Multiple Antibiotic–Resistant Bacteria in Long-Term-Care Facilities: An Emerging Problem in the Practice of Infectious Diseases

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Long-term-care facilities (LTCFs) are becoming a major component of the health care delivery system. The management of infections with antibiotic-resistant bacteria in elderly patients in LTCFs is presenting new challenges to our current therapeutic armamentarium. Among the enteric bacilli, resistance to ceftazidime, β-lactam/β-lactamase-inhibitor combinations, and trimethoprim-sulfamethoxazole present the foremost problems. Quinolone-resistant gram-negative and gram-positive bacteria are increasing in frequency because of the widespread use of these agents in empirical treatment. Among the resistant gram-positive organisms, methicillin-resistant Staphylococcus aureus, penicillin-resistant pneumococci, and vancomycin-resistant enterococci are the most feared pathogens. Education, antibiotic control measures, and fundamental epidemiological and scientific research are advocated as important preventive measures.
The first reported outbreak of bacteria resistant to cefazidime in the United States occurred among patients in a chronic-care facility in Massachusetts in 1990 [14]. The report of this outbreak described YOU-1 and YOU-2 (TEM-26 and TEM-12, respectively) located on highly mobile plasmids. In this LTCF, cefazidime-resistant bacteria were recovered up to 7 months after institution of an antibiotic-restriction policy, a finding that suggests that resistant phenotypes can readily become endemic in an LTCF. This was followed rapidly by a report of an SHV-type ESBL (SHV-7) from E. coli urinary tract isolates recovered from LTCF residents in New York [15]. Just 1 year later, an outbreak in a geriatric unit at the Cleveland Veterans Affairs Medical Center was also recorded [27]. Again, use of third-generation cephalosporins was associated with the emergence of TEM-6, another ESBL. It is interesting that the switch to use of piperacillin/tazobactam for patients in the medical center’s LTCF decreased the percentage of cefazidime-resistant isolates. The benefits of this strategy merit further investigation.

In a study of cefazidime-resistant E. coli and K. pneumoniae in Chicago, 31 of 35 patients from 8 nursing facilities harbored an ESBL-producing enteric pathogen. These strains were resistant not only to cefazidime but also to gentamicin and tobramycin. Ninety-six percent of the strains producing ESBLs were resistant to TMP-SMZ, and 41% were resistant to ciprofloxacin [28].

From these ominous reports, risk factors associated with colonization by ESBL-producing bacteria have been defined. These include (1) poor functional status (debilitated elderly patients), (2) percutaneous endoscopic gastrostomy tube placement, (3) pressure ulcers, (4) use of ciprofloxacin and/or TMP-SMZ, and (5) increased length of stay. Other studies have identified similar risk factors [17, 28]. These factors cannot be modified in LTCFs, in contrast to hospitals, to prevent emergence of resistance. By necessity, patients in LTCFs require many interventions.

Inhibitor-resistant β-lactamases. Normally, when gram-negative bacteria express TEM-1, SHV-1, and ESBLs, they are susceptible to inactivation by β-lactamase inhibitors (clavulanate, sulbactam, and tazobactam). In addition, β-lactamase inhibitors are potent inactivators of β-lactamase–producing anaerobic bacteria. In LTCF residents, among whom mixed gram-negative and anaerobic infections are common, β-lactam/β-lactamase inhibitors are ideal antibiotics. Unfortunately, plasmid-encoded β-lactamases found in E. coli, Klebsiella species, and Proteus species have also become resistant to inactivation by β-lactamase inhibitors [29, 30]. The majority of these have been recovered as pathogens in urinary tract infections [24].

### Table 1. Factors associated with the emergence of resistant pathogens in long-term-care facilities.

| Transfer of patients from tertiary care institutions who are colonized or infected with multiresistant pathogens |
| Excess use of broad-spectrum antibiotics that select for the emergence of resistant strains |
| Risk factors associated with recovery of resistant strains (percutaneous endoscopic gastrostomy feeding tubes, pressure ulcers, malnutrition, immunosuppression [age- and medication-related], prior antibiotic use) |
| Cycle of institutionalization and hospitalization |

### Table 2. Resistant pathogens recovered in long-term-care facilities.

| Cefazidime (ESBL)–resistant and β-lactamase-inhibitor-resistant gram-negative bacilli |
| Quinolone-resistant gram-positive and gram-negative bacteria |
| Sulfamethoxazole-resistant gram-negative bacilli |
| Aminoglycoside-resistant enteric bacilli |
| Methicillin-resistant Staphylococcus aureus |
| Penicillin-resistant pneumococci |
| Multiresistant enterococci (vancomycin-resistant, aminoglycoside-resistant, etc.) |

**NOTE.** ESBL, extended-spectrum β-lactamase.
Although inhibitor-resistant β-lactamases are inactivated poorly by clavulanic acid, organisms harboring these β-lactamases can be treated with cephalosporins or carbapenems. There is also experimental evidence that using tazobactam/β-lactam combinations may be an option [31].

