Original Article

Antimicrobial Stewardship in a Community Hospital: Attacking the More Difficult Problems

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ABSTRACT

Background: Antibiotic stewardship has been proposed as an important way to reduce or prevent antibiotic resistance. In 2001, a community hospital implemented an antimicrobial management program. It was successful in reducing antimicrobial utilization and expenditure. In 2011, with the implementation of a data-mining tool, the program was expanded and its focus transitioned from control of antimicrobial use to guiding judicious antimicrobial prescribing.

Objective: To test the hypothesis that adding a data-mining tool to an existing antimicrobial stewardship program will further increase appropriate use of antimicrobials.

Design: Interventional study with historical comparison.

Methods: Rules and alerts were built into the data-mining tool to aid in identifying inappropriate antibiotic utilization. Decentralized pharmacists acted on alerts for intravenous (IV) to oral conversion, perioperative antibiotic duration, and restricted antimicrobials. An Infectious Diseases (ID) Pharmacist and ID Physician/Hospital Epidemiologist focused on all other identified alert types such as antibiotic de-escalation, bug-drug mismatch, and double coverage. Electronic chart notes and phone calls to physicians were utilized to make recommendations.

Results: During 2012, 2,003 antimicrobial interventions were made with a 90% acceptance rate. Targeted broad-spectrum antimicrobial use decreased by 15% in 2012 compared to 2010, which represented cost savings of \$1,621,730. There were no statistically significant changes in antimicrobial resistance, and no adverse patient outcomes were noted.

Conclusions: The addition of a data-mining tool to an antimicrobial stewardship program can further decrease inappropriate use of antimicrobials, provide a greater reduction in overall antimicrobial use, and provide increased cost savings without negatively affecting patient outcomes.

Key Words—antimicrobial stewardship, data-mining tool, patient outcome metrics, process metrics, recommendations

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Antibiotic stewardship has been proposed as an important way to reduce antibiotic resistance and preserve the limited armamentarium of antibiotics. In many hospitals, antibiotic steward-

ship programs were implemented in response to an outbreak caused by multidrug-resistant (MDR) organisms. In 2001, Texas Health Presbyterian Hospital of Dallas implemented a Comprehensive Antimicrobial

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Management Program (CAMP) in the absence of an outbreak of MDR infections. It was conceived as a quality improvement project to address the growing concerns of antibiotic misuse.¹ Inappropriate antibiotic prescribing is a major concern as rates of health care–associated infections and antimicrobial resistance continue to rise. It has been estimated that up to 50% of antimicrobial use is inappropriate.² Prior to September 2011, interventions by CAMP were limited to conversion from intravenous (IV) to oral administration for highly bioavailable antimicrobials; discontinuation of perioperative antimicrobial prophylaxis at 24 hours for clean and clean-contaminated surgical procedures; and restriction of use of antibiotics that have a high risk for adverse events, have a high potential to promote resistance, or are expensive. Inappropriate utilization was not analyzed due to limited resources.

This program was successful in reducing antibiotic expenditures and was associated with modest improvements in antibiotic susceptibility.¹ However, it was largely noninterventional for monitoring antibiotic choice; it relied on physicians to voluntarily comply with policies on “restricted antibiotics.” After publication of the 2007 Infectious Disease Society of America (IDSA) practice guideline on antibiotic stewardship, it became clear that a more interventional program with rapid feedback was needed to ensure optimal use of antibiotics.³ With the advent of data-mining programs (eg, *Sentri7*, *TheraDoc*, *SafetySurveillor*) that interface with electronic health records (EHRs), it became possible to survey, in real-time, multiple different antibiotics, culture results, and clinical diagnoses. In *Sentri7*, the Infectious Disease (ID) Pharmacist has the administrative capability to create rules without the need for external or hospital information technology (IT) support. Currently, our EHR cannot data mine clinical microbiology information, and any additional rule build would require IT programming. Kullar and colleagues describe several other limitations with their EHR (*EPIC*).⁴

