Results of an antimicrobial control program at a university hospital

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During the mid-1990s, infectious diseases (ID) physicians and clinical pharmacists at the University of Kentucky Chandler Medical Center (UKCMC) were becoming concerned about the increasing resistance rates of key pathogens to commonly used antibiotics,[1] as well as the steady increase in the pharmacy's annual expenditures for antimicrobials. An internal evaluation indicated a high level of inappropriate prescribing of antimicrobials by clinicians throughout the medical center. These concerns led to a series of initiatives aimed at controlling antimicrobial use to minimize the development of antimicrobial resistance in nosocomial pathogens and reducing cost. This report describes the impact of the first five years (1998–2002) of an ongoing antimicrobial management program and antimicrobial management team and describes the use of antimicrobials and the annual expenditures for those agents at UKCMC.

Purpose. The results of the first five years of an ongoing antimicrobial control program are reported.

Methods. In 1998, a multidisciplinary antimicrobial subcommittee of the pharmacy and therapeutics committee of a university hospital was formed and charged with making formulary interventions in an effort to reduce rising antimicrobial resistance rates and drug expenditures. In 1999, a number of measures were implemented for controlling antimicrobial use. Selected antimicrobials with the potential for inappropriate use or whose inappropriate use had been documented were placed in the control of physicians in the infectious diseases (ID) division. Prior approval by an ID physician was required before the pharmacy could dispense these agents. Other key interventions included removal of ceftazidime and cefotaxime from the formulary, restriction of vancomycin and carbapenem use, and replacement of ciprofloxacin with levofloxacin as the sole fluoroquinolone on the formulary. Data regarding antimicrobial use and expenditures between 1998 and 2002 were compared and analyzed.

Results. Antimicrobial use was reduced by 80% for third-generation cephalosporins and 15% for vancomycin following the implementation of the new antimicrobial policies. Antimicrobial-resistance patterns for many important gram-negative pathogens, including *Pseudomonas aeruginosa*, demonstrated a reversal of previous increases. In addition, the rate of methicillin-resistant *Staphylococcus aureus* decreased by an average of 3% each year from 1999 to 2002. Pharmacy expenditures for all antimicrobials, including antiviral, antifungal, and antibacterial agents, decreased 24.7%, with a cumulative cost saving of $1,401,126, without inflation assumptions.

Conclusion. The implementation of an antimicrobial control program decreased the use of selected antimicrobial agents and resulted in substantial reduction of expenditures for antimicrobials.

Index terms: Antibiotics; Antifungals; Anti-infective agents; Antivirals; Carbapenems; Cefotaxime; Ceftazidime; Cephalosporins; Ciprofloxacin; Costs; Drug use; Economics; Formularies; Hospitals; Levofloxacin; Pharmacy and therapeutics committee; Prescribing; Protocols; *Pseudomonas aeruginosa*; Quinolones; Rational therapy; Resistance; *Staphylococcus aureus*; Vancomycin

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Methods

We initiated a formal antimicrobial control program at UKCMC in 1998 with the formation of a multidisciplinary antimicrobial subcommittee of the pharmacy and therapeutics (P&T) committee. Members of the subcommittee included representatives from surgery, pediatrics, internal medicine, transplantation, critical care, ID, pharmacy, and nursing. The antimicrobial subcommittee was charged with the following responsibilities: (1) develop and implement initiatives to ensure the appropriate use of antimicrobials by physicians in our institution and (2) review the existing formulary and recommend more cost-effective choices that will reduce the selection of anticrobial-resistant nosocomial pathogens.

In the fourth quarter of 1999, we began implementing a number of measures recommended by the antimicrobial subcommittee for controlling antimicrobial use. Selected antimicrobials with the potential for inappropriate use or whose inappropriate use had been documented were placed under the control of physicians in the ID division. Prior approval by an ID physician was required before the pharmacy could dispense these agents. These interventions, among others, are summarized below.

