaks of gastroenteritis in nursing homes, is one of the most common causes of epidemic gastroenteritis. The frequency of norovirus-associated outbreaks increased in 2002 on cruise ships and on land, which led the authors to try to identify a common strain or source. They conducted their investigation by using the reverse transcriptase polymerase chain reaction technique, which is more sensitive than traditional assays for norovirus detection and can provide information on the molecular epidemiology of outbreaks.

The authors identified the norovirus pathogen in 11 of 14 laboratory-confirmed outbreaks of gastroenteritis on cruise ships. Of these 11 cases, 7 involved a relatively new strain of the virus that was identified as the "Farmington Hills strain." The virus infected 2278 of 27 168 (8.3%) passengers, with transmission usually occurring from person to person.

Land-based outbreaks of norovirus infections occurred in many settings, including at a birthday party, daycare center, restaurant, and nursing home. The virus was transmitted from person to person or through contaminated food (primarily salads and sandwiches, not food that was heated); 1 community outbreak spread through a contaminated water supply. The Farmington Hills strain was implicated in 10 of 22 land-based outbreaks from May 2002 to December 2002. Current guidelines recommend the use of simple hygiene methods to control spread of the virus. This strategy is frequently ineffective, however, because 1) there are multiple mechanisms of transmission, 2) norovirus persists in stool for 2 weeks after recovery, and 3) the virus can persist on surfaces for more than 1 week. Of note, 3 of the cruise ship outbreaks were recurrences in ships that were removed from service for assiduous cleaning after previous norovirus contamination. This organism is clearly difficult to eradicate.

The authors also observed that norovirus gastroenteritis is generally characterized by vomiting and diarrhea that last for an average of 2 to 3 days; however, approximately 30% of people who are infected are asymptomatic carriers who therefore may go unidentified. To prevent widespread outbreaks, physicians should suspect possible norovirus infection when a common link is found among patients with vomiting and diarrhea. The widely varied features of the land-based outbreaks suggest that control measures should also address the possibility that the virus may be transmitted through food and water supplies.

Helicobacter pylori Infection

Helicobacter pylori Infection Was Associated with a Slightly Increased Prevalence of Heartburn but Not Gastroesophageal Reflux

Harvey RF, Lane JA, Murray LJ, et al. Randomised controlled trial of effects of Helicobacter pylori infection and its eradication on heartburn and gastro-oesophageal reflux: Bristol helicobacter project. *BMJ*. 2004;328:1417. [PMID: 15126313]

The investigators in this study wanted to better define the effects of Helicobacter pylori infection on the prevalence of heartburn and gastroesophageal reflux. They studied 10 537 persons between 20 and 59 years of age from 7 general practices in Bristol, England. All participants were given a ¹³C-urea breath test. Among the 2400 individuals with confirmed Helicobacter pylori infection, the investigators found increased occurrences of heartburn (odds ratio, 1.14 [CI, 1.05 to 1.23]); the prevalence of gastroesophageal reflux, however, was not increased in this group (odds ratio, 1.05 [CI, 0.97 to 1.14]). They then randomly assigned half of the Helicobacter pylori-infected patients to receive treatment with ranitidine and clarithromycin and the other half to receive placebo.

Infection with Helicobacter pylori was eradicated in 91% of the active treatment group, but the 2 groups had similar prevalences of heartburn (odds ratio, 0.99 [CI, 0.88 to 1.12]) and reflux (odds ratio, 1.04 [CI, 0.91 to 1.19]). Active treatment had no effect on preexisting symptoms of heartburn or reflux.

This study supported the belief that increased acid secretion associated with Helicobacter pylori infection increases the prevalence of heartburn but has no bearing on the mechanical integrity of the lower esophageal sphincter, which would explain

why reflux was not observed more frequently in this sample. Physicians should be aware that successful treatment of the infection will not offer relief to patients with preexisting heartburn or reflux symptoms.

Hepatitis B

Lamivudine Reduced the Risk for Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Infection

Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med.* 2004; 351:1521-31. [PMID: 15470215]

The investigators wanted to determine the utility of antiviral therapy for preventing disease progression in patients with chronic hepatitis B virus (HBV) infection and advanced fibrosis or cirrhosis. The study enrolled 651 patients (98% Asian and 85% men) with histologically confirmed cirrhosis or advanced fibrosis. Participants were randomly assigned in a 2:1 ratio to receive 100 mg of lamivudine per day (n = 436) or placebo (n = 215) for up to 5 years.

