Antibiotic Use in Hospitals 4

At any given time, 25 to 35 percent of hospitalized patients are receiving systemic antibiotics (Eickhoff, 1991) to treat active infections or to prevent potential infections. The heavy use of antibiotics in the hospital exerts enormous selective pressure for the emergence and spread of antibiotic-resistant bacteria. Consequently, many of the two million bacterial infections acquired in the hospital are antibiotic-resistant, and a few are resistant to every antibiotic currently approved for use. Some hospitals have reduced infections from antibiotic-resistant bacteria through a combination of infection control procedures that prevent the spread of the resistant organisms and through monitoring and control of antibiotic use.

This chapter 1) describes antibiotic use in hospitals and its contribution to the rise of antibiotic-resistant nosocomial infections, 2) discusses current efforts to control antibiotic-resistant infections, 3) explores medical and financial factors that make such efforts difficult to implement in hospitals, and 4) discusses some possible solutions.

INFECTIONS ACQUIRED IN THE HOSPITAL

The Centers for Disease Control and Prevention (CDC) estimates that 1 out of 20 patients (2 million per year) acquire infections in the hospital (Haley et al., 1985).[1] Nosocomial infections cost $4.5 billion a year (1992 dollars) in terms of extra treatment and days of hospitalization, directly cause 19,000 deaths, and contribute to 58,000 deaths annually (table 4-1). The 19,000 deaths per year directly caused by nosocomial infections makes them the 11th leading cause of death in the U.S. population (Martone et al., 1992).

Recent data from the National Nosocomial Infections Surveillance (NNIS) system show that nosocomial infections are increasing (figure 4-1). The number of blood stream infections increased 279 percent in small non-teaching hospitals, 196 percent in large non-teaching hospitals, by 124 percent in small teaching hospitals, and by 70 percent in large teaching hospitals during the 1980s. It might be discouraging that the rates of blood stream infections have been increasing

[1] Based on data from CDC's 1976 Study on the Efficacy of Nosocomial Infection Control (SENIC). This number is still widely quoted in recent reports (see, for example, IOM, 1992).

	Extra days		Extra charges		Deaths directly caused by infections	Deaths to which infections contributed
	Avg. per infection[a]	Est. U.S. total[b]	Avg. extra charges per infection in 1992 dollars[c]	Est. U.S. total in 1992 dollars[b]	Est. U.S. total[b]	Est. U.S. total[b]
Surgical wound infection	7.3	3,726,000	$3,152	$1,609,000,000	3,251	9,726
Pneumonia	5.9	1,339,000	$5,683	$1,290,000,000	7,087	22,983
Bacteremia	7.4	762,000	$3,517	$362,000,000	4,496	8,844
Urinary tract infection	1.0	903,000	$680	$615,000,000	947	6,503
Other site	4.8	1,946,000	$1,617	$656,000,000	3,246	10,036
All sites	4.0[d]	8,676,000	$2,100	$4,532,000,000	19,027	58,092

[a] Adapted from R.W. Haley et al., Extra days and prolongation of stay attributable to nosocomial infections: A prospective interhospital comparison. *American Journal of Medicine* 70:51, 1981, by pooling data from the three SENIC pilot study hospitals.

[b] Estimated by multiplying the total number of nosocomial infections estimated in the SENIC Project (R.W. Haley et al., The nation-wide nosocomial infection rate: A new need for vital statistics. *American Journal of Epidemiology* 121:159, 1985) by the average extra days, average extra charges, or percentage of infections causing or contributing to death, respectively.

[c] 1992 dollars estimated from R.W. Haley et al., *Amer. J. Med.* 70:51, 1981, by pooling data from the three hospitals and adjusting for the annual rate of inflation of hospital expenses from 1976 to 1992 (range 5.0 to 12.3 percent) obtained from the American Hospital Association's National Panel Survey. Estimates for inflation rates in 1991 and 1992 were projected from 1987 to 1990 trend.

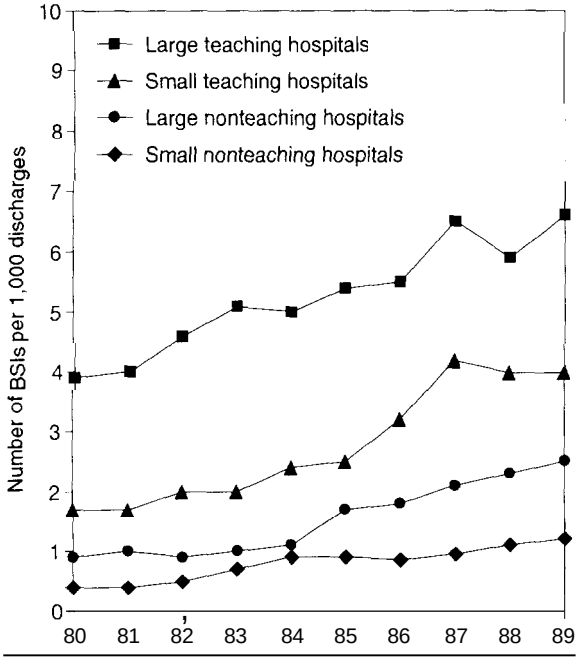
[d] Nationwide estimate obtained by summing the products of the site-specific estimate of the average extra days, average extra charges, or the percentage of infections causing or contributing to death, respectively, from the SENIC pilot studies (R.W. Haley et al., *Amer. J. Med.* 70:51, 1981), and the nationwide estimate of the proportion of nosocomial infections affecting the site from the main SENIC analysis (R.W. Haley et al., *Amer. J. Epidemiol.* 121:159, 1985).

SOURCE: W.J. Martone, W.R. Jarvis, D.H. Culver, et al. 1992. Incidence and nature of endemic and epidemic nosocomial infections. In: J.V. Bennett and P.S. Brackman (eds.) *Hospital Infections* Third edition. Boston, MA. Little, Brown and Company, pp. 593.

despite guidelines developed by CDC and the adoption of "universal precautions" to control infections. However, these increasing rates are partially due to recent advances in medicine. Increasing rates of surgery and catheterization provide opportunities for bacteria to penetrate into the body where they can cause infections. In addition, tissue and organ transplants, which are becoming more frequent and successful, require immunosuppression so that the foreign tissue is not rejected by the transplant recipient. Consequently, immunosuppressed patients are dependent on antibiotics to control bacterial infections.

Treatment with an antibiotic may suppress enough normal microbial flora (commensals) to leave a patient susceptible to infection by other organisms—especially antibiotic-resistant bacteria-unaffected by the antibiotic. Kollef (1 994) cites studies that show intensive care unit patients who had received antibiotics were more likely to develop ventilator-associated pneumonia caused by virulent species such as *Pseudomonas aeruginosa* or Acinetobacter, and that patients with those infections were almost twice as likely to die from them as patients infected with less virulent species.

FIGURE 4-1: Bloodstream Infection (BSI) Rates for All Pathogens in Various Types of Hospitals



SOURCE: S.N. Banerjee, T.G. Emori, D.H. Culver, et al, 1991. *American Journal of Medicine 91* (Suppl. 3B):86S-89S

THE RISE OF ANTIBIOTIC-RESISTANT INFECTIONS IN HOSPITALS

CDC operates the NNIS system that gathers voluntary information from approximately 200 hospitals, and through NNIS, CDC has documented increases in the number of nosocomial infections caused by antibiotic-resistant bacteria. Two important cases are the increasing numbers of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococci (VRE). Resistant strains of Klebsiella, Pseudomonas, *Escherichia coli,* and coagulase-negative Staphylococci also cause serious problems in hospitals.

Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Nosocomial *Staphylococcus aureus* infections have been a recurrent problem in hospitals for many years. This is partially due to the high rate of colonization in the population: about 50 percent of the population are intermittent carriers of *Staph. aureus,* and about 30 percent of the population are prolonged carriers of the bacteria in their nostrils or on their skin (Waldvogel, 1995). When these colonizing organisms enter internal organs of the body through invasive surgery, catheterizations, or other hospital procedures, they can cause infection. Strains resistant to penicillin were identified soon after its introduction (Spink and Ferris, 1945). Currently, more than 90 percent of all *Staph. aureus* are resistant to penicillin (Mandell and Sande, 1990). These strains of staphylococci were most likely resistant through the production of beta -lactamases that destroy penicillin and penicillin-like antibiotics.

The synthetic penicillin, methicillin, introduced in 1960, is not affected by many beta-lactamases. However, strains of staphylococci that

contain a chromosomal gene called *mec A* which encodes a modified penicillin-binding protein have been identified. These strains, commonly referred to as MRSA, are resistant to all beta-lactam antibiotics, and frequently also contain plasmid-encoded genes for resistance to other antibiotics (see chapter 2). MRSA were initially susceptible to the fluoroquinolones introduced in the 1980s, such as ciprofloxacin, but they quickly became resistant to these antibiotics. NNIS data document the increase in MRSA (figure 4-2). By 1992, more than 40 percent of *Staph. aureus* infections in large hospitals were methicillin-resistant. Some strains of MRSA are resistant to all antibiotics currently approved by the U.S. Food and Drug Administration (FDA), with the exception of vancomycin; others are susceptible to other antibiotics as well as vancomycin (see chapter 5).

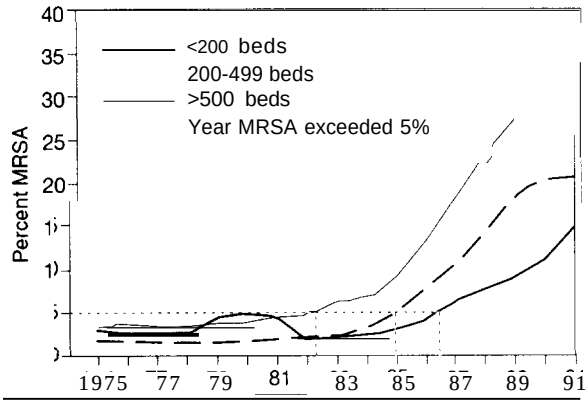
▮ Vancomycin-Resistant Enterococcus

Some strains of Enterococcus are resistant to ***all*** available antibiotics approved by FDA, and they are, therefore, untreatable with antibiotics. NNIS data showing the increase in VRE are presented in figure 4-3. As of 1994, almost 13 percent of enterococci acquired in intensive care units (ICUs) were resistant to vancomycin, and about 8 percent of enterococci acquired outside of ICUs were resistant. There is currently no FDA-approved antibiotic to treat many of these infections.[2]

▮ Vancomycin-Resistant MRSA?