Figure 1. This paradigm of the transfer of elderly patients within the health care system illustrates the movement of bacteria from one facility to another and to and from the community. SNF, skilled nursing facility.

The very property that confers resistance to inhibitors also affects the catalytic efficiency of the β-lactamase [32–34]. Inhibitor-resistant TEM β-lactamases (IRTs) (e.g., TEM-30) confer the property of clavulanic acid resistance because of the alteration of the side chain of an important amino acid. The arginine residue at position 244 of the TEM β-lactamase is altered to serine. This change in a single amino acid alters the binding and turnover of β-lactams and β-lactam inhibitors [34, 35].

Why TEM-33, -34, and -40, which have mutations at a different amino acid position (the methionine at position 69 is altered to a leucine, valine, or isoleucine), also confer resistance is still partially unexplained [36, 37]. It is believed that different factors influence inhibitor binding and turnover. The one clinical isolate of SHV resistant to inhibitors is SHV-10 [38]. This β-lactamase has a mutation at a different site (Ser130Gly) from the majority of TEM mutants. Postulates invoking the multiple interactions of this residue in the active site have been advanced concerning why this inhibitor-resistant SHV enzyme confers this property [39].

One wonders if the IRTs and SHV-10 are underestimated as a threat in LTCFs. Recently, inhibitor-resistant clinical strains of K. pneumoniae harboring TEM β-lactamase IRT-2 were found in residents of a nursing facility in France [40]. These isolates were recovered from rectal swabs, urine, and a foot biopsy specimen. All patients were previously treated with amoxacillin/clavulanic acid. The clinical isolates were identical or highly related by pulsed-field gel electrophoresis and had a 55-kb nonconjugative plasmid encoding a non–class 1 integron and the inhibitor-resistant β-lactamase gene. This problem may be unrecognized in residents of LTCFs in the United States. It is distressing that alerts to the presence of an inhibitor-resistant isolate are not routine in commercial laboratories.

Plasmid-encoded AmpC cephalosporinases. The production of a chromosomally mediated AmpC-type β-lactamase confers β-lactam resistance to several clinically important gram-negative bacilli (Enterobacter aerogenes, Enterobacter cloacae, Citrobacter freundii, Serratia marcescens, and Pseudomonas aeruginosa). Mutations in the regulatory mechanism controlling expression of these AmpC β-lactamase enzymes are well summarized ([41] and references therein). Important characteristics of these AmpC cephalosporinases are that they are able to inactivate all cephalosporins, including cefoxitin and ceftazidime. The only exception is possibly cefepime. As a rule, organisms with AmpC β-lactamases are susceptible to carbapenems (imipenem/cilastatin and meropenem). AmpC β-lactamases are generally resistant to inhibition by clavulanate and sulbactam.

In the past decade, the occurrence of plasmid-determined AmpC cephalosporinases has increased [42]. Many of these plasmid-borne AmpC cephalosporinases have been found in bacteria that have lost an outer-membrane protein [43]. In addition to being resistant to cefoxitin and ceftazidime, the host strain then becomes resistant to carbapenems. Are plasmid-borne AmpC-type cephalosporinases found in increasing numbers in the enteric bacilli that colonize and infect elderly patients in LTCFs? To date, no screening programs have been established to detect isolates that have plasmid-borne AmpC β-lactamases. In a study examining the clinical characteristics of patients infected with carbapenem-resistant K. pneumoniae, these multiresistant pathogens were recovered from patients (average age, 71 years) in a surgical intensive care unit who were critically ill [43]. In many respects the same factors accelerating the emergence of ESBLs in residents of LTCFs may be at work selecting for plasmid-determined AmpC β-lactamases. It is clear from limited surveillance studies performed at my facility that elderly patients admitted to an acute care ward were colonized with non-ESBL–producing ceftazidime-resistant gram-negative bacteria (author’s unpublished observations).

