Hospital-Based Strategies for Combating Resistance

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Selective pressures generated by the indiscriminate use of β-lactam antibiotics have resulted in increased bacterial resistance across all β-lactams classes. In particular, the use of third-generation cephalosporins has been associated with the emergence of extended-spectrum β-lactamase–producing and AmpC β-lactamase–producing Enterobacteriaceae and vancomycin-resistant enterococci. Conversely, β-lactams (e.g., cefepime, piperacillin-tazobactam, and ampicillin-sulbactam) have not demonstrated such strong selective pressures. Chief among institutional strategies to control outbreaks of multidrug-resistant bacteria are infection-control measures and interventional programs designed to minimize the use of antimicrobial agents that are associated with strong relationships between use and resistance. Successful programs include antimicrobial stewardship programs (prospective audit and feedback), formulary interventions (therapeutic substitutions), formulary restrictions, and vigilant infection control. Fourth-generation cephalosporins, such as cefepime, have proven to be useful substitutes for third-generation cephalosporins, as a part of an overall strategy to minimize the selection and impact of antimicrobial-resistant organisms in hospital settings.

The management of nosocomial infections has become an urgent health care priority. Hospital-acquired infections cause increases in mortality, morbidity, and length of hospital stay and have an enormous impact on health care costs. By one estimate, the average excess cost attributable to each such infection is $15,000 [1]. An increasing number of nosocomial infections are due to multidrug-resistant pathogens that may require the use of more expensive agents or may be treatable only with relatively toxic agents. The cost burden is further aggravated by such pathogens, because hospital stays are generally longer for patients with infections caused by resistant organisms [2]. Controlling the development and spread of multidrug-resistant bacteria in the hospital setting requires a combination of approaches that need to be applied in a disciplined and coordinated manner. This review will discuss selected experiences, as reported in the medical literature, of hospitals and health care facilities that have confronted the problems associated with nosocomial drug-resistant pathogens. The relative merits of hospital-based strategies for controlling outbreaks of resistant organisms and for treating the infections that they cause will also be discussed. A particular emphasis will be placed on approaches to the prevention and management of infections caused by extended-spectrum β-lactamase (ESBL)–producing and AmpC β-lactamase–producing bacteria.

**THE IMPORTANCE OF INFECTION-CONTROL MEASURES**

In general, antimicrobial resistance develops from a confluence of factors: failures of institutional hygiene; enhancement of resistance mechanisms in well-established clones through gene-capture genetic units, such as plasmids, integrons, or transposons; and facilitation of the coselective process under different selective pressures [3, 4]. At least one-third of all nosocomial infections, whether caused by susceptible or resistant pathogens, are thought to be preventable through infection-control programs [5].

In cases in which isolation precautions for controlling the dissemination of multidrug-resistant bacteria have been established, compliance may nevertheless be poor, which undermines the usefulness of such mea-
sures. A study in a Paris university hospital [6] found that, in general, caregivers poorly adhered to infection-control practices aimed at containing multidrug-resistant bacteria and that physicians wrote isolation orders for only 4 of 10 patients who required such measures. Personnel were also notably deficient in complying with hand-washing guidelines and with proper glove and gown use.

High rates of patient transfer between units and between hospitals may intensify an outbreak of resistant bacteria [7]. However, initiating barrier precautions to contain the spread of resistant organisms often is not practical for hospitals that must contend with a highly mobile patient population. A study of risk factors for colonization with ESBL-producing Escherichia coli and Klebsiella species found that the duration of hospitalization was the only independent risk factor for colonization with these organisms [8]. It was also noted that a large proportion of colonized patients had been admitted from another health care facility.

Interhospital transmission of resistant bacteria was demonstrated in a study of 15 hospitals in Brooklyn, New York [9]. Isolates of Acinetobacter baumannii and Pseudomonas aeruginosa were collected from the hospitals over the course of a 3-month period in 1999. A high proportion of A. baumannii isolates were multidrug resistant. Ribotyping revealed that a single clone accounted for >60% of the A. baumannii isolates, which were recovered from patients at all 15 hospitals. For P. aeruginosa, 3 clones accounted for nearly half of the multidrug-resistant isolates and were shared by most hospitals. In another report of clonal dissemination of a resistant pathogen, a hospital in Italy identified P. aeruginosa containing a metallo-β-lactamase gene; the strains appeared to be clonally related [10].