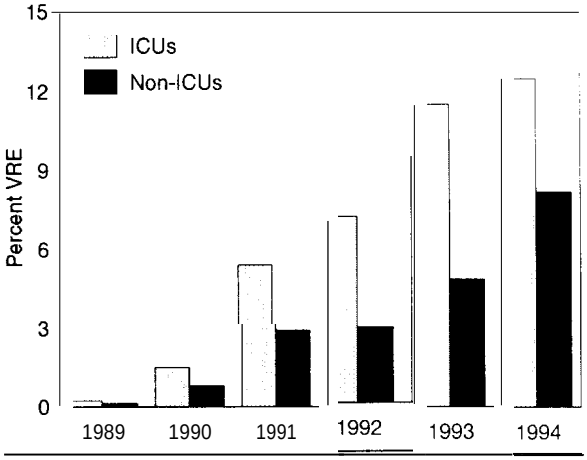
A huge fear among clinicians and epidemiologists is the possibility of the emergence of vancomycin-resistant strains of MRSA that are both highly virulent and untreatable. As this report goes to press, no confirmed vancomycin-resistant strain of MRSA has been reported to public health officials at CDC or elsewhere. However, Noble, Virani, and Cree (1992) demonstrated the transfer of a vancomycin resistance gene from an Enterococcus to *Staph. aureus* in the laboratory, indicating that the clinical emergence of vanco-

FIGURE 4-2: Methicillin-Resistant *Staphylococcus aureus* (MRSA) as a Percent of All *Staphylococcus aureus* in Hospitals of Different Sizes



SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA

FIGURE 4-3: Vancomycin-Resistant Enterococcus (VRE) as a Percent of All Enterococcus in Intensive Care Units (ICUs) and Non-ICUs



SOURCE: National Nosocomial Infections Surveillance System Centers for Disease Control, Atlanta, GA.

[2] **Chapter 5 describes two new drugs, quinupristin/dalfopristin and teicoplanin, currently in clinical trials that may have activity against some strains of VRE, These drugs are available from the manufacturers on a compassionate-use basis to patients with VRE infections (The *Medical Letter on Drugs and Therapeutics,* 1994, at p. 31).**

mycin-resistant MRSA is possible. The only treatment available for some strains of MRSA is vancomycin, and the emergence of vancomycin-resistant MRSA may be inevitable. It will present a crisis in treatment.

THE USES OF ANTIBIOTICS IN HOSPITALS

Prophylactic Use of Antibiotics

In large surgical hospitals, half of all antibiotics are used to prevent possible infections (prophylaxis) (Kernodle and Kaiser, 1990). More than 30 years ago, Burke (1961) showed that prophylactic use of antibiotics before surgery reduces postoperative infection rates. Classen et al. (1992) investigated the timing of administration of antibiotics for prophylaxis and confirmed that antibiotics can prevent infections when administered two hours prior to surgery. They also suggested that antibiotics given at times other than in the 2 hours before surgery (one-third of all prophylactic antibiotics were given earlier than 2 hours before surgery or after surgery in this study of 2,847 patients) are not as effective in preventing infections (see table 4-2). Approximately 12 percent of the patients received antibiotics more than 2 hours before surgery; and more than 70 percent of the antibiotics given had half-lives ranging from 0.7–1.9 hours (Wenzel, 1992), suggesting that these antibiotics washed out of the patients' system before surgery began. In these cases it is clear that the use of antibiotics was inappropriate and that appropriate use of antibiotics would reduce the rate of infections and their associated costs because of decreases in the number of days that a patient is hospitalized. Moreover, appropriate use would reduce antibiotic use and help control antibiotic resistance.

Studies raise questions about the effects of prophylactic antibiotic use other than to prevent surgical wound infections. Kollef (1994a) found that prophylactic use of antibiotics for selective digestive decontamination designed to reduce nosocomial pneumonia reduced the incidence of pneumonia, but it had no effect on mortality. Apparently this phenomenon occurred because antibiotic-resistant bacteria that colonized some patients following the prophylactic treatment were harder to treat.

Classen et al. (1992) reported that more than 50 percent of the nosocomial infections they

TABLE 4-2: Temporal Relation between the Administration of Prophylactic Antibiotics and Rates of Surgical-Wound Infection

Time of administration*	No. of patients	No. (%) of infections	Relative risk (95% CI)	Odds ratio** (95% CI)
Early	369	14 (3.8)‡	6.7 (2.9–14.7)	4.3[a] (1.8–10.4)
Preoperative	1708	10 (0.59)	1.0	
Perioperative	282	4 (1.4)[b]	2.4 (0.9–7.9)	2.1[c] (0.6–7.4)
Postoperative	488	16 (3.3)‡	5.8‡ (2.6–12.3)	5.8[d] (2.4–13.8)
All	2847	44 (1.5)	————————	————————

* For the administration of antibiotics, "early" denotes 2 to 24 hours before the incision, "preoperative" 0 to 2 hours before the incision, "perioperative" within 3 hours after the incision, and "postoperative" more than 3 hours after the incision.

** As determined by logistic-regression analysis.

‡ P<0.0001 as compared with preoperative group (all P values were determined by logistic-regression analysis).

[a] P = 0.001.

[b] P = 0.12 as compared with preoperative group.

[c] P = 0.23.

[d] P = 0.0001.

SOURCE: C. Classen, R.S. Evans, S.L. Pestotnik, et al. 1992. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *New England Journal of Medicine* 326(5):283.

studied were caused by organisms resistant to the antibiotic used. In these cases the infections may have been caused because the resistant organisms were able to multiply when the susceptible normal bacterial flora of the patients was inhibited by the prophylactic antibiotics. Siegel et al. (1980) reported an especially tragic example of prophylactic use gone awry based on examination of the results of giving a single dose of penicillin to ward off streptococcal infections in some 9,000 newborns. Although penicillin-sensitive infections were reduced by the prophylactic treatment, infections with penicillin-resistant bacteria were more frequent in the babies who received the antibiotic, and mortality was higher from the resistant infections (15 of 35) than from the sensitive infections (3 of 27). Overall, the death rate from streptococcus infections was 3 times higher in the babies that received penicillin (1.2/1,000 vs. 0.43/1,000 live births).

Antibiotic Use to Treat Active Infections

The remainder of antibiotic use in hospitals is for treatment of active infections. It takes at least two days to identify the bacteria causing an infection and to determine its antibiotic susceptibility (see chapter 6). Therefore, the physician often has to make an empirical judgment about the identity of the bacteria and prescribe an antibiotic before the laboratory test results are available. If a patient is very sick, the physician will often use multiple antibiotics. If the patient is improving when the laboratory tests arrive, the physician might ignore the results of the tests and continue the patient on the empiric antibiotics. It is difficult to determine inappropriate antibiotic use and how to improve use in such cases.

The appearance of unexpected resistant organisms in one patient may influence a physician to routinely prescribe newer or broader spectrum antibiotics. A letter to the editor of the *New England Journal of Medicine* (Lonks et al., 1995) illustrates a case where a patient suffered because he was infected with an unlikely resistant strain. Physicians knew that no highly resistant strains of pneumococci had been reported in Providence, Rhode Island; only 2.3 percent of isolates obtained in hospitals in 1990 and 1991 showed intermediate-level resistance to penicillin, and none was highly resistant. An otherwise healthy 33-year-old man, who lived a little more than 30 miles from the city, was treated in the hospital for a *Streptococcus pneumoniae* infection. Assuming that the strain was not ceftriaxone-resistant, doctors treated the patient with dexamethasone and ceftriaxone for the first four days. After initial improvement, encephalitis developed, and doctors switched drugs to vancomycin and rifampin based on antibiotic-susceptibility test results that showed the infecting strains were resistant to penicillin and ceftriaxone. The patient's condition eventually improved and he was sent home. Based on this experience, the authors concluded that "*all patients* with the presumptive diagnosis of pneumococcal meningitis should receive high-dose ceftriaxone (or cefotaxime) plus vancomycin, with or without rifampin, until the isolate is proved to be susceptible to penicillin or ceftriaxone" [emphasis added]. It may be true that following this advice will prevent a few adverse outcomes such as those described in the letter to the journal. However, if similar reasoning is applied in many cases, the widespread use of antibiotics such as vancomycin will increase the risk for the emergence of antibiotic-resistant organisms.

In a study of the reasoning strategies used by physicians in empiric antibiotic selection, Yu et al. (1991) found that unexpected organisms appeared in 3.8 percent of all blood cultures. In these cases, antibiotics had been prescribed which were not the antibiotics of choice based on logical reasoning, but which did cover the unexpected organisms. The authors comment that "[t]hese memorable situations may have a disproportionate influence in these physicians' future selection of antibiotic therapy." They further conclude that "our disturbing and unexpected finding is that reflex prescription of broad-spectrum antibiotic therapy that is so often decried by academicians may have a rational basis" and that "educational efforts that emphasize narrow, rather than broad-spectrum prescribing may be inadequate to change physician prescribing habits."

LEGAL ASPECTS OF ANTIBIOTIC USE

Malpractice concerns might provide an additional incentive to prescribe antibiotics. According to data published by St. Paul Fire and Marine Insurance Company, a large nationwide malpractice insurer, a significant number of claims are related to infection-related illnesses and antibiotic use (St. Paul Fire and Marine Insurance Co., 1995). It is reasonable to speculate that fear of malpractice litigation may contribute to prescription of overly broad spectrum antibiotics or of antibiotics in cases where the chance of a bacterial infection is small. Box 4-1 contains excerpts from a commentary in the medical journal *Lancet* discussing the medical and legal controversy over the use of prophylactic antibiotics to prevent neonatal bacterial sepsis caused by Group B streptococcus.

BOX 4-1: Group B Streptococcus: The Controversy

Group B streptococcus (GBS) is the leading cause of neonatal bacterial sepsis in the United States, infecting about 12,000 newborns annually. Some newborns infected with GBS may die or have permanent neurological damage from meningitis. In 1992, both the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) issued protocols regarding the screening of pregnant women to detect and treat carriers of GBS in an effort to prevent neonatal GBS sepsis.

AAP called for universal prenatal GBS screening for all pregnant women at 26–28 weeks' gestation. Because certain population groups are more likely to carry GBS, ACOG advocated for optional screening targeted to certain populations where the incidence of neonatal GBS infection is inordinately high, such as populations where sexually transmitted diseases are common.

Inasmuch as GBS is part of the normal gut flora of some women and may or may not become a pathogen during pregnancy, both AAP and ACOG recommended intrapartum (during delivery) antibiotic treatment only to women with positive cultures who have additional high-risk factors such as preterm labor or premature rupture of the membranes before 37 weeks' gestation, fever in labor, multiple births, rupture of membranes for more than 18 hours at any gestational age, or a previous affected child.

The AAP and ACOG protocols leave a number of issues unresolved that expose obstetricians, family practitioners, and nurse midwives to considerable medicolegal liability. Screening for GBS during pregnancy does not provide certainty as to whether or not intrapartum antibiotic treatment is warranted. A study found that in women who were culture-positive at 28 weeks' gestation, 30 to 50 percent were culture-negative at the time of delivery; in women who were culture-negative at 28 weeks, 8 to 15 percent were culture-positive at the time of delivery. Consequently, some women will be treated unnecessarily and some who need treatment will be ignored.

Moreover, if only certain groups are targeted for screening in keeping with ACOG's protocol, can excluded groups hold health care professionals responsible if their newborn babies developed undetected GBS sepsis? Further, would the withholding of treatment in a pregnant woman with a positive culture who has no additional risk factors absolve a health care professional from medicolegal liability if that baby were affected?

