

PRACTICE INSIGHTS

Key References in Infectious Diseases Pharmacotherapy

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Infectious Diseases Practice and Research Network Bibliography Group

Most health care practitioners are challenged to maintain knowledge of contemporary practice issues in many therapeutic disciplines. Like many other areas, infectious diseases pharmacotherapy continues to evolve because of new information regarding disease epidemiology and new treatment options. Emerging infections and resistance further compound the need for information. To assist clinicians in identifying such important new information, we compiled a list of key references on infectious diseases pharmacotherapy published over the last 2 years.

Key Words: bibliography, infectious diseases, pharmacotherapy.
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OUTLINE

Bacterial Infections
Emerging Infections
Human Immunodeficiency Virus
Invasive Fungal Infections
Bacterial Resistance

Knowledge regarding optimal infectious diseases pharmacotherapy is constantly changing. In contrast to other therapeutic areas that also are influenced by new findings regarding disease epidemiology, pathogenesis, and new drug development, the field of infectious diseases is affected by changes in pathogen susceptibility to

therapy. New and emerging infections also may significantly affect patient outcomes. Therefore, clinicians are urged to identify key investigative findings in infectious diseases pharmacotherapy that would significantly affect patient care. To assist with this process, the Infectious Diseases Practice and Research Network (ID-PRN) of the American College of Clinical Pharmacy undertook an initiative to identify and summarize key articles regarding infectious diseases pharmacotherapy.

In February 2004, members of the ID-PRN Bibliography Group were asked to identify recent publications containing reports or summaries of infectious diseases pharmacotherapy investigations whose findings had significantly affected patient care. Articles were identified by searching MEDLINE and meeting abstracts, and by personal knowledge. Members were asked to consider reports published within the last 2 years, and to identify a maximum of five publications in each of the following areas: bacterial infections, emerging infections, human immunodeficiency virus, invasive fungal infections, and bacterial resistance. Priority was given to peer-reviewed publications and consensus treatment recommendations. Summaries of key articles were submitted to an ID-PRN bibliography editorial board for review before submission to *Pharmacotherapy*.

We hope that readers of the journal find this bibliography useful, and we welcome feedback.

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Bacterial Infections

de Gans J, van de Beek D, for the European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002;347:1549–56.

Morbidity is high among adults with acute bacterial meningitis, with mortality rates up to 25%. Adjuvant treatment with corticosteroids has improved outcomes in animal studies of bacterial meningitis, but results in humans (especially adults) have been equivocal. The concern regarding administration of dexamethasone is that it may interfere with penetration of antibiotics into the subarachnoid space. To address the issues of safety and efficacy, investigators performed a prospective, randomized, double-blind, multicenter trial comparing dexamethasone with placebo in adults with bacterial meningitis. Intravenous dexamethasone 10 mg every 6 hours was administered for 4 days to 157 patients, with the first dose given before the start of antibiotic therapy; 144 patients received placebo. Dexamethasone treatment was associated with a significant reduction in unfavorable outcomes ($p=0.03$) and mortality ($p=0.04$) compared with placebo. The beneficial effect of dexamethasone was most apparent in patients with pneumococcal meningitis. No significant differences in adverse effects were noted between the two groups. The authors concluded that early treatment with dexamethasone improves outcomes in adults with bacterial meningitis. The question remains whether adjunctive dexamethasone therapy is appropriate for all adult patients with bacterial meningitis regardless of etiology.

Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* 2003;290:2588–98.

The typical duration of 2 weeks of antibiotic therapy for ventilator-associated pneumonia (VAP) is largely empiric because well-controlled clinical trials are lacking; the optimal treatment duration is unknown. A prospective, randomized, double-blind (until day 8) clinical trial was performed in intensive care patients diagnosed with VAP confirmed by quantitative cultures of bronchoscopic specimens. Patients received appropriate initial empiric antibiotic therapy and then were randomized to receive antibiotic therapy for either 8 (197 patients) or 15 days