INCORPORATING TECHNOLOGY

In June 2007, our institution implemented an EHR (*EPIC*, Madison, WI), including computerized physician order entry (CPOE). In 2011, CAMP was expanded to transition its focus from restricting antimicrobial use by requiring infectious diseases consultation to aiding judicious antimicrobial use, with interventions made as close to real-time as possible. Best practice alerts were not provided by the EHR. Addition of a data-mining tool (*Sentri7*;

PharmacyOneSource, Madison, WI) to the EHR created an efficient method to directly focus on inappropriate antibiotic-prescribing patterns. Criteria were developed to quickly identify and address opportunities for antibiotic streamlining, bug-drug mismatches, inappropriate double antibiotic coverage, and unwarranted antibiotic therapy. This permitted ongoing audit with intervention and direct feedback to physicians via EHR communication and/or phone calls as necessary. The goals of our program are to improve patient outcomes, improve patient safety, reduce costs, and minimize antimicrobial resistance.

INCORPORATING STRATEGY

Texas Health Presbyterian Hospital of Dallas is a not-for-profit, 890-bed community teaching hospital that includes 48 intensive care unit beds and has residents in medicine, surgery, obstetrics-gynecology, and psychiatry. In 2012, the hospital had 27,264 admissions and performed 7,069 inpatient and 5,826 outpatient surgeries. The emergency department had 83,566 visits. The data-mining tool was purchased and implemented by the pharmacy department to streamline workflow by identifying inappropriate antibiotic utilization. This tool fired alerts to the CAMP team when it identified patients with the institution’s 5 most commonly isolated bacterial pathogens, patients who were prescribed broad-spectrum antimicrobials, patients who had received antibiotics for more than 5 days, patients who had bug-drug mismatches, and patients for whom there was an opportunity to streamline to a narrower spectrum antibiotic. These alerts were presented in a dashboard format for ID Pharmacist review. The ID Pharmacist performed the initial screening of these alerts and determined the appropriateness of antibiotic use. There were 20 to 25 cases per day, of which 5 to 10 were referred to the ID Physician/Hospital Epidemiologist for further review. (See box, “Definitions of Antimicrobial Stewardship Intervention Types” for CAMP-defined intervention types.)

In the original CAMP, all components were performed by the ID Pharmacist. Gradually these responsibilities (IV to oral conversions, perioperative antibiotic duration, and use of restricted broad-spectrum antimicrobials) were transitioned to the decentralized pharmacists in addition to their responsibilities for processing medication orders to ensure proper dosing and safety. The hospital’s Pharmacy and Therapeutics Committee approved criteria for the pharmacists to automatically convert antibiotics from IV to oral and to discontinue postoperative

Definitions of Antimicrobial Stewardship Intervention Types

Antibiotic De-escalation: Streamline to a narrower spectrum antibiotic based on culture and susceptibility data

Antibiotic Dose Optimization: Optimize antimicrobial dose based on pharmacokinetic/pharmacodynamic parameters, causative organisms, and site of infection

Antibiotic Double Coverage: Inappropriate double gram-positive, gram-negative, or anaerobic coverage

Antibiotic Duration: Prolonged surgical prophylaxis or therapy that exceeds the recommended evidence-based duration of treatment

Antibiotic Recommendation: Recommendation to start antibiotic, based on documented diagnostic or clinical signs and symptoms of infection and culture reports

Bug-Drug Mismatch: Organism isolated is resistant to antibiotic prescribed

Inappropriate Therapy: Empiric or directed antibiotic therapy started in the absence of documented diagnostic or clinical signs and symptoms of infection and culture reports

Restricted Antimicrobial: Requires consultation by an Infectious Diseases physician to facilitate appropriate utilization

prophylactic antibiotics. By 2011, the ID Pharmacist and ID Physician/Hospital Epidemiologist were able to focus comprehensively on all new CAMP intervention types, such as antibiotic de-escalation and bug-drug mismatches, which had not been possible prior to the implementation of the data-mining tool. Our stewardship team rounded daily, Monday through Friday. All recommendations were supported by evidence-based guidelines, when they existed, or by professional experience and were communicated to the prescribing physicians by electronic chart notes and/or phone calls. Follow-up on recommendations was performed by the ID Pharmacist within 24 hours, thereby allowing 48 hours for acceptance. The outcome was placed in *Quantifi*, a PharmacyOneSource Web-based clinical intervention documentation and reporting tool.