Transmission of resistance to broad-spectrum β-lactams does not occur solely by migration of a single clone. In Japan, an outbreak of metallo-β-lactamase–producing P. aeruginosa resistant to broad-spectrum β-lactams and carbapenemas was found to have proliferated multifocally, by plasmid-mediated dissemination of the metallo-β-lactamase gene in pseudomonal strains of different genetic backgrounds [11]. On the basis of this and other evidence, the interhospital spread of resistant strains emphasizes why control measures aimed at suppressing the emergence of such strains are not merely the responsibility of a single hospital or localized group of medical centers [12].

In addition to large hospitals with mobile populations, long-term care facilities are another high-risk environment for bacteria with multidrug resistance. For residents in a skilled-care unit, Trick et al. [13] determined the frequency of and risk factors for colonization with several antimicrobial-resistant bacterial species. Approximately 1 of 4 residents who were culture positive for a resistant bacterial species also was co-colonized by >1 resistant species. Risk factors for colonization varied by pathogen, with total dependence on health care workers being a specific risk factor for colonization with ESBL-producing Klebsiella pneumoniae. A review of 74 published studies demonstrated significant commonality of risk factors across multidrug-resistant organisms, such as Staphylococcus aureus, vancomycin-resistant enterococci, Clostridium difficile, and ESBL-producing gram-negative bacilli [14]. Advanced age and interinstitutional transfer of patients, especially from a nursing home, were 2 of the major risk factors predicting nosocomial colonization or infection with individual multidrug-resistant organisms.

Paterson et al. [15] successfully controlled an outbreak of ESBL-producing E. coli organisms in a liver transplantation unit by means of gut decontamination with norfloxacin, contact isolation, and feedback on hand hygiene. In that case, the genotypic relatedness of all recovered isolates indicated horizontal transfer of the ESBL-positive strains [15]. Patients were isolated in individual rooms with sinks and nonmedicated soap. Nurses and other health care providers were stopped after leaving each room and were asked by the infection-control department to participate in a “teaching exercise.” The glove-juice sampling procedure indicated that nurses and physicians were culture positive (32% and 23%, respectively) for such organisms as methicillin-resistant S. aureus and vancomycin-resistant enterococci but not for ESBL-producing E. coli. Staff members were confidentially informed of their culture positivity and were educated about the significance of hand washing. Contact precautions (gloves and gowns) were required for all ESBL-positive patients and their environments, which lasted for their current and all future admissions. Norfloxacin (400 mg every 12 h for 5 days) was used to reduce the density of ESBL organisms in the stool samples of identified patients. The results of the decontamination effort were fleeting, because 40% of patients had positive cultures 14 days after receiving the last dose of norfloxacin, and 60% had positive cultures at 28 days. The strategy was successful in curtailing the outbreak of ESBL-producing isolates; however, the authors suggested caution in using so-called fluorquinolone decontamination regimens, because of the potential for high percentages of these organisms being quinolone resistant. Although there are some cases in which standard infection-control measures are inadequate and additional measures must be utilized [16], such programs are nevertheless integral for containing nosocomial transmission of organisms.

ASSOCIATION OF USE OF THIRD-GENERATION CEPHALOSPORINS WITH NOSOCOMIAL OUTBREAKS OF RESISTANT PATHOGENS

In the 1970s, Levy et al. [17] developed a biological model that demonstrated a clear relationship between antimicrobial use and drug-resistance selection among E. coli in humans. With regard to the development of ESBL-based resistance, total prior antibiotic use, including exposure to noncephalosporin anti-
biotics, has been identified as an important risk factor for infection with ESBL-producing *E. coli* or *K. pneumoniae* [18]. A more common observation is a strong correlation between antimicrobial resistance and the use of specific third-generation cephalosporins, especially among *K. pneumoniae* isolates [19–23]. In a study of hospitalized patients in Taiwan, the risk of infection with ESBL-producing *K. pneumoniae* was >13 times greater among patients who had been exposed to ceftazidime within the prior 30 days than it was among patients who had not been similarly exposed [24].

