Antimicrobial Stewardship: A Matter of Process or Outcome?

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The risk of antimicrobial resistance and superinfection is increasing alongside rates of hospital-acquired infection. Imprudent antibiotic use combined with few novel antimicrobials can speed resistance. Antimicrobial stewardship programs (ASPs) advocate for judicious use of available antimicrobials to preserve their usefulness. Decreased antibiotic expenditures was the backbone of early justification for ASPs, but the function of these programs has evolved into measuring the quality and appropriateness of antimicrobial use. Proper evaluation of an ASP helps to inform which methods work best for a particular institution and can help to define best practices at a more global level. Study design and duration limitations, however, can make it difficult to measure the impact of these programs. Process measures have been validated and can evaluate quality of care; however, they do not adequately describe the clinical impact of these programs at the patient level. Outcome measures also have limitations; they are not a direct measure of quality of care. Therefore, both process and outcome measures need to be defined and assessed when evaluating an ASP to confirm that goals of the intervention are attained and clinical objectives are met. Most available well-designed studies judging the effectiveness of ASPs use process measures alone. Adding improvements in clinical outcomes to process measures would theoretically attract the attention of a broader audience and provide additional support to expand current ASPs and develop novel ASPs.

Key Words: antimicrobial stewardship, measures, process, outcome.
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OUTLINE

Increasing rates of hospital-acquired infections are associated with increased costs, adverse events, antimicrobial resistance, and superinfection, as demonstrated in the 2004 National Nosocomial Infections Surveillance System Report.[1] Antimicrobial agents are unique relative to other drug classes in that increased use is associated with decreased utility secondary to selective pressure, thereby leading to antimicrobial resistance. This ability to change the ecology of an infection means that antimicrobial exposure and subsequent resistance in one individual may result in clinical failure in another individual despite having never been exposed

to the antimicrobial agent. This has been further complicated by the declining number of novel antimicrobial agents aimed at treating drug-resistant infections.[2]

The Infectious Diseases Society of America (IDSA) issued its "Bad Bugs, No Drugs" policy report in 2004 (with periodic updates thereafter) to encourage a community and legislative response to promote the development of new antimicrobials by increasing financial support to a level that matches that of other drug classes.[2] The original goal of 10 new antibacterials by 2020 may take decades, so more immediate efforts to conserve currently available resources are needed. Antimicrobial stewardship programs (ASPs) have been continuously evolving to facilitate the prudent use of antimicrobials in an effort to further preserve the effectiveness of currently marketed antimicrobials. In 2007, the IDSA and the Society for Healthcare Epidemiology of America (SHEA) published joint guidelines to aid institutions in developing programs to enhance antimicrobial stewardship.[3]

These guidelines identify the primary goal of antimicrobial stewardship as "to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as *Clostridium difficile*), and the emergence of resistance."[3] Recent expert reviews have identified strategies and barriers to implementing successful ASPs.[4–6] The purpose of this review is to discuss the effect of ASPs and the optimal measures of effectiveness, including both outcome and process measures.

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Literature Search

A comprehensive literature search for studies that evaluated the effect of ASPs was conducted by using the PubMed database and then was repeated in the Ovid MEDLINE database. Search terms included "antimicrobial stewardship," "antimicrobial prescribing" and "interventions," "antimicrobial management program," "antimicrobial control policy," and "antimicrobial control program" and "impact." These search terms were repeated with "antimicrobial" substituted with "antibiotic." The search was limited to English-language studies in adults aged 19 years and older. Additional studies were identified through bibliographies of review articles and other publications. Identified studies included those that evaluated antimicrobial use, resistance rates and/or susceptibility patterns, cost data, and other clinical outcomes such as length of stay, mortality, and *C. difficile* infection (CDI) rates. Studies that only evaluated compliance with ASP interventions were not included in this review. Uncontrolled before-and-after studies, studies that did not have interpretable data, or studies in which it was unclear how controls were chosen were excluded. Identified studies were included in the review if the full text was readily accessible through PubMed and/or the University of Rochester library system. Included studies were subsequently categorized on the basis of their outcomes evaluated including process measures only, process measures as primary outcomes with outcome measures as secondary outcomes, or outcome measures as primary outcomes with process measures as secondary outcomes.

