Management of Antibiotic-Resistant Bacteria

Dean C. Norman, MD

Optimizing the management of antibiotic resistance is an important strategy in improving outcomes for infectious diseases in older persons. Strategies that manage antibiotic resistance must take into account all clinical settings, because resistant pathogens previously seen only in acute care facilities are becoming increasingly common in long-term care facilities. Recently, modest improvement in therapeutic options for the treatment of infections due to resistant pathogens has become available because of the development of newer antibiotics. Some of these drugs are briefly discussed in this review, but the best strategy is to limit the potential for the development of resistance and transmission of these pathogens. This can best be accomplished by minimizing misuse of antibiotics and maximizing adherence to basic hygiene standards. **J Am Geriatr Soc 50:S242–S246, 2002.**

Key words: older; bacterial resistance; long-term care; pneumonia

Antibiotic resistance (AR) is an increasingly important factor in the outcome of infections in older people. Older patients represent a growing percentage of hospital admissions, and the number of older people residing in nursing homes is increasing. Infections in hospitals and nursing homes are more frequent in this age group because of the presence of comorbidities and age-related changes in host defenses, as well as other factors.[1] Nursing home residents have infection rates approximately equal to one infection per resident per year; frequently, they are transferred to acute care hospitals for management of acute illnesses and acute exacerbations of chronic illnesses. For these patients, acute care hospitalization leads to further risk of colonization and infection with nosocomial pathogens, including antibiotic-resistant bacteria (ARB). Moreover, hospitalized older patients are more likely to suffer iatrogenic complications such as the development of pressure ulcers, which also increases the risk of colonization and infection with ARB. Poor hygiene, antibiotic pressure, and mobile bacterial genetic elements that code for bacterial resistance are key factors that put the geriatric patient at risk of colonization and infection with ARB. Antibiotic misuse further exacerbates this problem.

Strategies to manage AR in older people must be effective in the nursing home and hospital settings (see Figure 1). Breakdowns in hygiene, misuse of antibiotics, and other patient care problems occurring in either setting will affect the other. In our experience, for example, nursing home patients who developed pressure ulcers during acute hospitalizations frequently became colonized, and sometimes infected, with ARB; they then carried these ARB back to the extended care facilities. As a result of this situation, a strategy was developed to improve these residents' nutritional status, increase their mobility, and develop pressure ulcer risk assessment tools for nurses, all of which improved this problem (unpublished data).

Colonization pressure is more important than antibiotic use in the spread of AR. Simply put, if the prevalence of patients colonized with ARB is high, then any breakdown in hygiene results in the high risk of spread of ARB to other patients. Intensive care units afford multiple opportunities for such breakdowns because of the frequency of contact between healthcare workers and patients. There is also a "tip of the iceberg effect," because there are more instances of patients being colonized with ARB than are actually reported. It is important to implement universal gloving in acute care settings, but gloving must also be performed correctly and in concert with adequate hand washing. It should be noted that the use of gowns does not appear to add much to prevention of transmission of AR.[2]

HAND WASHING

Surveys of healthcare providers demonstrate that 85% are aware that antibiotic misuse contributes to AR, but only 45% are aware that poor hand washing practices also contribute to this problem.[2] More than 150 years ago, Semmelweis established the effectiveness of adequate hand washing with disinfectant soap. He observed that pregnant women delivered by midwives fared much better than those delivered by physicians and medical students. Often, physicians would attend to deliveries shortly after performing autopsies, and Semmelweis postulated that materials carried from the autopsies on the hands of these doctors contributed to postdelivery fevers. After he initiated

From the University of California, Los Angeles, Los Angeles, California; and VA Greater Los Angeles Healthcare System, Los Angeles, California.

Address correspondence to Dean C. Norman, MD, Chief of Staff, VA Greater Los Angeles Healthcare System, 11201 Wilshire Boulevard, Los Angeles, CA 90073. E-mail: dean.norman@med.va.gov

0002-8614/02/$15.00

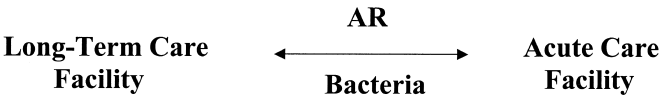

Figure 1. Antibiotic-resistant bacteria can be transmitted bidirectionally from acute to long-term care settings and vice versa.

measures to promote hand washing with soap before attending deliveries, maternal mortality was reduced from 18% to 3%, a rate that was comparable to the results observed for midwives. Unfortunately, at that time, the medical establishment rejected his findings, and even today inadequate hand washing by healthcare providers between patient contacts remains a fundamental problem in controlling AR.