The best approach to the management of GBS sepsis would be a rapid screening test during labor to determine whether antibiotic therapy is warranted, but the poor sensitivity of such tests currently renders them clinically useless. Until these tests are improved, health care professionals will most likely err on the side of caution and prescribe antibiotics even in extremely low-risk cases.

SOURCE: C.V. Towers, 1995, *Lancet* 346:197–198.

The following review of some malpractice suits exemplifies the dramatic consequences that can occur due to undertreating with antibiotics. In *Hellwig v. Potluri* (Case No. WL 285712, Ohio Court of Appeals 7th Circuit, 1991), the defendant emergency room physician was held liable for failing to prescribe antibiotics for the plaintiff who had stepped on a rusty nail at his home. The plaintiff developed osteomyelitis which forced him to "wear an appliance in his shoe and have an altered gait for the rest of his life." In *Toler v. United States of America* a plaintiff claimed that failure of a Veterans Administration (VA) hospital to administer an adequate course of antibiotics resulted in sepsis and death. In *Griffith v. West Suburban Hospital* (Case No. 86L-23904, Cook County, Illinois Circuit Court, 1993), a jury returned a $3.5-million verdict for failure to diagnose and timely treat a Group B Strep infection. In this case, a patient showed signs of respiratory distress shortly after birth, and although he was moved to an intensive care crib, antibiotics were not administered. Seven hours later, after being transferred to another hospital which then administered antibiotics, the patient died.

The medical and financial consequences of failing to prescribe prophylactic antibiotics for endocarditis can be considerable. In 1993, a dentist was held liable in *Orbay v. Castellanos* (Case No. 91-36124, Dade County Circuit Court, Miami, Florida, 1993) for failing to prescribe prophylactic antibiotics prior to tooth extraction. Soon after the tooth extraction, the plaintiff was diagnosed with bacterial endocarditis and underwent open heart valve replacement surgery. The defendant was held liable for failure to prescribe prophylactic antibiotics and failure to obtain a full medical history or medical clearance for a patient at risk of developing bacterial endocarditis. The jury awarded the plaintiff $1.24 million, which was reduced to $964,000 to reflect the decision that the plaintiff was 20 percent comparatively negligent for failure to take appropriate care of himself. However, a standard medical textbook comments:

> The issue of professional liability in the prophylaxis of endocarditis often has led to allegations of negligence and malpractice suits. . . . [It is hard] to prove that the failure of a physician or dentist to administer antibiotics was the direct cause of a patient acquiring endocarditis. If a strict demonstration of proximate cause were always required, it is doubtful that any claim based on the failure to administer prophylaxis could succeed, but juries are sometimes capricious in deciding liability in malpractice cases. . . (Mandell et al., 1990).

The "capricious" nature of the juries might bias physicians in favor of prescribing antibiotics, even when the risk of endocarditis (or other disease) is very minimal.

CONTROLLING THE EMERGENCE AND SPREAD OF ANTIBIOTIC RESISTANCE IN HOSPITALS

Part of the difficulty in controlling antibiotic resistance in hospitals is incomplete understanding of all the factors that contribute to the emergence and spread of antibiotic resistance in general. Most hospital personnel would agree that infection control is critical, but there are many disagreements about the benefits vs. cost of various infection control procedures. Few, if any, scientists disagree that the use of antibiotics is related to the emergence and spread of antibiotic resistance. Nevertheless, there are many controversies about how to implement programs to control the use of antibiotics.

Infection Control in Hospitals

In 1847, Ignac Semmelweis noticed that the rate of childbed fever in new mothers was much higher when the babies were delivered by obstetricians and medical students than by midwives and midwifery students. Semmelweis surmised that the high rate was due to the transmission of infectious particles from cadavers by the obstetricians and medical students and instituted the measure of handwashing in a chlorine solution. This measure greatly decreased the incidence of childbed fever (reviewed by Sanford, 1992).

In hospitals today, infection control procedures are considered absolutely essential. In 1976, CDC conducted a comprehensive Study on the Efficacy of Nosocomial Infection Control (SENIC) that measured the extent and effectiveness of infection control procedures in U.S. hospitals. The SENIC study included a survey of all hospitals in the United States and detailed interviews with representative hospitals. Twenty years later, the study remains the most comprehensive survey of the effectiveness of infection control procedures.[3] The study concluded that hospitals with intensive infection surveillance and control programs were able to reduce the rate of nosocomial infections by 32 percent (Haley et al., 1985). Yet the study found that only about 0.2 percent of U.S. hospitals had programs that effectively controlled all four of the major types of infections: surgical wound infection, urinary tract infection, primary bloodstream infection, and lower respiratory tract infection.

Infection Control Activities

The SENIC study concluded that a successful infection control program required leadership by a trained infection control physician, an infection control nurse for every 250 beds, organized infection surveillance efforts, and a system for reporting infection rates to practicing surgeons.

Handwashing and Other Precautions

Simple infection control procedures, such as handwashing and wearing gloves, reduce the spread of infections in hospitals, lowering the need for antibiotics and thereby reducing selective pressure for the spread of antibiotic-resistant bacteria. Health care workers have a large incentive to follow procedures such as universal precautions[4] because they were designed to protect them from infection from organisms such as the human immunodeficiency virus (HIV). However, in the hospital setting health care workers who respond to a life-threatening emergency often do not have time to put on gloves and follow proper infection control procedures. Willy et al. (1990) found that health care workers' perception of their own risk and potential spread of infections to patients is surprisingly low. In an anonymous nationwide survey of health care workers who might have frequent exposure to blood and other bodily fluids, only 55 percent of those responding reported routinely practicing universal precautions.

Human nature seems to prevent the full implementation of one of the simplest, yet most effective infection control method: handwashing. Handwashing is a proven method for reducing nosocomial infections, but the practice is not strictly followed. Handwashing compliance rates of less than 50 percent were observed in two studies of intensive care units (Simmons et al., 1990; Doebbeling et al., 1992). Goldmann and Larson (1992) make the following comments about the lack of compliance with handwashing:

> Experts in infection control coax, cajole, threaten, and plead, but still their colleagues neglect to wash their hands.... Education and persuasion do not generally lead to sustained improvement in handwashing. Physicians have been particularly refractory. Innovative approaches are needed desperately, but few have emerged.... There is so little confidence in hand-washing habits that hospital isolation policies now assume noncompliance.... [Original references not included].

Simmons et al. (1990) revealed one clue to handwashing noncompliance: nurses who were questioned about their handwashing practices believed they were washing their hands nearly

[3] SENIC data have the serious shortcoming that they were collected before implementation of current infection control procedures such as universal precautions, which were instituted beginning in 1985 largely because of the fear of transmission of the human immunodeficiency virus (HIV).

[4] Universal precautions include requirements that gloves be worn when handling bodily fluids, that needles and other sharp objects be disposed of in special containers to help prevent needle-stick accidents, and that health care workers with open or infected wounds have restricted contact with patients or patient care equipment (Garner, 1993).

90 percent of the time, when actual rates were between 22 and 29 percent.

Research into the seemingly simple question of which soap to use for washing hands may be useful in helping to prevent infections. Several studies have shown that a 7- to 10-second handwash with a non-antibacterial soap *increased* the transmission of bacteria due to the shedding of bacteria-laden skin cells, but that handwashing with antiseptic soaps reduces the rates of nosocomial infections (Martin, 1994). Rotter (1988) compared the efficacy of different antiseptics for washing hands and found that antiseptics containing isopropanol alcohol were significantly better at reducing skin bacteria than liquid soap.

Applying Infection Control Procedures to Control Antibiotic-Resistant Bacteria: Some Case Studies

Box 4-2 describes the successful countrywide control of MRSA in Denmark. The following case studies describe attempts to apply infection control procedures to control MRSA in nursing homes and hospitals in the United States.

Case 1: Successful control in a (mostly chronic care) VA medical center (Murray-Leisure et al., 1990)

The Lebanon, Pennsylvania, Medical Center is an 884-bed facility which successfully controlled an epidemic of MRSA patients during 1988–1989 within six months of instituting aggressive interventions. These interventions included confining known active MRSA carriers and MRSA-infected patients to one nursing unit, screening patients transferred into the facility for MRSA, using gown and glove isolation and treating both colonized and actively infected patients with topical and enteral antibiotics.

Case 2: Unsuccessful control in a VA medical center (Strausbaugh et al., 1992)

The Portland, Oregon, VA Medical Center Nursing Home Care Unit (NHCU) is a 120-bed facility that attempted to control MRSA primarily through administration of the antibiotics rifampin, trimethoprim-sulfamethoxazole, and clindamycin, used either alone or in different combinations, to asymptomatic carriers of MRSA. Other measures included restricting MRSA-infected or colonized patients to a small cluster of rooms, glove use to prevent the spread of any body fluids, and frequent environmental surface decontamination. The majority of MRSA patients in this facility remained either colonized or became recolonized during a 30-day follow-up period after treatment. Furthermore, a most disturbing byproduct of the Portland VA study was the emergence of resistance to rifampin after therapy.

Case 3: Coordination of infection control practices between a hospital and nursing homes to manage MRSA (Jewell, 1994)

The Christ Hospital and Medical Center, Oak Lawn, Illinois, is an 823-bed teaching hospital that serves many patients who live in regional nursing homes. Before 1991, nursing homes often required three successive test results showing the patient was not carrying MRSA before they would accept a patient from the hospital. This led to extended stays in the hospital for patients who were colonized with MRSA, but otherwise did not need to be in the hospital. A quality improvement team including clinicians, hospital administrators, and nursing home representatives adopted guidelines that allowed colonized patients to be returned to the nursing homes. When these new guidelines were adopted, the hospital did not see any change in the number of patients infected or colonized with MRSA. It did see an average decrease of over 10 days in the length of stay in the hospital, a reduction in the readmission rate of patients colonized with MRSA from 8.7 to 2.7 percent in 1992, and total cost savings of over $1.9 million.

These case studies illustrate the complexities in determining which infection control practices are the most likely to help control antibiotic-resistant bacteria such as MRSA. In the first case, a combination of isolation of patients colonized or infected with MRSA and antibiotic therapy seemed to control MRSA, but in the second case similar procedures failed to produce posi-

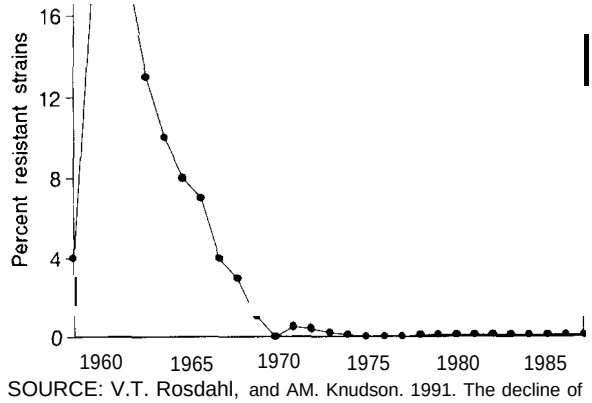
tive results. Further, the second case illustrates a danger in antibiotic-therapy for decolonization: the emergence of new antibiotic-resistant strains. And the third case illustrates that isolation of patients colonized with antibiotic-resistant bacteria can be taken too far: in this case allowing patients colonized with MRSA to return to nursing homes saved money and significantly reduced the length of hospital stays. Hospitals and nursing homes need to examine cases such as these along with specific conditions in their own facilities to determine the best practices for reducing the spread of antibiotic-resistant bacteria.

