Impact of an Antimicrobial Stewardship Program on Antimicrobial Utilization, Bacterial Susceptibilities, and Financial Expenditures at an Academic Medical Center

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ABSTRACT

Background: Antimicrobial stewardship programs (ASPs) have the potential to improve patient outcomes, decrease microbial resistance, increase patient safety, and decrease costs. However, to justify the costs involved with providing an ASP, it is necessary to assess its impact in achieving these outcomes on an ongoing basis.

Objective: The purpose of this study was to characterize the overall impact of the ASP at an academic medical center.

Methods: Quasi-experimental, before and after stewardship program implementation, retrospective analyses of quarterly antimicrobial utilization, bacterial susceptibilities, and antibiotic acquisition costs were utilized.

Results: Mean stewardship-focused antibiotic utilization was 510.3 defined daily doses (DDD) per 1,000 patient days for the pre-ASP period and 426.4 DDD per 1,000 patient days for the ASP period (16.4% decrease; $p < .001$). Significant changes in *Pseudomonas aeruginosa* susceptibility to tobramycin (8% increase; $p = .006$) and piperacillin-tazobactam (8% decrease; $p = .024$) were noted. Changes in susceptibility of *Staphylococcus aureus* to methicillin (7% increase, $p = .012$) were also observed. ASP-focused antibiotic expenditures decreased from \$4,028,068 in fiscal year (FY) 2010 to \$2,135,173 in FY2013 ($p = .01$).

Conclusions: ASP initiatives were associated with an observed reduction in stewardship-focused antibiotic utilization. Significant changes in susceptibilities of some bacteria were noted but did not seem to consistently reflect antibiotic utilization changes. Significant decreases in antimicrobial expenditures were observed. Observed outcomes are temporally related to shifts in antimicrobial selection through the initiation of stewardship program-driven antibiotic policy changes. These outcomes have been used to justify and expand our stewardship program moving forward.

Key Words—antibiotic cost, antibiotic use, antimicrobial stewardship, resistance

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BACKGROUND

Increases in antibiotic resistance combined with minimal market introduction of new classes of antibiotics have led to a multitude of initiatives to increase

awareness and institute solutions to address the problem termed “bad bugs, no drugs.”¹ The Infectious Disease Society of America (IDSA) has released and promoted the 10 x ‘20 initiative, which seeks to achieve

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10 new antibacterial drug approvals by the US Food and Drug Administration by 2020.² Additionally, the IDSA and the Society for Healthcare Epidemiology of America (SHEA) have released antimicrobial stewardship guidelines outlining the importance of antimicrobial stewardship programs (ASPs).³ In 2013, a publication from the Centers for Disease Control and Prevention (CDC) gave warning of antimicrobial resistance issues.⁴ The CDC's director, Dr. Tom Frieden, reflected on this publication and the issue of antimicrobial resistance at a press conference, saying, "If we are not careful, we will soon be in a post-antibiotic era. And, in fact, for some patients and some microbes, we are already there."⁵ These warnings were acknowledged on a national level on September 18, 2014, with the signing of the executive order Combating Antibiotic Resistant Bacteria by President Barack Obama that established the Task Force for Combating Antibiotic-Resistant Bacteria.⁶ Subsequently, the Task Force convened in March of 2015, releasing a national action plan.⁷ The White House hosted a National Antibiotic Stewardship Forum in June 2015 that brought together key stakeholders in the field to make commitments to combat antibiotic resistance.⁸ Most recently, on September 15, 2015, the US Department of Health and Human Services, the US Department of Defense, and the US Department of Agriculture appointed human and animal health experts to the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria such that recommendations can be made on preserving current antibiotics and decreasing the emergence of resistance.⁹