Evaluating Quality of Medical Care by Measuring the Impact of Antimicrobial Stewardship Programs

According to Dr. H. James Harrington, a pioneer in process improvement methodology, "measurement is the first step that leads to control and eventually to improvement."[7] Evaluating the quality of medical care through measuring the impact of ASPs can identify areas of deficiency and provide targets for intervention and improvement. Measuring the impact of ASPs can also help determine which strategies or methods of antimicrobial stewardship are most appropriate for individual institutions. Although the evidence to support antimicrobial stewardship is mounting, it is difficult to measure the true effect of these established methods due to

the complexity of ASPs, including the presence of potential confounders and limitations relative to study design and statistical methods used to analyze collected data. The ideal outcome variable to measure the effect of ASPs is debatable, so the question arises: is it a matter of process or outcome?

Process-Outcome Relationship

If the primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences, clinical outcomes must be measured to determine whether ASPs have achieved this goal. Commonly measured clinical outcomes that are reflective of the primary goal of antimicrobial stewardship include infection-related mortality, length of hospital stay, rates of readmission, rates of CDI, and antimicrobial resistance rates (Tables 1 and 2).[8–42] Clinical success rates, which may be measured by clinical cure or improvement, are less commonly measured but are of great importance. Often clinicians find it more difficult to measure these outcomes because they are more subjective secondary to the variability in the definition of these terms. According to Dr. Avedis Donabedian, renowned physician and expert in the study of quality in health care and medical outcomes research, "Outcomes… remain the ultimate validators of the effectiveness and quality of medical care."[43] Unfortunately, clinical outcomes may be difficult to causally relate to specific antimicrobial stewardship interventions, even when attempting to control for confounding factors and measuring outcomes over multiple time points.[5] As a result, process measures alone have often been used to measure the impact of such interventions (Table 3).[44–52]

In his groundbreaking article "Evaluating the Quality of Medical Care," Dr. Donabedian describes three aspects of quality in medical care: outcome, process, and structure.[43] Although dichotomous outcomes such as "alive or dead" are definite and easy to measure, other clinical outcomes are not so clearly defined and may be more difficult to quantify. The author emphasizes that they must be used with discrimination. It is important to consider potential confounders and the circumstances under which the outcome is measured, as it may not be a direct measure of the quality of care. For example, a patient may present to the emergency department with septic shock and suspected bacteremia and inappropriately receive empiric narrow-spectrum antibiotic therapy, and still survive if the administered antibiotic provides adequate coverage by chance. A potential way to minimize the possibility of a false conclusion being drawn about the quality of care based on an outcome measurement is by including associated process measures in the evaluation.

Infectious Diseases Society of America guidelines suggest that both process measures and outcome measures are useful in determining the impact of ASPs on antimicrobial use and resistance patterns.[3] However, a process measure is of value only when assumed to have a link to the outcome.[53] For example, if the purpose of a stewardship intervention is to decrease unnecessary exposure of patients to broad-spectrum antibiotics in order to decrease CDI rates, it would be imperative to measure the amount of unnecessary antibiotic consumption in addition to the primary outcome measure of CDI rate. Although antibiotic use is a surrogate marker, adequate measurement in the change from baseline use is essential to demonstrate the effectiveness of the targeted intervention. If broad-spectrum antimicrobial use did not decrease from baseline, then a decrease in CDI rate would not be attributed to the stewardship intervention because it was not effective.

Impact of Antimicrobial Stewardship Programs and Process Measures: Change in Antimicrobial Use and Time to Appropriate Therapy

Antimicrobial stewardship programs were traditionally justified by demonstrating significant cost savings. In accordance, ASPs have often directed interventions at changing antimicrobial use as a means to decrease costs associated with unnecessary antimicrobial therapy.[17, 44–47] Of the studies focusing on cost, intervention strategies consisted of both formulary restriction of targeted agents and education to providers in order to persuade prescribing behavior. One study showed an increase in appropriate dosing of parenteral cefazolin, clindamycin, and metronidazole through antibiotic order forms, resulting in cost savings for both consumables and labor saved by less frequent dosing of all three drugs.[45] Another study demonstrated $24,620 in monthly savings for all antimicrobials after substituting less expensive agents and reducing total use by using a three-tiered formulary classification system.[17] Tables 2 and 3 highlight significant studies that primarily used process measures to determine the impact of ASPs on antimicrobial use.