An investigation in a pediatric intensive care unit (ICU) found that previous treatment with third-generation cephalosporins and aminoglycosides, in addition to age <12 weeks, was independently associated with colonization or infection with multidrug-resistant *K. pneumoniae*. Patients who were exposed to the antibiotics had >30 times the risk of colonization or infection, compared with patients who were not similarly exposed [25].

Overall, the association of antibiotic use with the development of multidrug resistance underscores the fact that making suboptimal antimicrobial choices has global implications. The use of a particular antimicrobial agent may not only select for overgrowth of bacterial strains with innate resistance, but also may select for the development of diverse genetic vectors that encode and are capable of disseminating resistance mechanisms [12]. Genetic elements of this kind may spread widely through the world’s bacterial populations.

**ANTIBIOTIC RESTRICTION MEASURES**

The established connection between antibiotic use, particularly of third-generation cephalosporins, and the selection of ESBL- and AmpC-producing organisms has encouraged modifications in patterns of antimicrobial utilization. Selected changes have proven to be effective for minimizing the prevalence of these bacteria in health care facilities.

Patterson et al. [22] measured the prevalence of multidrug-resistant *K. pneumoniae* at 2 hospitals, before and after an acute intervention, which included restrictions on antibiotic use and physician education regarding the association between ceftazidime use and the presence of multidrug-resistant *K. pneumoniae*. Following the intervention, ceftazidime use decreased, and piperacillin-tazobactam use increased at both institutions. The changes were associated with a significant decrease in ceftazidime resistance among *K. pneumoniae* isolates. Similar observations were made in a retrospective analysis of data from 10 hospitals [26]; antimicrobial usage and antimicrobial resistance trends for prominent nosocomial pathogens were compared, as were antimicrobial control programs and policies, across all hospitals. A strong positive correlation was noted between ceftazidime usage and the prevalence of ceftazidime-resistant *P. aeruginosa* and of ceftazidime-resistant Enterobacteriaceae. Likewise, control programs and policies were associated with lower prevalence rates of some resistant bacterial strains and less antibiotic usage.

In another study, a high prevalence of ceftazidime-resistant *K. pneumoniae* in the hospital ICU prompted an intervention that included rigorously enforcing barrier precautions and ceftazidime restriction. Following the interventions, the susceptibility rate of *K. pneumoniae* increased by ~4-fold in isolates recovered in the ICU. Although the combined hand hygiene and antibiotic policy was only instituted in the ICU, a modest increase in the susceptibility of *K. pneumoniae* isolates among total hospital isolates occurred [23]. The benefits of antibiotic restriction for minimizing multidrug-resistant outbreaks are, however, not always apparent. This situation was described in a report by Toltzis et al. [27], who restricted ceftazidime use in a pediatric ICU; the result was a small, but not significant, reduction in the overall prevalence of ceftazidime-resistant gram-negative bacteria. However, if one looks at the organisms associated with AmpC β-lactamase production, where one would expect to see a difference, resistance decreased from 68.2% to 45.9% ($P<.05$).