Antimicrobial stewardship has been shown to impact the emergence of antimicrobial-resistant bacteria.³ In addition to achieving a reduction of

antimicrobial resistance, ASPs improve patient outcomes and safety and reduce health care financial expenditures.¹⁰ The measurement and evaluation of ASP clinical outcomes poses significant challenges. However, measures of antimicrobial utilization and financial expenditures are established and accessible outcomes for demonstrating the value contributed by ASPs. The effect of stewardship programs on cost avoidance and decreased antibiotic utilization is well described.¹⁰ As there are obvious limits to cost reduction or avoidance, the need to evaluate other important stewardship outcomes measures, including patient outcomes such as cure rates, length of stay, or antibiotic resistance changes, is increasingly important and, together with costs savings, may be used to continually justify ongoing support for ASPs. Although the existence of such programs will soon be mandated,^{6,11} the size and scope may well vary with their efficacy in meeting basic goals of optimizing anti-infective utilization and patient outcomes. The objective of this study was to quantify the impact of the program on antimicrobial utilization and related expenditures and to determine any impact on antibiotic resistance.

METHODS

The 709-bed academic medical center serves adults and pediatrics. The average daily census is 490, and annual admissions are 30,000. The ASP was implemented in late 2009. The program focuses on improving the use of antimicrobials in the adult inpatient population through a variety of preauthorization (front end) and prospective audit and feedback (back end) initiatives (Table 1), such as formulary restriction and dose optimization interventions,

Table 1. Examples of antimicrobial stewardship program initiatives

Year	Intervention	Description
2009	Prospective audit & feedback	Incorporation of a clinical decision support system
2010	Empiric therapy guidelines	Preferred antimicrobial agent changed from piperacillin-tazobactam and meropenem to cefepime on HAP/VAP/HCAP and febrile neutropenia clinical pathways, respectively
2011	Anti-infective restrictions	Ciprofloxacin use only in culture confirmed susceptibility except for select indications
	Formulary management	Exchange of micafungin for caspofungin as formulary agent
2012	Dose optimization	Extended infusion piperacillin/tazobactam as standard of care
2013	Clinical pathways	Re-drafting of bacteremia clinical pathway to include multiplex polymerase chain reaction

Note: HAP/VAP/HCAP = hospital-acquired pneumonia/ventilator-associated pneumonia/health care-associated pneumonia.

respectively. Additionally, preparation and implementation of empiric therapy guidelines, clinical pathways, and clinician education are used to pursue the program's goals. The program's clinician education focuses on providing in-services or grand rounds presentations to the medical staff for initiative rollouts or where areas of opportunity in prescribing practices are identified. During the study evaluation period, the staff of the ASP consisted of 1 full-time equivalent (FTE) infectious disease pharmacist and a 0.5 FTE infectious disease physician. The ASP is active from 8:00 a.m. to 5:00 p.m. on weekdays and also provides a 24-hour on-call service.

Outcomes

Outcomes for analysis included antimicrobial utilization, bacterial susceptibilities, and antimicrobial acquisition expenditures. Antimicrobial utilization was measured as defined daily doses (DDD), normalized for census. For the impact of the stewardship program, both total systemic antibiotics and ASP-focused antibiotics were considered. ASP-focused antibiotics were antibiotics routinely evaluated by the ASP team for appropriateness during therapy and the potential to optimize their appropriate use through policies, protocols, formulary restrictions, or clinician education. ASP-focused antibiotics included gentamicin, tobramycin, amikacin, ciprofloxacin, levofloxacin, moxifloxacin, piperacillin-tazobactam, cefepime, ertapenem, meropenem, imipenem-cilastatin, doripenem, vancomycin, linezolid, and daptomycin. Financial expenditures for antimicrobials were evaluated as both ASP-focused antibiotics and total systemic antibiotics. Susceptibilities were evaluated by organism and antibiotic as reported in the institutional antibiogram.