Table 1. Impact of Antimicrobial Stewardship Programs and the Use of Outcome Measures as Primary End Points and Process Measures as Secondary End Points

Antimicrobial Stewardship Team and Setting	Strategies and Interventions	Impact
ICU physicians; pediatric ICU in a university hospital[8]	Restriction: change in antibiotic policy from gentamicin to amikacin	Immediate significant reduction in the number of infections with multidrug-resistant *Enterobacter cloacae* by 7.5 cases/mo ($p<0.0001$) and sustained change in slope by 1 case/mo ($p=0.002$); no change in rates of confirmed nosocomial infection or mortality
ID M.D.; VA Medical Center[9]	Restriction of clindamycin use, requiring ID consultant approval for use	Immediate decrease in prevalence of CDAD by 26.3 cases/quarter ($p<0.001$) and a sustained decrease in slope by 3.8 cases/quarter thereafter ($p<0.001$); estimated cost savings of $2000 attributable to each case of CDAD avoided; cost of implementing the restriction not provided
ID M.D.; 500-bed hospital[10]	Restriction of routine cephalosporin use, requiring primary team to seek ID approval for use	80.1% reduction in hospitalwide cephalosporin use in 1996 compared with 1995; 44% reduction in incidence of ceftazidime-resistant *Klebsiella* infection and colonization throughout medical center ($p<0.01$), with 70.9% reduction in all ICUs ($p<0.001$) and 87.5% reduction in SICU; 68.7% increase in incidence of imipenem-resistant *Pseudomonas* infection throughout hospital ($p<0.01$)
Multidisciplinary ID service; 275-bed hospital[11]	Concurrent review with feedback; patients receiving inappropriate therapy randomized to study group vs control group; typed summary in patient's medical record within 2 hrs of randomization to study group	Length of stay lower (5.7 days vs 9 days, $p<0.0001$) and mortality rate lower (6.3% vs 12%, $p=0.175$) in study group vs control group
ID M.D.; tertiary care facility[12]	Restriction of third-generation cephalosporins, vancomycin, and clindamycin; encouraged use of piperacillin-tazobactam and ampicillin-sulbactam.	Significant decrease in MRSA and ceftazidime-resistant *Klebsiella* species; increased proportion of resistant *Acinetobacter* isolates
ICU physicians; University Medical Center ICU[13]	Antimicrobial cycling: 2-yr study in which first year had non–protocol-driven antibiotic use compared with second year, during which a quarterly rotating empiric antibiotic schedule was used	Decreased incidence of resistant gram-positive coccal infections (7.8/100 vs 14.6/100 admissions), gram-negative bacillary infections (2.5/100 vs 7.7/100 admissions), and mortality associated with infection (2.9 vs 9.6 deaths/100 admissions) ($p<0.0001$ for all) during antibiotic rotation; antibiotic rotation was an independent predictor of survival (OR 6.27, 95% CI 2.78–14.16)
(Team not specified); 800-bed hospital[14]	Restriction: antibiotic policy change from cefotaxime to ceftriaxone	Immediate increase in CDAD by 19.7 cases/quarter ($p=0.074$) and sustained increase in slope by 4.7 cases/quarter ($p=0.073$)
ID M.D., ID Pharm.D. 638-bed hospital[15]	Education and guidelines to decrease use of antibiotics associated with *Clostridium difficile* infections; provided alternative therapy recommendations and recommended shorter treatment duration based on IDSA guidelines	*C. difficile* incidence decreased 60% from 2003–2004 and 2005–2006; decrease in antibiotic consumption including total (23%) and targeted (54%) use; decrease in use of cephalosporins, clindamycin, macrolides, and ciprofloxacin; increase in use of "respiratory fluoroquinolones" and piperacillin-tazobactam
ICU staff, ID M.D., ID Pharm.D.; 24-bed combined ICUs[16]	Comprehensive clinical decision support system: ADVISE program implemented to increase appropriate antibiotic use	Improvement in susceptibility of *Pseudomonas* to imipenem: 18.3%/year ($p=0.009$) and gentamicin 11.6%/year ($p=0.02$) compared with preintervention trend; less clinically significant changes observed in rates of gentamicin and ciprofloxacin susceptibility in the inducible Enterobacteriaceae group