METHODS/STATISTICAL ANALYSIS

Cases analyzed in this program were hospital inpatients discharged during 2010 and 2012. Both 2010 and 2012 cohorts were filtered for the specific ICD-9 (*International Classification of Diseases, Ninth Revision*) principal diagnoses of pneumonia (community acquired and health-care associated), cellulitis, and urinary tract infection (UTI). The 2012 population was further analyzed to isolate cases where a CAMP intervention had been performed.

To evaluate the impact of our CAMP, we used quality metrics as defined by a 10-member expert panel from Canada and the United States.⁵ These quality metric indicators included antimicrobial consumption, antimicrobial resistance, and patient outcome measures. Data collected for these cases included

length of stay (LOS) in days, mortality determined by discharge disposition, diagnosis-related group (DRG) weight for use in computing case mix index (CMI), same-cause readmission (SCR) within 30 days of a prior admission based on the principal diagnosis, and direct cost of antimicrobials.

Because of disparities in size of the 2010 and 2012 populations, the populations were case mix adjusted using DRG weights. The American Hospital Directory describes the CMI as “the average relative weight for all cases reported in a Base MS-DRG” (Medicare Severity-Diagnosis Related Group).⁶ MS-DRGs at lower severity levels have lower relative weights and MS-DRGs at higher severity levels have higher relative weights. The CMI provides an index of patient mix among levels of acuity within a Base MS-DRG (http://www.ahd.com/definitions/ip_ms-drg.html). Mortality and SCR are then divided by this CMI to create a measure that is not influenced by population-specific acuity measures. The resulting numbers are referred to as CMI-adjusted numbers.

Pharmacy databases were used to obtain antimicrobial acquisition costs and data on antimicrobial doses charged to patient accounts, reflecting actual antibiotic utilization. 2013 antimicrobial costs were used for both 2010 and 2012 populations so that inflation would not affect the analysis.

The days of therapy (DOT) per 1,000 patient-days of targeted antimicrobials in the preimplementation period (2010) and postimplementation period (2012) were compared using unpaired *t* tests. DOT is defined as “the aggregate sum of days for which any amount of a specific antimicrobial agent was administered to an individual patient as documented in the electronic

medication administration record" (eMAR).⁷ Mortality, LOS, and SCR were compared using paired *t* tests. All statistical tests were 2-tailed. *P* values less than .05 were considered statistically significant. Statistical calculations were performed using Microsoft *Excel* 2010 and *GraphPad Prism*, version 6.

RESULTS (PROCESS METRICS)

Interventions

During 2012, the CAMP team made a total of 2,003 clinical interventions. Table 1 lists the number and types of recommendations. We allowed 48 hours in most cases to determine response to recommendations. Physicians accepted and acted upon 90% of our recommendations. Intravenous to oral switch of antibiotics and reminders to physicians of restricted antibiotics were not included in this

analysis, as the decentralized pharmacists performed these functions. The most common recommendations were for prolonged antibiotic duration (19.1%), antibiotic de-escalation (15.6%), and antibiotic recommendation (11%), respectively (Table 1). Seventy-five percent of CAMP antibiotic duration interventions were for prolonged treatment regimens, and 25% were for prolonged surgical prophylaxis. The existence of electronic postoperative order sets predominantly helped ensure timely discontinuation of surgical prophylaxis. This 25% reflected either manipulation of antibiotic duration within the order set or absence of order set use.