Formulary interventions. *Cephalosporins.* Ceftazidime and cefotaxime were removed from the formulary because of their reported association with the increased risk of developing multidrug resistance by gram-negative organisms[2-5] and selection of vancomycin-resistant *Enterococcus* species.[6-9] The use of ceftriaxone was largely limited to the treatment of community-acquired pneumonia (CAP), meningitis, and urinary tract infections. To further reduce the use of cephalosporins, penicillin-based regimens were endorsed for most infections. For example, in addition to a ceftriaxone-containing regimen for CAP, the new measures recommended a combination of ampicillin–sulbactam and a macrolide for the empirical treatment of hospitalized patients not in the intensive care unit. Piperacillin–tazobactam with or without an aminoglycoside or a fluoroquinolone was recommended to replace a ceftazidime-containing regimen for the treatment of nosocomial pneumonia. Cefepime was added to the formulary as an option for treating nosocomial infections in patients who cannot tolerate penicillin-based therapy, especially when *Pseudomonas aeruginosa* is suspected to be the offending pathogen.

Vancomycin. After an internal audit revealed poor adherence to the Centers for Disease Control and Prevention's Hospital Infection Control Practices Advisory Committee (HICPAC) guidelines,[10,11] staff pharmacists were instructed to dispense all orders for vancomycin and place an automatic 72-hour discontinuation in the pharmacy's computer system. This time frame was chosen because it gave practitioners ample time to examine culture and sensitivity data before mandatory discontinuation was imposed. Medical teams were notified of the automatic discontinuation either by the pharmacist conducting rounds with the team or the pharmacist assigned to the patient care area (for teams without pharmacy representatives attending daily rounds). The HICPAC guidelines were incorporated into a "vancomycin continuation form," which was placed in each patient's chart and to be completed by the treating physician.[12] If a patient met the criteria for vancomycin continuation, the form was completed and faxed to the pharmacy. If the patient did not meet these criteria before the 72-hour time frame, the agent was discontinued by pharmacy. An ID consultation was required to override this automatic discontinuation.

Fluoroquinolones. In May 2001, levofloxacin replaced ciprofloxacin as the sole fluoroquinolone on the formulary. Ciprofloxacin has been associated with antimicrobial resistance in many common pathogens, including *Staphylococcus aureus* and *P. aeruginosa*.[13-19] We had observed erosion in susceptibility rates to ciprofloxacin in these key pathogens before implementing this change. In 1991, only 6% of *P. aeruginosa* and 10% of *S. aureus* isolates were resistant to ciprofloxacin, compared with 27% and 56% in 2001, respectively.[1] Routine testing of levofloxacin's activity against these pathogens began in 2001. During that year, levofloxacin activity against *P. aeruginosa* was similar to that of ciprofloxacin, with 26% of isolates being reported as resistant. Levofloxacin was more active against *S. aureus*, however, with a 34% resistance rate. In addition to concerns over increasing pathogen resistance to ciprofloxacin, the total costs for fluoroquinolones at our institution had become prohibitive, reaching a high of $290,524 by 2000 when both ciprofloxacin and levofloxacin were being used. Because both agents were on our formulary, our market share for each agent was below the threshold that would have given us the best available acquisition cost for either drug. Adopting levofloxacin as the sole fluoroquinolone allowed us to receive the best possible acquisition cost for this agent.[20]

Carbapenems. The inappropriate use of carbapenems also has been associated with significant bacterial resistance in health care institutions, resulting in the emergence of multidrug-resistant isolates of *P. aeruginosa* and *Acinetobacter baumannii*, many of which are not susceptible to any of the commonly used antimicrobials, necessitating the use of potentially more toxic drugs, such as polymixin B and colistin.[2,21-27] We restricted the use of carbapenems to situations in which the infection was caused by a documented extended-spectrum β-lactamase-producing organism or an organism resistant to reasonable alternatives.

Amphotericin B formulations. The antimicrobial subcommittee recommended placing all lipid formulations of amphotericin B on the list of restricted agents. No clear therapeutic benefit had been demonstrated for the routine use of these formulations when compared with the conventional formulation of amphotericin B. In addition, the lipid formulations of these agents are much more expensive than the conventional formulation, making them excellent candidates for restriction. Pursuant to the recommendation of the subcommittee, the P&T committee required approval by an ID physician before clinicians were permitted to use these agents.

