Top Ten Publications of 2001

John G. Bartlett
Johns Hopkins University School of Medicine, Baltimore, Maryland

The occasion of Sydney Finegold’s 80th birthday is a time to reflect on the extraordinary life and accomplishments of this giant in the field of infectious diseases. For my contribution to this symposium, my decision was to review the most important publications in the field of infectious diseases for the year 2001. It should be acknowledged from the outset that there is a sparse contribution from those who have worked in the field of anaerobic infections and anaerobic bacteriology. This fact, by itself, is a great accolade to Dr. Finegold. During the early 1960s, he led the campaign to recognize, culture, and treat infections caused by anaerobes. At that time, Bacteroides fragilis was second only to Escherichia coli as a cause of gram-negative bacillary bacteremia at the Mayo Clinic, putrid lung abscesses were referred to as “non-specific lung abscess,” and appendicitis was routinely treated with penicillin plus gentamicin or cephalothin. The campaign led by Dr. Finegold penetrated deeply into the field of medicine. There were multiple symposia, clinical laboratories were persuaded to culture oxygen-sensitive forms, and pharmaceutical companies began testing their drugs for activity against anaerobes in vitro and in vivo. The effort was notably assisted by the introduction of the Gas-Pak jar, which facilitated detection of anaerobes; the taxonomy was finally placed in reasonable order; and clindamycin became a favored drug for management. These events transpired during the period 1965–1975. In retrospect, this is probably one of the most successful campaigns in the history of medicine, and it dramatically altered practice patterns. Dr. Finegold would probably say that it was very much the combined contributions of a large group, but there was never any doubt about its leader, who is a clinician, microbiologist, and scientist. All of this is to say that we are celebrating the career of a man who has done something that few in medicine accomplish. He took on a major issue, led the attack, and revolutionized practice patterns. Thus, the present review contains a large number of good papers—but sparse numbers from anaerobes, because most of the anaerobic story has been so well told.

With that background, the following is a brief summary of those papers that I consider to be the most important contributions to the medical literature in the field of infectious diseases for the period 1 January through 15 December 2001. There is no ranking, and they are presented in sequence as they were published, with a summary and a brief comment.

**Kyne L, Warny M, Qamar A, Kelly CP. Association between antibody response to toxin A and protection against recurrent Clostridium difficile diarrhoea.** *Lancet* 2001;357:189–93

The authors reviewed 44 patients with nosocomial *C. difficile*-associated diarrhea and measured serial serum antibodies against toxin A, toxin B, and nontoxin antigens. The results showed that serum anti–toxin A IgG on day 12 was substantially higher for the 22 patients who did not have relapse, compared with the 22 who had relapsing disease. The odds ratio for relapse associated with low concentrations of this antibody at 12 days after onset of symptoms was 48:1.

**Comment.** This is a sequel report from investigators at Beth Israel Deaconess Medical Center in Boston, who previously had reported that asymptomatic carriers of *C. difficile* have high concentrations of serum anti–toxin A IgG of *C. difficile* [1]. For years, there has been difficulty defining the reason why (1) some patients with *C. difficile* toxin A in stool have no disease whereas others have life-threatening pseudomembran-
uous colitis and (2) some patients develop debilitating relapses after therapy whereas most patients do extremely well with a single course of metronidazole or vancomycin. These 2 reports get us closer to a rational biologic explanation. To date, this observation has not been translated into a useful therapy that has used high-titer intravenous immunoglobulin.


The authors randomly selected 84 patients from the original study of Lyme disease in Lyme, Connecticut, including 25 with erythema migrans, 31 with facial palsy, and 28 with Lyme arthritis; there were 30 uninfected control patients. The 10–20-year follow-up study of the 3 groups of patients showed no differences, compared with controls, in terms of current symptoms or results of neuropsychological tests.

Comment. The original report of Lyme disease was by Steere et al. [2], and Dr. Steere is a coauthor of this study. The sequence of reports by Dr. Steere and colleagues led to the definition of clinical features, diagnostic tests, pathophysiologic mechanism, and management of Lyme disease. This probably represents one of the great accomplishments of the past 25 years in the field of infectious diseases. The importance of the report by Kalish et al. concerns the role that “post–Lyme disease syndrome” plays in chronic fatigue syndrome or fibromyalgia. In essence, there is none.


The authors reviewed the events that took place with the 1999 outbreak of West Nile virus (WNV) encephalitis in New York City. This event represents the first appearance of WNV in the Western Hemisphere. The initial event occurred on 23 August 1999, when Dr. Deborah Asnis notified Dr. Marcelle Layton of the New York City Health Department of 2 patients with fever, altered mental status, muscle weakness, and cerebrospinal-fluid changes suggestive of viral encephalitis. What followed was an aggressive pursuit of case finding, the establishment of diagnostic-testing resources, and development of a system to deal with the public. When it was all over, Fort Collins had received >2000 specimens during a 3-month period, the Health Department had distributed >400,000 cans of DEET, and a massive public health campaign included a hotline, manned by 25–75 staff at all times for 2 months, that received >150,000 calls.

