COMMENTARY

The Economics of Antimicrobial Stewardship: The Current State of the Art and Applying the Business Case Model

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Antimicrobial resistance (AR) among bacterial pathogens is an enormous burden for hospitals and a major public health concern, and it is considered to be a global crisis.[1] AR impacts healthcare delivery systems worldwide, because it is associated with healthcare-associated infections (HAIs).[2-5] Development of AR is linked with antimicrobial pressure, because substantial evidence demonstrates a causal relationship between antimicrobial use and the emergence of AR.[6-16] In most healthcare settings, AR is associated with increased morbidity, mortality, and healthcare costs.[6]

The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) recognize the gravity of AR and have published recommendations regarding the appropriate and optimal use of antimicrobial agents for more than 2 decades.[6,7,17] Evidence supporting institutional development of a formal antimicrobial stewardship program (ASP) is summarized in the latest IDSA/SHEA guidelines.[6] The authors of this document are unequivocal in stating that effective ASPs "can be financially self-supporting and improve patient care"[6(p162)] and cite 6 studies to illustrate this concept.[18-23] Much of the economic focus in these cited studies is on cost reductions in the pharmacy budget and is based on the argument that 30%–50% of antimicrobial use may be inappropriate.[24]

Infectious diseases clinicians are in agreement that improved patient care and healthcare outcomes are the ultimate goals of ASPs.[6] For these programs to be successful, they require ongoing personnel and administrative support. Analogous to infection control, ASPs are considered "cost centers" and not "revenue generators,"[25] and they are potential areas for budget cuts.[26] ASP directors must continually present a compelling argument to administrators regarding the financial impact of these programs. Merely monitoring pharmacy budgets may be insufficient and may not demonstrate the full economic impact of the program.

An alternative approach, a business case model, is based on the idea that appropriate antimicrobial selection may increase pharmacy costs but result in more rapid resolution of infection and subsequently shorten hospital length of stay (LOS), reduce the risk of developing resistant pathogens, and improve patient morbidity and mortality. The business model of improved efficiency of care may be the best economic argument in support of the development and maintenance of ASPs.

The ASP at Ohio State University Medical Center (OSUMC) has employed a business case model over the past 4 years that has been successful in promoting financial return on investments to the program. In this article, we review the economic studies that support the presence of ASPs to illustrate the diversity of study methods and the absence of a standardized approach, which limits attempts to build a compelling economic argument for these programs. We discuss the standard economic models available for analysis of the financial impact of ASPs and outline some of the current difficulties inherent in their application. Finally, we outline the use of a pragmatic business case model that we have successfully applied as a component of our ASP at OSUMC.

CURRENT STUDIES

In the IDSA/SHEA guideline, the authors emphasize that ASPs can be financially self-sustaining with an annual savings of $200,000–$900,000[6] and cite 6 studies to support this statement.[18-23] Despite diverse patient populations and study objectives, each of these studies relied on a reduction of antimicrobial (drug) costs as the primary metric for economic success. The impact on patient outcomes was either not examined or, if mentioned, not systematically included in the

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quantitative analyses. A summary of these studies is provided in Table 1.

The medical literature was further reviewed for the period after the IDSA/SHEA guideline was published. Many publications outlined strategies for ASP implementation that reviewed the principles delineated in the IDSA/SHEA guideline. Among the published studies that demonstrated outcomes, most focused on quantifying reductions in antimicrobial use, the impact of antimicrobial reductions on the prevalence of resistance or *Clostridium difficile* infection rates, or monitoring of process measures.[27-31] Some studies outlined demonstrable reductions in antimicrobial use and infection rates but did attempt to quantify cost savings.[27,29,31] One analysis went beyond calculations of cost savings from antimicrobial use alone to quantifying the impact of reductions in infection rates and total cost impact.[28] These authors appear to have applied some of the methods that we outline in our business case model below. These additional studies are also summarized in Table 1. There appears to be a paucity of studies that use standard economic models correlating cost with improved quality of care, which is a relationship that is not considered when only drug costs are measured. Furthermore, little is published on applying pragmatic business models, as we discuss in the last section of this article.