Antimicrobial Use and Cost

We evaluated DOT per 1,000 patient-days for targeted broad-spectrum antibiotics (Table 2). Use decreased by 15% from 282.8 DOT per 1,000

Table 1. Rate of acceptance of antimicrobial stewardship recommendations post implementation of program (January - December 2012)

Intervention	No. of accepted recommendations/suggestions (%)
Bug-drug mismatch	21/21 (100)
Antibiotic recommendation	209/220 (95)
Antibiotic de-escalation	297/313 (94.9)
Antibiotic dose optimization	204/215 (94.9)
Antibiotic double coverage	87/95 (91.6)
Antibiotic duration	350/382 (91.6)
Inappropriate empiric therapy	66/74 (89.2)
Restricted antimicrobial	521/612 (85.1)
Inappropriate directed therapy	56/71 (78.9)
Total	1,811/2,003 (90.4)

Table 2. Days of therapy per 1,000 patient-days of targeted broad-spectrum antimicrobials: pre vs post implementation

Antimicrobials	Pre implementation 2010	Post implementation 2012	Mean difference (95% CI)	<i>P</i>
Daptomycin	24.3	6.0	18.3 (14.1 to 22.5)	.0001
Quinolones	87.3	70.0	17.3 (10.9 to 23.8)	.0001
Carbapenems	34.2	27.9	6.3 (2.4 to 10.2)	.0029
Linezolid	13.9	7.7	6.2 (4.2 to 8.2)	.0001
Tigecycline	6.2	1.4	4.8 (3.4 to 6.2)	.0001
Piperacillin/tazobactam	44.6	44.4	0.2 (−3.9 to 4.3)	.0978
Vancomycin	72.3	83.6	−11.3 (−17.9 to −4.5)	.0022
Total	282.8	241.0		

*Determined by Student *t* test. Statistically significant at *P* < .05.

Table 3. Cost of targeted broad-spectrum antimicrobials (dollars): pre vs post implementation

Antimicrobials	Pre implementation 2010	Post implementation 2012	Savings
Daptomycin	1,213,798	273,996	939,802
Carbapenems	502,053	234,643	267,410
Linezolid	480,413	250,327	230,086
Tigecycline	163,159	34,655	128,504
Quinolones	142,462	95,075	47,387
Piperacillin/tazobactam	186,306	173,941	12,365
Vancomycin	101,799	105,623	-3,824
Total	2,789,990	1,168,260	1,621,730

patient-days in the preimplementation period to 241 DOT per 1,000 patient-days in the postimplementation period, which represents a cost savings of \$1,621,730 (Table 3). The overall cost of nontargeted drugs (such as aminoglycosides, aminopenicillins including ampicillin-sulbactam, antifungals, cephalosporins, and macrolides) decreased by \$314,142. However, these savings were driven by a decrease of \$324,333 in antifungal costs due to our hospital system's contract pricing for echinocandins. The cost of nontargeted antibacterials increased by \$10,191, which would be expected when recommendations to de-escalate therapy are made. Assuming that the majority of interventions for duration (350), double coverage (87), and inappropriate therapy (122) resulted in discontinuation of antibiotics, a total of 559 out of 1,811 (31%) interventions resulted in discontinuation. This compares with 297 out of 1,811 (16%) interventions that led to de-escalation. Thus, overall antimicrobial costs decreased by \$1,935,872 in the post-implementation period, representing a 55% decrease in antimicrobial expenditures.

RESULTS (PATIENT OUTCOMES METRICS)

Antimicrobial Susceptibility and Resistance

To evaluate the impact of changes in antimicrobial use on bacterial resistance, we focused on 5 isolates: *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus mirabilis*, and methicillin-resistant *Staphylococcus aureus* (MRSA). The isolates were further evaluated by source (urine vs non-urine) and the location of the patient at the time the culture was obtained (intensive care units vs non-intensive care units). We analyzed the susceptibility of these organisms to 4 antimicrobials targeted by CAMP (levofloxacin, meropenem, piperacillin-tazobactam, and vancomycin). Although inconsistent year-to-year variations in susceptibility patterns were noted,

none proved to be statistically significant using the Clinical and Laboratory Standards Institute M39-A3 standards.^{8,9} This was likely due to relatively small numbers of isolates and changes in susceptibility.

Impact on mortality, LOS, and SCR

To ensure that reductions in antibiotic usage were not associated with adverse patient outcomes, we looked for changes in mortality, LOS, and same cause readmission between the 2 cohorts. In addition, CMI-adjusted mortality and SCR and direct cost of antibiotics were calculated.