Resistance to Quinolones

Quinolone antibiotics have had a major impact on the treatment of nursing facility–acquired infections. It has become a common practice in LTCFs to use quinolones to treat urinary tract infections, upper and lower respiratory tract infections, skin and soft-tissue infections, and bone infections (diabetic and ischemic foot ulcers with or without associated osteomyelitis). In fact, they are among the most frequently used agents...
for treating nursing facility–acquired pneumonia [44]. The problem of quinolone resistance may be more severe in the nursing facility than it is in the hospital.

In a recent retrospective examination of antimicrobial susceptibility patterns among isolates from nursing-facility residents in Oklahoma, the frequency of quinolone resistance among gram-negative organisms ranged from 1% (E. coli) to 72% (Acinetobacter calcoaceticus subspecies anitratus) [45]. In a case-controlled study of patient risk factors for the acquisition of multiply resistant bacteria, Muder et al. discovered that 67%
of the *P. aeruginosa* isolates from LTCF residents were ciprofloxacin-resistant [46]. Excessive use of antibiotics may be responsible for this. In a retrospective analysis of the appropriate use of fluoroquinolones, only 25% of the treatment orders were judged to be appropriate [47].

In LTCFs, the frequency of quinolone-resistant bacteria may be linked to β-lactam resistance. In a prospective study of *K. pneumoniae* bacteremia, a significant percentage of ESBL strains were also ciprofloxacin resistant (18%) [48]. Again, prior use of quinolone antibiotics was associated with this finding. The close relationship between ciprofloxacin resistance and ESBL production is worrisome. Plasmid-mediated resistance of *K. pneumoniae* to ciprofloxacin has also been reported [49].

**TMP-SMZ-resistant gram-negative bacteria.** The widespread use of TMP-SMZ has resulted in the emergence of resistance to this combination. Bendall and Gruneberg described resistance to this agent in geriatric units as early as 1979 [50]. Major organisms now resistant to TMP-SMZ are *S. pneumoniae, Haemophilus influenzae*, and many enteric gram-negative bacilli (*E. coli, Klebsiella* species). Walker et al. [51] have also shown that cephalosporins and TMP-SMZ are significant risk factors for the asymptomatic carriage of *Clostridium difficile* in LTCFs. Knowing that resistance to TMP-SMZ is endemic in a particular institution has a significant impact on the choice of antibiotics for treatment against uropathogens.

### Resistance in Gram-Positive Bacteria

**MRSA.** Colonization and infection by MRSA or multiresistant *S. aureus* has proven to be one of the most problematic issues facing clinicians practicing in LTCFs [52]. Approximately 40% of staphylococci are resistant to methicillin. In certain settings (e.g., hospital intensive care units), the prevalence can be even higher. In addition, staphylococci resistant to methicillin (oxacillin) are also being found in the community [53]. Although MRSA is no more virulent than a methicillin-susceptible strain, the presence of MRSA in an LTCF leads to limited treatment options when infections occur.

MRSA is a frequent colonizer of debilitated patients. In a study performed by Bradley et al., the rate of colonization with MRSA was ~25% [52]. In contrast, infection rates were only 3%. Risk factors for MRSA colonization include (1) residence in a medical ward or medical intensive care unit or prolonged hospitalization (>3 weeks), (2) advanced age, and (3) history of invasive procedures [54]. Colonization by MRSA is often a hallmark of significant short-term disability. In a study by Niclaes et al., the RR of dying within 6 months was greater for MRSA carriers than that for noncarriers [55]. This RR remained stable even after adjustment for covariables.

In Veterans Affairs LTCFs, the prevalence of MRSA colonization is significantly higher than in the community nursing facilities [56]; however, a trend was noted toward higher rates of infection and mortality among colonized residents of the community nursing facilities than that among those in the Veterans Affairs LTCFs.

Rates of colonization of the nares and of wounds, the 2 most common sites, range from 8% to 53% and from 30% to 82%, respectively [57]. The routine use of surveillance cultures and antibacterials in an attempt to permanently eradicate MRSA colonization from nursing-facility residents has not been successful, and resistance to these topical agents has quickly emerged [58]. The current recommendation is that topical antibiotics, such as nasally administered mupirocin, should be reserved for use in an MRSA outbreak [57–59].

It is estimated that residents of LTCFs who are colonized with MRSA have a 4- to 6-fold increase in infection rate. In a study by Muder et al. [60], 25% of MRSA carriers had an episode of staphylococcal infection, versus only 4% of carriers of methicillin-susceptible staphylococci. These authors concluded that MRSA colonization might predict the development of staphylococcal infection in LTCFs. Unfortunately, once residents acquire MRSA, colonization is persistent.