BOX 4-2: Methicillin-Resistant *Staph. aureus* and Infection Control in Denmark

In Denmark the frequency of methicillin-resistant *Staph aureus* (MRSA) rose to 15 percent between 1967 and 1971, but decreased to 0.2 percent by 1984, and has remained at that low level (see figure).

Hans Jern Kolmos of the Hvidovre Hospital, University of Copenhagen, discussed the dramatic decline in MRSA at a recent meeting of the Association of Practitioners of Infection Control and Epidemiology. Kolmos attributes the decline to strict control of antibiotic use in hospitals. He acknowledges one of the fundamental dilemmas in antibiotic prescribing: "In a situation of doubt, where the clinician stands face to face with an ill patient, fear of overlooking an infection-or pressure from the patient—will often outweigh the fear of side effects in the doctor's mind, and the result will be prescription for safety's sake, " Kolmos stresses the value of including clinical microbiologists in the decision-making process: "In Denmark the clinical microbiologist is a medical doctor, who has a clinical education in addition to his laboratory education. This means that he takes part not only in laboratory work, but also in the treatment of patients, either bedside or at conferences with the clinical staff. Formally, he is only an advisor; it is the clinician who has the power to decide. However, the influence of the clinical microbiologist is great, partly because he is well-known from his frequent visits to the clinical units and partly because he has the same educational background as the clinicians. "

Frequency of Methicillin-Resistant *Staphylococcus aureus* (MRSA) in **Denmark**



SOURCE: V.T. Rosdahl, and AM. Knudson. 1991. The decline of methicillin resistance among Danish *Staphylococcus aureus* strains. *Infection Control and Hospital Epidemiology 12(2):83-88.*

The low rates of MRSA in Denmark may also be due to strict compliance with infection control procedures. Westh et al. (1992) note that "Isolation of a methicillin-resistant strain triggers an immediate visit to the patient involved and the staff caring for that patient by a microbiologist and an infection control nurse. Patients are isolated, and hygienic precautions are taken in an effort to prevent acquisition and carriage of the resistant strain by staff members. " They also comment that "Such precautions at institutions in countries not yet overwhelmed by high rates of isolation of methicillin-resistant S. *aureus* might likewise hinder the spread of these strains. "

SOURCES: V.T. Rosdahl and A.M. Knudson, 1991. The decline of methicillin resistance among Danish *Staphylococcus aureus* strains. *Infection Control and Hospital Epidemiology* 12(2):83-88; H. Westh, J.0. Jarlov, H. Kjersem, et al. 1992. The disappearance of multiresistant *Staphylococcus aureus in* Denmark: Changes in strains of the 83A complex between 1969 and 1989. *Clinical Infectious Diseases* 14(6) .1186-1194

HOSPITAL ACCREDITATION AND INFECTION CONTROL REGULATIONS UNDER MEDICARE

Current hospital accreditation and Medicare regulations recognize that each hospital must analyze conditions in its own facility to determine the best methods of infection control.

Loeb and O'Leary of The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) explain that

> The Joint Commission historically has used compliance with contemporary standards as its basic measure of health care quality in the accreditation process. In recent years, however, there has been growing interest in monitoring and evaluating the actual results of care. . .

JCAHO has recently developed a system for performance measurement called the Indicator Measurement System (IMSystem). Beginning in 1996, the system will include several measurements related to antibiotic use and infection control: timing of administration of prophylactic antibiotics, surveillance and prevention of surgical site infection, surveillance and prevention of ventilator-associated pneumonia, and surveillance and prevention of primary blood stream infections. JCAHO has recognized ". . . the already tremendous information burdens on most organizations" and therefore has designed

> ". . . the IMSystem to be parsimonious, that is, to collect only those data elements that are needed and to use all the elements that are collected. Whenever possible, the IMSystem uses data elements likely to be already collected by health care organizations" (IMSystem General Information, JCAHO).

Participation in this system, which is voluntary, has great potential to help hospitals identify specific problems in infection control.

Medicare regulations state that as a condition of participation in Medicare, hospitals must have a quality assurance program in which "nosocomial infections and medication therapy must be evaluated" (42 CFR 482.21a2). Further, "there must be an active program for the prevention, control, and investigation of infectious and communicable diseases" (42 CFR 482.42). This program includes the designation of an infection control officer who "must develop a system for identifying, reporting, investigating, and controlling infections and communicable diseases of patients and personnel" (42 CFR 482.42a1) and "must maintain a log of incidents related to infections and communicable diseases" (42 CFR 482.42a2).

In the past, regulations for accreditation and Medicare participation were more specifically worded, and specifically acknowledged the problems of antibiotic resistance: for example, hospitals had to have "measures which control the indiscriminate use of preventive antibiotics in the absence of infection, and the use of antibiotics in the presence of infection is based on necessary cultures and sensitivity tests" (42 CFR 405.1022c6 as of Oct. 1, 1983). However, based on past experiences such as those described in this chapter, specific regulations such as these may not be applicable to every facility.

Surveillance of Antibiotic-Resistant Bacteria

There is no national system for reporting the presence and pattern of antibiotic-resistant bacteria, leaving physicians and scientists in the dark about the prevalence of those organisms in different geographical areas. Although many in-hospital, small-scale surveillance systems, designed to track the spread of disease-causing organisms, including antibiotic-resistant bacteria, provide information to physicians about which antibiotics remain effective, there is no standard format for the collection and dissemination of data. Antibiotic prescriptions and microbiology test results are often recorded on separate slips of paper, making correlation of the two sets of data almost impossible. However, the increasing use of computer technology and the Internet provides increased opportunities for standardized record keeping in hospitals and easy database collection and access.

At the state level, the New Jersey State Department of Health started collecting data about antibiotic-resistant bacteria in 1991. The

system includes the 95 acute-care hospitals licensed by the State of New Jersey and uses data that are already routinely collected in hospital laboratories. All hospitals make monthly reports to the State Department of Health, which, in turn, disseminates its compilation of information to anyone on request. This system's tracking of vancomycin-resistant Enterococcus (VRE) spurred collaborative efforts involving private and public sector and academic organizations to evaluate risk factors for the disease, treatment options, effectiveness of infection-control procedures, and the in-vitro susceptibility of VRE to antimicrobial agents during the planning of clinical trials (MMWR, 1995). The system is inexpensive to operate and simple to maintain.

SCOPE, Surveillance and Control of Pathogens of Epidemiological Importance, is a national effort established by the University of Iowa and Lederle Laboratories (now Wyeth-Ayerst Lederle Laboratories) in 1995. The program expects to collect reports of all nosocomial bloodstream infections in 48 hospitals nationwide as well as samples of the organisms isolated from the infected patients. The reports will provide information about the spread of antibiotic-resistant bacteria in the participating hospitals. The bacterial samples will be banked at the University of Iowa, and the accuracy of bacterial identification and antibiotic resistance determinations will be verified for representative samples. For a fee, the University will test new antibiotics from any company against bacteria in its collection. The first hospital entered the program on April 1, 1995, and 40 had entered by June 30.

There are also other industry-funded surveillance systems. A number of academic and commercial laboratories conduct surveillance under contract to pharmaceutical companies, but they are not necessarily designed to obtain information most useful for public health purposes. Instead, and understandably, they collect information about the efficacy of producers' products.

The National Nosocomial Infection Survey (NNIS), which is run by CDC, is the single nationwide surveillance system that produces information about antibiotic-resistant bacteria. While it is limited to reports on nosocomial infections, it is the source for most of the data in this OTA report about MRSA, VRE, and other drug-resistant bacterial infections.

CDC is in the early stages of establishing nationwide surveillance of drug-resistant *Streptococcus pneumoniae* (DRSP), which will cover infections whether or not they occur in a hospital. The system requires that participating laboratories test all *S. pneumoniae* isolated from blood and cerebrospinal fluid for antibiotic susceptibility by using standard testing methods, and that all test results be reported to the state health departments. The CDC initiated this system in 20 laboratories in New Jersey in April 1995, and if funds are available, the organization expects that most of the nearly 2,000 hospital and commercial laboratories that now have computerized record keeping will be in the system by 1998. As laboratories add computer capabilities, CDC will encourage them to enlist in the system, and it expects that all of the nearly 5,000 laboratories in the country will participate. If the DRSP system works, CDC envisions expanding it to include other antibiotic-resistant bacteria. As an early step in setting up the DRSP system, and at CDC's request, the Council of State and Territorial Epidemiologists has recommended DRSP for inclusion on the list of notifiable diseases, and four states now report it.

WHONET, a surveillance project of the World Health Organization, was established and operated by two scientists, and it functions on a shoestring budget. The system collects information about resistance patterns in bacteria from about 100 hospitals all over the world, makes the data available to researchers, and provides much of the available information about the international flow of antibiotic-resistant bacteria.

One of WHONET's great strengths is that it has demonstrated that laboratories around the world can produce data that can be interpreted and incorporated into a system that provides results that are comparable from country to country. To do this, the network collects laboratory data, not interpretations of the data. While rules for interpreting susceptibility test results differ

among various countries, WHONET can make international comparisons based on the raw data.

Participating institutions also gain from WHONET. The network provides laboratories with a computer program, which can be taught in about six hours, and, where necessary, a computer. The software of WHONET, set up to identify unusual patterns of resistance, allows the infection control practitioner at the hospital to trace the spread of individual strains of bacteria and use that information to modify infection control procedures.

WHONET is inexpensive, it requires little supervision, and it obtains raw data, the data of most value to researchers (see chapter 6). It has been successful in obtaining information from developing countries as well as developed ones, and it provides an example of the feasibility of collecting and reporting antibiotic-resistance information for little money.