(204 patients). Initial antibiotic selection was left to the discretion of the treating physician. Streamlining of the initial antibiotic regimen was encouraged after receipt of culture results. The distribution of causative micro-organisms was similar between the two groups. No significant difference was noted in mortality or recurrent infection between the two groups. Patients treated for 8 days had significantly more antibiotic-free days than those treated for 15 ($p<0.001$). No significant difference was noted between the two groups in secondary outcomes (days free of mechanical ventilation, length of stay in the intensive care unit [ICU], number of days with no organ failure, rate of unfavorable outcomes, and mortality rate at day 60). The authors concluded that 8 days of treatment is as clinically effective as 15 days for patients who receive appropriate initial empiric therapy for VAP. Although no between-group difference was noted in unfavorable outcomes, a question arises as to whether 8 days of therapy for patients with nonfermentative gram-negative bacillus is adequate, since this subset of patients had a higher rate of recurrent pulmonary infection.

Saiman L, Marshall BC, Mayer-Hamblett N, et al. Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*: a randomized controlled trial. *JAMA* 2003;290:1749–56.

Macrolides may reduce microbial virulence factors or modulate host defenses. Increasing evidence indicates that this class of antibiotics may benefit patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* infection. This multicenter, randomized, double-blind, placebo-controlled trial compared the effects of azithromycin versus placebo on pulmonary function in patients with cystic fibrosis. For 3 days/week, 87 patients received azithromycin and 98 received placebo. Patients treated with azithromycin demonstrated significant ($p<0.009$) improvement in forced expiratory volume in 1 second (FEV₁) by day 168, as well as less risk of pulmonary exacerbation ($p<0.03$). However, patients receiving azithromycin experienced significantly more nausea, diarrhea, and wheezing than those receiving placebo. The authors concluded that azithromycin was associated with improvement in clinically relevant end points in patients with cystic fibrosis and chronic *P. aeruginosa* colonization or infection. This study provides evidence that macrolides, specifically azithromycin, could be

beneficial for patients with cystic fibrosis. The benefits are both clinical and economic, demonstrated as improvements in FEV₁ and reduced hospitalizations for pulmonary exacerbation. However, long-term azithromycin therapy has not been studied and needs to be investigated before adoption of this adjunctive therapy.

Harding GKM, Zhanel GG, Nicolle LE, Cheang M. Antimicrobial treatment in diabetic women with asymptomatic bacteriuria. *N Engl J Med* 2002;347:1576–83.

Asymptomatic bacteriuria is 3 times more common in women with (vs without) diabetes mellitus. Women with diabetes have an increased risk of pyelonephritis, bacteremia, and renal abscess formation. This trial compared symptomatic urinary tract infection (UTI) and UTI complication rates in adult women with diabetes and asymptomatic bacteriuria who received trimethoprim 160 mg–sulfamethoxazole 800 mg or ciprofloxacin 250 mg for resistant organisms. Fifty-five patients received antibiotic treatment, and 50 received placebo. The study design for the first 6 weeks was randomized and double-blind. During the follow-up period (mean 27 mo), no significant difference was noted in the frequency of symptomatic UTI in treated patients versus controls (42% vs 40%) or complication rates (pyelonephritis, 6 vs 11 patients; hospitalization for UTI, 3 vs 5 patients). The authors concluded that treatment of asymptomatic bacteriuria in women with diabetes does not appear to reduce complications.

Perl TM, Cullen JJ, Wenzel RP, et al. Intranasal mupirocin to prevent postoperative *Staphylococcus aureus* infections. *N Engl J Med* 2002;346:1871–7. Patients with *Staphylococcus aureus* colonization have an increased risk of nosocomial infection after surgery. The primary objective of this randomized, double-blind, placebo-controlled trial was to determine whether intranasal mupirocin treatment could reduce the rate of *S. aureus* infections after surgery. A total of 3864 patients were enrolled in the study. Overall, those who received mupirocin versus placebo had similar rates of surgical site infections (2.3% vs 2.4%). Of the subset of patients whose *S. aureus* cultures were positive, 444 treated with mupirocin had a significant reduction in nosocomial infection rate compared with 447 who received placebo (4.0% vs 7.7%, $p=0.02$). Therefore, prophylactic intranasal mupirocin did not significantly reduce the rate of *S. aureus*

surgical-site infections in all patients. However, mupirocin significantly reduced the rate of nosocomial *S. aureus* infections among those with nasal colonization of *S. aureus*.

