PRACTICE REPORT

Clinical and economic outcomes of a prospective antimicrobial stewardship program

MICHAEL A. NOWAK, ROBERT E. NELSON, JESSE L. BREIDENBACH, PAUL A. THOMPSON, AND PAUL J. CARSON

Purpose. A pre–post analysis of an antimicrobial stewardship program (ASP) involving the use of data-mining software to prospectively identify cases for ASP intervention was conducted.

Methods. The investigators evaluated clinical outcomes and cost metrics before and after implementation of the ASP, which entailed daily physician review of summary reports on all adult inpatients receiving antimicrobial therapy. The primary outcome measures were annual antimicrobial expenditures and rates of infections due to common nosocomial pathogens; secondary outcome measures included patient survival and length of stay (LOS) in cases involving the indicator diagnoses of pneumonia and abdominal sepsis.

Results. Antimicrobial expenditures, which had increased by an average of 14.4% annually in the years preceding ASP implementation, decreased by 9.75% in the first year of the program and remained relatively stable in subsequent years, with overall cumulative cost savings estimated at $1.7 million. Rates of nosocomial infections involving *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus,* and vancomycin-resistant enterococci all decreased after ASP implementation. A pre–post comparison of survival and LOS in patients with pneumonia (n = 2186) or abdominal sepsis (n = 225) showed no significant differences in those outcomes in either patient group, possibly due to the hospital's initiation of other, concurrent infection-control programs during the study period.

Conclusion. A prospective collaborative ASP employed automated reports to efficiently identify key data for ASP review. After ASP implementation, antimicrobial expenditures and rates of nosocomial infections caused by resistant pathogens dropped without significant changes in patient survival, LOS, and readmissions for the two studied illness categories.

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Health care-associated infections affect nearly 2 million people in the United States annually.[1] It has been suggested that over one third of these infections are preventable.[2] Over the last several decades, antimicrobial-resistant organisms have been responsible for an increasing percentage of nosocomial infections.[3-5] Infections involving resistant pathogens have been shown to increase hospital length of stay (LOS), costs, and mortality.[6-10] The World Health Organization (WHO) has labeled antimicrobial resistance as one of the three greatest threats to human health. However, the current antibiotic development pipeline offers little hope for improvement over current treatment options in the near future.[11-14]

While a direct relationship between antibiotic use and the sub-

MICHAEL A. NOWAK, PHARM.D., BCPS, is Assistant Professor of Clinical Science, College of Pharmacy, California Northstate University, Rancho Cordova; at the time of writing he was Pharmacy Practice Resident, Sanford Medical Center, Fargo, ND. ROBERT E. NELSON, PHARM.D., BCPS-ID, is Regional Medical Scientist, ViroPharma Incorporated, Fargo, ND; at the time of writing he was Pharmacy Clinical Manager, Sanford Medical Center. JESSE L. BREIDENBACH, PHARM.D., is Director of Acute Care Pharmacy, Sanford Medical Center, Fargo, ND. PAUL A. THOMPSON, PH.D., is Director of Methodology and Data Analysis Center, Sanford Research and University of South Dakota, Sioux Falls. PAUL J. CARSON, M.D., is Chairman, Department of Infectious Disease and Pulmonary Medicine, and Director of Research, Sanford Medical Center.

Address correspondence to Dr. Nowak at the College of Pharmacy, California Northstate University, 10811 International Drive, Rancho Cordova, CA 95670 (mnowak@calpharm.org).

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sequent development of resistance is widely accepted, the majority of antibiotic use continues to be regarded as inappropriate.[15-17] In spite of a number of authors and organizations expressing concern about the inappropriate use of antibiotics over the last decade or more,[18-20] little change in prescribing behaviors has been observed over this period.[21-23] Recognizing that the effects of antimicrobial resistance adversely impact all health care settings, good stewardship over the use of antimicrobials has been identified as a key strategy to control the emergence and transmission of antimicrobial-resistant organisms.[12,20,24,25]

The term *antimicrobial stewardship* refers to a multidisciplinary approach to selecting the optimal drug, dosage, and duration of therapy that will result in the best clinical outcome for the prevention or treatment of infection, with minimal toxicity to the patient and minimal development of resistance.[20]

In 2007 the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America published guidelines on the development of antimicrobial stewardship programs (ASPs) within health care institutions.[20] These guidelines support the use of a physician specialist in infectious diseases (ID) and a clinical pharmacist with ID training as core ASP members. ID physicians and pharmacists are optimally positioned in the patient care process to control inappropriate antimicrobial use within health care institutions.[26] ID physician and pharmacist review of anti-infective therapy could help to reduce common errors, including use of an agent with an inappropriate spectrum, prescribing of antibiotic medications when there is little evidence of bacterial infection, unnecessarily prolonged courses of therapy, and overuse of i.v. agents.