Although restriction of third-generation cephalosporins is nevertheless an effective method for controlling outbreaks of ESBL-producing bacteria, such measures must be undertaken cautiously. A formulary change that restricts cephalosporins, as well as other antimicrobials, may sometimes promote the emergence of pathogens with new and different resistance profiles. This phenomenon was observed following a formulary change that was instituted to limit an outbreak of vancomycin-resistant enterococci. The change resulted in a decrease in usage, not only of cephalosporins, but also of imipenem, clindamycin, and vancomycin. To compensate, an emphasis was placed on the use of β-lactam/lactamase-inhibitor combinations [28]. Significant reductions were observed in the monthly number of patients colonized with methicillin-resistant *S. aureus* and ceftazidime-resistant *K. pneumoniae*. However, the proven clonal spread of these strains via person-to-person transmission, a decrease in patient density and in the average length of hospital stay, and the marked decrease in the overall use of antimicrobial agents could have confounded these data [29]. Nonetheless, there was a significant increase in the number of patients for whom cultures were positive for ceftotaxime-resistant *Acinetobacter* species [28]. A study of a 500-bed urban teaching facility in New York City successfully illustrated the relationship between antimicrobial use and resistance selection [30]. The effects of various countermeasures used to contain both the endogenous selection and horizontal transmission of resistant gram-negative bacilli were also documented. An initial series of infections caused by *A. baumannii* (multidrug resistant but ceftazidime susceptible) led to the increased use of ceftazidime. From this reliance on ceftazidime, significant numbers of in-
fections due to both ceftazidime-resistant *A. baumannii* (in 1988) and ceftazidime-resistant (ESBL-producing) *K. pneumoniae* (in 1993) arose, requiring the greater use of imipenem. To gain perspective, between 1993 and 1995, 37% of all *K. pneumoniae* strains isolated produced ESBLs. The resultant increase in imipenem use and continued selective pressure exerted by ceftazidime and cefotetan culminated with the development of *A. baumannii* strains that are resistant to imipenem and ceftazidime; *K. pneumoniae* that now are resistant to ceftazidime (an ESBL), cefotetan (an ACT-1 plasmid-mediated AmpC-type β-lactamase), and imipenem (via outer membrane porin loss); and imipenem-resistant *P. aeruginosa*. Selective pressure exerted by both ceftazidime and imipenem undoubtedly contributed to the genesis of these resistant organisms, and, once established, horizontal transmission amplified their dissemination.

Quale et al. [31] reported that an advanced outbreak of ESBL-producing *K. pneumoniae* was occurring in 2002 in the New York City area. They collected 281 ESBL-producing isolates of *K. pneumoniae* from 15 hospitals in the Brooklyn area. Isoelectric points suggested a predominance of SHV-5 enzymes mixed with other smaller numbers of other enzymes, including the plasmid-mediated AmpC β-lactamase ACT-1. For the isolates, susceptibilities (expressed as percentages) to several antimicrobial agents were reported, including ceftazidime (13%), cefotaxime (13%), ciprofloxacin (42%), ceftriaxone (48%), piperacillin-tazobactam (55%), amikacin (57%), cefepime (86%), and imipenem (99%). The high rate of resistance to cefepime (66%) and the low rate of resistance to cefepime strongly suggest the copresence of AmpC and ESBL enzymes. Antimicrobial utilization data indicated that the use of cefalosporins (as a group) and aztreonam correlated strongly with the prevalence of ESBL-producing strains at each institution via multivariate analysis (P = .014).

Neighboring hospitals in Brooklyn, New York, also experienced significant outbreaks of ESBL-producing Enterobacteriaceae and *Acinetobacter* species. From their experience arose a case-control study of their clinical outcomes [9]. Longer hospital stays following the infection were noted for patients infected with ESBL-producing *K. pneumoniae*, compared with control subjects (median of stay, 29 vs. 11 days [P = .03]; mean ± SD, 37 ± 25 vs. 15 ± 10 days [P = .04]). Patients infected with ESBL-producing isolates had a higher, but not statistically significant, mortality rate than did control subjects (44% vs. 34%) [9].

Once an outbreak of ESBL-producing strains has been effectively managed at the hospital level, it is important to recognize that these organisms have likely disseminated into the surrounding community, including long-term care facilities [30, 32, 33]. Strains can be reintroduced to the hospital from these venues, which further emphasizes the importance of effective and prospective infection-control programs for ESBL control.