Data Collection and Analysis

Utilization data for antimicrobials were obtained for 2008 to 2013 from a previously created database that was established using the hospital pharmacy computer system (McKesson, San Francisco, CA) and transferring the data to a spreadsheet (Excel; Microsoft, Redmond, WA) with subsequent data de-identification. Medication orders were summed per medication per quarter in grams using the total number of doses and dose per administration. The grams were then converted to census-normalized DDD (defined as grams per 1,000 patient days) using World Health Organization (WHO) definitions¹² and institution-specific definitions where discrepancies occurred (Table 2). Totals for all ASP-focused and all systemic

Table 2. Comparison of World Health Organization (WHO) and antimicrobial stewardship program (ASP) defined daily doses^a

Antibiotic	WHO	ASP
Amikacin	1	1
Cefepime ^b	2	6
Ciprofloxacin (PO/IV ^b)	1/0.5	1/1.2
Daptomycin ^b	0.28	0.56
Doripenem	1.5	1.5
Ertapenem	1	1
Gentamicin	0.24	0.24
Imipenem	2	2
Levofloxacin	0.5	0.5
Linezolid	1.2	1.2
Meropenem ^b	2	3
Moxifloxacin	0.4	0.4
Piperacillin-tazobactam ^b	14	13.5
Tobramycin	0.24	0.24
Vancomycin	2	2

Note: PO/IV = oral/intravenous.

^aDefined daily doses reported as grams per day.

^bInstitution-specific definition used.

antibiotics were calculated per quarter. Changes in utilization were evaluated for the year before the ASP implementation and the fourth year of the program. These years, 2008 and 2013, were defined as Pre-ASP and ASP analysis periods, respectively. Quarterly antimicrobial cost data were obtained and evaluated for fiscal years (FY) 2010 and 2013 from pharmacy purchase records. Cost data for the complete FY2009, the year before the start of the program, or earlier were unavailable. FY data at the institution begins in July (ie, FY2010 begins July 1, 2009). All antimicrobial cost data were adjusted for inflation to the last time period in the study. Antiviral agent data were excluded from all analyses. Antifungal agent data were included for the calculation of the total of all systemic antibiotics. Susceptibility data were obtained from the institution's annual antibiograms for years 2008 and 2013. Organisms were utilized for comparison if present on both antibiograms and thus meeting the CLSI minimum requirement of 30 first isolates per organism.¹³ The list of organisms evaluated included *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Acinetobacter baumannii*, *Staphylococcus aureus*, coagulase-negative

staphylococci, *Enterococcus faecalis*, *Enterococcus faecium*, and *Streptococcus pneumoniae*. Changes in susceptibility were evaluated for ASP-focused antibiotics only. No changes in interpretative susceptibility testing were adopted during this period. For statistical analysis, categorical variables were evaluated using chi-square test or Fisher's exact test as appropriate. Continuous variables were evaluated using the Student's *t* test. A *p* value of .05 or less was considered statistically significant. SPSS (version 22; SPSS Inc., Chicago, IL) was utilized for all data analyses.

RESULTS

In our study, the means of ASP-focused antibiotic utilization were 510.3 DDD per 1,000 patient days and 426.4 DDD per 1,000 patient days for the Pre-ASP and ASP periods, respectively, which is a 16%

decrease ($p < .001$). Overall antibiotic utilization decreased by 2% ($p = .46$). Other notable significant findings in utilization between the periods included a 56% decrease in fluoroquinolone use ($p < .001$) and a 31% decrease in carbapenem use ($p = .003$). Additional utilization observations can be found in **Table 3**. The financial impact of the ASP, measured as total systemic antibiotic expenditures, decreased from \$4,765,075 in FY2010 to \$2,887,118 in FY2013 ($p = .02$). ASP-focused antibiotic expenditures decreased from \$4,028,068 in FY2010 to \$2,135,173 in FY2013 ($p = .01$) (**Figure 1**). A review of the policy changes initiated by the ASP revealed approximately \$1.3 million in annual savings concurrent with the exchange of meropenem and piperacillin-tazobactam for cefepime on the febrile neutropenia and hospital-acquired pneumonia (HAP),

Table 3. Pre antimicrobial stewardship program (Pre-ASP) and ASP defined daily doses of stewardship-focused antibiotics