Numerous studies have demonstrated that ASPs may both confer a financial benefit and increase the susceptibility of pathogens to specific antimicrobial classes in the laboratory.[27-30] However, the primary goal of any stewardship effort is optimal antimicrobial treatment for the patient, with subsequent improvement of clinical outcomes; to date, few studies have demonstrated such benefits. Gross et al.[31] demonstrated an ASP-associated improvement in cure rates and a decline in failure rates in 180 hospitalized patients. Select studies have shown significant reductions in LOS and reduced infection-related mortality with ASP use.[32,33] Likewise, a small number of ASPs have been demonstrated to have a favorable impact on the frequency of nosocomial infections.[34-36] These reductions in infections may be more relevant to clinical practitioners than the commonly described improvements in laboratory susceptibilities. Improvements in pathogen susceptibilities to specific antimicrobial classes in vitro may simply be "squeezing the resistance balloon"; that is, they may be accompanied by declines in susceptibility to other agents.[37-39]

While a number of studies have shown benefits resulting from ASP implementation efforts, the results have been quite variable, a reflection of the fact that nearly all stewardship efforts are unique in their design and application, making comparisons difficult. A prospective, interventional review of every patient receiving antimicrobials may provide the best option for achieving the goals of any ASP; however, such programs are also likely to require the most resources. In the study described here, we evaluated the clinical and economic outcomes of a comprehensive prospective program that made efficient use of limited human resources by relying on automated reports generated from the electronic medical record (EMR) via data-mining software.

Background

Sanford Medical Center Fargo is an integrated tertiary care referral center consisting of a network of clinics and providers in three states that refer patients to a large community teaching hospital in the upper Midwest. The hospital has 583 beds and an average daily census of 312 patients. Yearly, the system encounters over 17,000 surgical cases, nearly 52,000 emergency department visits, and over 25,000 admissions.

Before the inception of the ASP described here, multiple strategies, mostly passive, were being used to optimize antimicrobial therapy within the hospital. Provider education and antimicrobial prescribing pathways (algorithms for antimicrobial selection based on suspected diagnosis, risk factors, and illness severity) were being used to aid physicians in selecting appropriate treatments to prevent or treat infections. Based on criteria specified by hospital policy, pharmacy staff provided automatic i.v.-to-oral conversions for qualifying patients and also monitored patients receiving medications requiring dosage adjustment on the basis of renal function. Before formal ASP implementation, pharmacists also provided dosage adjustments based on individualized pharmacokinetic evaluations (i.e., for patients receiving vancomycin and aminoglycosides). Preauthorization of the use of formulary-restricted antimicrobials required an ID physician's approval.

Development of current ASP efforts

In early 2007, we began using data-mining software (Crystal Reports, SAP Business Objects, Newtown Square, PA) to develop automated reports to capture key pharmacy, clinical, and microbiological data on all adult hospital inpatients receiving antimicrobials. The customized reports included patient demographics and information on allergies, pertinent laboratory values, medications, and portions of the

medical history. Initially, the reports included only immunosuppressive medications and antimicrobials. Likewise, reported laboratory values were limited to the white blood cell count, counts of segmented neutrophils and bands, the serum creatinine concentration, blood urea nitrogen level, and positive culture results for *Clostridium difficile*. The software in use at the time also allowed the reporting of microbiological culture and susceptibility data.

Residency-trained pharmacists, working on a weekly rotation schedule, were responsible for performing the duties described above, although none had formal ID training (i.e., a postgraduate year 2 residency, fellowship, or ASP certification). The ASP pharmacist on rotation reviewed the software-generated antimicrobial therapy reports, which contained information on approximately 60–80 patient cases daily. Using EMR data, the pharmacist was able to update the reports by adding physician progress notes, diagnostic test results, and other pertinent information as needed. Patients who were considered to be appropriately treated and clinically improved were labeled for review at a later date (usually the targeted discontinuation date). A revised final report (covering about 20 cases daily) was then reviewed with an ID physician, and written recommendations were given to providers on a standardized form. On each distributed form, educational comments provided a rationale for the recommendations; this served the function of an abbreviated ID consultation. The form used for this purpose stated that the physician's comments did not constitute a formal consultation, that recommendations were based on a review of limited data available from the EMR, and that the provider's clinical judgment should take precedence in clinical decision making.

The data-mining software was also used to generate an additional automated report to facilitate screening for pneumococcal and influenza vaccination candidates. Some of the key issues targeted in these reports included

- Properly classifying patients with pneumonia as having community-acquired, health care-associated, hospital-acquired, or ventilator-associated pneumonia and then recommending appropriate empirical therapy based on guidelines jointly issued by IDSA and the American Thoracic Society,[40]
- Identifying cases of abdominal sepsis as community-acquired or health care-associated and, in the case of the former, advising the preferential use of ceftriaxone and metronidazole rather than broader-spectrum antibiotics such as carbapenems and piperacillin–tazobactam,
- Automatically switching patients receiving highly bioavailable antimicrobials such as the quinolones, metronidazole, and fluconazole from i.v. to oral therapy in cases involving the use of enteral nutrition,
- "Deescalating" broad-spectrum antibiotics to narrower-spectrum and less expensive first-line antibiotics as appropriate once culture and sensitivity data were available,
- Advising the preferential use of alternatives to quinolone therapy in appropriately selected patients (e.g., those with urinary tract or abdominal infections) in order to decrease overall quinolone use, and
- Recommending the discontinuation of antibiotics after an adequate duration of therapy (per applicable IDSA guidelines and deemed clinical status).