### More Targeted Use of Carbapenems

The carbapenems have been important antimicrobial agents for treating nosocomial gram-negative infections, especially those caused by ESBL-producing organisms. Surveillance data from the Meropenem Yearly Susceptibility Test Information Collection on antimicrobial resistance in gram-negative isolates from European ICUs found that the 2 most frequently used members of this antibiotic class—meropenem and imipenem—have remained highly active against important species of gram-negative bacteria recovered from European ICUs that actively use meropenem [34]. The susceptibility of Enterobacteriaceae to carbapenems was generally >98%, whereas that of *P. aeruginosa* and *A. baumannii* was 68%–82%.

Although carbapenems are still highly effective against ESBL-producing bacteria, carbapenem-resistant strains are beginning to emerge, probably because of the increased reliance by clinicians on this class of antimicrobials. The prevalence of multidrug-resistant *A. baumannii*, including strains with resistance to carbapenems, has increased markedly, along with the prevalence of carbapenem-resistant strains of *P. aeruginosa*. A single carbapenem-resistant epidemic strain of *A. baumannii* was recently reported to have infected patients at 5 hospitals in Buenos Aires, Argentina [35]. A concurrent outbreak of multidrug-resistant *P. aeruginosa* and *A. baumannii* was reported in 15 hospitals in Brooklyn, New York [9]. Ribotyping revealed that a relatively small number of clones accounted for the majority of patient isolates of these 2 bacterial species. For *A. baumannii*, 53% of isolates were resistant to meropenem and/or imipenem. In an Italian study of 8 *P. aeruginosa* isolates recovered from 7 patients in different wards of a single hospital, all isolates showed high levels of resistance to carbapenems; 7 of the 8 isolates appeared to be clonally related [10].

The latest issue to concern the carbapenems is the description of geographically isolated outbreaks of enterobacteriaceae (particularly *K. pneumoniae*) that possess carbapenem-hydrolyzing enzymes belonging to the KPC family of β-lactamases [36]. In some KPC-producing isolates, additional porin channel alterations were noted [37]. The isolation of these organisms has, thus far, been limited to certain geographic regions, and these organisms certainly pose a therapeutic challenge in centers that deal with infections caused by them. Because carbapenem resistance due to KPC-producing organisms can be difficult to detect with automated susceptibility testing methods, vigilance should be maintained in terms of monitoring for treatment failures when carbapenems are used [37].

In summary, the increased use of carbapenems to combat the growing prevalence of multidrug-resistant bacteria, particularly ESBL-producing strains, shows early signs of eroding the
effectiveness of the carbapenems. A more highly targeted and restrained use of these drugs, aimed at preserving their antimicrobial activity, is probably warranted.

**HOSPITAL CASE STUDIES: REPLACEMENT OF CEFTAZIDIME WITH CEFEPIME**

Recognizing that exposure to third-generation cephalosporins plays a role in the selection of multidrug-resistant organisms, a number of studies have evaluated the effect of substitution of the fourth-generation cephalosporin ceftazidime for third-generation cephalosporins on susceptibility patterns. Empey et al. [38] reviewed antibiotic use and antimicrobial resistance before and after a university hospital formulary change that was aimed at reducing utilization of third-generation cephalosporins. After the formulary change to cefepime, the use of ceftazidime and cefotaxime underwent a combined decrease of 89%. Cefepime use was associated with a significant decrease in infections due to ceftazidime-resistant *K. pneumoniae* and *P. aeruginosa*.

Because cefepime MICs are less affected by the expression of AmpC β-lactamases, replacing third-generation cephalosporins with cefepime appears to be effective in reversing reduced hospital-wide susceptibility to hyperproducers of this β-lactamase. The gene encoding the AmpC β-lactamase is naturally present in many species of Enterobacteriaceae and in some nonfermentative gram-negative bacilli, including *Serratia marscescens*, *P. aeruginosa*, indole-positive Proteae (e.g., *Morganella* species), *Citrobacter* species, and *Enterobacter* species.