Emerging Infections

Naimi TS, LeDell KH, Como-Sabetti K, et al. Comparison of community- and healthcare-associated methicillin-resistant *Staphylococcus aureus* infection. *JAMA* 2003;290:2976–84.

Unlike methicillin-resistant *S. aureus* (MRSA) infections in patients treated in health care institutions, community-associated MRSA infections appear to occur in otherwise healthy persons with no known risk factors for MRSA. The recent increase in community-associated MRSA infections may alter empiric antimicrobial prescribing patterns in the outpatient setting. The authors prospectively reviewed 1100 MRSA cases from several institutions in Minnesota; 131 (12%) were classified as community associated (CA-MRSA), 937 (85%) as health care associated, and 32 (3%) could not be classified. Comparisons between CA-MRSA and health care-associated infections revealed that patients with CA-MRSA tended to be younger ($p<0.001$). Skin and soft tissue infections occurred more often in the CA-MRSA group (odds ratio [OR] 4.25, 95% confidence interval [CI] 2.97–5.90). The CA-MRSA isolates were more often susceptible to four different antibiotics, such as ciprofloxacin, clindamycin, gentamicin, and trimethoprim-sulfamethoxazole (adjusted OR 2.44, 95% CI 1.35–3.86) and usually had different molecular features and distinct toxin gene profiles. The authors concluded that patients with CA-MRSA differ demographically, microbiologically, and clinically from those with health care-associated disease. This supports the hypothesis that CA-MRSA strains do not arise in the health care setting. The authors also concluded that β -lactam antimicrobials may no longer be the optimal empiric therapy for outpatients with suspected staphylococcal infections.

Manocha S, Walley KR, Russell JA. Severe acute respiratory distress syndrome (SARS): a critical care perspective. *Crit Care Med* 2003;31:2684–92.

The authors searched MEDLINE and reviewed the epidemiology, clinical features, etiology, diagnosis, and management of severe acute respiratory distress syndrome (SARS) from a critical care perspective. The mortality rate worldwide for SARS was approximately 10.5% in

2003. This article also includes an analysis of five published studies reporting that 107 (26%) of 417 patients with SARS required admission to the ICU. Of those patients, 71% required mechanical ventilation, and 19% died. Recommendations for management of SARS in the ICU are provided, such as important infection control measures. Management of SARS consists of respiratory isolation, contact precautions, empiric treatment with broad-spectrum antibiotics, and ventilatory support as needed. Anecdotal evidence suggests that corticosteroids may be beneficial. Although ribavirin has been used for treatment, it has been associated with significant toxicity in many patients with SARS; in vitro testing suggests that ribavirin is inactive against the SARS coronavirus. Further research is needed to determine the efficacy of ribavirin in outcomes for patients with confirmed SARS.

Petersen LR, Martin AA, Gubler DJ. West Nile virus. *JAMA* 2003;290:524–8.

This concise report reviews the epidemiology, pathogenesis, clinical presentation, and treatment of West Nile virus infection. The only preventive method is reducing contact with infected mosquitoes. Insect repellents containing *N*, *N*-diethyl-*m*-toluamide (DEET) or permethrin are effective for preventing infection. Currently, treatment of West Nile virus infection is largely supportive. Anecdotally, ribavirin, intravenous γ -globulin, interferon alpha-2b, corticosteroids, anticonvulsants, and osmotic diuretic agents have been used for treatment of encephalitis. However, no controlled trials have evaluated the efficacy of these therapies. An inactivated human vaccine is in development.

Nicholson, KG, Wood JM, Zambon M. Influenza. *Lancet* 2003;362:1733–45.

Influenza has had major effects on morbidity, mortality, and economics worldwide. The yearly immunologic drift and intraspecies spread of viral strains novel to humans continue to produce concern that a major pandemic of human infection will occur in the near future. This article reviews the epidemiology, immunology, and diagnosis of influenza infection worldwide. Pharmacology, indications, and limitations of vaccines and influenza-specific antiviral drugs are discussed. Influenza vaccine remains the major intervention in the control of influenza. Drugs for prevention and treatment are the M2 protein inhibitors amantadine and rimantadine, and the neuraminidase inhibitors oseltamivir and

zanamivir. The authors provide background information to enable clinicians to evaluate and select prophylactic and therapeutic agents in epidemic and pandemic settings.