STANDARD ECONOMIC MODELS

Economic models that examine cost and relate cost to quality are ideal for supporting the development and maintenance of ASPs. These complex types of analyses traditionally have been the domain of healthcare economists. There are 3 standard types of objective economic analyses used to compare health outcomes and costs: cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis.[25,32-34] The economic premise for these approaches is that, if limits on resources exist and if resources used for one activity are not available for another activity, then the activity that yields the greatest benefit is desirable.[32] Allocating resources to a less beneficial activity is, therefore, considered harm.

Cost-benefit analysis measures the outcomes strictly in terms of monetary units.[25,35] If a proposed intervention costs less than the benefit's monetary value, then the intervention is considered worthwhile. Cost-effectiveness analysis measures the outcomes in units that more directly reflect benefit (eg, increased survival, disability-days saved, or cases avoided).[25,32,34] This method examines the monetary cost of the intervention relative to the measure of effectiveness. Cost-utility analysis is a special type of cost-effectiveness analysis in which quality of life is considered as the measure of effectiveness, expressed as quality-adjusted life-years (QALYs).[25,34] A QALY is a measure to correct an individual's life expectancy on the basis of the level of health-related quality; it is the arithmetic product of life expectancy and a weighted quality measure.[36] Among health economists, cost-effectiveness analysis and cost-utility analysis are considered to be the standard methods for economic analysis in healthcare.[35]

Studies evaluating the impact of ASPs using these standard economic models are very limited. A study published in 2009 examined the impact of ASP interventions on reducing morbidity and mortality associated with healthcare-associated bacteremia.[37] A decision-analysis model compared costs and outcomes among patients with bacteremia who did and did not receive an ASP consultation. The cost for patients with bacteremia who received an ASP consultation was $39,737 (95% confidence interval [CI], $27,272–$53,017) per patient, and the cost for patients with bacteremia who did not receive an ASP consultation (ie, those who received standard care) was $39,563 (95% CI, $27,164–$52,797). The difference in effectiveness between the 2 strategies was 0.08 QALYs, with $2,367 per QALY gained. The authors concluded that maintaining an ASP to improve care for patients with bacteremia was cost-effective from the hospital perspective.

Infection control programs also struggle to demonstrate their economic value to hospital administration. One analysis of 70 infection control interventions audited these studies with a data collection tool that contained 23 data elements from the Harvard Cost-Effectiveness Analysis.[38,39] Most of the studies were deemed simple cost analyses. The authors outlined their efforts to standardize the methods and reporting of economic evaluations of healthcare technology[40-43] and conclude that "the analyses we audited were for the most part much less sophisticated and did not meet the recommended standards."[38(p104)] It is likely that a similar conclusion would be drawn from studies in the ASP economic literature.

There may be several barriers for ASPs to conduct these more rigorous economic analyses. The primary barrier is likely access to trained healthcare economists who can assist with the data collection and modeling. Academic medical centers may have access to these individuals, but most community-based programs will not. Additional barriers that may be confronted are adequate personnel to conduct the analyses outlined here and ready access to economic and patient data. The absence of electronic means for data collection, which requires that data be collected manually, may also provide a significant barrier.

BUSINESS CASE MODEL

A core principle in developing a successful business plan for ASPs is outlined by Ward et al.[44] Simply put, it focuses on "asset and capacity management by improving throughput to optimize investment in fixed costs."[44(p95)] Hospitals have very high fixed costs, on the order of 85%–90% in the short term,[45] which leaves a very small amount of variable costs to be impacted by cost savings. Thus, ASPs with a primary focus on saving through reducing antimicrobial expenses will have a limited and nonsustainable impact on variable costs and essentially no impact on fixed costs. To confirm this conclusion, a recent analysis demonstrated that, because the fixed

costs are so high, most clinical improvement programs cannot reduce expenses enough to cover these high fixed costs.[46]

According to Ward et al,[44] the key is employing a "cost efficiency strategy" in which more patients can receive care with the same investment in fixed costs. This is particularly true in the setting of third-party payers, in which a fixed amount is paid per patient on the basis of diagnosis or diagnosis-related group (DRG). Shortening a patient's hospital stay, for example, allows a new patient with a new DRG payment to occupy that same bed, providing coverage for the hospital's fixed costs that may not have been covered by the former patient, especially if that patient had a prolonged hospital stay attributable to complications, such as HAI.