Periodic monitoring. The antimicrobial susceptibility rates of key pathogens were closely monitored from 1998 through 2002 via quarterly reports from the clinical microbiology laboratory. The financial officer of the pharmacy department monitored antimicrobial expenditures (including all antibacterial, antiviral, and antifungal agents) and provided quarterly reports to the antimicrobial subcommittee. These expenditures were compared with baseline data (gathered in 1998) and with projected expenditures for each year, assuming a 10% inflation rate in drug acquisition costs. Antimicrobial purchases were also monitored in defined daily doses per 1000 patient days to standardize the amount of each agent purchased to accommodate any fluctuation in the number of admissions each year. The defined daily doses used for each agent corresponded to those used by Project ICARE.[28]

Results

Antimicrobial expenditures. From 1998 through 2002, we were able to reduce antimicrobial expenditures by 25% at our institution. A total saving of $1,401,126, assuming no inflation in drug costs, was realized from 1999 through 2002 (Table 1). Figure 1 compares the expected versus actual total antimicrobial expenditures for each year, using a 10% inflation rate. Cumulative cost savings increased to an estimated $4,438,825. The number of defined daily doses per 1000 patient days purchased in 1998–2002 for key agents is listed in Table 2.

Antimicrobial susceptibility and resistance. Overall, the susceptibility of *P. aeruginosa* to key antimicrobials remained constant or improved slightly over the five-year period. Susceptibility to piperacillin increased from 82% in 1998 to 85% in 2002, despite a 64% increase in the number of defined daily doses per 1000 patient days of piperacillin plus piperacillin–tazobactam purchased. Susceptibility to ceftazidime increased from 81% in 1998 to 85% in 2001 before decreasing slightly to 82% in 2002. Susceptibility to the carbapenems improved during the study period, increasing from 86% in 1998 to 91% in 2002. Fluoroquinolone susceptibility decreased from 70% in 1998 to 66% in 2002. The reduction in multidrug-resistant *P. aeruginosa* isolates (defined as susceptible to no more than one of the commonly used antimicrobials) is illustrated in Figure 2.

Methicillin resistance in *S. aureus* isolates is shown in Figure 3. Resistance peaked at 40% in 1999 but has decreased an average of 3% per year since that time.

Ceftazidime resistance in *Klebsiella pneumoniae* is shown in Figure 4.

Table 1.
Annual Expenditures Related to Antimicrobials in 1998–2002

Variable	Year				
	1998	1999	2000	2001	2002
Antimicrobial expenditures ($)	2,550,455	2,486,697	2,336,522	2,056,251	1,921,224
Reduction in expenditures[a] ($)	. . .	63,758	213,933	494,204	629,231
Inpatient days	120,626	122,323	128,326	122,651	118,302
Antimicrobial cost per inpatient day ($)	21.14	20.33	18.21	16.77	16.24

[a]Compared with expenditures in 1998.

Table 2.
Defined Daily Doses per 1000 Patient Days Purchased in 1998–2002

Antimicrobial(s)	Year					% Change[a]
	1998	1999	2000	2001	2002	
Ceftazidime, cefotaxime, and ceftriaxone	194.5	100.6	56.4	48.1	39.2	–79.8
Cefepime	0	26.3	33.2	33.6	25.1	. . .
Piperacillin and piperacillin–tazobactam	30.9	50.2	47.6	48.8	50.7	64.1
Imipenem and meropenem	6.3	6.4	5.7	3.0	8.1	28.6
Vancomycin	50.2	52.0	47.2	45.4	42.7	–14.9
Ciprofloxacin and levofloxacin	74.7	109.2	138.2	194.1	160.5	114.9

[a]Data from 2002 compared with 1998 data.

Figure 1. Expected (gray bars) and actual (black bars) antimicrobial expenditures, assuming 10% inflation per year and adjusted for fluctuations in inpatient days.