ID = infectious diseases; ADVISE = Antibiotic Decision Support for the Victorian Infectious Diseases Service; CDAD = *C. difficile*–associated diarrhea; CI = confidence interval; ICU = intensive care unit; IDSA = Infectious Diseases Society of America; MRSA = methicillin-resistant *Staphylococcus aureus*; OR = odds ratio; SICU = surgical intensive care unit.

Table 2. Impact of Antimicrobial Stewardship Programs and the Use of Process Measures as Primary End Points and Outcome Measures as Secondary End Points

Antimicrobial Stewardship Team and Setting	Strategies and Interventions	Impact
ID approval system; 1208-bed hospital[17]	Formulary restrictions; 3-tiered classification system	Monthly savings for all antibiotics: $24,620 ($p<0.03$) as a result of both substituting less expensive agents and reducing total use; no associated changes in inpatient mortality or length of stay
ID fellow, ID Pharm.D.; 600-bed hospital[18]	Concurrent review with intervention through nonpermanent medical record note in patients receiving 1 of 10 target antimicrobials for > 3 days (intervention group vs standard of care group)	85% of suggestions implemented; annual cost savings: $390,000; no significant differences in clinical or microbiologic outcomes
MICU physicians; 146-bed hospital[19]	Restrictive guidelines: patients received standard initial therapy for suspected VAP with i.v. ciprofloxacin for 3 days; after 3 days, if CPIS < 6, treatment was stopped in the study group	Significant differences observed in the study group vs control group: proportion of patients who received antibiotics for > 3 days (28% vs 97%), length of ICU stay (9.4 vs 14.7 days, $p=0.04$), and antimicrobial resistance and/or superinfection (15% vs 35%)
ID M.D., ID Pharm.D., clinician educators; 697-bed hospital[20]	Education: academic detailing provided to ordering M.D. about appropriate antibiotic use; computerized flagging of levofloxacin and ceftazidime orders to determine appropriateness	37% reduction in number of days of unnecessary levofloxacin and ceftazidime use/2-wk interval; 41% reduction in use of levofloxacin and ceftazidime over an 18-wk period ($p<0.001$ for both); no significant differences in length of stay, ICU transfers, or in-hospital deaths ($p \geq 0.10$ for all)
ID Pharm.D., ID M.D.; 174-bed hospital[21]	Prospective audit with intervention and feedback (choice of antibiotic, duration, i.v. to p.o. conversion)	22% decrease in use of i.v. broad-spectrum antibiotics ($p<0.0001$) despite 15% increase in acuity of patient care over 7 yrs; decrease in incidence of *Clostridium difficile* from 2.2 to 1.4 cases/1000 patient-days ($p=0.002$); no significant changes in MRSA or VRE infection rates
ID M.D., ID Pharm.D., bacteriologist; 600-bed hospital[22]	Local prescribing guideline; formulary restriction; audit with intervention and feedback	Initial decrease in unjustified prescriptions from 6% to 0% ($p<0.001$), with subsequent increase to 3% ($p<0.05$) and stabilization; prevalence of ESBL-producing Enterobacteriaceae decreased from 12.5% to 3.6% over 3 yrs ($p<0.001$); prevalence of MRSA and ceftazidime-resistant *Pseudomonas* did not change significantly
ID M.D., ID Pharm.D.; 725-bed hospital[23]	Restriction and ID approval: increasing restriction on vancomycin and third-generation cephalosporin use over 10-yr period	85.5% decrease in third-generation cephalosporin use; VRE prevalence increased steadily from 17.4% to 29.6% during the 10-yr period ($p<0.001$); clindamycin use associated with VRE prevalence ($r=0.75$, $p=0.01$)
ID M.D., ID Pharm.D.; 250-bed hospital[24]	Antibiotic order forms, review and feedback, formal antibiotic prescription policy, active revision of inappropriate prescriptions; stepwise interventions over 6 mo	Sustained reduction of antibiotic consumption ($R^2=0.6885$, $p=0.01$); total cost savings of $913,236; third-generation cephalosporin resistance/18 mo: *Escherichia coli* and *Klebsiella* nonsignificant changes, *Proteus* 32.5% reduction, *Enterobacter cloacae* 80% reduction; ampicillin-sulbactam resistance/18 mo: *E. coli* nonsignificant changes; imipenem-cilastatin resistance/18 mo: *Pseudomonas* 100% reduction; cefepime resistance/18 mo: MRSA 36.3% reduction