Terriff CM, Schwartz MD, Lomaestro BM. Bioterrorism: pivotal clinical issues. Consensus review of the Society of Infectious Diseases Pharmacists. *Pharmacotherapy* 2003;23:274–90.

This article examines the emerging threat of biologic agents used as terror weapons. Epidemiology, microbiology, diagnosis, and control measures are discussed for five major biologic agents that have been or could become terror threats. Included are overviews of anthrax, botulinum toxin, plague, smallpox, and tularemia. Therapeutic and preventive uses of pharmaceuticals and vaccines are reviewed to assist clinicians in contributing to policy and clinical decision making. A list of Web-based resources is also included. The integral role pharmacists can play in disaster preparedness and response is described.

Human Immunodeficiency Virus

DeJesus E, Grinsztejn B, Rodriquez C, et al. Efficacy and safety of atazanavir and ritonavir or saquinavir versus lopinavir-ritonavir in patients who have experienced virologic failures on multiple HAART regimens: 48 week results from BMS AI424-045. Presented at the 11th conference on retrovirus and opportunistic infections, San Francisco, California, February 8–11, 2004.

Many protease inhibitors have been associated with hyperlipidemia. Atazanavir is the first protease inhibitor to exhibit a favorable adverse effect profile with a reduced frequency of hyperlipidemia. This open-label, randomized, controlled trial was the first to compare atazanavir and either ritonavir or saquinavir with lopinavir combined with “boosted-dose” ritonavir. The study involved 358 patients with numerous previous virologic failures and experience with protease inhibitors. Each treatment was combined with tenofovir and another nucleoside reverse transcriptase inhibitor (NRTI). This 48-week study demonstrated similar antiretroviral efficacy between atazanavir-ritonavir and lopinavir-boosted-dose ritonavir, and less efficacy with atazanavir-saquinavir. Mean change in plasma human immunodeficiency virus (HIV)-1 RNA from baseline was -1.93 (atazanavir-ritonavir), -1.87 (lopinavir-boosted-dose ritonavir), and -1.55 (atazanavir-saquinavir)

log₁₀ copies/ml. The CD4⁺ count increased from baseline by 110, 121 and 72 cells/mm³ with the three treatments, respectively. Fewer lipid abnormalities were noted with atazanavir-ritonavir than lopinavir-boosted-dose ritonavir, especially with fasting triglyceride levels (+30% vs -4%, respectively, $p \leq 0.005$). Diarrhea (11% of patients) was more common with lopinavir-boosted-dose ritonavir, whereas hyperbilirubinemia (49%), jaundice (6%), and scleral icterus (3%) were more common with atazanavir-ritonavir. With similar efficacy and less hyperlipidemia, atazanavir-ritonavir may be an option in patients with cardiac risk factors for heart disease.

Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. *AIDS* 2003;17:2045–52.

This open-label, randomized, controlled trial assigned 180 patients in equal numbers to one of three regimens: NRTI based (abacavir, stavudine, and didanosine), protease inhibitor based (ritonavir, saquinavir, lamivudine, and zidovudine), or protease inhibitor–non-NRTI (NNRTI) based (nelfinavir, nevirapine, lamivudine, and zidovudine). Patients in the NRTI group failed to reach an undetectable viral load at 48 weeks at a rate of 57% versus 38% ($p < 0.01$) and 31% ($p < 0.05$) in the protease inhibitor and protease inhibitor–NNRTI groups, respectively. Severe adverse events (grade 3–4) occurred at rates of 28% in the NRTI group versus 26% and 17% in the protease inhibitor and protease inhibitor–NNRTI groups, respectively ($p = \text{NS}$). Neuropathy was more frequent in the NRTI group (27%, $p < 0.001$); lactate levels also were increased, with a median level of 1.8 mmol/L versus 1.1 mmol/L ($p < 0.01$) and 1.3 mmol/L ($p < 0.05$), respectively, in the protease inhibitor and protease inhibitor–NNRTI groups. This is one of four pivotal trials demonstrating the inferior efficacy of a triple NRTI regimen in antiretroviral-naïve patients compared with regimens also consisting of NNRTIs and/or protease inhibitors.