The density of normal bacterial flora on skin is 100 to 1,000 colony-forming units per square centimeter. Bacteria further accumulate during episodes of patient contact. To decontaminate hands properly, they must be washed with disinfectant soap for at least 10 to 15 seconds. This is a significant period of time, often not achieved by busy practitioners. Hand washing is also required after degloving. In a landmark study by Pittet et al., more than 2,800 opportunities for proper hand washing were observed in a Swiss hospital. Rates of hand washing were 52% for nurses, 47% for nursing aides, and only 30% for physicians. Noncompliance with hand washing correlated with the intensity of care that in turn correlated with more opportunities for hand washing. Proper use of disposable gloves was observed only 12% of the time.[3]

The lack of availability of suitable hand washing areas and the length of time it takes for hand washing to be effective (10–15 seconds) make the use of alcohol rubs, usually packaged with emollients, more attractive. These certainly have excellent antibacterial activity, save time, and are well accepted by staff.

ANTIBIOTIC MISUSE

The misuse of antibiotics, including overuse and underuse, is a major obstacle in controlling AR. Underuse includes failure to properly cover the causative pathogens with empirical antimicrobial therapy. Underuse increases the risk of a poor outcome, and inadequate dosing or length of treatment increases the risk of the development of AR. The failure to establish a diagnosis, determine the microbial etiology of infection, or aim for a cure further contributes to the problem. Some strategies for reducing the misuse of antibiotics include establishing a restricted formulary, using clinical guidelines with individual provider feedback, and supplying order forms with next-day reviews and computerized physician order entry with automatic feedback.[2]

A restricted formulary, carefully reviewed by infectious diseases specialists, is effective in significantly reducing cost and increasing susceptibility of bacteria to beta-lactam and quinolone drugs. Moreover, a restricted formulary appears to have no adverse effect on outcomes.[4]

A potential strategy is to rotate the use of antibiotics in certain care units. One study, for example, demonstrated that replacing ceftazidime with ciprofloxacin reduced ventilator pneumonia from 4.0% to 0.9% and antibiotic-resistant gram-negative bacteremia from 1.7% to 0.3% in a cardiothoracic surgery unit.[5] Another study showed that substitution of a beta-lactam/beta-lactamase inhibitor for third-generation cephalosporins reduced vancomycin-resistant *Enterococcus* (VRE) colonization from 47% to 15%.[6]

Physician order entry computer systems, which allow physicians to computerize their orders, offer an exciting new approach. Currently, one such system is widely distributed in the medical centers of the Department of Veterans Affairs. These systems are capable of using software that provides instructions, current antibiotic resistance data, and decision support algorithms. Such systems allow easy review for performance improvement and provider-specific feedback.

SPECIAL PROBLEMS IN CONTROLLING ANTIBIOTIC RESISTANCE IN LTCFs

Taking the driving forces of AR into consideration (poor hygiene, antibiotic overuse, and mobile genetic elements that code bacterial resistance mechanisms), key infection control recommendations include ongoing surveillance for AR, molecular typing of isolates when rates of AR increase, hygiene controls to limit spread of single clonal strains, antibiotic controls to limit spread of multiple strains of AR bacteria, adequate administrative support and resources, monitoring adherence to control measures with appropriate feedback, and appropriate screening and cohorting of colonized and infected patients (see Table 1).

In long-term care facilities (LTCFs), ongoing surveillance for AR is mandatory (as indicated in Table 1). Nevertheless, implementation of infection control measures in nursing homes is often problematical. This is because antibiotic controls are difficult to establish; the provision of administrative support and resources is variable; and screening and cohorting of colonized and infected patients

Table 1. Key Strategies to Reduce the Effect of Antibiotic Resistant Bacteria: Acute Versus Long-Term Care

Proven Acute Care Strategy	Feasibility of Strategy in Long-Term Care
Ongoing surveillance for antibiotic resistance	Mandated
Molecular typing of isolates when rates of AR increase	Rarely done as routine
Hygiene controls to limit spread of single clonal strains	Mandated
Antibiotic controls to limit spread of multiple (polyclonal) strains of antibiotic resistant bacteria	Difficult to accomplish
Administrative support/ resources	Limited, variable
Monitoring adherence to control measures with feedback	Achievable
Screening and cohorting of colonized and infected patients	Cohorting often impossible

are often not practical. Furthermore, limited availability of diagnostic testing makes diagnosis difficult, and diagnosis is often based on limited clinical findings. Culture data may not be available, and physician inaccessibility may be a problem. Other factors that make infection control difficult in LTCFs include empirical therapy with broad-spectrum antibiotics that may not be modified appropriately because of lack of culture data, different treatment goals for LTCF residents, limited resources for infection control (e.g., part-time infection control practitioner), and lack of availability of molecular typing of isolates in LTCF.

