Practice Report: Antimicrobial Stewardship Program

Clinical and economic outcomes of a prospective antimicrobial stewardship program

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Health care-associated infections affect nearly 2 million people in the United States annually. It has been suggested that over one third of these infections are preventable. Over the last several decades, antimicrobial-resistant organisms have been responsible for an increasing percentage of nosocomial infections. Infections involving resistant pathogens have been shown to increase hospital length of stay (LOS), costs, and mortality. 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.

While a direct relationship between antibiotic use and the sub-

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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sequent development of resistance is widely accepted, the majority of antibiotic use continues to be regarded as inappropriate. In spite of a number of authors and organizations expressing concern about the inappropriate use of antibiotics over the last decade or more, little change in prescribing behaviors has been observed over this period. 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.

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.

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. 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. 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. 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. 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. Likewise, a small number of ASPs have been demonstrated to have a favorable impact on the frequency of nosocomial infections. 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.

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, intervention trial 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). Prior authorization 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 quasi-experimental 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-
**Antimicrobial stewardship program**

Historic costs 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 that year.

**Statistical analysis.** SAS, version 9.2 (SAS Institute Inc., Cary, NC) and EpInfo (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)

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

\(*\)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, *Clostridium 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
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-

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

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

\(^a\)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.
Antimicrobial stewardship program

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., 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. 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, 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


PRACTICE REPORT

Antimicrobial stewardship program