Perencevich et al[25] published a seminal paper outlining a step-by-step approach for a business case model for infection control. The cost efficiency concepts and principles outlined above are integral to this approach, and the format outlined for infection control programs is equally applicable to ASPs. We developed our business plan independently of this approach but recognized retrospectively how this approach could be aligned with our business model. The steps include (1) framing the problem, (2) meeting with key administrators, (3) determining the costs of administering the proposed program, (4) determining the costs that can be avoided, (5) determining the specific costs associated with the problem of interest at the hospital, (6) calculating the financial impact, (7) including the additional financial or health benefits, (8) making the business case, and (9) prospectively collecting cost and outcome data. The final step, which focuses on local outcome data, specifically hospital LOS or intensive care unit (ICU) LOS, is critical and provides the data that argue for the ongoing economic impact of the program.

Healthcare epidemiologists are defining the attributable cost of HAIs[47,48] and infections with multidrug-resistant organisms (MDROs)[49,50] in an effort to build a business case for infection control efforts. The Centers for Disease Control and Prevention (CDC) developed a comprehensive document, *The Direct Medical Costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention* (available at http://www.cdc.gov/ncidod/dhqp/pdf/scott_costpaper.pdf), that provides the average attributable costs per patient for specific HAIs. These types of data are critical for step 4 by helping to define the potential costs associated with problems being directly addressed by ASP or infection control programs. These attributable costs often account for fixed hospital costs due to HAIs or infections with MDROs that result in prolonged hospitalizations and are not covered. Upon implementation of the ASP, these estimated costs should be replaced by the actual outcome and cost data that were prospectively collected from local data.

In early 2008, we sought to expand the impact of antimicrobial stewardship at OSUMC and developed a business plan that independently followed the principles outlined by Perencevich et al.[25] After the development of our plan, we recognized that the steps presented, although developed for infection control, aligned well with the strategy that we followed. We framed the problem by assessing those areas in the medical center in which we felt we could have the greatest initial impact (step 1). We developed a 5-year plan and estimated the number of personnel who would be required over that period. We calculated the actual personnel and operating costs of the program, accounting for additional infectious diseases specialty practice pharmacists, a data manager, and a microbiology technologist to be added during the early years of the 5-year plan (step 3).

We determined that costs could be avoided in 4 areas (step 4). First, we projected that cost savings would result from improved antimicrobial use throughout the medical center by applying the evidence-based principles of feedback auditing and prior authorization outlined in the IDSA/SHEA guidelines.[6] This would result in some reductions in overall antimicrobial costs. We recognized that there was a limitation to the expected antimicrobial cost reductions and that these alone could not sustain the economic impact of our program. Second, we estimated the reduction in the number of *C. difficile* infections that would result from antimicrobial optimization using published attributable cost data to make cost estimates. Third, we projected that interventions designed to optimize antimicrobial management, specifically in the ICUs, would result in reductions in hospital LOS. The LOS reduction allowed lower costs for patient care given fixed reimbursement, thereby enhancing the institution's revenue under prospective payment. This was a direct application of the cost efficiency strategy described and was likely the most important cost factor that we considered. Fourth, we projected additional reductions in targeted MDROs by integrating the ASP with ongoing infection control activities. We again used the published attributable cost data to make estimates of cost reductions. In making the cost estimates, we attempted to use institutional cost data as much as possible but often had to rely on published data.

Combining the projected costs of the program with the estimated cost reductions, we created a 5-year budget plan outlining the financial impact (step 6). We projected that the program would cover expenses and be cost saving during the proposed 5-year budget time period. We met with our key administrators and financial staff (step 2) and made the business case based on our projections (step 8). Upon approval by administration and medical staff leadership, we implemented the business plan. We had a preexisting part-time infectious diseases specialty practice-trained pharmacist, and we hired 2 full-time infectious diseases specialty-trained pharmacists and a data manager during the first year. We added a third full-time infectious diseases specialty-trained pharmacist during the second year. We have since added a clinical microbiology technologist to assist with laboratory-related ASP issues.