Compared with placebo, lamivudine therapy produced statistically significant improvements in patients with disease progression (8% vs. 18%) and hepatocellular cancer (4% vs. 7%). Significant changes in the Child-Pugh score (3% vs. 9%) were also seen. The improvement was less substantial in those patients with lamivudine resistance caused by YMDD mutations, but results in this subset were still significantly better than among controls. The rate of adverse reactions was greater in the placebo group, suggesting that long-term treatment with lamivudine was safe.

Pegylated Interferon- α 2a Was More Effective than Lamivudine for Management of Chronic HBV Infection

Marcellin P, Lau GK, Bonino F, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med.* 2004;351:1206-17. [PMID: 15371578]

An alternative to lamivudine therapy for the treatment of HBV infection is interferon. Published after Liaw and colleagues' paper, this study addressed the relative merits of 48 weeks of therapy with pegylated interferon- α 2a, lamivudine, or both for hepatitis B e antigen-negative chronic hepatitis B. Outcomes were assessed at 72 weeks. Pegylated interferon- α 2a, either alone or in combination with lamivudine, was superior to lamivudine alone for reducing levels of serum alanine aminotransferase and for suppressing HBV DNA. Patients receiving interferon monotherapy also had fewer adverse effects and were more likely to experience seroconversion of hepatitis B surface antigen, an important outcome relative to risk for end-stage liver disease and hepatocellular carcinoma. No long-term benefits were seen in patients receiving lamivudine monotherapy or combination therapy. More large-scale trials are required to gauge the long-term effectiveness of pegylated interferon and lamivudine therapy for HBV infection. Although lamivudine therapy may prevent disease progression, interferon monotherapy may also offer better long-term outcome.

Prion Disease

Variant Creutzfeldt-Jakob Disease Was Possibly Transmitted by Blood Transfusion

Llewelyn CA, Hewitt PE, Knight RS, et al. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet*. 2004; 363:417-21. [PMID: 14962520]

Variant Creutzfeldt-Jakob disease (CJD) is a prion disease thought to be caused by ingestion of beef from cows that are infected with bovine spongiform encephalitis. Abnormal prion protein in the beef somehow traffics from the gastrointestinal tract to the brain, where it causes deformation of normal prion protein and an amyloid-like reaction. People who are homozygous for methionine at codon 129 of the prion gene are susceptible to this disease. The United Kingdom recorded 180 000 cases of bovine spongiform encephalitis among cows and about 150 cases of variant CJD; the United States has recorded 1 or 2 cases of bovine spongiform encephalitis and no cases of variant CJD. Epidemiologic evidence does not suggest that sporadic CJD is transmitted from person to person, but this evidence may not apply to variant CJD. The long incubation period for variant CJD, which is estimated to be 5 to 10 years, suggests that individuals could possibly transmit the disease unknowingly.

The investigators in this paper reviewed data from the Office of National Statistics in Cambridge, United Kingdom, to determine if patients with variant CJD were blood donors and, if so, what happened to recipients of their donations. The investigators identified 15 donors who were later found to have variant CJD and who were the source of blood products for 48 recipients. Of these 48 recipients, 1 individual was found to have variant CJD 6.5 years after receipt of a red cell transfusion from a patient who developed variant CJD 3.5 years after the donation. A probability analysis indicated that the probability of variant CJD developing in the recipient in the absence of transfusion-transmitted infection ranged from 1 in 15 000 to 1 in 30 000. The authors concluded that the infection in the recipient could have come from past dietary exposure to bovine spongiform encephalitis but probably came from the blood transfusion.

Later in 2004, Peden and associates (6) reported a case of preclinical variant CJD that was transmitted from a blood transfusion. The recipient died 4 years after the transfusion without evidence of variant CJD; however, the abnormal prion protein was detected in the patient's lymph nodes and spleen. Unlike other patients with the disease who are homozygous for the prion protein gene at codon 129, this recipient was heterozygous at codon 129. This finding implied that heterozygous carriers of the prion protein might transmit variant CJD through a donation of blood or organs, thus making the pool of potentially infectious persons much larger than if it were restricted only to homozygous carriers.