Controlling the Use of Antibiotics

Much evidence links the use of antibiotics to the emergence and spread of antibiotic resistance. Table 4-3 summarizes some studies which demonstrate relationships between *increased* use of antibiotics and prevalence of resistance in hospital organisms. There are also many examples where the prevalence of resistance in hospital organisms *decreased* when the use of antibiotics was *decreased* (table 4-4). McGowan (1994) recently asked the question: "Do intensive hospital antibiotic control programs prevent the spread of antibiotic resistance?" and concluded that

TABLE 4-3: Some Studies Demonstrating a Temporal Relationship Between *Increased* Usage of Antimicrobial Agents and *Increased* Prevalence of Resistant Hospital Organisms

Year	Reference	Setting for use of antimicrobials	Organism(s)	Antimicrobial(s) used
1953	1	General use	*Staphylococcus aureus*	Erythromycin
			S. aureus	Penicillin
			S. aureus	Chlortetracycline
1956	2	Burn ward	*S. aureus*	Chloramphenicol
			S. aureus	Chlortetracycline
1967	3	Surgical prophylaxis	*S. aureus*	Neomycin cream
1971	4	Burn ward	*Pseudomonas aeruginosa*	Gentamicin
1978	5	Surgical prophylaxis	*P. aeruginosa*	Gentamicin
			Serratia	Gentamicin
1979	6	Postoperative use	*Serratia*	Gentamicin

1. M.H. Lepper, B. Moulton, H.F. Dowling, et al. 1953. Epidemiology of erythromycin-resistant staphylococci in a hospital population—effect on the therapeutic activity of erythromycin. In: H. Welch and F. Martí-Ibáñez (eds.) *Antibiotics annual 1953–1954*. New York, NY. Medical Encyclopedia, pp. 308–313.

2. C.D. Gibson, Jr., and W.C. Thompson, Jr. 1956. The response of burning wound staphylococci to alternating programs of antibiotic therapy. In: H. Welch and F. Martí-Ibáñez (eds.) *Antibiotics annual 1955–1956*. New York, NY. Medical Encyclopedia, pp. 32–34.

3. P.M. Rountree, M.A. Beard, J. Loewenthal, et al. 1967. Staphylococcal sepsis in a new surgical ward. *British Medical Journal* 1:132–137.

4. J.A. Shulman, P.M. Terry, and C.E. Hough. 1971. Colonization with gentamicin-resistant *Pseudomonas aeruginosa*, pyocine type 5, in a burn unit. *Journal of Infectious Disease* 124(suppl):S18–23.

5. N.J. Roberts, Jr., and R.G. Douglas, Jr. 1978. Gentamicin use and *Pseudomonas* and *Serratia* resistance: effect of a surgical prophylaxis regimen. *Antimicrobial Agents and Chemotherapy* 13:214–220.

6. V.L. Yu, C.A. Oakes, K.J. Axnick, et al. 1979. Patient factors contributing to the emergence of gentamicin-resistant *Serratia marcescens*. *American Journal of Medicine* 66:468–472.

SOURCE: J.E. McGowan, Jr. 1983. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. *Reviews of Infectious Diseases* 5(6):1033–1048.

TABLE 4-4: Some Studies Demonstrating a Temporal Relationship Between *Decreased* Usage of Antimicrobial Agents and *Decreased* Prevalence of Resistant Organisms

Year	Reference	Setting for use of antimicrobials	Organism(s)	Antimicrobial(s) used
1953	1	General use	*Staphylococcus aureus*	Chloramphenicol
1954	2	General use	*S. aureus*	Erythromycin
1956	3	Burn ward	*S. aureus*	Chlortetracycline
			S. aureus	Chloramphenicol
1960	4	General use	*S. aureus*	Penicillin
1960			*S. aureus*	Tetracycline
1966	5	Pediatric ward	*S. aureus*	Erythromycin
1967	6	Surgical prophylaxis	*S. aureus*	Neomycin cream
1970	7	General use	*Escherichia coli*	Streptomycin
			Klebsiella, Enterobacter	Streptomycin
1970	8	Neurosurgical unit	*Klebsiella*	"All"
1970	9	General use	*S. aureus*	Erythromycin
			S. aureus	Novobiocin
1971	10	Burn ward	*Pseudomonas aeruginosa*	Gentamicin
1972	11	Burn ward	*"Enterobacteriaceae"*	Carbenicillin
			Pseudomonas aeruginosa	Carbenicillin
1973	12	Nursery	*"Enterobacteria"*	Carbenicillin
1974	13	Urology ward	*"Gram-negative bacilli"*	5 agents
1975	14	Nursery	*E. coli*	Kanamycin
1978	15	Surgical prophylaxis	*Pseudomonas aeruginosa*	Gentamicin
	16		*Serratia*	Gentamicin

1. W.M.M. Kirby, and J.J. Ahern. 1953. Changing pattern of resistance of staphylococci to antibiotics. *Antibiotics and Chemotherapy* 3:831–835.
2. M.H. Lepper, B. Moulton, H.F. Dowling, et al. 1953. Epidemiology of erythromycin-resistant staphylococci in a hospital population—effect on the therapeutic activity of erythromycin. In: H. Welch and F. Martí-Ibáñez (eds.) *Antibiotics annual 1953–1954*. New York, NY. Medical Encyclopedia, pp. 308–313.
3. C.D. Gibson, Jr., and W.C. Thompson, Jr. 1956. The response of burning wound staphylococci to alternating programs of antibiotic therapy. In: H. Welch and F. Martí-Ibáñez (eds.) *Antibiotics annual 1955–1956* New York, NY. Medical Encyclopedia, pp. 32–34.
4. M. Barber, A.A.C. Dutton, M.A. Beard, et al. 1960. Reversal of antibiotic resistance in hospital staphylococcal infection. *British Medical Journal* 1:11–17.
5. A.W. Bauer, D.M. Perry, and W.M.M. Kirby. 1960. Drug usage and antibiotic susceptibility of staphylococci. *Journal of the American Medical Association* 173:475–480.
6. J.O. Forfar, A.J. Keay, A.F. Maccabe, et al. 1966. Liberal use of antibiotics and its effect in neonatal staphylococcal infection, with particular reference to erythromycin. *Lancet* 2:295–300.
7. P.M. Rountree, M.A. Beard, J. Loewenthal, et al. 1967. Staphylococcal sepsis in a new surgical ward. *British Medical Journal* 1:132–137.
8. R.J. Bulger, E. Larson, and J.C. Sherris. 1970. Decreased incidence of resistance to antimicrobial agents among *Escherichia coli* and *Klebsiella-Enterobacter*: observations in a university hospital over a 10-year period. *Annals of Internal Medicine* 72:65–71.
9. D.J.E. Price, and J.D. Sleigh. 1970. Control of infection due to *Klebsiella aerogenes* in a neurosurgical unit by withdrawal of all antibiotics. *Lancet* 2:1213–1215.
10. M. Ridley, D. Barrie, R. Lynn, et al. 1970. Antibiotic-resistant *Staphylococcus aureus* and hospital antibiotic policies. *Lancet* 1:230–233.
11. J.A. Shulman, P.M. Terry, and C.E. Hough. 1971. Colonization with gentamicin-resistant *Pseudomonas aeruginosa*, pyocine type 5, in a burn unit. *Journal of Infectious Disease* 124(suppl):S18–23.
12. E.J.L. Lowbury, J.R. Babb, and E. Roe. 1972. Clearance from a hospital of gram-negative bacilli that transfer carbenicillin-resistance to *Pseudomonas aeruginosa*. *Lancet* 2:941–945.
13. J.A. Franco, D.V. Eitzman, and H. Baer. 1973. Antibiotic usage and microbial resistance in an intensive care nursery. *American Journal of Diseases of Children* 126:318–321.
14. H. Søgaard, C. Zimmermann-Nielsen, and K. Siboni. 1974. Antibiotic-resistant gram-negative bacilli in a urological ward for male patients during a nine-year period: relationship to antibiotic consumption. *Journal of Infectious Disease* 130:646–650.
15. J.B. Howard, and G.H. McCracken, Jr. 1975. Reappraisal of kanamycin usage in neonates. *Journal of Pediatrics* 86:949–956.
16. D.L. Palmer. Epidemiology of antibiotic resistance. 1980. *Journal of Medicine* 11:255–262.

SOURCE: J.E. McGowan, Jr. 1983. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. *Reviews of Infectious Diseases* 5(6):1033–1048.

> . . . in a few institutions there has been an increase in susceptibility to antimicrobials following intensive control or monitoring . . . in a few hospitals, intensive antibiotic control for selected drug-organisms pairs was associated with a high prevalence of susceptibility, and the proportion susceptible fell abruptly when control or monitoring was relaxed or removed.

This latter finding indicates that the decrease in resistance may not be stable: reintroduction of the antibiotic can cause the resistance to immediately return.

There are also counterexamples where antibiotic control programs do not increase susceptibility. In one example, resistance patterns in *Enterobacter cloacae* but not *Pseudomonas aeruginosa* were related to ceftazidime use in 18 different hospitals in different geographical locations (Ballow and Schentag, 1992). Silber et al. found that "facilities with restriction programs were as likely as those without to have had a case of VRE bacteremia." In Denmark the use of methicillin *increased* substantially in the 1970s while the prevalence of MRSA *decreased* substantially. The decrease in MRSA was correlated with a decrease in the use of tetracycline and streptomycin (Rosendal et al., 1977). This might be explained by the use of tetracycline and streptomycin selecting for bacteria with multi-resistant plasmids (see chapter 2) also containing genes for resistance to methicillin. Taken together, these examples indicate that it is not simple to determine the specific relationship between antibiotic use and antibiotic resistance.

CDC recently began a systematic study of the relationship between antibiotic use and antibiotic resistance. In the initial phase of the I-CARE (Intensive Care Antimicrobial Resistance Epidemiology) project, eight pilot hospitals monitored the use of antibiotics and the numbers of antibiotic-resistant bacteria. The results for MRSA (shown in figure 4-4) indicate that some hospitals use large amounts of methicillin and have high frequencies of resistant organisms (hospital B), while others use very little methicillin, but still have high frequencies of resistant organisms (hospital E).

One possible explanation for this is suggested by the Klebsiella results in figure 4-5: hospital E may be receiving many patients from another hospital (or nursing home) that uses a lot of methicillin. Hospital H is interesting in that it has one of the lowest rates of MRSA and the highest use of methicillin of any of the eight pilot hospitals. This result might be related to a recent result from a French 15-year study (Loulergue et al., 1994) that showed the prevalence of MRSA was unrelated to cloxacillin (a semisynthetic penicillin derivative closely related to methicillin) use on some wards of a hospital where none of the staff was a carrier of MRSA. This study indicated that carriage of MRSA by hospital staff is one risk factor for patients becoming infected with MRSA. The data from I-CARE correlate the emergence and spread of antibiotic resistance with different causes in different hospitals. Moreover, the pilot study demonstrates how useful a system such as I-CARE can be in comparing an individual hospital to national trends and using that comparison to design antibiotic use and infection control procedures specifically tailored to the problems in the individual hospital.Antibiotics are widely used by physicians in community practice as well as by physicians in the hospitals. In one study (table 4-5), about half of the cardiac surgery patients colonized with cefazolin-resistant strains of bacteria were colonized upon admission to the hospital.[5] Therefore, some antibiotic-resistant strains arise in the community, indicating that antibiotic use must be

[5] Cefazolin is commonly administered to cardiac patients as prophylaxis to prevent infections during the surgery. The risk of developing a *Staph. aureus* infection after cardiac surgery has been estimated as 15-44 percent (Mandell, Bennet, Dolin, page 2747). Colonization of the patient or attending staff with cefazolin-resistant strains would be a significant risk factor for surgical infections when cefazolin is used for prophylaxis.

FIGURE 4-4a: Percent of *Staphylococcus Aureus* Resistant to Methicillin

SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA.