Other events during the study period that could have influenced the evaluated outcomes (described below) included a change in our pneumonia pathway and order set in 2006 whereby ceftriaxone and azithromycin or doxycycline replaced quinolones as the preferred agents for community-acquired pneumonia. Also, in 2008, privileges to prescribe linezolid in the hospital for the empirical and definitive treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia were extended beyond the ID physicians to include critical care physicians.

Methods

Clinical outcomes. A quasiexperimental study design was used to analyze the clinical outcomes of the ASP by comparing data for designated periods before (January 2003–December 2006) and after (April 2007–December 2010) ASP inception. Postimplementation data collection excluded the first two months of the service in order to allow for transition time. Throughout the study time frame, comparisons were made to assess any differences in outcomes between patients for whom ASP recommendations were accepted and those for whom ASP recommendations were rejected. The impact of the ASP on nosocomial infections involving MRSA, vancomycin-resistant enterococci (VRE), and *C. difficile* was determined by following the occurrence rates before and after ASP inception. Data on VRE rates before 2004 were not available.

Clinical outcomes including LOS, mortality, and 30-day readmission rates (where applicable) were collected for all eligible patients. For comparison, we evaluated clinical outcomes for two common disease states: pneumonia and abdominal sepsis. These disease states were chosen because they were frequent targets of ASP intervention and are associated with high morbidity and mortality; thus, they were considered to be the diseases most amenable to the demonstration of any positive ASP effects on parameters such as LOS and mortality. Patients were identified by cross-referencing our ASP database to a list of all hospitalized patients using the most common *International Classification of Diseases, 9th Revision, Clinical Modi-*

fication codes indicative of pneumonia and abdominal sepsis (28 and 12 such codes, respectively, were used in our study).

Economic outcomes. The acquisition costs of all i.v. and oral antimicrobial, antifungal, and antiviral agents were collected and compared over an eight-year time frame. Current acquisition prices were used for all cost comparisons to account for any changes in those costs over the studied period. Additionally, daily inpatient census data were used to calculate antimicrobial cost as a function of patient-days of care. Only data from inpatient units serving patients needing medical or surgical interventions were included; data from the palliative care, neonatal intensive care, and psychiatry units were excluded. Data regarding drug consumption were gathered from our antimicrobial charge history database and reported in terms of defined daily doses (DDDs), as recommended by the WHO Collaborating Centre for Drug Statistics Methodology[41]; DDD values for drugs included in institutional dosing protocols (e.g., extended-infusion β-lactams) were calculated separately.

Total expenditures for all antimicrobials were calculated and divided by the applicable total number of patient-days to derive a figure for "antimicrobial dollars per patient-day" (ADPD). Actual cost savings related to the ASP were calculated by subtracting the ADPD for each of the four study years (2007–10) from the ADPD for 2006, the baseline year (i.e., the year before the launch of the ASP); each difference was then multiplied by the number of patient-days for the specific year. Cost savings related to the ASP were projected by assuming that the trend of cost increases noted before the ASP would have continued in the years after ASP implementation (i.e., the "post-ASP years"). This was done by performing a linear regression analysis of the trend in ADPD for the period 2003–06 and projecting further rises through 2010. The ADPD for a given post-ASP year was then subtracted from the projected ADPD, and the result was multiplied by the number of patient-days for that year.

Statistical analysis. SAS, version 9.2 (SAS Institute Inc., Cary, NC) and EpiInfo (Centers for Disease Control and Prevention, Atlanta, GA) were used to perform statistical analyses. Clinical outcomes were compared using tests of means (days and years) or independent proportions (readmission rate and survival). The *t* test was applied for log-transformed LOS data, and chi-square testing was used to assess survival in patients before and after ASP inception and the impact of acceptance versus rejection of ASP recommendations. Nosocomial infection frequency data and antibiotic consumption and cost for the preimplementation and postimplementation periods were compared using regression methods.

To ensure that autocorrelation was not present, a Durbin-Watson test was used; results were nonsignificant for each infection class (for MRSA, $r = -0.18$, $p = 0.34$; for VRE, $r = -0.14$, $p = 0.51$; for *C. difficile*, $r = 0.03$, $p = 0.21$). Thus, ordinary regression methods (without correction for autocorrelation) were used for subsequent evaluations.

The pre- and post-ASP periods were compared for time-related changes in nosocomial infection rates, antimicrobial consumption, and ADPD by analyzing slopes and regression interaction terms. The overall levels of infection were compared between the pre- and post-ASP periods through analysis of variance. The a priori level of significance was 0.05.