Despite their limited resources, LTCFs are now presented with patient care problems similar to those of resource-rich acute care facilities. Some LTCFs contain intermediate care units or immediate post-acute care programs that deliver care to patients with tracheostomies, patients on ventilators, patients undergoing hemodialysis, and patients with a variety of chronic indwelling vascular and other catheters. Because patients with ARB are transferred back and forth between LTCF and acute care institutions, and because infections in nursing homes are common and antibiotic use is frequent, it is likely that ARB encountered in the acute care setting will also be encountered in LTCFs. Methicillin-resistant *Staphylococcus aureus* (MRSA), VRE, extended-spectrum beta-lactamase–producing bacteria, quinolone-resistant bacteria, penicillin-resistant pneumococcus (PRP), and other forms of AR are increasingly encountered in LTCFs. Some of these pathogens will be discussed in more detail below.

Despite the growing problem of AR in LTCFs, there is no evidence that patients colonized with ARB should be denied admission to LTCFs.[7] Unfortunately, our local experience in Los Angeles County is that, despite Los Angeles County infection control advisories to the contrary, some nursing homes are reluctant to take such patients, even when the source of the problem is actually the LTCF. This leads to ethical abuses, such as trying to temporarily eradicate a resistant strain of bacteria that is only transiently colonizing a patient in order to transfer the patient to an extended care facility.

Recommendations for meeting at least minimal standards for infection control in LTCFs include the hiring and appropriate training of an infection control practitioner, the establishment of a surveillance program that includes monitoring of hand washing, and the establishment of an infection control program aimed directly at limiting the development and spread of ARB. Antibiotic appropriateness should be monitored. It should also be emphasized that there is solid evidence that vaccinating patients against influenza and tetanus and of employees against influenza and hepatitis B is good practice. Although the data are less compelling for the effectiveness of pneumococcal vaccine in this patient population, it is recommended that LTCF residents be vaccinated against pneumococcal disease.

HAND WASHING IN LTCFS

Unfortunately, basic hygiene practices such as hand washing and proper glove use are lacking in LTCFs. One observational study based in a university-associated LTCF found that, although gloves were used in 82% of patient care actions, they were changed appropriately only 16% of the time. The conclusion of the study was that microbial transmission to patients by healthcare workers could have occurred in 82% of 193 observed interactions.[8]

MISUSE OF ANTIBIOTICS IN LTCFS

Antibiotic pressure exacerbated by misuse is a key driver of AR in LTCFs. In a study by Muder et al.,[9] the use of ampicillin and the presence of pressure ulcers were associated with multi-drug-resistant Enterobacteriaceae. *Pseudomonas aeruginosa* resistance was associated with the use of all antibiotics. Several retrospective reviews of the appropriateness of antibiotic use in LTCFs can be summarized. Jones et al.[10] observed that of 120 infections in 96 patients, antibiotic use was deemed appropriate in only 49% of cases. In another study of two LTCFs, the majority of purported infections did not have objective evidence indicating that antibiotics should be given.[11] Furthermore, in an extensive study of more than 4,100 patients in 53 LTCFs observed for 1 year, 54% of residents received antibiotics, but only 44% had documented physical examinations, and only 11% met minimal criteria for evaluation of an infection.[12] In these cases, 20% of antibiotics were given for minor upper respiratory tract infections and asymptomatic bacteriuria that in general should not be treated with antibiotics.[12] Finally, one study examining the prescribing of ciprofloxacin in an academic extended care facility over a 3-year period found that in only 25% of the cases was the prescription appropriate. Appropriateness was reduced further to the very low rate of 11% when duration of therapy was taken into account.[13] Clearly, the misuse of antibiotics is rampant in LTCFs.

Often the goals for the treatment of acute disease in residents of LTCFs differ between acute care facilities and LTCFs. Table 2 gives recommendations for optimal antibiotic use in long-term care. Furthermore, although antibiotics may be empirically initiated to treat a suspected infection, a specific diagnosis should be sought whenever possible. Excellent guidelines for the evaluation of the febrile nursing home resident have been published recently.[14] Cure should be the goal of therapy once the decision to initiate antibiotics has been made. Culture data are essential and provide the opportunity to switch to a narrow-spectrum agent once the culture results are known.