Herpes Simplex Virus

Valacyclovir Significantly Reduced the Risk for Transmission of Genital Herpes

Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med*. 2004;350: 11-20. [PMID: 14702423]

Therapy with antiviral agents like valacyclovir has been shown to suppress shedding of herpes simplex virus (HSV)-2 on the genital mucosal surfaces of infected patients; consequently, this treatment might have a role in the prevention of sexual transmission

of HSV-2 infection. This study was designed to determine if maintenance valacyclovir administration to patients with genital HSV-2 infection effectively prevents transmission to sexual partners.

This trial involved 1484 immunocompetent, heterosexual, monogamous couples who were serologically discordant for symptomatic genital HSV-2. The couples were randomly assigned to receive valacyclovir (500 mg/d) or placebo for 8 months. The susceptible partner was evaluated monthly for signs and symptoms of genital herpes. A subset of participants who were monitored for recurrences of genital herpes (n = 89) also had viral cultures to determine the frequency of daily HSV viral shedding in genital secretions. Couples were counseled on safer sex practices and were offered condoms.

At the end of the study, the incidence of HSV transmission to the healthy partner was significantly lower among the valacyclovir recipients than among the controls; outcomes were determined by the presence of HSV symptoms (0.5% vs. 2.2%), incidence of newly acquired HSV seropositivity (1.9% vs. 3.6%), and evidence of viral shedding (2.9% vs. 10.8%). The authors concluded that once-daily suppressive therapy with valacyclovir reduced the frequency of HSV transmission to sexual partners.

On the basis of these findings, the U.S. Food and Drug Administration (FDA) approved valacyclovir for prevention of HSV transmission as well as prevention of outbreaks of HSV infection (7). However, physicians should remain aware that these new indications cannot be expanded to include nonheterosexual persons or those who are immunocompromised until more research is conducted. These findings do raise the promising possibility that valacyclovir could have a role in preventing transmission of HIV because of the large risk associated with HSV-induced ulcers.

Rabies

The First Documented Recovery from Clinical Rabies in a Patient Who Had No History of Prophylaxis

Recovery of a patient from clinical rabies-Wisconsin, 2004. *MMWR Morb Mortal Wkly Rep.* 2004;53:1171-3. [PMID: 15614231]

Rabies is nearly always fatal without proper postexposure prophylaxis. There have been 5 previous reports of survival following postexposure prophylaxis and clinical rabies, but all 5 patients experienced significant, permanent neurologic deficits. This report is the first in the history of medicine to describe survival of a patient without the use of rabies vaccine.

The patient was a 15-year-old Wisconsin girl who was bitten by a bat on her left hand in October 2004. She did not seek immediate treatment. No symptoms developed until 1 month later, at which time she first experienced fatigue and paresthesias. Over the next week, she developed typical symptoms of rabies, including tingling at the site of the bite, unsteady gait, and a sixth cranial nerve palsy. The patient was hospitalized after antibodies to the rabies virus were detected in her serum and cerebrospinal fluid. As Willoughby and colleagues reported in a later analysis of the case (8), postexposure prophylaxis was not given because of concerns regarding potential adverse reactions. Instead, ketamine was administered to induce coma, and ventilator support and high-

dose amantadine therapy were begun. Results of a lumbar puncture revealed an increase in antirabies IgG from 1:32 to 1:2048 during the time the patient was kept comatose. She was extubated on day 33 and sent to a rehabilitation unit for recovery; the patient continues to make progress and has returned to high school as a full-time student.

Beyond its historical importance, this report provides us with a useful reminder that rabies in domestic animals is a focus of concern, although cases are very rarely seen in developed countries (rabid dogs are now found almost exclusively in developing countries). Bats are believed to be the source of a large majority of rabies cases in the United States, and most of these patients had no apparent bite.

Although health care workers worry that the rabies virus may be transmitted through contact with infected patients, no instance of human-to-human transmission of the virus has been reported (9). According to current guidelines, prophylaxis for health care workers is recommended if they suspect percutaneous or mucocutaneous contamination with saliva, tears, cerebrospinal fluid, or neurologic tissue from an infected person.