FIGURE 4-4b: Grams of Methicillin Used per 1,000 Patient Days

SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA.

FIGURE 4-4c: Percent of *Staphylococcus aureus* Resistant to Methicillin/Methicillin Use

SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA.

controlled by community physicians as well as by hospital physicians in order for hospital-based programs to be fully effective. (For more information about antibiotic-resistant bacteria and antibiotic use in the community, see chapter 3.

Improving Antibiotic Use

Antibiograms

To guide physicians in the use of antibiotics, many hospitals provide "antibiograms" that describe the susceptibility of commonly encountered bacteria to various antibiotics. As shown in table 4-6, the vast majority of causes of bacterial infections in both inpatients and outpatients remain sensitive to the modern antibiotics. On the other hand, many *Staph. aureus*, coagulase-negative Staphylococci, and *S. pneumoniae* are resistant to many commonly used antibiotics, and some Enterococcus are resistant to all antibiotics.

Formularies

The use of all drugs in hospitals is increasingly controlled by hospital formularies, which were set up to control the costs of drugs. The formularies may have the added benefit of helping to control the use of antibiotics and the antibiotic resistance problem. In Denver, Colorado, area hospitals (North, 1993), a formulary is combined with a computerized antibiotic order form. This system restricts some antibiotics to approved indications, and use of others requires approval by specialists in infectious disease. This system has saved the hospitals money, and allowed them to easily change the formulary when susceptibility testing indicated a problem of increased resistance to a specific antibiotic) .

Physician Education

Physician education is crucial to avoid mistakes made by inadequate knowledge of antibiotic

FIGURE 4-4a: Percent of *Staphylococcus Aureus* Resistant to Methicillin

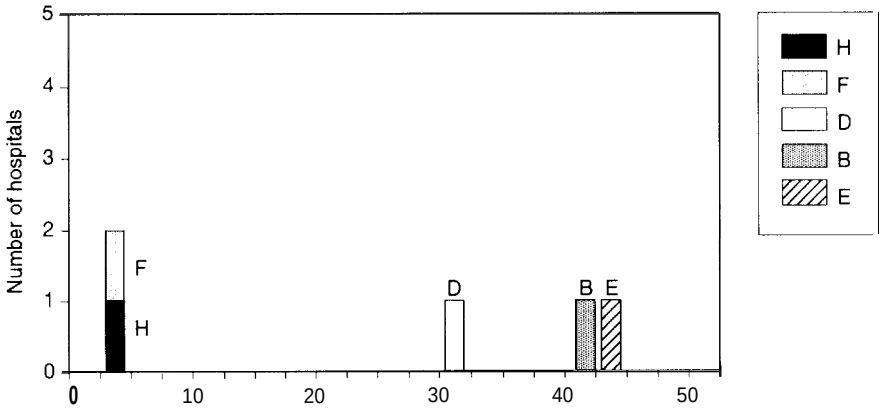


FIGURE 4-4b: Grams of Methicillin Used per 1,000 Patient Days

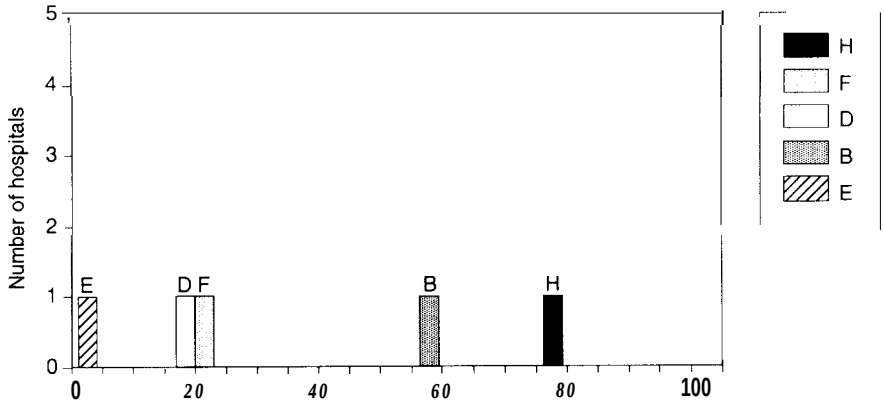
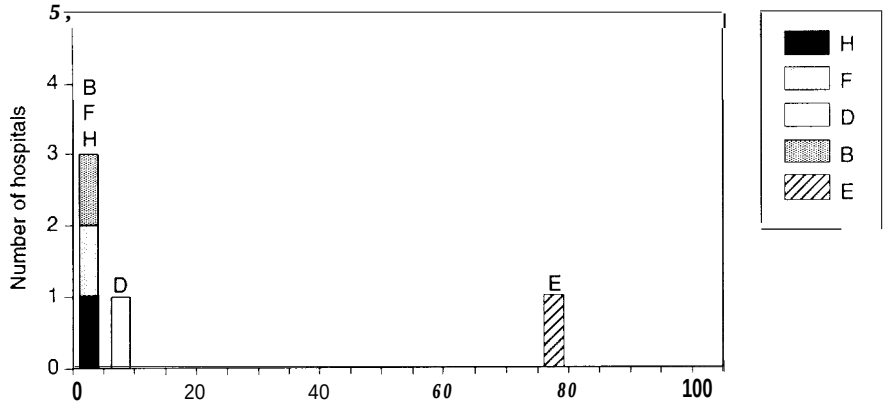
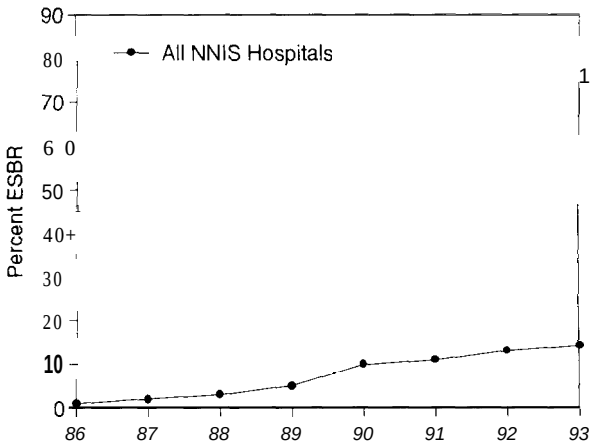


FIGURE 4-4c: Percent of *Staphylococcus aureus* Resistant to Methicillin/Methicillin Use



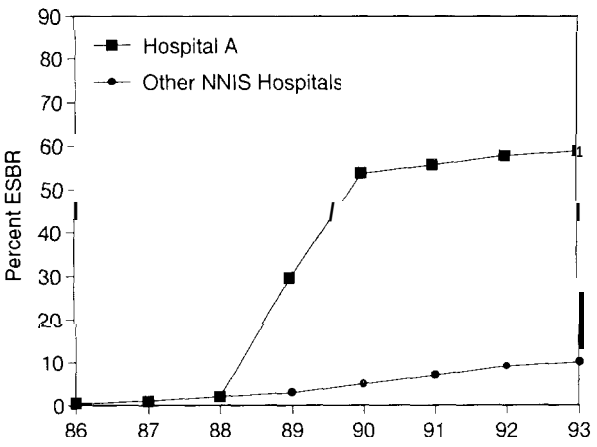
SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA.

FIGURE 4-5a. All Hospitals in the National Nosocomial Infection Surveillance System



SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA.

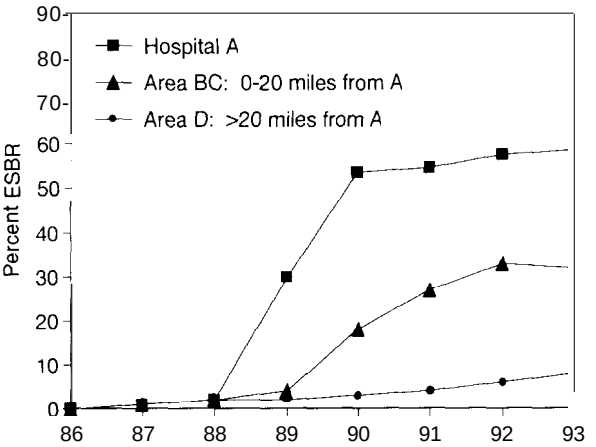
FIGURE 4-5b: Hospital A and All NNIS Hospitals



SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA.

controlled by community physicians as well as by hospital physicians in order for hospital-based programs to be fully effective. (For more information about antibiotic-resistant bacteria and antibiotic use in the community, see chapter 3.

FIGURE 4-5c. Hospital A and Surrounding Areas



SOURCE: National Nosocomial Infections Surveillance System, Centers for Disease Control, Atlanta, GA.

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TABLE 4-5: Characteristics of Cardiac Surgery Patients Colonized with Cefazolin-Resistant Gram-Negative Bacilli

Species	Number of patients colonized (n = 87)	Location at first positive culture (% patients)			Percent of colonization due to horizontal transmission	Percent developing clinical infection
		At admission	48–72 hr into CSICU	> 72 hr into CSICU		
Enterobacter species	58	50	34	16	16	21
Citrobacter species	37	49	22	29	?	3
Pseudomonas aeruginosa	33	55	12	33	9	27
Serratia marcesens	7	43	57	0	29	29

KEY: CSICU = cardiac surgery intensive care unit; ? = unknown (no typing system used).

SOURCE: Adapted from D.M. Flynn, R.A. Weinstein, and S.A. Kabins. 1988. Infections with gram-negative bacilli in a cardiac surgery intensive care unit: The relative role of *Enterobacter*. *Journal of Hospital Infections* 11:367.

tion about susceptibilities of different organisms. Physicians must learn to check other reliable up-to-date sources of information about antibiotics such as *The Medical Letter On Drugs and Therapeutics* (New Rochelle, NY: The Medical Letter, Inc.) and to consult with infectious disease experts who are aware of susceptibility patterns in the specific hospitals.

Computerized Systems for Antibiotic Monitoring

The LDS Hospital in Salt Lake City, Utah, has developed a computerized antibiotic monitoring system, which is part of a larger computerized patient record system that automatically collects surveillance data and generates antibiograms (see table 4-6) (Evans and Pestotnik, 1994). When the microbiology laboratory results are entered into the computer, the computer checks the susceptibilities of the organisms against the antibiotic prescribed for the patient and generates an alert when an antibiotic is inappropriate. In one year, the system generated an alert for 32 percent of the patients. However, many physicians did not change the antibiotic based on the alert, often because the patient was clinically improving even though the susceptibility results indicated that the antibiotic was inappropriate.[6] The system also notifies physicians of the optimum time for administration of prophylactic antibiotics. Use of the system saved $42 per patient in the first year of use, with a projected reduction in the costs of prophylactic antibiotics of over $89,000 per year in a single hospital (Evans et al., 1990).

Another part of the antibiotic monitoring system at the LDS hospital is a computerized antibiotic consultant (Evans et al., 1994). This system uses surveillance data together with information about the site of the infection and patient allergies to determine the best choice of empiric antibiotic therapy. The computer consultant was better at choosing antibiotics than the physicians in the hospital. The computer chose antibiotics to which the infecting bacteria were susceptible 94 percent of the time; the physicians chose correctly 77 percent of the time.