Results

Survival, LOS, and readmission. The charts of a total of 2186 patients treated for pneumonia and 225 patients treated for intraabdominal sepsis during the 3 years before and the 3 years after ASP implementation were reviewed. The mean ± S.D. age of patients with abdominal sepsis was 62.2 ± 19.3 years and 61.7 ± 16.2 years in the pre- and post-ASP periods, respectively ($p = 0.82$). There was a significant difference in the mean age of patients with pneumonia between the two periods (71.9 ± 16.2 years and 69.1 ± 17.3 years for the pre- and post-ASP periods, respectively; $p \leq 0.001$). Survival, LOS, and 30-day readmissions for either type of infection did not differ significantly between the two periods (Table 1).

Accepted versus rejected recommendations. From April 2007

Table 1.
Clinical Outcomes for Patients With Selected Infections Before and After Implementation of an Antimicrobial Stewardship Program (ASP)

Outcome	Pre-ASP	Post-ASP	*p*
Intraabdominal Sepsis			
Fraction (%) pts survived	111/123 (90.2)	97/102 (95.1)	0.17
Mean ± S.D. length of stay (days)	7.2 ± 7.1	7.4 ± 8.3	0.52
Fraction (%) pts readmitted[a]	22/111 (19.8)	16/97 (16.7)	0.54
Pneumonia			
Fraction (%) pts survived	1118/1163 (96.1)	985/1023 (96.3)	0.85
Mean ± S.D. length of stay (days)	5.9 ± 4.9	5.5 ± 7.8	0.21
Fraction (%) pts readmitted[a]	163/1118 (14.6)	146/985 (14.8)	0.88

[a]Readmission within 30 days for any cause.

through December 2009, 1596 recommendations were made to providers to alter therapy; of those, 1277 (80%) were accepted within 48 hours. The most commonly made recommendations called for more appropriate empiric antimicrobial therapy, de-escalation of therapy (as appropriate) once cultures results were available, discontinuation of antibiotics if an infection was not clearly documented, and a change to an appropriate duration of therapy.

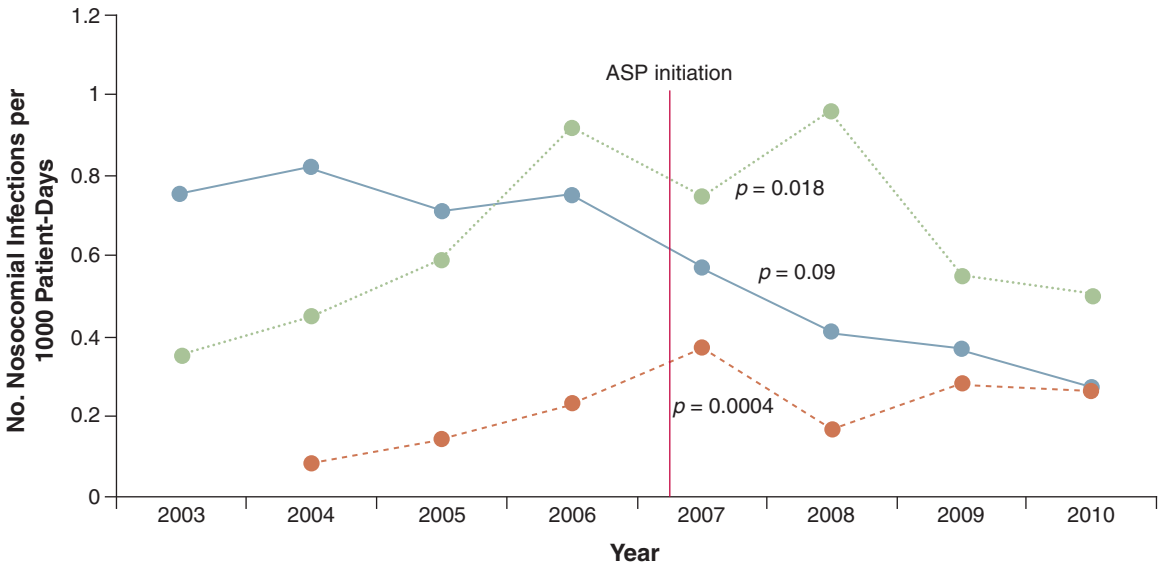
Survival among patients for whom ASP recommendations were accepted (91.9%) was not significantly different from that among patients with rejected recommendations (90.3%, $p = 0.37$). The mean LOS of patients with accepted ASP recommendations (11.6 days) did not differ significantly from that of patients for whom recommendations were not accepted within 48 hours (10.4 days, $p = 0.21$).

Nosocomial infection. Nosocomial infection rates for MRSA, *C. difficile*, and VRE trended downward after ASP implementation (Figure 1). There were significant differences between the pre- and post-ASP periods in quarterly changes of the rates of nosocomial infections involving *C. difficile* ($p = 0.018$) and VRE ($p = 0.0004$). The between-period difference in rates of nosocomial MRSA infections was not significant ($p = 0.09$) possibly because rates were already starting to fall immediately before ASP inception.