Lalezari JP, Henry K, O’Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med* 2003;348:2175–85.

Enfuvirtide, the first of a new antiretroviral drug class called entry or fusion inhibitors, interferes with entry of HIV-1 into cells by inhibiting fusion of viral and cellular membranes.

This is one of the key clinical trials to demonstrate enfuvirtide’s efficacy in treatment-experienced patients. Patients were randomly assigned to receive subcutaneous enfuvirtide 90 mg twice/day plus an optimized background regimen or an optimized background regimen alone. Drug resistance was tested to determine which drugs in the optimized background regimen had demonstrated superior activity in vitro, since enrolled patients had documented antiretroviral failure and resistance. At 24 weeks, the viral load had decreased 1.696 log₁₀ copies/ml with the enfuvirtide regimen versus 0.764 log₁₀ copies/ml with the optimized background regimen alone ($p < 0.001$). A significant increase was noted in mean CD4⁺ count in the enfuvirtide group (76 cells/mm³) vs the optimized background regimen group (32 cells/mm³) ($p < 0.001$). These data are consistent with other studies through 48 weeks of follow-up.

Panel on Clinical Practices for the Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents, November 10, 2003. Available from <http://www.aidsinfo.nih.gov/guidelines/>. Accessed February 12, 2004.

These comprehensive HIV treatment guidelines are available online and are frequently updated. Information is presented in algorithms, tables, and text, and supporting evidence is systematically evaluated throughout the document. Included are treatment algorithms, timing of antiretroviral therapy, goals of therapy, and tables of pharmacologic agents (e.g., adverse reactions and drug interactions, therapeutic drug monitoring, drug adherence, resistance testing, acute HIV infection, and considerations for pregnancy). Treatment regimens are differentiated into specific definitions of preferred and alternative categories, and the list of “not recommended” antiretroviral components and combinations is expanded. The guidelines are updated to include new antiretroviral agents and clinical trial data.

Invasive Fungal Infections

Pappas PG, Rex JH, Sobel JD, et al. Guidelines for treatment of candidiasis. *Clin Infect Dis* 2004;38:161–89.

The 2000 guidelines from the Infectious Diseases Society of America for the treatment of invasive candidiasis have been updated. The authors discuss the role of the microbiology laboratory in providing information concerning

in vitro susceptibility testing and identification of the infecting organism. In addition, treatment recommendations for 16 forms of invasive candidiasis are reviewed. In general, amphotericin B (including lipid formulations), fluconazole, and caspofungin all play a role in the treatment of invasive candidiasis. In general, fluconazole is considered the mainstay for the treatment of candidiasis. However, the choice of agent depends on the clinical status of the patient, identification of infecting species or susceptibilities, drug toxicity, related patient characteristics (e.g., concurrent drugs), and previous exposure to antifungal therapy. Prophylactic strategies for the prevention of invasive candidiasis in high-risk patients with prolonged neutropenia or who have received a solid organ transplant are discussed. In general, these patients are at significant risk for developing invasive candidiasis, and prophylaxis with an azole (e.g., fluconazole or itraconazole) is warranted during periods of highest risk.

Ostrosky-Zeichner L. New approaches to the risk of *Candida* in the intensive care unit. *Curr Opin Infect Dis* 2003;16:533–7.

The rationale for prophylaxis against invasive candidiasis in the intensive care setting is thoroughly reviewed. In general, prophylaxis in this setting is most beneficial in institutions, specific areas of an institution, or patient populations with a high rate of fungal infections. Some risk factors for invasive candidiasis in intensive care patients are length of stay in the ICU, receipt of broad-spectrum antibiotics, receipt of total parenteral nutrition, gastrointestinal perforation or surgery, and hemodialysis. The three major studies of antifungal prophylaxis in the intensive care setting are reviewed. The potential benefit from reducing the frequency of invasive candidiasis in the intensive care setting must be weighed against increased drug therapy, which increases drug expenditures and the potential for selection of resistant organisms. Knowledge in this area is evolving; a more extensive evaluation with a multicenter approach is being conducted.