Comment. This article is a contribution to the section of Clinical Infectious Diseases that was devoted to bioterrorism. In this context, it is important to emphasize that the “index case” of WNV was first detected by an alert infectious diseases physician, Dr. Asnis, as also was true for the first case of anthrax, which was detected by Dr. Larry Bush [3]. This review is also a great tribute to Dr. M. Layton, who rigorously pursued the early clue of an unusual form of encephalitis, and the methods to deal with the public response were masterful in the sense of providing good information in a timely fashion. These are aspects of bioterrorism preparedness that are usually absent in the pre-event planning process.


The authors performed a randomized, double-blind, placebo-controlled trial in 76 centers during the winter of 1998–99, to determine the efficacy of oseltamivir for the prevention of influenza in household contacts. There were 377 indexed cases and 955 household contacts; the household contacts were randomly assigned to a regimen of oseltamivir, 75 mg daily for 7 days, within 48 h of the onset of symptoms in the index cases. The results showed a protective efficacy of 89%, the drug was well tolerated, and no resistance to oseltamivir was detected in the influenza isolates.

Comment. This article was selected because (a) the new treatments available for influenza A and B are noteworthy, (b) influenza itself is the leading infectious disease cause of death in the United States, and (c) the study is an interesting twist compared with multiple studies that have demonstrated the efficacy of these agents in patients with symptoms. For practical purposes, the clinician will often not detect influenza early enough to use these drugs, but this article shows a way to deal more effectively with the rest of the family. The obvious concern is cost—for a regimen of oseltamivir at 75 mg daily for 7 days, the average wholesale price is about $30.


This report, from the National Institute of Child Health and Human Development Network of Maternal–Fetal Medicine, addresses the issue of treatment of T. vaginalis during pregnancy, to reduce the frequency of preterm delivery. There were 617
women with asymptomatic trichomoniasis at 16–23 weeks gestation who were randomized to receive metronidazole or placebo. Follow-up cultures showed that this treatment was effective in eliminating *T. vaginalis* in 93% of the metronidazole recipients. Preterm delivery at <37 weeks gestation occurred in 60 (19%) of 315 of metronidazole recipients and in 31 (11%) of 289 in the placebo group. The relative risk for preterm delivery with metronidazole was 1.8:1.

**Comment.** This is a provocative report that addresses the issue of treating asymptomatic trichomoniasis in pregnant women, on the basis of (a) the observation that this infection is a risk factor for preterm delivery and (b) the assumption that its treatment would eliminate the risk; instead, the authors showed the opposite. It should be noted that bacterial vaginosis, presumably an anaerobic infection that reflects dysbiosis of the genital flora, is another condition associated with preterm delivery. Again, the assumption was that treatment would eliminate the risk, but prior studies of bacterial vaginosis have also shown no benefit or even increased risk [4]. Thus, the conclusion is that there appears to be a subset of women in whom the risk of adverse outcomes of pregnancy is actually increased by antibiotic treatment.

**Dowell SF, Peeling RW, Bowman J, et al. Standardizing Chlamydia pneumoniae assays: recommendations from the Centers for Disease Control and Prevention (USA) and the Laboratory Centre for Disease Control (Canada). Clin Infect Dis 2001;33:492–503**

This report is of a meeting at the Centers for Disease Control and Prevention, which was attended by a large group of experts in the field known as the “C. pneumoniae Workshop Participants” who reviewed current diagnostic tests for *C. pneumoniae*. The group defined the methods to document infection by *C. pneumoniae* by use of serology, culture, PCR, and immunohistochemistry. The most common test is serological, and the endorsement was for the microimmunofluorescence, with the demonstration of a 4-fold rise, in IgG or IgM, to a titer ≥1:16 in samples separated by 4–6 weeks. Single titers to define acute infection are “discouraged.” For PCR, the group endorsed the reagents for 4 of 18 currently published assays.

**Comment.** This study was selected because of the enormous confusion that has been created about *C. pneumoniae* and its role in community-acquired pneumonia (CAP), atherosclerotic disease, and multiple sclerosis. For CAP, most studies have shown that *C. pneumoniae* causes 10%–30% of cases, but the evidence to support this has generally been based on serological tests that are inadequate according to the definition used here. Similarly, with coronary artery disease, cerebrovascular disease, and multiple sclerosis, the evidence to support *C. pneumoniae* as an etiologic factor has been highly variable, and much of the variation may be due to differences in methods to document the role of *C. pneumoniae*. Thus, this paper has the potential to establish diagnostic standards to facilitate communication and to improve our ability to more definitively judge the role of *C. pneumoniae* in diverse conditions.


This report, from Toronto, concerns an outbreak of fluoroquinolone-resistant *S. pneumoniae* that occurred in 16 patients hospitalized in a 30-bed respiratory ward from 1995 to 1996. There were 13 cases of exacerbations of chronic bronchitis and 3 cases of pneumonia, all nosocomially acquired. The initial cluster included 9 infections during a 2-month period in patients hospitalized in 2 rooms, and then there were 7 new cases identified during the next 17 months. The initial infections involving *S. pneumoniae* showed reduced sensitivity to fluoroquinolones, attributed to the parC mutation; the second group showed high levels of resistance attributed to the combination of parC and gyrA mutations. Treatment showed that 10 of 10 patients treated with drugs active in vitro (ceftriaxone or erythromycin) were cured, but in 7 (87.5%) of 8 patients treated with drugs resistant in vitro (cefuroxime or ciprofloxacin) the treatment was considered to be a failure, and 1 of these 7 patients died.