Antibiotic group	Pre-ASP ^a	ASP ^a	% Change	<i>p</i> value
Aminoglycosides	61.7	55.3	-10.3	.280
Amikacin	1.0	2.9		
Gentamicin	7.8	8.8		
Tobramycin	52.7	43.6		
Carbapenems	51.3	35.4	-31.0	.003
Doripenem	0	0		
Ertapenem	2.1	6.5		
Imipenem	0.2	3.3		
Meropenem	49.0	25.6		
Fluoroquinolones	131.4	57.5	-56.2	<.001
Ciprofloxacin	92.4	29.0		
Levofloxacin	3.6	4.8		
Moxifloxacin	35.4	23.7		
MRSA	162.2	155.4	-4.2	0.092
Daptomycin	7.0	7.8		
Linezolid	17.9	27.2		
Vancomycin	137.3	120.4		
Non-carbapenem antipseudomonal β-lactams	103.7	122.8	+18.4	.002
Cefepime	10.9	54.1		
Piperacillin/tazobactam	92.8	68.7		
Total	510.3	426.4	-16.4	<.001

Note: Pre-ASP and ASP values reported as adjusted per 1,000 patient days. MRSA = methicillin-resistant *Staphylococcus aureus*.

^aMean of period. Aggregates are shown in bold.

Figure 1. Financial trends of stewardship-focused antibiotics. Fiscal Year (FY) for following year begins in July of the previous calendar year.

health care-associated pneumonia (HCAP), and ventilator-associated pneumonia (VAP) clinician order sets, respectively.

Susceptibility changes were noted between the pre-ASP and ASP periods for *S. aureus*, *P. aeruginosa*, *E. coli*, *S. marcescens*, and *A. baumannii* (Tables 4 and 5). *S. aureus* susceptibility to methicillin increased by 7% ($p = .012$). Significant susceptibility changes in *P. aeruginosa* susceptibility to tobramycin (increased 8%; $p = .006$) and piperacillin-tazobactam (decreased 8%; $p = .024$) were observed. Finally, susceptibility changes were noted for *E. coli* (amikacin increased 3%; $p = .014$), *S. marcescens* (tobramycin decreased 16%; $p = .026$), and *A. baumannii* (meropenem increased 21%; $p = .003$ and gentamicin increased 23%; $p = .001$).

DISCUSSION

This study aimed to characterize changes in antibiotic-utilization patterns and temporally related changes in bacterial susceptibility and drug expenditures that occurred in our institution following the introduction of an ASP. Observed changes included alterations in antibiotic utilization, antibiotic financial expenditures, and bacterial susceptibilities. ASP interventions designed to achieve these changes included formulary restrictions, prospective audits and feedback, dose optimizations, intravenous to oral conversions, development of empiric therapy guidelines and clinical pathways, and clinician education. Following the introduction of the ASP, mean ASP-focused antibiotic utilization decreased by 16%. This is similar to results from other studies evaluated in

Table 4. Percent susceptible of antimicrobial stewardship program (ASP)-focused antibiotics between pre-ASP and ASP periods for gram-positive organisms

Organism	<i>S. aureus</i>			CoNS			<i>E. faecalis</i>			<i>E. faecium</i>		
	Pre-ASP (n=693)	ASP (n=607)	<i>p</i>	Pre-ASP (n=200)	ASP (n=155)	<i>p</i>	Pre-ASP (n=110)	ASP (n=93)	<i>p</i>	Pre-ASP (n=67)	ASP (n=44)	<i>p</i>
Gentamicin	—	—	—	—	—	—	81	74	0.25	97	98	1.0
Linezolid	100	100	—	99	100	.21	100	100	—	100	100	—
Methicillin	49	56	.012	35	44	.09	—	—	—	—	—	—
Moxifloxacin	82	81	.67	62	68	.26	—	—	—	—	—	—
Vancomycin	100	100	—	100	100	—	100	97	0.09	27	27	—

Note: *S. aureus* = *Staphylococcus aureus*; CoNS = coagulase-negative staphylococci; *E. faecalis* = *Enterococcus faecalis*; *E. faecium* = *Enterococcus faecium*.