Hospenthal DR, Murray CK, Rinaldi MG. The role of antifungal susceptibility testing in the therapy of candidiasis. *Diagn Microbiol Infect Dis* 2004;48:153–60.

The goal of standardized in vitro susceptibility testing is to assess the likelihood of a successful response when an agent is used to treat an

infection and, perhaps more important, when failure can be predicted. Unlike such testing for many bacteria, routine use of in vitro antifungal drug susceptibility testing is in its infancy. This article reviews the key principles used in in vitro susceptibility testing of antifungals and the potential role for this testing in the clinical setting. Data for available antifungal agents are summarized. The authors conclude that susceptibility testing for selected organism-drug combinations (in particular, the azole antifungal agents against *Candida* sp) is useful in the treatment of fungal infections.

Steinbach WJ, Stevens DA. Review of newer antifungal and immunomodulatory strategies for invasive aspergillosis. *Clin Infect Dis* 2003;37(suppl 3):S157–87.

The past 5 years have seen great advances in the pharmacotherapy of invasive aspergillosis. This review article thoroughly describes current antifungal therapy with available agents approved by the Food and Drug Administration, and investigational antifungal agents in late stages of development. The authors also discuss antifungal susceptibility testing and the current and future role of immunomodulatory agents (granulocyte-macrophage colony-stimulating factor, interferon- γ , and granulocyte transfusions) in the management of invasive aspergillosis. Key points reviewed include the in vitro potency of voriconazole compared with amphotericin B against various *Aspergillus* sp, and voriconazole's superior safety and efficacy in animal models and clinical trials of invasive aspergillosis.

Revankar SG, Patterson JE, Sutton DA, et al. Disseminated phaeohyphomycosis: review of an emerging mycosis. *Clin Infect Dis* 2002;34:467–76.

Disseminated phaeohyphomycosis, or black mould, is an uncommon infection that appears to be increasing, particularly in immunocompromised patients. The common feature among these organisms is the presence of melanin in their cell walls, which imparts the characteristic dark color. This review addresses 72 cases of disseminated phaeohyphomycosis, 75% of which were reported from 1992–2001. Risk factors for infection were immunosuppression, malignancy, organ transplant, and valve replacement. The outcome with antifungal therapy was poor. However, the extended-spectrum triazoles—voriconazole, posaconazole, and ravuconazole—possess favorable in vitro activity against pathogens responsible for phaeohyphomycosis

and appear to hold promise for improving the therapy of these infections.

Bacterial Resistance

Chang S, Sievert DM, Hageman JC, et al. Infection with vancomycin-resistant *Staphylococcus aureus* containing the *vanA* resistance gene. *N Engl J Med* 2003;348:1342–7.

For many years, vancomycin was an antimicrobial to which resistance in *Staphylococcus* sp had not yet emerged. In 1997, the first reported *S. aureus* isolate expressing reduced intermediate resistance to vancomycin was isolated. This article summarizes clinical information and genetic testing data from the first reported case of vancomycin-resistant *S. aureus* (VRSA). The patient, who had diabetes mellitus and received hemodialysis, was treated for recurrent foot ulcers with several courses of antibiotics, including 6.5 weeks of vancomycin. Initial wound cultures revealed oxacillin-susceptible *S. aureus*; later, MRSA and vancomycin-susceptible *Enterococcus faecalis* were isolated. Subsequent catheter-related MRSA bacteremia developed. Both VRSA and vancomycin-resistant *E. faecalis* (VREF) were isolated from the catheter site and from foot ulcers. Surveillance cultures of health care providers, personal contacts, and potential patient contacts were performed, but none revealed VRSA. The VRSA contained the *vanA* gene, most likely acquired from VREF during bacterial conjugation. Based on this mode of bacterial resistance, determinant transfer, and prevalence of VREF, additional VRSA infections are likely to occur.

Neuhauser MM, Weinstein RA, Rydman R, et al. Antibiotic resistance among gram-negative bacilli in U.S. intensive care units. *JAMA* 2003;289:885–8.