The different MRSA strains that circulate in LTCFs often mirror the strains found in local referring hospitals. Surveillance of MRSA colonization status is not necessary when these universal barrier precautions are applied to the care of all patients. If an increase in the rate of MRSA infections is documented, more intensive infection-control measures should be implemented. Physicians should be aware that they are also a source of MRSA. The need to instruct physicians regarding hand washing has been a serious, perennial problem.

**Glycopeptide-resistant *S. aureus.** The occurrence of vancomycin resistance by *S. aureus* (defined by an MIC of 8–16 µg/mL) in the United States has recently been described. In May 1996, the first clinical infection was reported from Japan [61]. So far, vancomycin-resistant strains have been recovered from three patients in the United States (Michigan, New York, and New Jersey). All of these patients were very similar to those cared for by geriatricians in LTCFs. It has been shown that glycopeptide-resistant strains have increased extracellular material (a thicker extracellular matrix, as demonstrated by electron microscopy) associated with their cell walls. In addition, these strains possess increased levels of penicillin binding proteins, decreased autolysis, and increased cell wall precursors [62, 63]. There is some small comfort in knowing that this resistance determinant is not transferable on a plasmid. Given that the spread of glycopeptide-resistant staphylococci may mimic that of MRSA, containment of a virulent strain would be exceptionally difficult in an LTCF.

**Penicillin-resistant pneumococci.** Pneumonia due to *Streptococcus pneumoniae* is one of the most frequent causes of lower respiratory tract infection in elderly patients. Penicillin has been the mainstay of therapy for pneumococcal pneumonia. However, penicillin-resistant pneumococci have now emerged as a significant problem in the treatment of pneumonia in the elderly. This threat stems from the fear of outbreaks of pneumococcal...
infection in institutional settings. The earlier study reports by Millar et al. [64] and Denton et al. [65] were among the first to describe penicillin-resistant pneumococcal infection in elderly institutionalized and debilitated patients.

A significant outbreak of penicillin-resistant pneumococci in an LTCF in rural Oklahoma was reported [66]. In this outbreak, the predominant strain was serotype 23F, a serotype associated with penicillin resistance worldwide. Pneumonia developed in 13% of the residents in this nursing facility, and the mortality rate in the outbreak was 23%. Resistant isolates were recovered from 64% of residents with pneumonia (type 23F) and from 23% of noninfected residents. It is surprising to note that the pneumococcal vaccination rate was very low in this LTCF. Low rates of vaccination in other nursing facilities have been reported [67].

Penicillin resistance has occurred mainly in serotypes 6B, 9V, 14, 19A, 19F, and 23F [68, 69]. One can partially protect against invasive infection by the strains that are penicillin-resistant by immunizing with the 23-valent pneumococcal polysaccharide vaccine. Unfortunately, this practice has not gained universal acceptance. In addition to questions concerning efficacy, the difficulty in ascertaining correct immunization history has dampened enthusiasm for this practice [70, 71].

The treatment of penicillin-resistant pneumococcal meningitis in the elderly is most worrisome. The poor penetration of penicillin through the meninges makes it difficult to achieve sufficient levels in the CSF. Hence, for the treatment pneumococcal meningitis, the use of vancomycin, ceftriaxone or cefotaxime, and rifampin is advocated. Meropenem may prove to be the treatment agent of choice for penicillin-resistant pneumococci [72, 73].

The concern raised by many regarding the increasing prevalence of high-level resistance of penicillin and ceftriaxone (and the fear of treatment failure) has focused attention on the use of fluoroquinolones (e.g., levofloxacin, moxifloxacin, and gatifloxacin) in the treatment of pneumonia [74–76]. Whether excessive use of fluoroquinolones will have an impact on the colonizing flora of nursing facility residents remains to be established.

Vancomycin-resistant enterococci (VRE). According to recent national nosocomial-infection surveillance studies, enterococci are the second most common organisms recovered in nosocomial infections [77]. Intrinsic resistance to virtually all antibiotics makes these organisms highly “successful” in the LTCF environment. Numerous reports have suggested that there is facile transfer of VRE between institutions [78]. It appears that VRE can spread by direct patient-to-patient contact or indirectly via transient carriage on the hands of personnel, contaminated environmental surfaces, and patient care equipment. The prevalence of colonization with VRE in patients admitted to acute-care hospitals from LTCFs may be as high as 47% [79].