Setting up a comprehensive patient data system requires significant financial investment by hospitals. However, the hospitals will realize cost savings just from improvement in the use of antibiotics. Forty to fifty percent of hospital

[6] Many patients recover from bacterial illnesses on their own without the help of an antibiotic.

TABLE 4-6: Antibiotic Susceptibility of Common Organisms (Numbers Indicate Percent Susceptible) January–December 1994 (Page 1 of 2)

IN PATIENTS	Staph. aureus (1080)	Coagulase-neg. Staph. (647)	Strep. pneumoniae (75)	Enterococcus spp. (612)	E. coli (808)	K. species (396)	C. diversus (35)	C. freundii (42)	Enterobacter species (309)	Serratia species (55)	Proteus mirabilis (100)	P. aeruginosa (520)	A. anitratus (60)	X. maltophilia (42)	H. influenzae (128)	B. fragilis group (30)
Penicillin	5	6	86													3
Ampicillin				88	54	0	0	0	0	0	91				75	
Ampicillin-sulbactam	***	***			58	59	91	50	15	13	97		54	0		93
Oxacillin	70	26														
Ticar-clavulante*	***	***			77	75	96	62	61	88	100	67	58	52		100
Cephalothin**	***	***			73	71	97	3	1	0	94					
Cefazolin	***	***			88	78	97	7	3	0	97					
Cefotetan	***	***			99	88	97	68	55	92	99					70
Cefuroxime	***	***													99	
Cefotaxime	***	***	93		99	95	97	77	66	94	99				100	76
Ceftazidime												84	69	23		
Imipenem	***	***						100	100				96	0		
Chloramphenicol															99	
Erythromycin			91													
Trimeth-sulfa	83	39	77		80	77	100	58	88	93	95		70	90	88	
Ciprofloxacin	70	54		21	99	98	100	100	96	99	100	82	61	14		
Nitrofurantoin				87	96	61			45		15					
Gentamicin					97	91	95		93	100	98	84	66	50		
Amikacin****					100	98			99			84	91	35		
Clindamycin	72	48														92
Metronidazole																100
Vancomycin	100	100		99												

* Piperacillin-tazobactam was added to the formulary late in the year. Its activity is equivalent to or somewhat superior to ticarcillin-clavulanate.

** Tested for the oral cephalosporins, cephalexin and cephradine.

*** Oxacillin-resistant staphylococci are also resistant to beta-lactamase inhibitor combinations, cephalosporins, and imipenem; oxacillin-susceptible staphylococci are susceptible to those agents.

**** Amikacin reported only on Gentamicin resistant isolates.

TABLE 4-6: Antibiotic Susceptibility of Common Organisms (Numbers Indicate Percent Susceptible) January–December 1994 (Page 2 of 2)

OUT PATIENTS	Staph. aureus (966)	Coagulase-neg. Staph. (320)	Strep. pneumoniae (103)	Enterococcus spp. (632)	Escherichia coli (2558)	K. species (405)	C. diversus (76)	C. freundii (48)	E. species (136)	Serratia species (46)	Proteus mirabilis (244)	P. aeruginosa (234)	Salmonella species (25)	Shigella species (51)	H. influenzae (121)
Penicillin	4	13	83												
Ampicillin				94	53	2	0	6	2	0	89		92	33	72
Ampicillin-sulbactam	***	***			72	75	95	81	37	12	97				
Oxacillin	89	52													
Ticar-clavulante*	***	***			90	90	100	90	92	93	100	85			
Cephalothin**	***	***			65	86	96	3	3	0	94				
Cefazolin	***	***			90	91	97	13	4	0	93				
Cefotetan	***	***			99	97	100	91	83	90	100				
Cefuroxime	***	***													100
Cefotaxime	***	***	92		99	98	100	94	92	94	100		100		100
Ceftazidime												95			
Chloramphenicol													92	87	100
Erythromycin			84												
Trimeth-sulfa	92	54	80		81	83	100	61	94	88	93		100	70	94
Ciprofloxacin	88	72		24	99	97	97	92	97	96	99	87	100	100	
Nitrofurantoin				91	99	62	91	90	51	0	0				
Gentamicin					99	96	100	97	98	95	95	93			
Amikacin****					93						100	93			
Clindamycin	91	76													
Vancomycin	100	100		100											

* Piperacillin-tazobactam was added to the formulary late in the year. Its activity is equivalent to or somewhat superior to ticarcillin-clavulanate.
** Tested for the oral cephalosporins, cephalexin and cephradine.
*** Oxacillin-resistant staphylococci are also resistant to beta-lactamase inhibitor combinations, cephalosporins, and imipenem; oxacillin-susceptible staphylococci are susceptible to those agents.
**** Amikacin reported only on Gentamicin resistant isolates.

KEY: Staph. = Staphylococci
Strep. = Strephcoccus
K. species = Klebsiella species
C. diversus = Citrobacter diversus
C. freundii = Citrobacter freundii
E. species = Enterobacter species
P. aeruginosa = Pseudomonas aeruginosa
A. anitratus = Acinetobacter anitratus
X. = Xanthomonas maltophilia
H. influenzae = Haemophilus influenzae
B. tragillis group = Bacteroides tragillis group

SOURCE: University Health System, San Antonio, TX, 1994. With permission of J.H. Jorgensen.

BOX 4-3: "Food-Borne" Outbreak of Expensive Antibiotic Use in Community Teaching Hospital

To the Editor—Drug utilization review assures cost-effective use of medications in hospitals. We present an example of drug utilization review that began with the identification of an "index case" of a costly therapeutic decision. Subsequent investigation lead to the identification of a prescribing outbreak as well as its probable source.

Report of a Case—A 32-year-old man had been on a camping trip and noted an insect bite at the top margin of his sock. The next day he noted redness and swelling at the site of the bite. The third day he was febrile and the redness began to spread. On the fourth day, red streaks extended 15 cm above the site of injury. He felt ill and came to the emergency department. His examination demonstrated a temperature of 39.4°C, sickly appearance, and a tender cellulitis of his lower leg. Blood pressure was normal and he did not have a truncal rash. Therapy with a new, expensive, broad-spectrum antibiotic was initiated. When asked about his antibiotic choice, the admitting intern noted at morning report that he had planned on giving penicillin or nafcillin, but had been overruled by the supervising resident who insisted on a "more modern choice for a severely ill patient."

Comment—Following discussion of this case, we evaluated the use of the new antibiotic in our hospital. We found that use had transiently increased following its addition to our formulary in February 1994, then abruptly increased in June and July. After conducting interviews with our house officers, it was revealed that an extravagant dinner party had been held for incoming and current house staff the third week of June. The sponsor of this dinner was the manufacturer of the antibiotic. The increase in use of this agent bore a striking temporal association with this dinner. Furthermore, the prescribing resident had attended the dinner and directed the admitting intern to use the drug instead of nafcillin.

The prescribed antibiotic exhibits a broad spectrum of activity, including β-lactamase-producing strains of staphylococci, *Haemophilus influenzae*, anaerobes, and facultative gram-negative rods. The agent would be expected to be effective in most settings where nafcillin might be used. Although this agent is not contraindicated in treating uncomplicated cellulitis, it is much more expensive ($183.20 per day) than other effective drugs such as nafcillin ($84 per day). In this single case, the daily excess cost of therapy would approximate $100. The relationship between pharmaceutical marketing maneuvers and prescribing is controversial. Previous ecological studies have found an association between educational "enticements" and hospital formulary additions and prescribing trends. However, we are not aware of a detailed case description where a more expensive therapeutic choice was made when less expensive therapeutic alternatives were indicated. We do not know if the resident's attendance at the dinner caused his therapeutic choice. However, the striking epidemiological association between resident attendance at this drug company-sponsored event and the subsequent changes in hospital-wide prescribing practices should prompt training programs to be wary of such outside sources of medical education.

SOURCE: Quoted from R.I. Shore and W.L. Greene, letter to the editor, *Journal of the American Medical Association* 273(24):1908. Copyright 1995, American Medical Association.

FIGURE 4-6: An Antibiotic Advertisement from a Medical Journal

SOURCE: A major pharmaceutical company.

pharmacy budgets are for antibiotics, and one-fourth of that in some hospitals is for vancomycin alone (*Modern Healthcare*, 1994). Eliminating unnecessary use of antibiotics will decrease total pharmacy expenditures. Treating infections with appropriate antibiotics and administering prophylactic antibiotics with appropriate timing will also increase the quality of patient care and decrease the number of days spent in the hospital. (OTA's report *Bringing Health Care Online: The Role of Information Technologies*, September 1995, discusses costs and benefits of computerized patient record systems.)

Practice Guidelines

Practice guidelines, or practice protocols, are medical guidelines that "encompass a broad range of strategies designed to assist practitioners in the clinical decision-making process" (Shanz, 1993). More specifically, they are "standardized specifications for care developed by a formal process that incorporates the best scientific evidence of effectiveness with expert opinion" (Leape, 1990). These guidelines are set by experts from specific areas of the medical profession to advise about recommended standards of care. For example, the goal of practice guidelines established by the Agency for Health Care Policy and Research, a federal agency empowered to establish practice guidelines, is to encourage physicians and other health care providers to change their practice behavior, thus improving patient care, patient outcomes, and quality of life (AHCPR, 1994).

Practice guidelines on infection control or the prudent use of antibiotics might be helpful in controlling antibiotic resistance. For example, practice guidelines might specify that older antibiotics such as amoxicillin be tried for community-acquired infections before newer, broader spectrum antibiotics are used. Under managed care, insurers may adopt guidelines such as these because they will save money as older antibiotics are generally much less expensive than newer antibiotics.

Practice guidelines may also be of use in medical malpractice litigation. A major difficulty in medical malpractice cases is establishing the appropriate standard of care before "layperson" decision-makers on juries. Practice guidelines have the potential to reduce such difficulties. By establishing an unbiased standard of care, practice guidelines should "significantly reduce the most vexing problem in malpractice litigation: the battle of the experts" (West, 1994). In theory, a physician could rely on the practice guideline as the appropriate standard of care without having to worry whether a judge or jury, in a medical malpractice case, would consider the care administered appropriate. The only remaining issues to be determined in medical negligence litigation would be whether the practice guideline "is relevant to the case at hand, and whether it is appropriate to use the [guideline] to establish the standard of care" (West, 1994).

On the other hand, practice guidelines which suggest any benefit from the use of antibiotics may be used as evidence against the physician in the case of a bad outcome. For example, a guideline on the treatment of otitis media with effusion published by the Agency for Health Care Policy and Research concludes:

> Meta-analysis for Guideline development showed a 14 percent increase in the probability that otitis media with effusion would resolve when antibiotic therapy was given versus no treatment. . . . When this small improvement in resolution of otitis media with effusion is weighed against the side effects and cost of antibiotic therapy, antibiotic therapy may not be preferable to observation in management of otitis media with effusion in the otherwise healthy young child. . . . To assist in making choices for management of otitis media with effusion, health care providers need to inform parents fully as to the side effects and costs of antibiotic therapy, as well as the benefits and harms of other options for care (AHCPR, 1994).