A recent intervention at our institution illustrates the effective application of the business case model and cost efficiency strategy.[51] In March 2009, we instituted a polymerase

TABLE 1. Summary of Antimicrobial Stewardship Program (ASP) Studies Demonstrating Cost Savings

Study	Setting	Type of ASP intervention	Outcome of ASP intervention	Estimated cost savings
Schentag et al 1993[18]	Community-based hospital, Buffalo, New York	Active feedback auditing. Application of customized software linking mismatches between antibiotic orders and microbiology results. Pharmacists contacted prescribing clinicians.	Over 90% of recommended prescribing changes were implemented.	Real-dollar expenditures for antimicrobial agents decreased by greater than $200,000 per year.
Carling et al 2003[19]	University-affiliated teaching hospital, Boston, Massachusetts	Multidisciplinary approach to reduce antimicrobial use to control *Clostridium difficile* infections. A physician and physician and pharmacist recommended alternative therapies.	Compliance with recommendations exceeded 85% within 6 months and reached 93% by the end of the intervention with a 22% decrease in broad-spectrum antimicrobial use and a significant decrease in *C. difficile* infections.	The estimated net savings in drug acquisition costs was $200,000–$250,000 per year.
LaRocco 2003[20]	Small community hospital, West Monroe, Louisiana	Concurrent medical record reviews with feedback auditing 3 times weekly.	There were 488 recommendations made; 336 (69%) were accepted and 126 (26%) were rejected.	The average antimicrobial cost per patient decreased from $18.21 to $14.77; total estimated cost reduction of $177,000.
Ansari et al 2003[21]	Tertiary university hospital in Tayside, Scotland	Concurrent feedback auditing by pharmacists; antimicrobial use monitored by interrupted time series analysis during a 2-year study.	Changes in slope of 0.27 defined daily doses per 100 bed-days per month and £1,908 per month.	The overall estimated impact was significant at £572,448 over 24 months.
Ruttimann et al 2004[22]	University-affiliated teaching hospital, Basel, Switerzland	Quasi-experimental design; combination of formulary restriction, continued education, and implementation of guidelines.	Total antimicrobial consumption decreased by 36% ($P < .001$) and intravenous consumption decreased by 46% ($P < .01$).	Overall antimicrobial expenditures decreased by 53%, equating to $100 per patient admitted.
Lutters et al 2004[23]	University hospital for geriatric patients, Geneva, Switzerland	Drug use reviews of antimicrobial use before, during, and after the educational program; enrolled 3,383 patients.	15% reduction in the proportion of patients exposed to antimicrobial agents ($P = .08$); 26% decrease in the number administered ($P < .001$).	54% decrease in cumulative daily antimicrobial costs.

Lipworth et al 2006[27]	Two university-affiliated hospitals, Philadelphia, Pennsylvania	Formulary restriction of ceftazidime and ceftriaxone; target to decrease extended spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae.*	86% to 97% decrease in targeted agents; 22% to 45% decrease in infections with targeted organisms.	No cost estimates calculated for the noted reductions in antimicrobial agents and rates of infection.
Fishman 2006[28]	Hospital at the University of Pennsylvania, Philadelphia, Pennsylvania	Audit feedback; prior authorization.	Improvement in the appropriate selection of agents from 32% to 90%; increase in cure rate from 55% to 91%; decrease in prevalence of resistance from 9% to 1%.	Savings of $302,400 for antimicrobial costs, $533,000 for infection-related costs, and >$4.25 million in total costs.
Valiquette et al 2007[29]	Secondary and tertiary care hospital, Quebec, Canada	Interventions to control *C. difficile* infections: education, guidelines, feedback auditing.	Targeted antimicrobial consumption decreased by 54% and total by 23%; incidence of infection decreased from 2–3 to 1–1.5 cases/1000 patient-days.	No cost estimates calculated for the noted reductions in antimicrobial agents and rates of infection.
Ohl and Luther 2011[30]	Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina	Multifactorial and comprehensive implementation of ASP strategies.		Cost savings in 2002 of $215,000 with significant reduction in cost per patient-days.
Slain et al 2011[31]	West Virginia University Hospitals, Morgantown, West Virginia	Combination efforts of feedback auditing, formulary restrictions, guidelines, education, antimicrobial cycling, de-escalation of therapy. Focused impact on *Pseudomonas aeruginosa* susceptibilities and antimicrobial use.	Reduction of intravenous ciprofloxacin and ceftazidime decreased from 148 and 62.5 defined daily doses/1000 patient-days to 40 and 24.5 defined daily doses/1000 patient-days, respectively. No impact on resistant rates was noted.	No cost estimates calculated for the noted reductions in antimicrobial agents.