Antimicrobial use and cost savings. Antimicrobial consumption before and after ASP inception is shown in Figure 2. Antimicrobial consumption, expressed as DDDs per 1000 patient-days, had risen in the years before ASP inception. After the initiation of the ASP in 2007, DDD values generally declined; the year-to-year change in DDD values differed significantly between the pre- and post-ASP periods ($p = 0.0057$). ADPD, which had risen steadily before ASP inception, decreased by 9.7% in the first year after ASP implementation (2007), remained steady in 2008 and 2009, and rose slightly in 2010; this trend was due almost exclusively to the increased use of linezolid experienced over a period of several years (Table 2). The year-to-year change in ADPD (slope) differed significantly between the pre- and post-ASP periods ($p = 0.0086$). For 2007–10, the actual cost savings attributable to ASP activities ranged from $24,377 to $179,088. The cumulative projected cost savings for 2007–10 (the years after ASP implementation)—based on the assumption that cost increases would have continued at the pre-ASP pace—was more than $1.7 million (Table 2).

The use of almost all antibiotic classes trended downward in the years after ASP inception. Notably, average total quinolone use in the four pre-ASP years was 159.3 DDDs per 1000 patient-days; overall quinolone use fell 44% to an average of 114.9 DDDs per 1000 patient-days in the four post-ASP years. Vancomycin use steadily rose to a peak of 105.8 DDDs per 1000 patient-days

Figure 1. Nosocomial infection rates for methicillin-resistant *Staphylococcus aureus* (solid line), *Clostridium difficile* (dotted line), and vancomycin-resistant enterococci (dashed line) before and after implementation of an antimicrobial stewardship program (ASP). The *p* values are for comparisons of slopes of quarterly trend lines before and after ASP implementation.



in the years leading up to 2006 and then steadily fell to a low of 76.1 DDDs per 1000 patient-days in 2010 (a decrease of 28%). Similar trends were seen in the use of carbapenems and piperacillin–tazobactam, whereas the use of first-line antimicrobials such as cefazolin, ceftriaxone, metronidazole, and doxycycline remained flat or increased slightly; a notable exception was an increase in the use of linezolid (5.5, 10.0, 13.1, and 21.7 DDDs per 1000 patient-days in 2007, 2008, 2009, and 2010, respectively). As previously mentioned, institutional privileges to prescribe linezolid for the empirical or definitive therapy of MRSA pneumonia were expanded in 2008 to include critical care physicians; the easing of the prescribing restriction was based on studies suggesting the drug's superiority to vancomycin in those situations.[42-45]

Discussion

The study described here mea-

Figure 2. Antimicrobial use before and after implementation of an antimicrobial stewardship program (ASP), expressed as defined daily doses (DDDs) per 1000 patient-days (bars) and antimicrobial dollars per patient day (ADPD, indicated by solid line). The dotted line represents the hypothetical continuation of the pre-ASP regression line for ADPD.

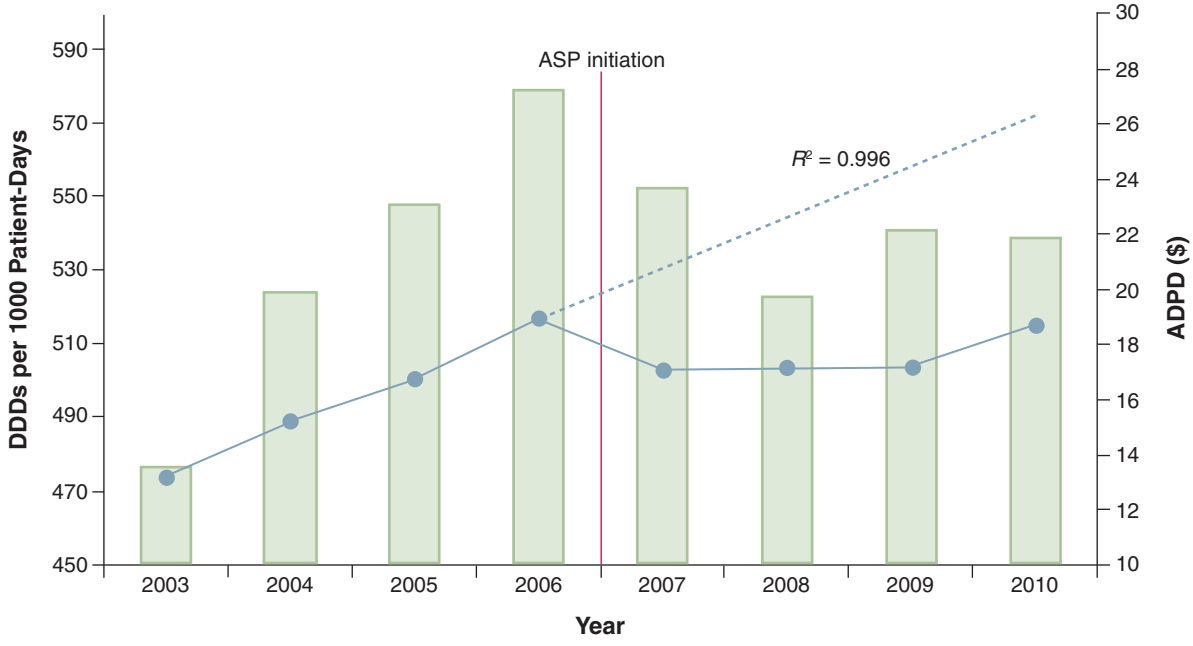


Table 2.
Estimated Cost Savings Associated With an Antimicrobial Stewardship Program (ASP)