In one hospital, the use of a ceftazidime-glycopeptide combination as initial empirical therapy for neutropenic fever resulted in a 75% reduced rate of susceptibility to ceftazidime among Enterobacteriaceae with AmpC β-lactamase–mediated resistance [39]. After a cefepime-amikacin combination was used as an alternate empirical therapy, a significant improvement was observed in the susceptibility of inducible Enterobacteriaceae to ceftazidime. Susceptibility to amikacin, cotrimoxazole, and ciprofloxacin increased as well, and the reduced susceptibility to ceftazidime exhibited by noninducible Enterobacteriaceae (e.g., *Klebsiella* species) was also reversed. After formulary replacement of ceftazidime with cefepime as empirical therapy for febrile neutropenia, Orrick et al. [40] also reported improvements in susceptibility of AmpC β-lactamase-producing organisms, in this case, to ceftazidime and to ticarcillin-clavulanate. A similar pattern of significantly improved antimicrobial susceptibility among inducible Enterobacteriaceae was reported after a switch to cefepime in a medical/surgical ICU [41].

The improvements in antimicrobial susceptibility observed following implementation of programs to restrict third-generation cephalosporins can produce clinically significant benefits. In a study of outcomes among critically ill patients, a 27% reduction in third-generation cephalosporin use was accompanied by a dramatic increase in cefepime use. The new treatment program led to a significant decrease in the infection-related hospital-wide mortality rate, from 36% to 19% [42]. The improved outcomes were associated with an increase in the antimicrobial susceptibilities of *E. coli* and *Klebsiella* species.

Rotation is another strategy used to limit antimicrobial exposure to minimize selection of resistant organisms. In a rotation scheme, changes in the choice of antibiotic administered for a condition occur cyclically, according to a prearranged schedule. Gruson et al. [43] studied the effect of a combination of antibiotic restriction and rotation on the incidence of ventilator-assisted pneumonia. Their scheme restricted the use of ciprofloxacin and ceftazidime through a multistage program in which a β-lactam and an aminoglycoside were prescribed empirically. The chosen β-lactam was cefepime, piperacillin-tazobactam, imipenem, or ticarcillin-clavulanic acid. Each was the preferred choice of empirical therapy for ~1 month, at which time the next β-lactam, in predetermined order, became the preferred choice. The β-lactams were variously associated with one of several aminoglycosides. Comparison of the 2 years before and after the program showed a significant decrease in the number of cases of ventilator-assisted pneumonia. The total number of potentially resistant gram-negative bacteria responsible for ventilator-assisted pneumonia decreased, whereas the antimicrobial susceptibilities of these bacteria increased.

Taken together, the results of these studies suggest that, by substituting cefepime for third-generation cephalosporins, the resistance profile of gram-negative bacteria producing common ESBLs and AmpC β-lactamases can, in some cases, be reversed. The CTX-M type ESBLs, which hydrolyze cefepime efficiently and are of growing importance outside (but not, as yet, inside) the United States, suggest that continued monitoring of cefepime susceptibilities and enzyme characteristics will be important [44]. Substituting cefepime for third-generation cephalosporins appears to offer an alternative to treatment with carbapenems in selected cases of nosocomial infection due to multidrug-resistant organisms.

**COST ISSUES: ANALYZING HOSPITAL CONVERSION FROM CEFTAZIDIME TO CEFEPIME**

A comprehensive review of hospital-based strategies for combating drug-resistant nosocomial infections must address the issue of treatment and hospitalization costs and how they might be minimized. A workshop entitled “Measuring the Economic Costs of Antimicrobial Resistance in Hospital Settings,” sponsored by Emory University and the Centers for Disease Control and Prevention, was conducted in November 2000 [45]. At the workshop, the excess direct costs of treating a patient with a nosocomial infection caused by a resistant pathogen were delineated. Because infections due to resistant pathogens result
in longer hospital stays, usually as a result of failure of initial therapies, excess per-bed daily costs contribute substantially to the costs of treating such infections. Other excess costs derive from the need for patient isolation, additional costs associated with the acquisition and administration of antimicrobials, and the costs of other infections and complications that often are associated with infection with resistant pathogens. Additional procedures and laboratory costs, as well as physician staff time and infection-control staff, are further costs associated with nosocomial infections due to resistant organisms.