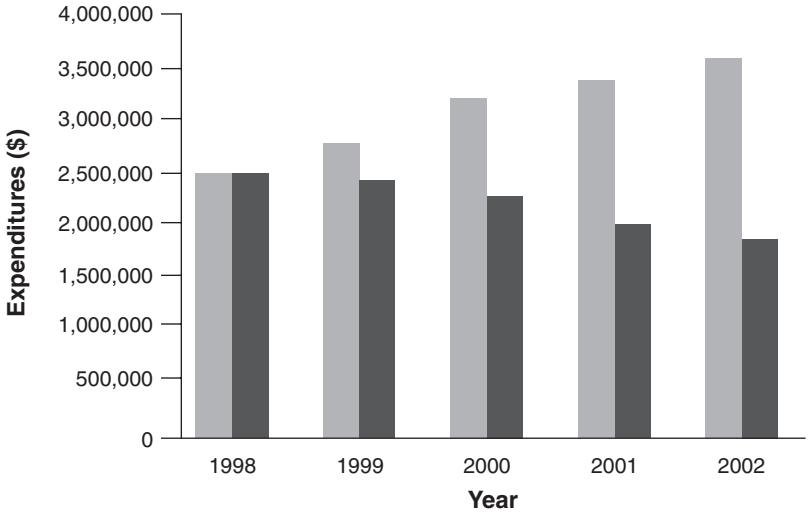


Figure 2. Patients with multidrug-resistant *Pseudomonas aeruginosa* isolates. Multidrug-resistant was defined as susceptible to one or none of the following agents: piperacillin–tazobactam, cefepime, ceftazidime, aztreonam, meropenem, imipenem, tobramycin, gentamicin, amikacin, ciprofloxacin, and levofloxacin. Duplicate patients were excluded.

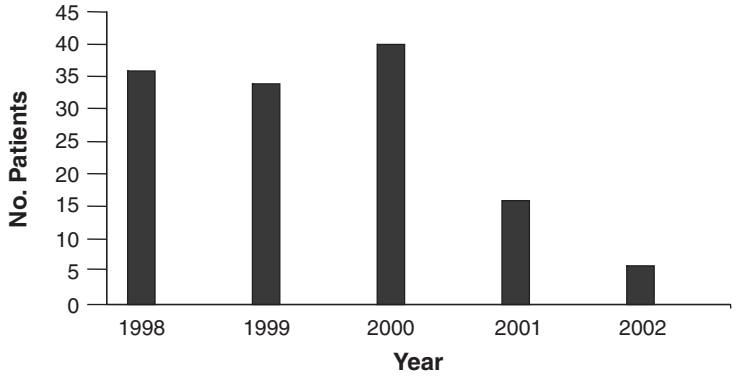
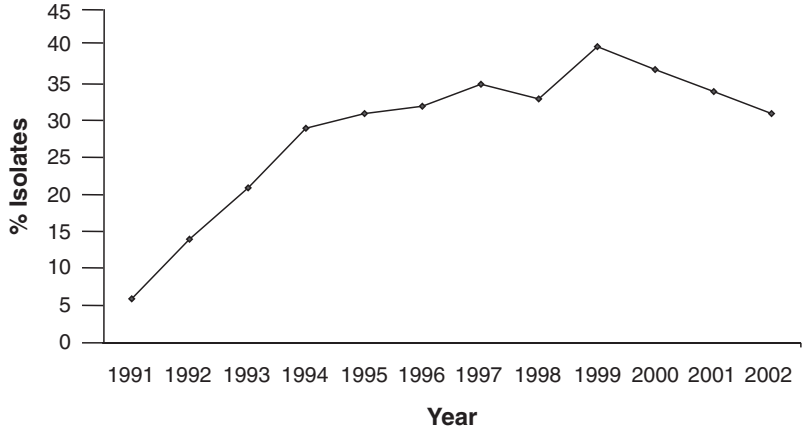


Figure 3. Percentage of all *Staphylococcus aureus* isolates resistant to methicillin.