New concerns were recently raised when rabies infection was reported in 3 patients who received transplanted organs (liver and kidneys) from an individual who was later found to be infected (10); transmission was believed to have occurred through contact with neuronal tissue. Consequently, the Centers for Disease Control and Prevention has begun to work with organ procurement agencies to determine if screening guidelines should be revised.

Avian Influenza

Clinical Features of Avian Influenza Documented in Vietnamese Patients

Tran TH, Nguyen TL, Nguyen TD, et al. Avian influenza A (H5N1) in 10 patients in Vietnam. *N Engl J Med.* 2004;350:1179-88. [PMID: 14985470]

In order for a global pandemic to occur, a strain of the influenza virus needs 3 things: a vulnerable population lacking immunity, the capability to infect humans, and the capability of person-to-person transmission. Avian influenza virus had never been transmitted from poultry to humans before 1997, when an outbreak in Hong Kong infected 18 people and caused 6 deaths. The Hong Kong outbreak met the first 2 criteria, but there was weak evidence of person-to-person transmission for this particular strain (influenza A [H5N1]). Geneticists advised that a viral mutation could eventually lead to human-to-human transmission, so Hong Kong health authorities culled the chickens in an effort to stop the virus.

The strain cited here recurred anyway, and it is now endemic in the bird population of 8 Asian countries. This report, which included 10 patients in Vietnam, was selected because it is one of the first reports to characterize the clinical features of avian influenza A. The patients' mean age was 13.7 years. All patients were critically ill, with a mean temperature of 39.2 °C and a mean respiratory rate of 52 breaths/min. Of 10 patients, 8 reported a history of handling poultry. Most patients died.

Autopsies showed necrotizing hemorrhagic pneumonia, which was similar to the pathologic findings associated with the Spanish influenza outbreak from 1918 to 1919.

The Spanish influenza virus was reconstructed and found to have a virulence factor at the hemagglutinin and cleavage site, which is also found in the H5N1 strain; the virulence factor confers resistance to interferon and causes death by a cytokinetic storm. This accounts for the fact that both the Spanish influenza and avian influenza A cause death most frequently in young patients.

To date, avian influenza A has infected about 126 people and caused about 65 deaths. This is an unforeseen rate of mortality from influenza (approximately 2% of infected patients died during the aforementioned outbreak of Spanish influenza). Consequently, the validity of the reported mortality rate associated with H5N1 infection has been questioned. Although reports of some asymptomatic cases of avian influenza A could be viewed as encouraging because they would reduce mortality rates, such reports also mean that more people are infected-increasing the probability of a global epidemic.

If the H5N1 strain led to a flu pandemic, the Centers for Disease Control and Prevention has estimated that it could kill 2 million to 7 million people; the World Health Organization has estimated that it could kill 20 million to 100 million people. There has been no sustained case of human-to-human transmission of H5N1, but there is substantial concern that more human-to-human transmission is possible. This is an influenza strain that affects a very broad range of species; whereas most viruses of poultry stay in poultry, this one has been found to infect not only chickens but also ducks, cats, tigers, and pigs. The drug oseltamivir has shown in vitro activity against the strain, but its clinical efficacy is unclear; amantadine and rimantadine have not shown any activity against the virus.

Although it remains possible that the H5N1 will never mutate into a pathogen that is transferable from human to human in a sustained fashion, the world needs to be prepared for that possibility. A group in Memphis has produced H5N1 vaccine by reverse genetics, a unique way of reconstructing the virus and separating out the hemagglutination cleavage site that is responsible for its virulence. By using the backbone of a standard influenza virus, they created an attenuated H5N1 viral vaccine and produced it within 1 month (much faster than the traditional splitvirus technique). Nevertheless, this new technology will still require a full review by the FDA.