Table 5. Percent susceptible of antimicrobial stewardship program (ASP)–focused antibiotics between pre-ASP and ASP periods for gram-negative organisms

Organism	<i>P. aeruginosa</i>		<i>E. coli</i>		<i>K. pneumoniae</i>		<i>E. cloacae</i>		<i>S. marcescens</i>		<i>A. baumannii</i>	
	Pre-ASP (n=197)	ASP (n=193)	p	Pre-ASP (n=161)	ASP (n=215)	p	Pre-ASP (n=94)	ASP (n=83)	p	Pre-ASP (n=43)	ASP (n=42)	p
Amikacin	86	90	.19	97	100	.01	99	100	.35	98	100	.32
Cefepime	85	86	.73	95	95	.95	96	89	.17	95	100	.16
Ciprofloxacin	74	79	.28	69	72	.50	97	94	.36	88	95	.25
Gentamicin	81	80	.72	85	87	.60	90	92	.43	95	98	.57
Meropenem	88	81	.57	100	100	—	99	100	.63	98	100	.34
Piperacillin-tazobactam	90	82	.02	93	95	.48	75	75	.15	88	71	.89
Tobramycin	87	95	<.01	82	88	.18	90	93	.13	95	79	.58
												.02
												.90
												.100
												.54

Note: *P. aeruginosa* = *Pseudomonas aeruginosa*; *E. coli* = *Escherichia coli*; *K. pneumoniae* = *Klebsiella pneumoniae*; *E. cloacae* = *Enterobacter cloacae*; *S. marcescens* = *Serratia marcescens*; *A. baumannii* = *Acinetobacter baumannii*

a meta-analysis that showed 11% to 38% reduction in DDD per 1,000 patient days due to stewardship interventions.¹⁴ Total systemic antibiotic financial expenditures showed an annual savings of \$1,877,956. The financial observations presented herein are consistent with a more recent ASP study from Beardsley and colleagues that reported an average annual cost savings of \$920,070 to \$2,064,441.¹⁵ However, our study differs with the aforementioned study, as their savings were based on the difference of projected and actual expenditures. In contrast, our study more conservatively compared with the baseline and therefore the actual savings are possibly greater than reported. Similarities between the 2 studies include utilization of both infectious diseases-trained PharmD and MD providers and relatively similar FTE allocations (1 PharmD / 0.5 MD and 0.8 PharmD / 0.5 MD) for our study and Beardsley and colleagues' study, respectively. The settings were also similar as both institutions were academic medical centers, with 880 beds at their institution and 709 beds at ours.

Several ASP-initiated changes to clinical pathways occurred during the observed periods that we believe contributed to shifts in therapy and thus antibiotic utilization. Two such changes included a shift in the preferred empiric therapies for febrile neutropenia and HAP/VAP/HCAP. These changes represented a savings opportunity in switching to cefepime from piperacillin-tazobactam and meropenem that coincided with our antibiogram showing nearly equal activity for cefepime, piperacillin-tazobactam, and meropenem against *P. aeruginosa*. With cefepime as the preferred agent in both clinical pathways, non-carbapenem antipseudomonal β -lactam (cefepime and piperacillin-tazobactam use combined) use increased 18% with a corresponding decrease in carbapenem use of 31%. Further breakdown of the utilization reflected that meropenem and piperacillin/tazobactam use decreased by 48% and 26%, respectively, while cefepime increased by approximately 4-fold. These findings further support our observed qualitative changes in antibiotic use, which translated into financial savings. However, these changes in preferred agent did not consistently translate into susceptibility changes, as we noted an 8% decrease in *P. aeruginosa* susceptibility to piperacillin-tazobactam despite decreased use. This is not necessarily surprising, because the relationship between antibiotic use and susceptibility rates has been inconsistent in a variety of studies.^{16,17} It is worth noting that our observation is similar to North American surveillance trends

leading up to this period reflecting approximately a 4% decrease in *P. aeruginosa* susceptibility to piperacillin-tazobactam.¹⁸ Finally, the decrease in meropenem use coincided with a 21% increase in *A. baumannii* susceptibility to meropenem, which is in contrast to United States surveillance trends.¹⁹