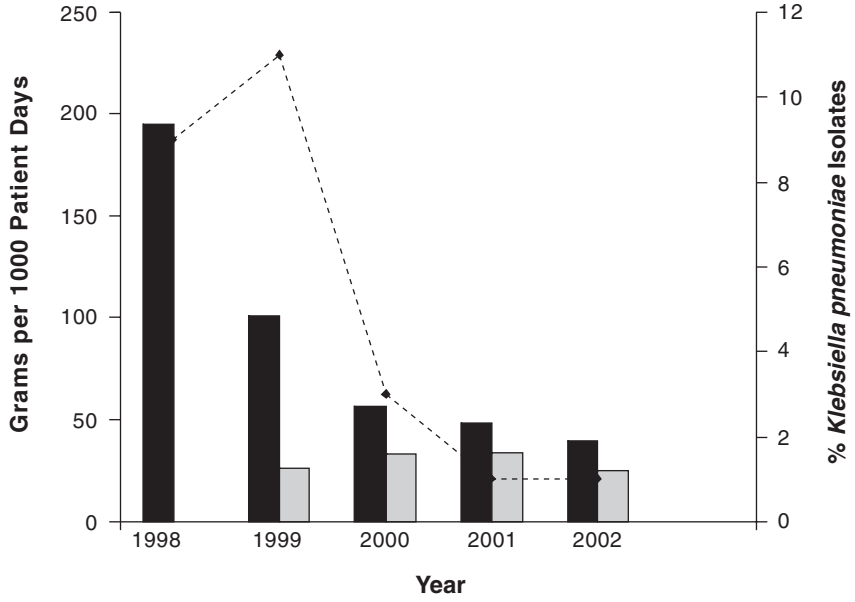
Ceftazidime resistance decreased dramatically after ceftazidime was removed from the formulary.

Discussion

The key objectives of our antimicrobial control program were accomplished with variable degrees of success. The program led to a reduction in the use of selected antimicrobials over the five-year period. Most striking was the decrease in the use of third-generation cephalosporins. This intervention was deemed the most crucial, given the well-documented history of the effect of these agents on antimicrobial flora and resistance rates. As has been reported in other institutions, the reduction in the use of these agents resulted in a dramatic decrease in ceftazidime resistance in *K. pneumoniae* isolates.[2,5] This phenomenon is important because it implies extended-spectrum β-lactamase production, prompting clinicians to increase the use of carbapenems due to the risk of increased rates of multidrug-resistant gram-negative bacteria, including *P. aeruginosa* and *A. baumannii*.[2,23,25,26,29]

Much thought and discussion have been devoted to the effects of antimicrobial restriction of certain classes or agents in favor of others. While antimicrobial use in general can be reduced to an extent, the restriction of some agents typically leads to increases in the use of unrestricted classes of antimicrobials. The most obvious example of this phenomenon at our institution is the increased use of piperacillin–tazobactam in response to the removal of ceftazidime and cefotaxime from the formulary. The key to minimizing the impact of this substitution on susceptibility rates is to select the agent least likely to promote resistance. Multiple reports have illustrated the positive effect of substituting piperacillin–tazobactam for third-generation cephalosporins on various bacteria.[2,4,8,9,22] Some authors have suggested that an open formulary allows for heterogeneity

Figure 4. Defined daily doses per 1000 patient days of third-generation cephalosporins (black bars) and cefepime (gray bars) purchased compared with ceftazidime-resistant *Klebsiella pneumoniae* isolates (dashed line).



of antimicrobial use and avoids significant increases in the use of any one class of agents.[30]

Our institution also observed a 3% decrease in the rate of methicillin-resistant *S. aureus* from 1999 through 2002, a reversal of the trend seen throughout the 1990s. Although we cannot definitively determine the interventions that may have caused this decrease, third-generation cephalosporins have been implicated in the selection of methicillin-resistant *S. aureus*,[4] as has ciprofloxacin.[13,15,17]

The most dramatic outcome observed in this antimicrobial control program has been in cost savings to the institution. In an era of decreasing reimbursement and increasing health care costs, most institutions are challenged by budget restrictions, and pharmacy costs are certainly no exception. The implementation of our antimicrobial control program was associated with a significant reduction in antimicrobial expenditures. Using the most conservative of estimates and assuming no inflation of drug costs, we saved more than $1,400,000 cumulatively over the five-year period analyzed. When 10% inflation is introduced and expenditures are standardized to inpatient days, the estimated saving increases dramatically to more than $4,400,000. In addition to normal inflation, we did not consider the availability of new, expensive antimicrobials, such as quinupristin–dalfopristin and linezolid. We view this savings as significant, given that no new personnel were added to support this program until 2001. Not all of the reduction in antimicrobial expenditures can be attributed to decreased use of antimicrobials. As we have previously described elsewhere, selection of single agents within a therapeutic class can have a dramatic impact on contract pricing.[20] For example, nearly all of our fluoroquinolone cost savings was due to the endorsement of levofloxacin as the sole fluoroquinolone on our formulary. We have similarly adopted amphotericin B lipid complex (Abelcet, Liposome, Princeton, NJ) as our sole lipid formulation of amphotericin B on the formulary.