Year	Total Antimicrobial Expenditures ($)	Patient-Days	ADPD ($)[a]	Actual Savings Compared With 2006 ($)[b]	Projected ADPD ($)[c]	Projected Savings ($)[d]
2006	1,758,433	92,873	18.93			
2007[e]	1,657,295	96,990	17.09	179,088.20	20.70	171,309.80
2008	1,729,034	100,667	17.18	176,968.55	22.60	369,071.65
2009	1,579,291	91,798	17.20	158,788.23	24.50	510,971.77
2010	1,707,946	91,494	18.67	24,377.38	26.30	673,968.82

[a]ADPD = antimicrobial dollars per patient-day.
[b]Calculated by subtracting the year's ADPD from 2006's ADPD and multiplying the result by the number of patient-days for the year. Total actual savings for 2007–10, $539,222.36.
[c]Projection of cost in the absence of an ASP. Determined by linear regression of changes in costs for 2003–06, before the ASP was implemented.
[d]Calculated by subtracting the year's projected ADPD from 2006's ADPD and multiplying the result by the number of patient-days for the year. Total projected savings for 2007–10, $1,725,322.04.
[e]First full year of the ASP.

sured clinical outcomes and costs before and after the implementation of an ASP. The implementation of the ASP was associated with a decrease in the overall use of antimicrobials and a decrease in antimicrobial expenditures. The calculated cost savings were substantial—especially relative to a hypothetical scenario of continued growth in antimicrobial use at the pre-ASP rate. ADPD and overall antimicrobial use (in terms of DDDs per 1000 patient-days) did not correlate perfectly, as seen in Figure 2, because the cost calculations depended on both overall use and the proportionate use of more expensive third-line antibiotics and less expensive generic first-line antibiotics. For example, our ASP was able to reduce overall antimicrobial use (relative to 2006 levels) in all four years after ASP inception, but the associated costs began to rise again in 2010 because of the frequency with which the critical care services were prescribing linezolid instead of generic vancomycin.

As the data-mining software used for our study was previously used for other clinical purposes, the implementation cost of the program was negligible, entailing only the time required to design and create the newly required ASP reports and database. Existing pharmacist and ID physician personnel were able to provide the new service successfully, rotating as needed. The greatest cost of the ASP was the cost of ASP pharmacist time. The pharmacist on duty typically spent three to four hours daily reviewing and augmenting the automated reports; this relatively high time requirement was primarily due to the need to manually extract some EMR data elements that were not readily amenable to extraction with the data-mining software. Once the reports were completed, ID physician review time was minimal (usually 30–60 minutes daily).

Although our study did not demonstrate significant ASP-related improvements in LOS or mortality and readmission rates, it may be considered a positive sign that no worsening in these measures was observed with an increased frequency of recommendations to de-escalate or discontinue antimicrobial therapy. Although reductions in antimicrobial resistance (as measured by hospital laboratory antibiograms) are desirable, one ultimate goal of stewardship efforts is to reduce actual nosocomial infections. The results of our study strongly support the association between ASP use and reductions in these infections.

In an observational study such as ours, it is difficult to tell what interventions or outcomes may have contributed to the falling rates of nosocomial infection. It is interesting to note that in a study by Valiquette et al.,[45] a *C. difficile* outbreak did not abate with the use of various infection-control interventions but ultimately did abate after the implementation of a nonrestrictive ASP, which produced a substantial reduction of overall antibiotic use. That study, and others, documented an increased frequency of *C. difficile* and MRSA infections with increased use of quinolones.[46,47] In our study, quinolone use was not a particular target of the ASP but did fall substantially in the postimplementation period. In keeping with a previously reported association between the use of vancomycin and the occurrence of VRE,[48] in our study the frequencies of VRE and vancomycin use both decreased after ASP implementation.

We believe the key to the success of the ASP was the prospective nature of the audits via a collaborative effort of the pharmacist and the ID physician. No improvements in the outcomes we measured were evident in the years before such collaboration, when only the passive strategies of formulary restriction, educational efforts, and development of clinical pathways were in place. We also believe that our ASP was greatly facilitated by the use of data-mining software to develop automated reports that consolidated large amounts of pertinent clinical information into an abbreviated report. This allowed the ID physician to review large numbers of cases in a relatively short time without manually perusing each patient's medical record.