SPECIFIC ARB ENCOUNTERED IN LTFCs

Vancomycin-Resistant *Enterococcus*

Most strains of VRE are *E. faecium* (VREF), usually type Van A or Van B. An abnormal cell-wall ligase confers AR.

Table 2. Optimal Use of Antibiotics in Long-Term Care Facility

Antibiotics should only be used to *minimize:*
Suffering
Untimely death
Adverse drug effects
Antibiotic resistance
Medical costs

Note: Adapted from reference 12.

In one study of 36 colonized patients, investigators found only three cases that were acquired in the LTCF, with the rest acquired in an acute care facility. This study noted the carriage time to be several months, and the patient-to-patient transmission rate was low. Symptomatic infection occurred in only one case over an observation period of 2.5 years. Furthermore, attempts at eradication only increased carriage time, and patients were frequently colonized with other ARB. The incidence and prevalence of VRE colonization/infection appeared to be less in this extended care facility than the rates reported in certain acute care facilities because established VRE risk factors, such as recent surgery and intensive care unit stays, were not factors in the nursing home studied.[15] In another study, VREF was isolated from a LTCF resident's urine during a hospital admission. A subsequent review of 285 residents from the same facility yielded four additional residents who were colonized with the same Van B-type VREF.[16] Precautions to limit VRE transmission were initiated and required the use of gowns and gloves and limiting contact between colonized residents and other residents without imposing the hardship of social isolation. Colonized residents were issued their own personal hygiene equipment, and there was intense cleaning of rooms. Over the next few years, two of the four died of unrelated causes and two cleared their VRE. An initial brief trial of bacitracin failed to clear the pathogen, but, at 9 months, there were no new cases. Additionally, infection control costs were modest, $12,061 Canadian. This included the cost of materials such as gowns and paper towels, plus staff time and education. Most of the costs were in the extra staff time and the cultures and typing of pathogens.

Methicillin-Resistant *Staphylococcus aureus*

MRSA is another multidrug-resistant pathogen frequently encountered in LTCFs. In an early study, Muder et al.[17] found that infection developed in 15% of MRSA carriers per 100 days. Risk factors for symptomatic infection included duration of carriage, dialysis, and the intermediate care setting. A subsequent study of 341 LTCF patients found that the MRSA colonization rate was 23% per month, with 25% of cases colonized in the acute care facility before admission to the extended care unit. Only 10% appeared to acquire MRSA in the extended care unit.[18] Nevertheless, in contrast to the previous study, only nine patients (3% of those colonized) actually developed infection, and none died. The author's conclusion was that, in the absence of dialysis or residence in an intermediate care unit, although MRSA colonization was common and was particularly associated with wounds and low functional status, the actual infection rate appears to be low. Furthermore, given the high prevalence of MRSA colonization, but the low rate of infection, the limiting of social contacts and the cohorting of patients to reduce colonization rates is not practical. Subsequently, the same group demonstrated that topical mupirocin when applied daily to wounds and nares reduced the MRSA colonization rate by 50%. However, recurrence and resistance were problematic, and, given the low infection rates, mupirocin should only be used to limit outbreaks of symptomatic infection.[19]

NEWER ANTIBIOTICS FOR THE TREATMENT OF INFECTIONS DUE TO ARB

Streptogramins

Streptogramins are a new class of antibiotics that act on the bacterial ribosome, inhibiting early and late protein synthesis. Synercid®, the first drug of this class approved for use in this country, is composed of the synergistic compounds quinupristin and dalfopristin. The drug is bactericidal against methicillin-susceptible *Staphylococcus aureus* and MRSA but is only bacteriostatic against *E. faecium*. Its only indication is for VRE bacteremia, and it is available only as an intravenous preparation. VRE resistance to this drug has already been reported. No adjustment in dosage is necessary for older patients.

Oxazolidinones

The oxazolidinones are members of a new class of antibiotics active against antibiotic-resistant gram-positive bacteria. These drugs act by a unique mechanism of action that inhibits bacterial protein synthesis. Linezolid (Zyvox) is available in oral and intravenous preparations and is the first of the oxazolidinones to be released. The drug is active against MRSA, PRP, and VRE and has an indication for community-acquired and hospital-acquired pneumonia, skin and soft tissue infection, and gram-positive bacteremia. Side effects include monoamine oxidase inhibition and bone marrow suppression. The usual dose is 600 mg intravenously or orally every 12 hours.

The above two new classes of antibiotics focus primarily on the treatment of resistant gram-positive bacteria. Unfortunately, fewer options exist for resistant gram-negative pathogens. Given that there is significant expense and toxicities with these drugs, streptogramins and oxazolidinones should only be used in accordance with appropriate clinical guidelines and in consultation with an infectious diseases specialist.