Our results are consistent with previous studies showing that a well-designed and well-implemented antimicrobial control program can lead to substantial cost savings.[31-36] As at our institution, most of the financial gains in these studies resulted from intervention policies that reduced the number of antimicrobials.[37-40]

Our analysis of the program's success has some obvious limitations. First, most of the data have been collected through retrospective review. There are, therefore, data points that are simply unavailable or require additional analysis. For instance, we only began routinely performing susceptibility testing for levofloxacin in 2001. In addition, we believe that susceptibility reporting for specific intensive care or other patient care units is extremely important, but we only began such reporting in 2001. The largest limitation of this analysis is the fact that, to date, we have yet to analyze the clinical outcomes (e.g., clinical success, length of stay) before and after the implementation of these interventions. We are currently evaluating the impact of many of our policies on clinical outcomes related to specific disease states, but those results have not been analyzed.

We attribute the success of our program to several factors. First, the program was largely conceived and implemented by a multidisciplinary team effort. Identification of the need for intervention evolved as a result of close collaboration between ID physicians, clinical pharmacists, and physicians on medical and surgical services who were concerned about risk of resistant pathogens and antimicrobial expenditures. The antimicrobial subcommittee consulted extensively with faculty in the ID division, infection control practitioners, hospital administrators, representatives of the clinical microbiology laboratory, and clinical pharmacists. In addition, significant input was obtained from physicians working on clinical services, especially those who prescribed large numbers of antimicrobial agents, including those on the

critical care and transplant teams. These consultations facilitated physicians' acceptance of the subcommittee's recommendations. Second, periodic feedback to prescribing physicians about the benefits of our program reinforced their acceptance of it. Third, the goals of our program were focused; interventions were targeted only at antimicrobials that had the potential for inappropriate use as determined by a previous internal review. As a result, our program was not perceived as punitive or as unnecessary interference with physicians' autonomy.

Because of the ongoing success of this program, we have obtained institutional support for a full-time clinical pharmacist and a half-time ID physician to comprise the antimicrobial management team, whose responsibilities include monitoring antimicrobial use and resistance, educating clinicians about the rationale for antimicrobial restrictions, evaluating new antimicrobials for formulary inclusion, and organizing meetings of the antimicrobial subcommittee. The team currently accomplishes these goals in several ways, including the use of a pocket reference for clinicians at our institution, the *University of Kentucky Guide to Empiric Antimicrobial Therapy*. This pocket guide, the principal educational tool used by the team, includes treatment guidelines for commonly encountered infections (e.g., CAP, meningitis, endocarditis, urinary tract infections). It combines available national guidelines, expert clinical experience, and our local formulary and includes antimicrobial susceptibilities. The guide was first published in July 2002 and distributed to all physicians (faculty, interns, residents, and fellows), nurse practitioners, physician assistants, pharmacists, and medical students. We are currently evaluating the guide's effects on clinician prescribing habits. In 2002, the antimicrobial management team developed a Web-based information source for University of Kentucky practitioners (www.hosp.uky.edu/pharmacy/amt). This program, while still in its early stage, has proven extremely helpful for clinicians in selecting the appropriate antimicrobial for their patients. Its contents include a link to an electronic copy of the *University of Kentucky Guide to Empiric Antimicrobial Therapy,* the hospital antibiogram, formulary antimicrobials and applicable restrictions, and links to national guidelines, organizations, and key ID-related journals.

Conclusion

The implementation of an antimicrobial control program decreased the use of selected antimicrobial agents and resulted in substantial reduction of expenditures for antimicrobials.

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