For cellulitis, the mortality rate was too low to analyze (0 of 310 in the 2010 cohort compared to 1 of 206 in 2012). There was a borderline increase in LOS in 2012 (6.05) compared to 2010 (5.18) ($P = .0562$). The direct antibiotic cost per day in 2012 (\$51.04) was significantly lower than in 2010 (\$65.64) ($P = .0056$).

For community-acquired pneumonia, crude mortality increased from 28/393 (7.1%) in 2010 to 10/112 (8.9%) in 2012 ($P = .0051$). However, when mortality was CMI adjusted, it decreased from 19.69 to 5.99 ($P = .003$). Crude and CMI-adjusted SCR both decreased from 6/393 (1.5%) (CMI adjusted 4.69) to 1/112 (0.8%) (CMI adjusted 0.4422) ($P = .0086$). Direct antibiotic costs per day were unchanged. For health care-associated pneumonia, there were no significant differences in crude mortality, CMI-adjusted mortality, LOS, SCR, or direct antibiotic costs per day.

For UTIs, the mortality rate was too low to analyze (1/402 in 2010 compared to 1/85 in 2012). LOS was identical. SCR increased from 7/402 (1.7%) to 2/85 (2.35%) ($P = .0086$). However, when CMI adjusted, it decreased from 7.45 to 1.85 ($P = .016$). The clinical significance of such change is uncertain because of the small numerical changes. Direct antibiotic costs per day were unchanged.

Although the small number of patients precluded any conclusions, there was no diagnosis for which actual or adjusted mortality, LOS, SCR, or direct antibiotic cost all increased.

DISCUSSION

We instituted CAMP in 2001 at a time when there was less concern about the selection of MDR organisms and there were few published models for antibiotic stewardship. Although the success of this program was gratifying, it lacked audit of antimicrobial use and feedback to prescribers as advocated by IDSA.³ With the availability of a data-mining program, it became possible to construct rules for screening cases by diagnosis, microorganism, antibiotic, and duration of therapy, which in turn allowed prompt feedback to prescribing physicians.

Several patterns of antibiotic misuse emerged from this program. The vast majority were overuse of broad-spectrum agents when a narrow spectrum agent was appropriate and excessive duration of antibiotics. There were a few situations in which we had to recommend higher doses or more active antibiotics. Occasionally we informed physicians of an unrecognized infection for which treatment was indicated but had not been given.

For 7 of the most commonly used or costly drugs or classes of drugs (daptomycin, carbapenems, piperacillin/tazobactam, quinolones, tigecycline, linezolid, vancomycin), there were remarkable 1-year cost savings totaling almost 1.7 million dollars, comparing 2010 to 2012. However, some of the daptomycin savings cannot be attributed to our interventions, because the physician who was the primary user left the institution. Also, there was a correction in the laboratory methodology for vancomycin minimum-inhibitory concentration (MIC) testing on MRSA, resulting in a dramatic reduction in frequency of vancomycin MICs of 2 or more, one of the major indications for daptomycin.^{10,11} Because of the reduction in the use of linezolid, daptomycin, and tigecycline for the treatment of MRSA infections, there was the expected increase in vancomycin usage. Despite the reduction in use of carbapenems and quinolones, remarkably there was no increase in the use of piperacillin/tazobactam. When the costs of nontargeted antimicrobials are included, the overall 1-year cost reduction of greater than 1.9 million dollars has not been demonstrated in any other program, to the best of our knowledge.^{12,13}

Although dramatic savings in antibiotic expenditure and usage occurred, there was no improvement in antibiotic susceptibility in the first full year of

implementation. This was not surprising because the baseline level of resistance was not high, and it likely takes more than 1 year to have an effect on the microbial ecosystem of a large hospital. To demonstrate statistically significant changes in antimicrobial susceptibility, either large numbers of isolates are needed or there need to be dramatic changes in susceptibility of smaller numbers of isolates. Neither of these criteria was met. Of note, there were also no significant changes in susceptibility among the nontargeted antibiotics.