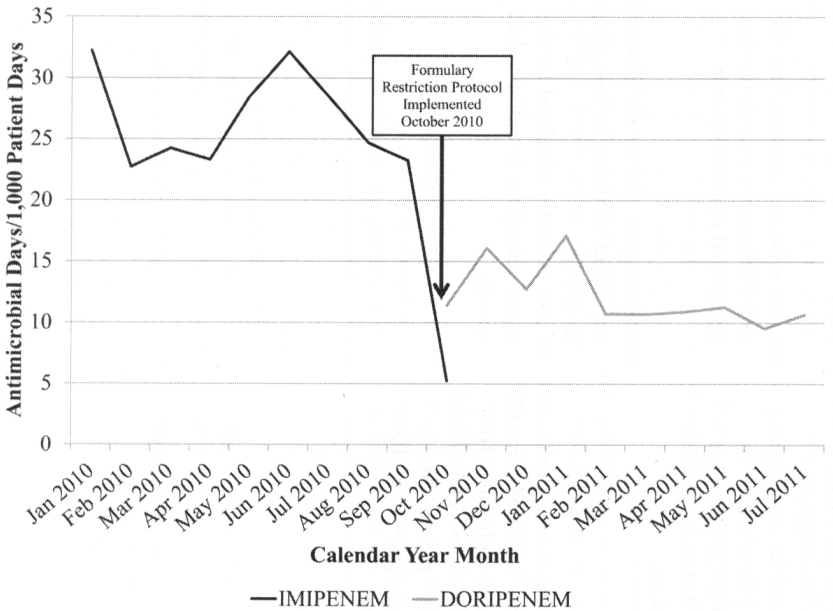

FIGURE 1. Antimicrobial-days per 1,000 patient-days, imipenem and doripenem, January 2010–April 2011. These data are obtained from the antimicrobial data mart as outlined in the text. A switch from feedback auditing for imipenem to prior authorization for doripenem is indicated by the arrow.

chain reaction (PCR) test for rapid identification of *Staphylococcus aureus* (methicillin-susceptible *S. aureus* [MSSA] and methicillin-resistant *S. aureus* [MRSA]) and coagulase-negative staphylococci in blood cultures. As soon as growth with gram-positive cocci appeared in the blood culture bottles, the PCR test was applied. We compared the preintervention time period to the intervention time period. When the PCR results were available, the clinical microbiology technologist paged an ASP pharmacist who contacted the clinician providing care for the patient and provided real-time guidance on optimal antimicrobial therapy. Key outcomes measured were time to appropriate antimicrobial therapy, LOS, and hospital costs. The mean time to switching to optimal therapy was shorter in the intervention group, as was the mean hospital LOS (6.2 days less), with an estimated decrease in hospital costs of $21,387 per patient. There was some reduction in pharmacy costs in the intervention time period, but the major cost reductions were from decreased ICU LOS, which had a significant financial impact on fixed hospital costs through improvements in cost efficiency. ASP interventions that continue to improve the cost efficiency of care will produce these positive economic results.