Results of a national in vitro surveillance study analyzing 35,790 gram-negative isolates from 1994–2000 are presented in this article. A decline in ceftazidime susceptibilities in *Klebsiella pneumoniae* (93% to 87%) and *Enterobacter* sp (67% to 63%) was observed from 1990–1993 to 1994–2000. Ciprofloxacin susceptibilities decreased from 86% in 1994 to 76% in 2000; the greatest reduction occurred in *Pseudomonas aeruginosa*, from 89% in 1990–1993 to 68% in 2000. This decrease was correlated with an increase exceeding 2.5-fold in fluoroquinolone use. Cross-resistance to ceftazidime and/or gentamicin was seen in more than 39% of ciprofloxacin-resistant *P. aeruginosa* isolates,

Enterobacter sp, and *K. pneumoniae*, whereas imipenem cross-resistance occurred in 37.6% of ciprofloxacin-resistant *P. aeruginosa* isolates. Continuing surveillance and judicious fluoroquinolone use were recommended to preserve these agents.

Carling P, Fung T, Killion A, et al. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect Control Hosp Epidemiol* 2003;24:699–706.

Antibiotic use and resistance before (1988–1991) and after (1991–1998) implementation of a pharmacist- and physician-managed antimicrobial program are summarized in this article. Intervention consisted of education on appropriate antibiotic therapy by team members. Recommendations for antibiotic streamlining, discontinuation, and changing from intravenous to oral administration were suggested by informal chart consult (i.e., inclusion of recommendations in the written or electronic medical chart that do not become part of the permanent record), with 98% acceptance. Although patient acuity (as reflected by the Medicare case-mix index) increased 15%, use of targeted antimicrobials (i.e., third-generation cephalosporins, aztreonam, intravenous fluoroquinolones, and imipenem-cilastatin) decreased 22%. An overall cost reduction was observed. There was a significant decrease in *Clostridium difficile* infection and in resistant Enterobacteriaceae, and a nonsignificant decrease in vancomycin-resistant *Enterococcus* sp. There was no change in MRSA. Antibiotic management programs and education affect judicious antibiotic use and can decrease the frequency of some resistant pathogens.

Lim S, Bast D, McGeer A, de Azavedo J, Low DE. Antimicrobial susceptibility breakpoints and first-step *parC* mutations in *Streptococcus pneumoniae*: redefining fluoroquinolone resistance. *Emerg Infect Dis* 2003;9:833–7.

Fluoroquinolone resistance in *Streptococcus pneumoniae* remains at a relatively low magnitude, but significant concerns exist regarding an apparent increase in global resistance. Thus, some investigators have explored alternative methods that might better describe the true scope of fluoroquinolone resistance. These authors analyzed 115 *S. pneumoniae* isolates with a levofloxacin minimum inhibitory concentration (MIC) of 2 µg/ml or greater sampled from 6076 isolates collected in a 1993–1998 surveillance study. The regions of *parC* and *gyrA* determining

quinolone resistance were sequenced to identify mutations in the genes encoding the fluoroquinolone target sites topoisomerase IV and DNA gyrase, respectively. Of isolates with an MIC of 4 µg/ml, 63% displayed a *parC* mutation, and 38% possessed mutations in *parC* and *gyrA*. More important, 59% of isolates with an MIC of 2 µg/ml (characterized as susceptible according to National Committee for Clinical Laboratory Standards clinical breakpoints) harbored a *parC* mutation. This study calls into question the utility of MIC testing alone as a reliable method for surveillance of fluoroquinolone susceptibility in *S. pneumoniae*.

Phillips I, Casewell M, Cox T, et al. Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data. *J Antimicrob Chemother* 2004;53:28–52.

This review summarizes the evidence linking antibiotic use in food animals with development of bacterial resistance. Numerous studies have reported isolation of antimicrobial-resistant bacteria in retail ground beef, chicken, and pork from animals that had been given antibiotics for growth promotion. As a result of concerns regarding the necessity of routine administration of antibiotics to animals, several countries have banned antibiotic use for growth promotion. After such changes were made, an increase in prudent antibiotic use, a decrease in total antibiotic use in animal feed, and a decrease in animal food production were observed. The authors recommend improving hygiene practices to decrease bacterial isolation. They concluded that no evidence indicates that antibiotic use in animals increases the frequency of resistant pathogens in humans.