Newer Quinolones

Newer fourth-generation quinolones include gemifloxacin, gatifloxacin, and moxifloxacin, all of which differ somewhat from earlier-generation quinolones in that they have expanded activity against anaerobes.

CONCLUSION

Colonization and infection with ARB is an increasingly important clinical problem in geriatric medicine. Strategies to reduce the effect of this problem must be effective in acute and long-term care settings. Newer, more effective antibiotics are becoming available to treat patients infected with ARB. Nevertheless, the most effective strategies to reduce the effect of ARB on older people include strict adherence to basic hygiene, minimizing antibiotic misuse, and the establishment of effective infection control programs in acute care facilities and LTCFs.

REFERENCES

1. Yoshikawa TT. Epidemiology of aging and infectious diseases. In: Yoshikawa TT, Norman DC, eds. Infectious Disease in the Aging: A Clinical Handbook. Totowa, NJ: Humana Press, 2001, p 36.
2. Weinstein RA. Controlling antimicrobial resistance in hospitals: Infection control and use of antibiotics. Emerg Infect Dis 2001;7:188–192.

3. Pittet D, Mourouga P, Perneger TV. Compliance with handwashing in a teaching hospital. Infection Control Program. Ann Intern Med 1999;130:126–130.
4. White AC, Jr, Atmar RL, Wilson J et al. Effects of requiring prior authorization for selected antimicrobials: Expenditures, susceptibilities and clinical outcomes. Clin Infect Dis 1997;25:230–239.
5. Kollef MH, Vlasnik J, Sharpless L et al. Scheduled change of antibiotic classes: A strategy to decrease the incidence of ventilator-associated pneumonia. Am J Respir Crit Care Med 1997;156:1040–1048.
6. Quale J, Landman D, Saurina G et al. Manipulation of a hospital antimicrobial formulary to control an outbreak of vancomycin-resistant enterococci. Clin Infect Dis 1996;23:1020–1025.
7. Smith PW, Rusnak PG. Infection prevention and control in the long-term–care facility. Infect Control Hosp Epidemiol 1997;18:831–849.
8. Thompson BL, Dwyer DM, Ussery XT et al. Handwashing and glove use in a long-term–care facility. Infect Control Hosp Epidemiol 1997;18:97–103.
9. Muder RR, Brennen C, Drenning SD et al. Multiply antibiotic-resistant gram-negative bacilli in a long-term care facility: A case-control study of patient risk factors and prior antibiotic use. Infect Control Hosp Epidemiol 1997;18:809–813.
10. Jones SR, Parker DF, Liebow ES et al. Appropriateness of antibiotic therapy in long-term care facilities. Am J Med 1987;83:499–502.
11. Katz PR, Beam TR, Jr, Brand F et al. Antibiotic use in the nursing home. Physician practice patterns. Arch Intern Med 1990;150:1465–1468.
12. Warren JW, Palumbo FB, Fitterman L et al. Incidence and characteristics of antibiotic use in aged nursing home patients. J Am Geriatr Soc 1991;39: 963–972.
13. Pickering TD, Gurwitz JH, Zaleznik D et al. The appropriateness of oral fluoroquinolone-prescribing in the long-term care setting. J Am Geriatr Soc 1994;42:28–32.
14. Bentley DW, Bradley S, High K et al. Practice guideline for evaluation of fever and infection in long-term care facilities. Clin Infect Dis. 2000;31: 640–653.
15. Brennen C, Wagener MM, Muder RR. Vancomycin-resistant *Enterococcus faecium* in a long-term care facility. J Am Geriatr Soc 1998;46:157–160.
16. Evans MA, Litt M, McArthur MA et al. Control of transmission of vancomycin-resistant *Enterococcus faecium* in a long-term care facility. Infect Control Hosp Epidemiol 1999;20:312–317.
17. Muder RR, Brennen C, Wagener MM et al. Methicillin-resistant staphylococcal colonization and infection in a long-term care facility. Ann Intern Med 1991;114:107–112.
18. Bradley SF, Terpenning MS, Ramsey MA et al. Methicillin-resistant *Staphylococcus aureus*: Colonization and infection in a long-term care facility. Ann Intern Med 1991;115:417–422.
19. Kauffman CA, Terpenning MS, He X et al. Attempts to eradicate methicillin-resistant *Staphylococcus aureus* from a long-term–care facility with the use of mupirocin ointment. Am J Med 1993;94:371–378.