Methicillin-Resistant Infection

Skin Breaks May Have Facilitated Spread of Methicillin-Resistant Staphylococcus aureus Infection among Football Teammates

Begier EM, Frenette K, Barrett NL, et al. A high-morbidity outbreak of methicillin-resistant Staphylococcus aureus among players on a college football team, facilitated by cosmetic body shaving and turf burns. Clin Infect Dis. 2004;39:1446-53. [PMID: 15546080]

This was a retrospective cohort study of a Connecticut football team that experienced an outbreak of methicillin-resistant Staphylococcus aureus (MRSA) infections of soft tissue. The investigators compared risk factors for infection among patients and controls. The affected individuals were 10 previously healthy men between 17 and 22 years of age who had received treatment for 13 MRSA infections. The infections comprised 9 abscesses and 4 instances of cellulitis between 6 August 2003 (the first day

of football camp) and 1 October 2003. Study controls were 90 other team members or people who had interacted with the team in some way during the same time period. The investigators found that players whose position required substantial body contact accounted for 8 of the 10 cases; men who played the positions of cornerback (relative risk, 17.5 [CI, 3.8 to 81.0]) and wide receiver (relative risk, 11.7 [CI, 2.4 to 56.8]) reported the most infections. Turf burns (relative risk, 7.2 [CI, 1.0 to 54.5]) and body shaving (relative risk, 6.1 [CI, 1.7 to 22.0]) also presented substantial risk. The investigators also found an increased prevalence of infection in players who used the facility whirlpool 2 or more times per week (relative risk, 12.2 [CI, 1.4 to 109.2]). Whirlpool water was disinfected with diluted povidoneiodine but was not drained between uses.

The outbreak was attributed to a strain of MRSA called USA 300, a community-acquired strain that differs from that encountered in hospitals. Nasal cultures were negative in 97 of the 100 participants. The strain carried the unique molecular markers (genes for Panton-Valentine leukocidin, a marker of virulence, and the staphylococcal chromosome cassette mec type IV element for methicillin resistance) that are characteristic of community-acquired MRSA; the organism was sensitive to fluoroquinolones, tetracycline, clindamycin, and trimethoprim-sulfamethoxazole.

The USA 300 strain is relatively new, global, and clonal. It most commonly causes furunculosis but may also cause necrotizing fasciitis and necrotizing pneumonia. Outbreaks have been reported in prison inmates, military recruits, injection drug users, homosexual men, and athletes (wrestlers and football and rugby players). Major risks for transmission are poor hygiene and crowding. As in this study, infection is usually community acquired, nasal colonization is rare, and the organism is sensitive to many non- β -lactam antibiotics.

Epidemic control measures include avoiding contact with sites of infection (which can be accomplished by promptly cleaning and dressing soft-tissue infections) and good hygiene. Such measures should include washing hands with antibacterial soap and laundering towels and worn clothing in water temperatures of at least 71 °C. Soft tissue infections are usually treated with drainage; if antibiotics are needed, β -lactam drugs should be avoided in favor of trimethoprim-sulfamethoxazole or clindamycin.

Antibiotic Development

Decline in Antibiotic Development Documented

Spellberg B, Powers JH, Brass EP, et al. Trends in antimicrobial drug development: implications for the future. *Clin Infect Dis.* 2004;38: 1279-86. [PMID: 15127341]

In an effort to determine why so few new antibacterial agents are being developed, the authors reviewed FDA approvals, public data for the 15 largest pharmaceutical companies, financial reports for 10 pharmaceutical companies, and relevant published data. They found that the FDA approved 30 new antibacterial agents between 1983 and 1992 (an average of 3 per year), 10 new agents between 1993 and 1997 (2 per year), and 9 between 1998 and 2003 (1.5 per year). With the notable exception of linezolid, no new products with a unique mechanism to stop infection have been developed since 1970. Data from the 15 largest pharmaceutical companies-whose research yielded 53 of

the last 57 new antibiotics-indicated that antibacterial drugs account for only 5 of 315 new molecular entities in development.

The authors cite fewer prospects for cost recovery as the reason behind this decline. Development costs for a single agent range from \$400 million to \$800 million, and an average of 8 years elapse from the time clinical trials begin until the product is launched. After this investment, antibacterial products are typically taken for 7 to 14 days whereas drugs prescribed for chronic diseases need to be taken for life. In addition, public health messages have successfully helped to reduce the use of antibacterial agents, particularly new antibiotics. The potential cost recovery for a new antibiotic to be used for resistant gram-positive cocci is \$100 million per year, compared with \$1.1 billion per year for a neuromuscular drug that can be used on a long-term basis.