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Table 2 (continued)

Antimicrobial Stewardship Team and Setting	Strategies and Interventions	Impact
ICU M.D.; 860-bed hospital with 11-bed ICU[25]	Guidelines: algorithm to determine ICU antibiotic use with periodic review of appropriateness of antibiotic selection, oral quinolone use, aminoglycoside duration limitation as dual therapy	Costs of antibiotic use progressively decreased (by 100% in 1994, 81% in 1995, 65% in 1998); antibiotic selective pressure diminished from 940 (in 1994) to 610 (in 1998) days of antibiotic use/1000 days, $p<0.00001$; significant decrease in nosocomial infections due to antimicrobial-resistant microorganisms from 37% (in 1994) to 15% (in 1998) of all nosocomial infections ($p<0.00001$) after 3 yrs of implementation; MRSA: 79% reduction/4 yrs; ceftazidime resistance: Enterobacteriaceae 52% reduction/4 yrs, *Pseudomonas* nonsignificant change; ESBL: Enterobacteriaceae nonsignificant change
ID M.D., ID Pharm.D., internal medicine department head; 80-bed hospital[26]	Formulary restriction requiring antibiotic approval; comprehensive educational program with lectures and handbooks for prescribers; biannual feedback on prescribing practices; guidelines for antibiotic selection; antibiotic selection checklist	Short-term analysis showed decrease in total antibiotic consumption (DDD)/hospitalized patient by 36% ($p<0.001$) and i.v. DDDs decreased by 46% ($p<0.01$); antibiotic withheld for URI more frequently after intervention (47% vs 27%, $p=0.04$); decrease in delivery of broad-spectrum antibiotics (10% vs 23% of treatment, postintervention vs preintervention groups)
ID M.D. and antimicrobial subcommittee; University hospital[27]	Formulary restriction of select antimicrobials, removal of cefotaxime and ceftazidime from the formulary, replacement of ciprofloxacin with levofloxacin as sole fluoroquinolone	Antimicrobial use decreased by 80% for third-generation cephalosporins and 15% for vancomycin; antimicrobial resistance patterns for *Pseudomonas aeruginosa* demonstrated reversal of previous increases; MRSA rate decreased by average of 3%/year from 1999–2002; antimicrobial expenditures decreased 24.7%, with a cumulative cost savings of $1,401,126 without inflation assumptions
ID M.D., ID Pharm.D.; 731-bed hospital[28]	Formulary restriction and review with feedback; restricted agents required ID approval; controlled agents reviewed within 48 hrs and feedback provided	Significant reduction in total antimicrobial use; no significant change in antimicrobial susceptibility
ICU staff, ID M.D., ID Pharm.D.; 24-bed combined ICUs[29]	Comprehensive clinical decision support system: ADVISE program implemented to increase appropriate antibiotic use	Decreased use of carbapenems ($p=0.04$), third-generation cephalosporins ($p=0.001$), and vancomycin ($p=0.05$) after risk adjustment; decrease in total antibiotic utilization by 10.5%; fewer susceptibility mismatches for initial antibiotic therapy ($p=0.02$); increased deescalation to narrower-spectrum antibiotics

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Table 2 (continued)