**Comment.** There needs to be at least 1 paper dealing with antibiotic resistance, and this is a good one. Others have pointed out the problem of increasing resistance of *S. pneumoniae* to fluoroquinolones due to a perceived abuse of these drugs [5], but the rate of fluoroquinolone resistance by *S. pneumoniae* remains <1% [6], and the clinical significance of pneumococcal in vitro resistance has been subject to controversies in interpretation. This report describes a rare outbreak, but it is important in the sense that it is one of the relatively few studies to have shown a nosocomial outbreak of pneumococcal pulmonary infections, a high-level fluoroquinolone resistance in the epidemic strain, and good clinical correlations between in vitro and in vivo activity.


The author, from Hadassah University Hospital in Jerusalem, reports studies of urine samples, from prion-infected British...
cows, patients, and experimentally infected hamsters, that showed the PrP isoform long before clinical evidence of disease. They propose this test as a method to detect incubating prion disease in animals and people.

Comment. The prion is a fascinating pathogenic mechanism that violates all the rules of infectious diseases in the sense that these are the only infectious agents without nucleic acid. The recent epidemic of variant Creutzfeldt-Jakob disease illustrates the clinical importance and challenge of prions and the diseases they cause. The total toll is unknown because of the prolonged incubation period, which is estimated at 10–17 years [7], and the estimated number of human infections varies from several hundred to several million [8]. It is obviously important, but incredibly difficult, to identify infections in cows, in order to prevent unnecessary slaughter of thousands, and in people who are destined for an inevitably progressive neurologic disease. This report, although preliminary, shows that there is great promise that these goals can be achieved.


The authors, from the Minnesota Health Department and Indian Health Service, reviewed 354 cases of community-acquired infections involving methicillin-resistant S. aureus (MRSA) in Minnesota from 1996 to 1998. Of these, 299 (84%) were skin and soft-tissue infections, most were in patients age <30 years, and most of the isolates were susceptible to clindamycin, ciprofloxacin, gentamicin, tetracycline, and trimethoprim-sulfamethoxazole. Molecular subtyping showed “striking” clonality in >80% of the isolates. Of the 354 patients, 103 (29%) were hospitalized and 282 (80%) were initially treated with antibiotics, primarily β-lactams, that were not active in vitro.

Comment. This is an important report on a subject of substantial current concern: MRSA acquired in the community. The initial assumption was that the escalating rate of MRSA in the community represented dispersal of nosocomial strains, but it appears that these strains are different, by molecular typing and by in vitro sensitivity testing. This is obviously an important concept in terms of our understanding of resistance and its epidemiological spread. Also of interest is the observation that 80% of the patients were treated with about the only class of antibiotics that was inactive: β-lactams.


The authors performed a retrospective study that used data from Express Scripts Patient Treatment Episode Registry, which has >2 million subscribers. The analysis was done with the ICD-9 code for acute sinusitis and was correlated with antibiotic treatment and outcome. The antibiotics were classified as “first-line” (amoxicillin, sulfa-trimethoprim, or erythromycin) or “second-line” (clarithromycin, azithromycin, amoxicillin-clavulanate, cephalosporin, or fluoroquinolone). The total number of patients studied was 29,102, 60% of whom received first-line agents and 40% of whom received second-line agents. The results showed that the overall success rate was 90%, the failure rate was 3%, and the relapse rate was 6%; there was no difference, in outcome, between first-line and second-line agents.

Comment. This study does not address the issue of antibiotic indications for acute sinusitis but does deal with antibiotic selection. A prior report, from the Cochrane Library, showed that, according to prior therapeutic trials, no antibiotic was superior to amoxicillin [9], despite the presumed role of Haemophilus influenzae and penicillin-resistant S. pneumoniae. Thus, amoxicillin is the preferred drug according to guidelines from the American College of Physicians, the Infectious Diseases Society of America, the Centers for Disease Control, and the American Association of Otolaryngologists [10–12]. Nevertheless, only 40% of the patients were treated with amoxicillin. This article was selected because it deals with one of the most common infections encountered in clinical practice, an infection that is subject to the perception of great antibiotic abuse.

The present review is obviously arbitrary, but it does deal with important contributions in the field of infectious diseases that are considered most topical, including antibiotic resistance, bioterrorism, 3 newly recognized pathogens (Lyme disease, C. difficile, and C. pneumoniae) during the past 25 years, the role of infectious agents in chronic disease, the continued underplayed importance of influenza, prion disease, and the importance of microbiology in establishing etiologic diagnosis to improve patient care. The stringent methodology and discipline of infectious-disease study has moved this field in an extraordinary way, and Dr. Sydney Finegold has been a notable contributor to this progress.
References