A physician who elects not to prescribe an antibiotic, foregoing the 14-percent increased probability that the condition "would resolve," might be held legally liable for any negative outcome. Such potential liability might encourage physicians to prescribe antibiotics even when

they may not be necessary. Further, the above guidelines do not instruct physicians to consider the spread of antibiotic resistance in the decision to prescribe antibiotics. If practice guidelines are going to have an effect on promoting prudent antibiotic use, they have to acknowledge that the benefit to a few patients from routine use of newer and broader spectrum antibiotics may be outweighed by the public health benefits expected from reducing the prevalence of antibiotic-resistant bacteria.

One concern of practice guidelines relevant to antibiotic use is that national standards of conduct do not adequately reflect the localized aspect of antibiotic-resistant bacteria outbreaks. The National Health Lawyers Association addressed this concern in its 1995 Colloquium Report on Legal Issues Related to Clinical Practice Guidelines, which conceded that "[s]ome local adaptation of national guidelines is probably inevitable and may be useful, because even well-developed guidelines may have gaps and may not foresee significant local objectives or constraints" (National Health Lawyers Association Colloquy, 1995). One solution may be the use of an online computer system that allows health care practitioners in a particular geographic area to consult with each other and local experts concerning appropriate local adaptations to practice guidelines (Meyers, 1995). Such a system would also allow health care practitioners to disseminate the specifics of their cases, as well as establish a record of compliance with the practice guidelines in the event of future litigation (Meyers, 1995).

COSTS OF CONTROLLING THE EMERGENCE AND SPREAD OF ANTIBIOTIC-RESISTANT BACTERIA

Hospitals cannot charge costs of infection control procedures and the monitoring of antibiotic-resistant bacteria directly to insurance companies. As a result, although these procedures improve the quality of patient care, hospitals' efforts to minimize costs may retard spending on them. Haley et al. (1987) commented that hospitals might not be placing enough emphasis on infection control because "the direction and magnitude of the financial incentive to prevent nosocomial infections are not clear to many hospital administrators." They analyzed the financial incentives for hospitals to prevent nosocomial infections under the prospective payment system and concluded that

> Assuming an average nosocomial infection rate of 5.7 percent, one would expect. . . a hospital with 10,000 admissions annually to have approximately 570 nosocomial infections per year in the absence of an effective infection control program. If the average 1985 marginal cost of providing extra care for a nosocomial infection were approximately $1800, the total cost of treating these infections would amount to approximately $1 million per year, not counting physicians' fees or medicolegal losses. . . . From the nationwide SENIC project evaluation, we know that at least 32 percent of the infections can be prevented, thus indicating that an effective infection control program could produce a gross financial savings of approximately $305,000 per year. . . nearly five times the costs of the program.

A computerized antibiotic monitoring system, such as that of the LDS Hospital, reduces costs both by controlling the use of antibiotics and reducing the length of hospital stays, but the LDS system has been in development for 20 years, it is based on obsolete computer technology, and it is not exportable. Developing a system on current computer technology will take a significant investment in research and development. Given all the costs involved in control and monitoring, it would be useful to calculate the total cost to hospitals of antibiotic resistance to judge whether infection control procedures and monitoring of antibiotic-resistant bacteria will have a financial payoff.

Many different factors can be considered in a calculation of the cost of antibiotic-resistant bacteria: the direct cost of time in the hospital, the costs of extra physician visits when antibiotics are ineffective, the extra hospitalizations due to community-acquired resistant infections, and the costs of newer antibiotics to replace antibiotics

such as penicillin to which organisms have become resistant. To those must be added the indirect costs to patients from lost days of work, increased illness, and, at worst, death. It is difficult to estimate the costs of all of these factors.

Phelps (1989) made such an estimate and concluded that antibiotic-resistant bacteria cost the nation between $0.1 billion and $30 billion annually. Use of different values for the value of a life accounted for almost all of the 300-fold range in the estimate. The National Foundation for Infectious Disease (1990) estimated that the costs of nosocomial infections caused by antibiotic-resistant bacteria could be as high as $4 billion annually, and CDC has estimated the costs of all nosocomial infections at $4.5 billion per year, an estimate that includes costs from both antibiotic-resistant and susceptible infections.

Here, OTA estimates the effects of antibiotic-resistant bacteria on the costs of some hospitalizations. The national costs of five classes of nosocomial infections—surgical wound infections, pneumonia, bacteremias, urinary tract infections, and others—are taken from the results of the SENIC project (see table 4-1). Those costs are shown on the first data line in table 4-7 (for instance, the cost of all surgical wound infections is $1.6 billion annually). The calculation of the costs of each of the infections caused by each of six different antibiotic-resistant bacteria is illustrated by the example of MRSA-associated surgical wound infections. *Staph. aureus* is associated with 19 percent of all surgical wound infections, and 15 percent of all *Staph. aureus* is MRSA. Therefore, the hospital cost of MRSA-associated surgical wound infections is $50 million [$1.6 billion × 0.19 × 0.15 = $50 million]. Repeating this process for the five kinds of infections and the six different antibiotic-resistant bacteria produces an annual total of $661 million (1992) for hospital costs.

Using the estimate of Holmberg, Solomon and Blake (1987) that antibiotic resistance doubles the cost of nosocomial infections, the *minimum* extra cost of antibiotic-resistant bacteria in hospitals is $661 million annually (1992 dollars) and the *minimum* total cost of antibiotic-resistant bacteria in hospitals is $1.3 billion annually (1992 dollars). The actual hospital costs are bound to be much higher as this calculation considers only six species of bacteria, and in some cases considers strains of bacteria that are resistant to only one antibiotic and not other strains of the same bacteria that are resistant to other antibiotics. Further, the trends in antibiotic resistance indicate that the number of antibiotic-resistant infections is likely to be increasing rapidly. Finally, the OTA estimate considers only one factor among many that increase the costs of antibiotic-resistant bacteria; it ignores costs of other infections, costs of days of work lost, and post-hospital care, and other major costs. For these reasons, the OTA estimate of $1.3 billion must be considered a **minimum** estimate .

CONCLUSIONS

Twenty-five to 35 percent of all hospitalized patients receive antibiotics, which produces enormous pressure for the selection of antibiotic-resistant bacteria. The result of that pressure is increasing frequencies of antibiotic-resistant bacteria in hospitals: Some strains of vancomycin-resistant Enterococcus are now resistant to all FDA-approved antibiotics, and some strains of *Staphylococcus aureus*, a common cause of nosocomial infections, are resistant to all antibiotics except vancomycin. Many experts fear the emergence and spread of *Staph. aureus* strains resistant to all antibiotics, including vancomycin, which would pose a major health care crisis.

Two avenues are open to reduce the spread of antibiotic-resistant bacteria. One is infection control to reduce the rate of hospital infections, and the other is the reduction in the use of antibiotics to reduce selection pressures. While infection control programs have worked well in some institutions, similar programs have produced no positive results elsewhere. The mixed results indicate that more research into what makes systems work and why is needed to guide infection control efforts. Formularies, lists of drugs that are available for use in a hospital, were established to control drug costs, but they can be tied

TABLE 4-7: Costs of Stays in Hospital Associated with Antibiotic-Resistant Bacteria

	Surgical wound infection	Pneumonia	Bacteremia	Urinary tract infection	Other	Total
Total cost of nosocomial infections[a]	1.6	1.3	0.36	0.61	0.66	4.5
Staph. aureus	19%	20%	16%	2%	17%	
Methicillin resistant	15%	15%	15%	15%	15%	
Cost of MRSA[b]	50	40	10	1.8	20	122
Enterococcus	12%	2%	9%	16%	5%	
Vancomycin resistant	7.9%	7.9%	7.9%	7.9%	7.9%	
Cost of VRE[b]	20	2	2.6	10	2.4	37
Pseudomonas	8%	16%	3%	11%	6%	
Imipenem resistant	7.8%	16.9%	10.3%	6.9%	12.5%	
Cost of impenem-resistant pseudomonas[b]	10	40	1	4.6	5	61
Coagulase-negative Staphylococcus (CoNS)	14%	2%	31%	4%	14%	
Methicillin resistant	50%	50%	50%	50%	50%	
Cost of methicillin-resistant CoNS[b]	112	13	56	12	46	239
E. Coli	8%	4%	5%	25%	4%	
Ampicillin resistant	35%	35%	35%	35%	35%	
Cost of ampicillin-resistant *E. Coli*[b]	45	18	6	5	9	83
Enterobacter	7%	11%	4%	5%	4%	
Resistant	37%	37%	37%	37%	37%	
Cost of resistant enterobacter[b]	41	52	5	11	9.7	119
TOTAL COST[b]						661

[a] In billions of 1992 dollars.

[b] In billions of 1992 dollars.

NOTE: The costs were estimated by multiplying the total cost of nosocomial infections from a specific category (e.g., urinary tract infections) by the fraction of infections in that category caused by a specific organism (e.g., *E. coli*) and the fraction of the organism resistant to one specific antibiotic (e.g., ampicillin). The data from the fraction of infections caused by specific organisms and organisms resistant to a specific antibiotic were taken from the CDC/NNIS system. This calculation represents a minimum estimate of the costs of antibiotic resistant bacteria: it only accounts for charges in a hospital for nosocomial acquired infections due to six different antibiotic resistant species.

SOURCE: Office of Technology Assessment, 1995, based on data from the Centers for Disease Control, National Nosocomial Infections Surveillance (CDC/NNIS) System, Atlanta, GA.

to information about antibiotic susceptibility produced by the hospital microbiology laboratory to inform physicians' prescription decisions. Positive results have been reported in the few places this has been tried, but more evaluation will be necessary before it is widely adopted.

Surveillance systems are designed to collect and disseminate information to physicians and others about the presence and prevalence of antibiotic-resistant bacteria. They are common in hospitals, but far less common between and among hospitals and across larger geographical units. New Jersey has the only statewide system

in the country, and CDC is only now establishing a nationwide system for one kind of antibiotic-resistant bacterium. In addition, a number of privately supported surveillance systems collect data for pharmaceutical companies, but, understandably, those systems collect information for their clients rather than for general public health information. On the international level, WHONET collects data from over 100 institutions around the world. Chapter 1 discusses some features that could be built into a national surveillance system directed at antibiotic-resistant bacteria and offers an option for its implementation.

One estimate of the total costs associated with antibiotic-resistant bacteria had a range of $100 million to $30 billion annually, with most of the 300-fold range in cost coming from varying estimates of the value of a human life, and another estimate said that the costs could be up to $4 billion annually. OTA estimates the minimal extra hospital costs associated with five kinds of nosocomial infections caused by antibiotic-resistant bacteria to be $1.3 billion per year. The total costs would certainly be certainly higher when hospital costs of other antibiotic-resistant bacterial infections and non-hospital costs are considered.

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