The virtually empty antibiotic pipeline will pose significant challenges in the management of emerging resistance in organisms such as MRSA, vancomycin-resistant *Enterococcus* species, *Pseudomonas aeruginosa*, *Acinetobacter* species, extended-spectrum β -lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli*, *Stenotrophomonas maltophilia*, multidrug-resistant tuberculosis, and drug-resistant *Bacillus anthracis*. Potential solutions to these disincentives in development exist on a policy level. Economic incentives, such as patent extensions and tax breaks, or reduction in FDA regulatory demands may help to spur development of much-needed new agents that would otherwise offer small returns on investment.

Tigecycline Was Active against a Variety of Resistant Gram-Positive Cocci and Respiratory Tract Pathogens

Fritsche TR, Kirby JT, Jones RN. In vitro activity of tigecycline (GAR-936) tested against 11 859 recent clinical isolates associated with community-acquired respiratory tract and gram-positive cutaneous infections. *Diagn Microbiol Infect Dis.* 2004;49:201-9. [PMID: 15246511]

Tigecycline is a new FDA-approved broad-spectrum glycylglycyl cycline that is related to tetracycline. Unlike other drugs in its class, however, tigecycline has a structure that subverts the major ribosomal protection and efflux mechanisms that make many strains of common bacteria resistant to tetracycline derivatives.

This study found that tigecycline was active in vitro against all 11 859 recent bacterial strains (in 2000 and 2002) that were isolated and studied in association with cases of community-acquired respiratory tract infections and gram-positive cutaneous infections. These included 1881 strains of MRSA, 1111 strains of coagulase-negative methicillin-resistant *Staphylococcus* species, 122 strains of vancomycin-resistant *Enterococcus* species, 232 strains of penicillin-resistant *Staphylococcus pneumoniae*, 249 strains of β -lactamase-positive *Haemophilus influenzae*, and 474 strains of *Moraxella catarrhalis*. In other testing, vancomycin was active against all the strains except vancomycin-resistant enterococci, and linezolid was universally active.

These findings confirmed that tigecycline is a potent broad-spectrum antibiotic that is effective against resistant gram-positive cocci; common respiratory tract pathogens; and most gram-negative bacilli, except strains of *Pseudomonas aeruginosa* and *Proteus* species that were not included in this review. Although more research is needed, the

drug offers another choice to physicians with patients who have complicated, multidrug-resistant infections.

Other Key Developments

Management of Respiratory Tract Infections

As a result of concern regarding the spread of SARS, the Centers for Disease Control and Prevention and other authorities have recommended that health care workers use more caution when managing respiratory tract infections in the office and in the hospital emergency department. The agency advises that both patient and provider wear a surgical mask during all interactions and that patients with respiratory infections should be separated from other patients by at least 3 feet. The recommendations are intended to help prevent transmission of influenza, parainfluenza virus, rhinovirus, coronavirus, adenovirus, respiratory syncytial virus, *Mycoplasma pneumoniae*, and other infections throughout health care facilities.

Emerging Pathogen Seen in Veterans of the Iraq War

A multidrug-resistant strain of *Acinetobacter* species is an emerging pathogen that has become a problem for some hospitals and for soldiers returning from Iraq with war injuries. Some of these strains are sensitive only to colistin, a drug that has not been used for 40 years because of concerns regarding toxicity.

New Vaccines

A new acellular vaccine for pertussis appears to provide universal protection to adolescents and adults and could possibly be administered as part of a diphtheria-pertussis-tetanus or diphtheria-tetanus booster. Researchers are presently emphasizing that adolescents receive the new vaccine. There is also a new meningococcal C vaccine, which will also probably be reserved for use in adolescents and in outbreaks. Experience with the protein-conjugated pneumococcal vaccine, which is indicated for children younger than 2 years of age, suggests that fewer unvaccinated adults may acquire pneumococcal infection if their children received the vaccine; consequently, vaccination of children may be one of the best ways to reduce these infections in adults.

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[Author Affiliation]

John C. Bartlett, MD

[Author Affiliation]

From Johns Hopkins University School of Medicine, Johns Hopkins Hospital, Baltimore, Maryland.

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Requests for Single Reprints: John G. Bartlett, MD, Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21205-2191; e-mail, jb@jhmi.edu.