ASP-initiated changes in our formulary led to significant shifts in antimicrobial use, specifically with fluoroquinolones, as recently described elsewhere.²⁰ In 2011, a formulary restriction was placed on ciprofloxacin use based on dramatically declining susceptibility of *Escherichia coli* from 2006 to 2010 (20.7%-32.8% nonsusceptible; $p = .025$). This change was consistent with recommendations on avoiding empiric agent use in settings of high resistance as per the 2010 Infectious Disease Society of America and European Society for Microbiology and Infectious Diseases international clinical practice guidelines for treatment of acute uncomplicated cystitis and pyelonephritis in women.²¹ This restriction effectively limited the agent's use to a short list of mostly prophylactic indications and culture-directed therapy (susceptibility must have been demonstrated). Through regression analysis, this approach revealed a positive association between ciprofloxacin use and *E. coli* resistance rates. For the comparison periods in that study, susceptibility of *E. coli* to ciprofloxacin increased 8.7%. For the present study's analysis, in evaluating our pre-ASP and ASP periods, a 56% decrease in overall fluoroquinolone use was observed. We noted a 7% decrease in *methicillin-resistant Staphylococcus aureus* (MRSA) among staphylococci cultures within this period. Additionally, during this period, MRSA agent use had a nonsignificant decrease of 4%. While we did not evaluate this relationship in our study, statistical correlations between fluoroquinolone use and MRSA rates in our institution have been established previously.^{22,23} This phenomenon has also been described in a study by Madras-Kelly and colleagues with levofloxacin restriction leading to 50% reduction in MRSA.²⁴ These reports suggest that the decrease in MRSA rates is correlated with decrease in fluoroquinolone use.

Aminoglycoside use was evaluated with the ASP-focused antibiotics; it was suspected that utilization might have been affected by initiatives with other antibiotics such as the ciprofloxacin restriction. However, we observed a decrease in aminoglycoside use of 10%. This downward trend is consistent with national reports of use from 2002 to 2009 showing aminoglycoside use has decrease by 41%.²⁵ It has

been suggested that the decreased use in aminoglycosides relates to the availability of other agents with gram-negative activity and superior safety profiles.²⁶ Corresponding to our decreased aminoglycoside use, we observed increased susceptibility to aminoglycosides with *P. aeruginosa*, *E. coli*, and *A. baumannii*. However, *S. marcescens* showed decreased susceptibility. The increased susceptibility differs from trends observed nationally leading up to this period.¹⁹

This study is not without limitations. While ASP outcomes of resistance, antibiotic utilization, and financial impact were evaluated, important ASP clinical goals of improving the safe and efficacious use of antibiotics for improving patient outcomes were not. The lack of a measurement of clinical outcomes limits the conclusion on the overall effectiveness of this ASP in that regard. The financial analysis did not attempt to address the cost avoidance changes inherent with some antibiotics achieving generic status during the study period or changes occurring with purchase contracts. The evaluations on susceptibilities centered on stewardship-focused antibiotics and thus may have missed selective pressure for resistance on antibiotics not targeted by our program. Finally, although generally absent in the stewardship literature, our study did not account for changes that occurred in our infection control and prevention program or the potential impact of drug shortages during the study period that could have had measurable effects on resistance, antibiotic utilization, and antibiotic financial expenditures.

In conclusion, following the initiation of an ASP, significant decreases in utilization, increases in cost savings, and an unexpected decrease in MRSA rates occurred. These outcomes are consistent with the goals of decreasing unnecessary antibiotic exposure to patients, decreasing rates of resistance, and reducing avoidable health care financial expenditures. Such findings are utilized in the ongoing justification for maintaining and expanding our stewardship program, and this evaluative exercise serves as an example that can be employed by other similar stewardship programs.

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The authors declare no conflict of interests.

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