Our study was limited by its quasiexperimental design, and our findings could therefore suggest an association between ASP activities and reduced nosocomial infection rates but could not establish definite causality. However, we believe the use of that design methodology was appropriate, as the random assignment of patients to an experimental group is generally not feasible when investigating the impact of a systemwide change in protocol, as was the case in our study. During the same years as those covered by our study, other systemwide changes were made, including an increased emphasis on hand hygiene and intensive care unit "bundling" practices (i.e., the use of several preventive measures in combination) for the prevention of ventilator-associated pneumonia and central line-associated bacteremia; these factors may have contributed to the declines in infection rates we documented.

Moreover, our study was not a true cost–benefit analysis but instead only provided an overview of the program's implementation, resource utilization, and observed benefits.

Conclusion

A prospective collaborative ASP employed automated reports to efficiently identify key data for ASP review. After ASP implementation, antimicrobial expenditures and rates of nosocomial infections caused by resistant pathogens dropped without significant changes in patient survival, LOS, and readmissions for the two studied illness categories.

References

1. Klevens RM, Edwards JR, Richards CL Jr et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep.* 2007; 122:160-6.
2. Yokoe DS, Mermel LA, Anderson DJ et al. A compendium of strategies to prevent health care-associated infections in acute care hospitals. *Infect Control Hosp Epidemiol.* 2008; 29(suppl 1):S12-21.
3. Fridkin SK, Steward CD, Edwards JR et al. Surveillance of antimicrobial use and antimicrobial resistance in United States hospitals: project ICARE phase 2. Project Intensive Care Antimicrobial Resistance Epidemiology (ICARE) hospitals. *Clin Infect Dis.* 1999; 29:245-52.
4. Gaynes R, Edwards JR. Overview of nosocomial infections caused by gram-negative bacilli. *Clin Infect Dis.* 2005; 41:848-54.
5. Klevens RM, Edwards JR, Tenover FC et al. Changes in the epidemiology of methicillin-resistant *Staphylococcus aureus* in intensive care units in US hospitals, 1992–2003. *Clin Infect Dis.* 2006; 42:389-91.
6. Wilson SJ, Knipe CJ, Zieger MJ et al. Direct costs of multidrug-resistant *Acinetobacter baumannii* in the burn unit of a public teaching hospital. *Am J Infect Control.* 2004; 32:342-4.
7. Qavi A, Segal-Maurer S, Mariano N et al. Increased mortality associated with a clonal outbreak of ceftazidime-resistant *Klebsiella pneumoniae:* a case-control study. *Infect Control Hosp Epidemiol.* 2005; 26:63-8.
8. Song X, Srinivasan A, Plaut D et al. Effect of nosocomial vancomycin-resistant enterococcal bacteremia on mortality, length of stay, and costs. *Infect Control Hosp Epidemiol.* 2003; 24:251-6.
9. Tam VH, Rogers CA, Chang KT et al. Impact of multidrug-resistant *Pseudomonas aeruginosa* bacteremia on patient outcomes. *Antimicrob Agents Chemother.* 2010; 54:3717-22.
10. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis.* 2006; 42(suppl 2):S82-9.
11. Boucher HW, Talbot GH, Bradley JS et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis.* 2009; 48:1-12.
12. Spellberg B, Blaser M, Guidos RJ et al. Combating antimicrobial resistance: policy recommendations to save lives. *Clin Infect Dis.* 2011; 52(suppl 5):S397-428.
13. The 10 × 20 Initiative: pursuing a global commitment to develop 10 new antibacterial drugs by 2020. *Clin Infect Dis.* 2010; 50:1081-3.
14. Coates AR, Halls G, Hu Y. Novel classes of antibiotics or more of the same? *Br J Pharmacol.* 2011; 163:184-94.
15. Livermore D. The zeitgeist of resistance. *J Antimicrob Chemother.* 2007; 60(suppl 1):i59-61.
16. Hecker MT, Aron DC, Patel NP et al. Unnecessary use of antimicrobials in hospitalized patients: current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. *Arch Intern Med.* 2003; 163:972-8.
17. Werner NL, Hecker MT, Sethi AK et al. Unnecessary use of fluoroquinolone antibiotics in hospitalized patients. *BMC Infect Dis.* 2011; 11:187.
18. Shlaes DM, Gerding DN, John JF Jr et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. *Clin Infect Dis.* 1997; 25:584-99.
19. Marr JJ, Moffet HL, Kunin CM. Guidelines for improving the use of antimicrobial agents in hospitals: a statement by the Infectious Diseases Society of America. *J Infect Dis.* 1988; 157:869-76.
20. Dellit TH, Owens RC, McGowan JE Jr et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis.* 2007; 44:159-77.
21. Lautenbach E, Larosa LA, Kasbekar N et al. Fluoroquinolone utilization in the emergency departments of academic medical centers: prevalence of, and risk factors for, inappropriate use. *Arch Intern Med.* 2003; 163:601-5.