A pharmacoeconomic analysis conducted in a French university hospital group found that, on a daily basis, the most costly antibiotic treatments were prescribed for ICU patients, patients with device-related nosocomial pneumonia, and patients with multidrug-resistant bacterial infections [46]. Undocumented nosocomial infection accounted for ∼20% of overall antibiotic costs. The authors of that study concluded that antibiotic treatment for nosocomial infection represents a significant part of hospital expenditure, which should be moderated by controlling the use of highly expensive prescriptions.

An analysis by Owens, Jr., et al. [47] concluded that significant cost savings might be realized by a formulary switch from the third-generation cephalosporin ceftazidime to ceftazime. The survey was based on antibiotic usage patterns and treatment costs encountered at Hartford Hospital in Connecticut. Significant savings could be realized by following the different dose recommendations of the Food and Drug Administration for ceftazime (twice-daily administration) and ceftazidime (thrice-daily administration), which are also supported by pharmacokinetic-pharmacodynamic differences between the 2 cephalosporins [48]. On the basis of these factors and of the then-current usage patterns and drug acquisition costs, the investigators estimated that replacing ceftazidime on the hospital formulary could result in a potential annual savings of >$50,000.

In addition to decreased direct drug costs, greater savings might derive from an increase in clinical efficacy gained by switching from ceftazidime to ceftazime. When ceftazidime and ceftazime treatment were compared in a study of 100 patients with hospital-acquired pneumonia, ceftazidime was indeed found to be more cost effective [49]. The mean drug-specific cost of ceftazime treatment was $266.59, versus $339.93 for ceftazidime. In addition to the cost of the 2 antibiotics, the figures also reflected the significantly lower costs of concomitant medications in the ceftazime group. The lower costs, in turn, reflected the higher rates of clinical efficacy (78% vs. 60%; P = .05) and microbiological efficacy (77% vs. 55%; P = .04) reported in that study for ceftazime and ceftazidime, respectively [49].

ANTIMICROBIAL STEWARDSHIP PROGRAMS

The use of the term “antimicrobial stewardship program” implies a multidisciplinary, programmatic, prospective interventional approach to optimizing the use of anti-infectives. Antimicrobial stewardship programs should be multidisciplinary and should involve an infectious diseases physician and an infectious diseases clinical pharmacist, both of whom should be compensated for their time. Additional team members should optimally include a microbiologist, a data analyst, and a representative of the infection-control department. The Infectious Diseases Society of America’s guidelines for antimicrobial stewardship programs, which have been endorsed by multiple societies, will be published soon and will provide more details about the rationale, benefits, and implementation and coordination of such programs. A variety of prospective programmatic strategies have been proposed, but, in reality, they can be simplified into 1 of 2 main categories: prior authorization and concurrent review with feedback [50]. Of course, the 2 categories are not mutually exclusive, and hybrid programs using a blend of the central strategies have been created. Why are programmatic multidisciplinary strategies important? Carling et al. [51] demonstrated that, among similarly matched hospitals, only hospitals that used the programmatic prospective interventional programs were able to significantly affect parenteral antimicrobial use patterns and costs, in contrast to hospitals that relied solely on passive strategies. These passive or adjunctive interventions may, in our opinion, serve as tools to augment the 2 main strategies and may include the use of stop orders, antibiotic order forms, closed formularies, selective susceptibility reporting, educational sessions, and restriction of pharmaceutical promotional activities. The outcomes and implementation methods for antimicrobial stewardship programs have been extensively reviewed elsewhere [52]. In brief, these programs have demonstrated reductions in both inappropriate and overall antimicrobial use, decreased expenditures, and improved patient safety; some of them have even demonstrated improved antibiotic susceptibilities [53–57].