Antimicrobial Stewardship Team and Setting	Strategies and Interventions	Impact
ID M.D., antibiotic management program team; 350-bed hospital[30]	Education, introduction of antibiogram, antibiotic prescription forms, prescribing restrictions	Decreased antibiotic prescription rate by 24% (640 vs 400 prescriptions/1000 admissions, $p<0.001$); decreased rate of inappropriate antibiotic use (42% vs 20%, $p<0.001$); sustained reduction in antibiotic use ($R^2=0.692$, $p<0.001$); decreased rates of third-generation cephalosporin use (31 vs 18 DDDs/1000 patient-days, $p<0.001$) and glycopeptide use (3.2 vs 2.4 DDDs/1000 patient-days, $p=0.002$); increased rates of cefazolin use (3.5 vs. 8.2 DDDs/1000 patient-days, $p<0.001$) and fluoroquinolone use (0.68 vs 1.15 DDDs/1000 patient-days, $p<0.001$); decreased incidence of MRSA infections (48% vs 33.5%, $p<0.001$), ESBL-producing *E. coli* (33% vs 21%, $p<0.001$), ESBL-producing *Klebsiella pneumoniae* (30% vs 20%, $p<0.001$), and third-generation cephalosporin-resistant *Acinetobacter baumanii* (27% vs 19%, $p<0.001$); total cost savings of $32,231 during the study period
ID M.D., ID Pharm.D., microbiologist; 900-bed hospital[31]	i.v. to p.o. conversion for select highly bioavailable antimicrobials; cessation of perioperative prophylaxis within 24 hrs; ID consultation before continuing administration of select antimicrobials beyond 48 hrs	Overall physician compliance 76%; cost/patient-day decreased by 31%, from $13.67 in 2000 to $9.41 in 2003; total acquisition cost savings of $1,841,203/3-yr period; ceftazidime resistance: *Klebsiella* 73% reduction/3 yrs, *E. coli* (UTI) 2% increase/3 yrs; cefepime resistance: *E. coli* (non-UTI) 2% increase/3 yrs; ceftriaxone resistance: *Klebsiella* 75% decrease/3 yrs; cefuroxime resistance: *Klebsiella* 68% decrease/3 yrs; levofloxacin resistance: *Klebsiella* 78% decrease/3 yrs
ID M.D., ID Pharm.D.; 648-bed hospital[32]	Electronic monitoring of all restricted antibiotic orders to alert for inadequate antimicrobial therapy compared with control group	Team intervened in 16% of patient cases in intervention group vs 8% in control group; less time spent with intervention group; hospital expenditures of $285,812 vs $370,000 in control group over 3 mo; no significant difference in mortality rate or rate of *C. difficile* after 3 mo between groups
Infection control M.D., infection control R.N.; 78-bed, acute care geriatric ward[33]	Review and feedback, education, restriction; narrow-spectrum antibiotic policy and information on *C. difficile* and MRSA infection rates	Significant decrease in amoxicillin-clavulanate and cephalosporin use at the time of the intervention and after the intervention; significant increase in long-term benzyl penicillin use; sudden change in amoxicillin use; decrease in *C. difficile* infection rate (IRR 0.35, 95% CI 0.17–0.73, $p=0.009$) but no significant changes in MRSA infection rate (control outcome) (IRR 0.79, 95% CI 0.49–1.28, $p=0.32$)

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Table 2 (continued)