Other OSUMC ASP interventions focus on feedback auditing on targeted antimicrobials (linezolid, daptomycin, colistin, tigecycline, and imipenem) conducted Monday through Friday by ASP pharmacists and physicians. We added formulary restriction for targeted agents (doripenem replaced imipenem; fidaxomicin added) by instituting a dedicated ASP pager available from 8 AM to 10 PM 7 days a week. To monitor the impact of these interventions on targeted antimicrobial use, we partnered with the OSUMC information warehouse (IW). The IW is a long-standing clinical data repository that facilitates the acquisition and analysis of patient-level data.[52] We employed the IW to create data marts, which allowed ready access to targeted antimicrobial use data by unit, antimicrobial agent, or prescribing physician. The scope includes monitoring antimicrobial use on the patient and drug levels, aggregate data on the number of antimicrobial doses, prescribing timelines, and antimicrobial use based on billing information. Some aspects of the antimicrobial data mart have been recently published.[53]

As an example of its usefulness, the antimicrobial data mart was recently employed to monitor the restriction of doripenem upon its addition to our formulary. Doripenem 4-hour extended infusions replaced imipenem 30-minute infusions to enhance carbapenem activity against increasingly resistant gram-negative pathogens. Imipenem was monitored by feedback auditing but did not require prior authorization. Mean doripenem use was significantly lower than prior mean imipenem use (11 antimicrobial-days per 1,000 patient-days vs 27 antimicrobial-days per 1,000 patient-days; $P = .0008$; Figure 1).

As outlined by the critical step 9 of the Perencevich business case model,[25] major ongoing projects prospectively collect cost and outcome data and emphasize impact on hospital and ICU LOS as part of the cost efficiency strategy. One such example of an ongoing project at OSUMC is the implementation of extended infusion of β-lactam antimicrobials to optimize the pharmacodynamics of these classes of drugs. Lodise et al[54] demonstrated that optimizing the pharmacodynamics

of piperacillin-tazobactam through use of 4-h extended infusions improved patient outcomes among critically ill patients. Mortality rate decreased from 31.6% to 12.2%, and hospital LOS decreased from 38 days to 21 days among patients with an Acute Physiological and Chronic Health Evaluation II score greater than 17.

Our ASP began using extended-infusion piperacillin-tazobactam administered at a dosage of 4.5 g intravenously every 8 h, with each dose infused over a 4-h period on August 1, 2008. As the result of an interim analysis of OSUMC data for piperacillin-tazobactam for patients with *Pseudomonas aeruginosa* bacteremia, ASP began the use of extended-infusion cefepime and doripenem. Outcomes studies with an emphasis on these agents for *P. aeruginosa* bacteremia and/or pneumonia are currently ongoing. The major metric is the impact of this intervention on total hospital LOS and ICU LOS determined by applying the same cost efficiency model illustrated in our rapid staphylococcal PCR intervention.[51]

Another ASP initiative aimed at optimizing patient care relates to the management of candidemia. Clinical microbiology laboratory personnel page an ASP pharmacist during normal business hours when yeast is detected on Gram stain from a blood culture specimen. The pharmacist ensures that the patient initiates appropriate antifungal therapy and recommends infectious diseases and ophthalmology consultations. The ASP pharmacist is also alerted when peptide nucleic acid fluorescence in situ hybridization (PNA FISH; Biomérieux) results, which provide identification at the species level, are available for each specimen, thereby enabling early tailoring of therapy. The same cost efficiency outcomes measures are gathered.

ASPs that rely solely on continuing reductions in pharmaceutical costs to justify program costs may not be financially sustainable after a few years. In addition, decreases in pharmacy budgets likely do not demonstrate the full economic impact of ASP activities. This article emphasizes that ASPs should employ a pragmatic business model based on a cost efficiency strategy to remain viable. We outlined the development of our ASP built on these principles and provided concrete examples from our ASP interventions in which this model is applied. Our focus on cost efficiency strategy with the collection of appropriate patient outcome data has allowed us to demonstrate, each year since the inception of the ASP interventions, continuing cost reductions attributable to those ASP interventions. Application of this business case model has been highly successful and has provided sufficient data to maintain the confidence and support of our medical staff and hospital leadership.

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