A recent example of this programmatic approach evaluated the impact of an interventional program on antimicrobial use, cost savings, and antimicrobial resistance. The multidisciplinary team consisted of an infectious diseases physician, 2 pharmacists, a microbiologist, a laboratory technologist, an internal medicine physician, and a computer systems analyst [58]. Interventions included an antibiotic order form, providing clinicians with feedback based on the data collected, and verbally communicating with prescribers about new orders for third-generation cephalosporins and carbapenems centered around antimicrobial selection, specifically the collateral resistance potential associated with third-generation cephalosporin and carbapenem use [58]. Over the course of the study, an increased
rate of cefepime use, relative to use of third-generation cephalosporins, was associated with decreasing rates of resistance to third-generation cephalosporins among Proteus mirabilis and Enterobacter cloacae but not among E. coli and K. pneumoniae. The increased rate of aminopenicillin-sulbactam use relative to the third-generation cephalosporins, in conjunction with a sustained reduction in vancomycin use, was associated with a reduction in methicillin-resistant S. aureus rates [58]. In addition, P. aeruginosa rates of resistance to carbapenems decreased to zero. This decrease was strongly associated with the reduction in carbapenem consumption over time.

A joint committee of the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America has developed a set of recommendations for the prevention and reduction of antimicrobial resistance in hospitals [59], as follows:

1. Hospitals should have a system for monitoring antimicrobial resistance of both community-acquired and nosocomial isolates (by hospital location and patient site) on a monthly basis or at a frequency appropriate to the volume of isolates recovered,
2. Hospital locations or prescribing services should monitor the use of antimicrobials on a monthly basis or at a frequency appropriate to the prescription volume,
3. Hospitals should monitor the relationship between antimicrobial use and resistance and should assign responsibility through practice guidelines or other institutional policies, and
4. Hospitals should apply contact precautions to specific patients known or suspected to be colonized or infected with epidemiologically important microorganisms that can be transmitted by direct or indirect contact.

These recommendations can serve as talking points in the initiation of programs supported by hospital administration and managed by infectious diseases experts.

CONCLUSION

The problem of increasing antimicrobial resistance, which is due, in part, to suboptimal antimicrobial use, coupled with the fact that a growing number of pharmaceutical companies have abandoned anti-infective research and development, has resulted in a growing public health crisis. Because hospitals are characterized by high-density antibiotic use, they are target-rich venues for proactive interventions to improve antimicrobial use. Reasons for suboptimal infection control and antimicrobial use in modern times are similar: insufficient resources (both human and financial), apathy, and ignorance. With regard to gram-negative organisms, the emergence of ESBL-producing K. pneumoniae and E. coli and AmpC-producing Enterobacteriaceae, such as Enterobacter species and S. marcescens, has resulted in increased morbidity and mortality, as well as increased health care costs. With little to no help on the way from the antimicrobial pipeline for the most resistant gram-negative bacterial infections, antimicrobial resistance needs to be considered a priority by clinicians and administrators alike.

McGowan, Jr., et al. [60] stated recently that guidelines for the prevention and control of antimicrobial resistance must target specific drug-organism combinations, because the risks and predictors for them are dissimilar. Minimizing or eliminating the use of certain antimicrobial agents has been shown to be an effective strategy for dealing with third-generation cephalosporin-resistant gram-negative bacilli. To pretend that we know the absolute method for the treatment of the evolving β-lactamase crisis within the world of gram-negative bacilli is the antithesis of science. However, the literature is now replete with the negative effects of certain agents (e.g., third-generation cephalosporins) on the ecological profiles of hospital and institutional flora. This has led many institutions to remove these agents from the formulary or to place restrictions on their use, as well as to introduce more heterogeneity into their antimicrobial prescribing habits. It has also become clear that not all cephalosporins are equal with regard to their inherent resistance selection potential and their usefulness in treating resistant organisms. The fourth-generation cephalosporins, such as cefepime, appear to be capable of being used, in place of third-generation cephalosporins, for the empirical and definitive treatment of infections without adversely affecting resistance profiles or the environment. We must continue to be proactive and study strategies for the containment and treatment of infections caused by antimicrobial-resistant organisms, as well as to modify and expand our approaches when more information becomes available.

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