VRE have become a serious challenge in LTCFs. How does one distinguish colonization from infection in wounds and urine? What is the best therapy for urinary tract infections, bacteremia, colonization, and infected pressure ulcers caused by VRE in LTCFs [70]? The translocation of elderly residents from tertiary-care institutions to LTCFs and back again can easily spread VRE from the hospitals to the nursing facilities. In a study done by Edmond et al., the mortality attributable to bacteremia due to VRE was 37%, and patients with such bacteremia were twice as likely to die as closely matched controls [81]. In a prospective 5-year study of 163 episodes of bacteremia in an LTCF, 36 episodes of bacteremia were polymicrobial and 14 involved an enterococcal species. It is almost imperative now that clinicians consider VRE as a significant pathogen in elderly patients residing in LTCFs [82].

As an example of the difficulty presented by colonization with VRE in LTCFs, the epidemiology of colonization with VRE in a 400-bed LTCF for veterans was described [79]. Twenty-four of 36 patients were colonized with VRE when they were transferred from an acute-care hospital to the Veterans Affairs LTCF. VRE persisted for 67 days and was associated with antibiotic administration.

The recommendations for containment of VRE in hospitals have proved to be impractical in nursing facilities. The financial, social, and psychological burdens associated with implementation of these guidelines are significant. The use of barrier precautions and isolation practices is not feasible in LTCFs. The Society for Healthcare Epidemiology of America recommends that patients colonized with VRE be isolated in private rooms until these organisms have “cleared”—a status usually determined on the basis of 2–3 negative stool culture results, each obtained 1 week apart. Modified contact isolation (with the use of gloves, a gown, and a private room, if available) is also strongly encouraged [83].

Infection Control and Antibiotic Use

Recommendations by the Society for Healthcare Epidemiology of America have been drafted to help control antibiotic resistance in LTCFs. These recommendations include antibiotic restriction practices, nontreatment of asymptomatic bacteremia, minimal use of topical antibiotics, hand washing, and barrier precautions for wound care [84]. I propose that at LTCFs, the following additional actions be specifically stressed: (1) regular education of nursing and physician personnel and (2) surveillance at the time of admission for antibiotic resistance.

Continuing medical education concerning the imprudent use of antibiotics needs to be the first step. Alerting staff to the dangers of excess antibiotic use and the epidemiology of current outbreaks will help with enforcing infection-control guidelines in the community. Education of the physician and nursing staffs is also needed to determine whether infection is present. Use of the definitions of infection in residents of LTCFs developed by McGeer et al. [85], which can serve as a guide, is encouraged.
Nursing personnel instructed in the use of these guidelines can assist physicians with treatment decisions. Infection-control surveillance also helps to identify the presence and spread of resistance.

I believe that identifying patients coming from hospitals where penicillin-resistant pneumococci, VRE, and ESBLs are endemic should be an infection-control policy for nursing facility physicians. Identifying patients who have been treated with advanced-generation cephalosporins, quinolones, or vancomycin in a hospital will alert nursing facility personnel to this potential problem. Although not proven in prospective studies, screening high-risk patients for colonization by antibiotic-resistant bacteria, particularly ESBLs, may help contain a potential outbreak [86]. Screening for VRE should also be a consideration in high-risk LTCFs.

Conclusions

In conclusion, clinicians should be “ecologically responsible” in their prescribing of antibiotics. The unnecessary use of broad-spectrum antibiotics to treat against susceptible organisms should be strongly discouraged. There should be clear guidelines in place for the use of antibiotics in the nursing facility. Limits to the length of antibiotic administration should also be enforced. Use of third-generation cephalosporins and quinolones in LTCF residents only when they are necessary in the treatment of urinary tract infections or upper/lower respiratory tract infections may limit the emergence of multiresistant gram-negative bacilli and VRE.

It is not clear whether restricting antibiotic formularies for LTCFs will prove to be effective in halting the emergence of resistance. Alerting physicians to the number of treatment courses of broad spectrum antibiotics used can stem overprescribing. Treatment algorithms are not yet a common practice in the nursing facility and should be developed.

Taken together, these steps have the potential to have an impact on the spread of resistance determinants in LTCFs. Most important, these are quality-of-care issues that preserve the environment for the care of a growing segment of our population.

References

11. Strausbaugh LJ, Crosseley KB, Nurse BA, Thrupp LD. Antibacterial-resistant bacteria, particularly ESBLs, may help contain a potential outbreak [86]. Screening for VRE should also be a consideration in high-risk LTCFs.