Strengths of the program included greater than 90% compliance with our recommendations despite the lack of any leverage to require implementation; consistent reductions in usage and cost of antibiotics across multiple classes of drugs and in multiple diagnoses; and documentation of no consistent adverse effects on mortality, LOS, or SCR. The use of CMI adjustment clarified the lack of any adverse effects on outcomes.

A number of weaknesses of the program were identified. First, reporting after only 1 year of implementation might be considered premature. Second, we did not attempt to measure the impact on the frequency of *C. difficile* or MRSA infections. Finally, small numbers of outcomes precluded meaningful comparisons of benefits or harms attributable to our program other than cost savings.

There were also several weaknesses in communication: Our pharmacy communication notes were not always in conspicuous locations in the EHR and were often not noticed by busy physicians; those physicians who made rounds early in the day did not see the EHR communication notes until the next day, making timely responses less likely; and phone calls to doctors' offices were intrusive and time consuming for both parties. Texting to physicians' cell phones would be a quicker and less obtrusive way to communicate recommendations, but this is not compliant with the Health Insurance Portability and Accountability Act (HIPAA) without special provisions. We are investigating the development of a HIPAA-compliant "smart phone" application that would allow nurses and pharmacists to communicate directly with physicians and improve the timeliness of responses.

It must be acknowledged that implementing a program such as ours requires a significant upfront investment, is very labor intensive, and requires a complex data-mining program. EHRs are not necessarily capable of data mining. Not all institutions have the resources to allow the pharmacy to devote a full-time

employee to antibiotic stewardship. Many institutions struggle to justify funding for a data-mining tool and for the physician champion. Even fewer institutions have a physician able and willing to commit the time and effort to review data and offer recommendations. In addition, such “free consultations” could be harmful to a physician’s medical practice, either by reducing requests for consultation or alienating referring physicians by offering unsolicited recommendations. In our institution, practitioners in the dominant ID physician group who were not a part of the CAMP observed no reduction in consults (personal communication, November 2013). In retrospect, we were able to secure the resources needed based on our program’s previous successes coupled with use of data from drug use evaluations to prospectively estimate the likely return on investment.

The availability of a data-mining program was essential to the success of our program. Manual review of the EHR to identify those patients on targeted antibiotics would have been prohibitively time consuming. Although the annual cost of such a program is daunting (\$100,000 for software, \$114,400 for the PharmD [1 FTE], and \$71,300 for the physician [.31 FTE]), the return on investment of 7:1 (\$1.9 million) in the first year more than made up for the costs. It is important to note that future savings are likely to be incrementally less year after year as physicians’ prescribing patterns change in response to our consistent recommendations for their patients.

For hospitals with fewer resources, there are still options available to improve antibiotic utilization.^{14,15} Examples include IV to oral conversions by pharmacists, stopping prophylactic perioperative antibiotics at 24 hours or sooner, and requiring indications on prescriptions for antibiotics. When there is no ID physician affiliated with the hospital, options might include contracting with such a physician at a remote site to assist the pharmacy department in implementation of a restricted formulary. If properly indemnified and compensated, such a physician might also provide consultations to other physicians via phone or e-mail. Also, pharmacists without specialized training in ID can complete a stewardship certification program through organizations such as Making a Difference in Infectious Diseases (MAD-ID) Pharmacotherapy or the Society of Infectious Diseases Pharmacists (SIDP).^{16,17}

Antibiotic stewardship is likely to become a required component of hospital quality improvement programs. Therefore, all hospitals will be working to control the escalating misuse of antibiotics and to prevent its consequences, such as multidrug resis-

tance and *C. difficile* infection. The addition of a data-mining tool to an antimicrobial stewardship program can further decrease inappropriate use of antimicrobials, provide a greater reduction in overall antimicrobial use, and provide increased cost savings without negatively affecting patient outcomes. Going forward, we would like to further expand the role of our decentralized pharmacists with additional training in the newer CAMP intervention types. We would also like to use our experience to “systematize” antimicrobial stewardship across our entire hospital system – Texas Health Resources – which is composed of 14 community hospitals of varying sizes and patient types.

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