22. Lawton RM, Fridkin SK, Gaynes RP et al. Practices to improve antimicrobial use at 47 US hospitals: the status of the 1997 SHEA/IDSA position paper recommendations. Society for Healthcare Epidemiology of America/Infectious Diseases Society of America. *Infect Control Hosp Epidemiol.* 2000; 21:256-9.
23. Nyquist AC, Gonzales R, Steiner JF et al. Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis. *JAMA.* 1998; 279:875-7.
24. Anderson DJ, Kaye KS. Controlling antimicrobial resistance in the hospital. *Infect Dis Clin North Am.* 2009; 23:847-64,vii-viii.
25. American Society of Health-System Pharmacists. ASHP statement on the pharmacist's role in antimicrobial stewardship and infection prevention and control. *Am J Health-Syst Pharm.* 2010; 67:575-7.
26. McQuillen DP, Petrak RM, Wasserman RB et al. The value of infectious diseases specialists: non-patient care activities. *Clin Infect Dis.* 2008; 47:1051-63.
27. Kaki R, Elligsen M, Walker S et al. Impact of antimicrobial stewardship in critical care: a systematic review. *J Antimicrob Chemother.* 2011; 66:1223-30.
28. Owens RC Jr, Fraser GL, Stogsdill P. Antimicrobial stewardship programs as a means to optimize antimicrobial use. Insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy.* 2004; 24:896-908.
29. Patel D, Lawson W, Guglielmo BJ. Antimicrobial stewardship programs: interventions and associated outcomes. *Expert Rev Anti-Infect Ther.* 2008; 6:209-22.
30. Wong-Beringer A, Nguyen LH, Lee M et al. An antimicrobial stewardship program with a focus on reducing fluoroquinolone overuse. *Pharmacotherapy.* 2009; 29:736-43.
31. Gross R, Morgan AS, Kinky DE et al. Impact of a hospital-based antimicrobial management program on clinical and economic outcomes. *Clin Infect Dis.* 2001; 33:289-95.
32. Bantar C, Sartori B, Vesco E et al. A hospitalwide intervention program to optimize the quality of antibiotic use: impact on prescribing practice, antibiotic consumption, cost savings, and bacterial resistance. *Clin Infect Dis.* 2003; 37:180-6.
33. Gentry CA, Greenfield RA, Slater LN et al. Outcomes of an antimicrobial control program in a teaching hospital. *Am J Health-Syst Pharm.* 2000; 57:268-74.
34. Carling P, Fung T, Killion A et al. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect Control Hosp Epidemiol.* 2003; 24:699-706.
35. Khan R, Cheesbrough J. Impact of changes in antibiotic policy on *Clostridium difficile*-associated diarrhoea (CDAD) over a five-year period in a district general hospital. *J Hosp Infect.* 2003; 54:104-8.
36. Apisarnthanarak A, Danchaivijitr S, Khawcharoenporn T et al. Effectiveness of education and an antibiotic-control program in a tertiary care hospital in Thailand. *Clin Infect Dis.* 2006; 42:768-75.
37. Rahal JJ, Urban C, Segal-Maurer S. Nosocomial antibiotic resistance in multiple gram-negative species: experience at one hospital with squeezing the resistance balloon at multiple sites. *Clin Infect Dis.* 2002; 34:499-503.
38. Peterson LR. Squeezing the antibiotic balloon: the impact of antimicrobial classes on emerging resistance. *Clin Microbiol Infect.* 2005; 11(suppl 5):4-16.
39. Burke JP. Antibiotic resistance—squeezing the balloon? *JAMA.* 1998; 280:1270-1.
40. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med.* 2005; 171:388-416.
41. Collaborating Centre for Drug Statistics Methodology, World Health Organization. Guidelines for ATC classification and DDD assignment. www.whocc.no/atc_ddd_publications/guidelines (accessed 2012 Apr 24).
42. Kollef MH, Rello J, Cammarata SK et al. Clinical cure and survival in gram-positive ventilator-associated pneumonia: retrospective analysis of two double-blind studies comparing linezolid with vancomycin. *Intensive Care Med.* 2004; 30:388-94.

43. Wunderink RG, Mendelson MH, Somero MS et al. Early microbiological response to linezolid vs vancomycin in ventilator-associated pneumonia due to methicillin-resistant *Staphylococcus aureus. Chest.* 2008; 134:1200-7.
44. Wunderink RG, Rello J, Cammarata SK et al. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest.* 2003; 124:1789-97.
45. Valiquette L, Cossette B, Garant MP et al. Impact of a reduction in the use of high-risk antibiotics on the course of an epidemic of *Clostridium difficile*-associated disease caused by the hypervirulent NAP1/027 strain. *Clin Infect Dis.* 2007; 45(suppl 2):S112-21.
46. Paterson DL. "Collateral damage" from cephalosporin or quinolone antibiotic therapy. *Clin Infect Dis.* 2004; 38(suppl 4):S341-5.
47. Owens RC Jr, Donskey CJ, Gaynes RP et al. Antimicrobial-associated risk factors for *Clostridium difficile* infection. *Clin Infect Dis.* 2008; 46(suppl 1):S19-31.
48. Recommendations for preventing the spread of vancomycin resistance. Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR Recomm Rep.* 1995; 44(RR-12):1-13.