Antimicrobial Stewardship Team and Setting	Strategies and Interventions	Impact
ICU M.D., infection control M. D., ID Pharm.D., microbiologist; 12-bed neurosurgical ICU[34]	Guideline for empiric treatment with antibiotics in the ICU for nosocomial pneumonias	Significant decrease in total antibiotic use from 949.8 to 626.7 DDDs/1000 patient-days; reduced consumption of second-generation cephalosporins (−100.6 DDDs/1000 patient-days), imidazoles (−100.3 DDDs/1000 patient-days), carbapenems (−33.3 DDDs/1000 patient-days), penicillin–β-lactamase inhibitors (−33.5 DDDs/1000 patient-days) and glycopeptides (−30.2 DDDs/1000 patient-days); decreased MRSA rate from 8.4% to 2.9%; significant decrease in total antibiotic costs/patient-day from 13.16 to 7.31 euros/patient-day; no change was noted in mortality rate from pneumonia
Antibiotic management program, general surgeons, ICU M.D.; 390-bed hospital[35]	Guidelines that used quantitative bronchoscopy or mini–bronchoalveolar lavage for diagnosis; empiric treatment for VAP was based on epidemiology and timing of infection, tailoring therapy after culture results available	Increase in use of appropriate definitive therapy from 80.4% to 89.4% (p=0.001); decrease in mean duration of therapy from 12 days to 10.7 days (p=0.0014); therapy more frequently tailored on basis of quantitative culture results from 61.3% to 68.9% (p=0.034)
Drug and therapeutics committee; 365-bed hospital[36]	Computerized antimicrobial approval system for ordering restricted antibiotics	Decreased gradient DDDs/1000 bed-days before and after the intervention: third- and fourth-generation cephalosporins (−0.05 and −0.39, p<0.01), glycopeptides (+0.27 and −0.53, p=0.09), carbapenems (+0.12 and −0.24, p=0.21), aminoglycosides (+0.15 and −0.27, p<0.01), and quinolones (+0.76 and +0.11, p=0.08); increased use of extended-spectrum penicillins (+0.16 and +1.16, p<0.01); trends in improved susceptibility of *Staphylococcus aureus* to methicillin and improved susceptibility of *Pseudomonas* to many antibiotics observed; no increase in adverse events in patients with gram-negative bacteremia
ID M.D., ID Pharm.D.; 953-bed hospital[37]	Education: academic detailing to 6 medicine teams randomized to intervention group (compared with 6 randomized medicine teams given indication-based guidelines for prescription of broad-spectrum antimicrobials)	Intervention group had 9% increase in appropriate empiric antimicrobial use (p=0.005), 39% increase in appropriate definitive antimicrobial use (p<0.001), and 24% increase in appropriate end antimicrobial use (overall) (p<0.001)
ID Pharm.D.; 1150-bed tertiary care facility[38]	Microbiology testing: rPCR MRSA blood culture test; outcomes were compared during two time frames: before rPCR testing was implemented (pre-rPCR) and after rPCR testing was implemented (post-rPCR)	Post-rPCR MSSA group demonstrated a shorter mean time to switch from empiric vancomycin to cefazolin or nafcillin by 1.7 days (p=0.002); post-rPCR MSSA and MRSA groups had a shorter mean length of stay by 6.2 days (p=0.07), and mean hospital costs were $21,387 lower (p=0.02)

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Table 2 (continued)

Antimicrobial Stewardship Team and Setting	Strategies and Interventions	Impact
ID Pharm.D.; 903-bed hospital[39]	Prospective audit with intervention and feedback; education; implementation of antimicrobial stewardship care bundle	Increased compliance of quality indicators for antibiotic use, including documented indication for antibiotic therapy (p=0.12), appropriate cultures collected (p=0.09), appropriate empiric therapy (p=0.06), appropriate deescalation (p=0.01), and with all quality indicators (combined) (p<0.001)
Team not specified; 531-bed hospital with 4 ICUs[40]	Prospective audit with intervention and feedback; formulary restriction with preauthorization; educational conferences; guideline pocket cards; VAP antimicrobial cycling protocol; deescalation of therapy	Decrease in antipseudomonal agent use from 412 to 346 DDDs /1000 patient-days/yr from 2004–2007 (increased to 456 in 2010); decreases in i.v. ciprofloxacin use (from 148 to 40 DDDs/1000 patient-days/yr) and ceftazidime use (from 62.5 to 24.5 DDDs/1000 patient-days/yr) correlated with a decrease in resistant *P. aeruginosa* rates: from 56.2% to 18.4% and from 31.2% to 18.4%, respectively (resistance rates increased in 2010 when use of these agents increased)
ID Pharm.D., pediatric M.D.; 180-bed pediatric hospital[41]	Prospective audit with intervention and 1-on-1 feedback; enforcement of formulary restriction and prior authorization; guideline pocket cards distributed	Decreases in antimicrobial use (doses administered/1000 patient-days/yr) from 2003–2007: from 3089 to 1904 for all antimicrobials, from 1250 to 988 for targeted antimicrobials (broad-spectrum and costly), and from 1839 to 916 for nontargeted antimicrobials (narrow-spectrum and less expensive); resistance rates to broad-spectrum antimicrobials among most common gram-negative bacilli did not significantly change over time
ID Pharm.D., microbiologist; 495-bed hospital[42]	Guidelines to promote the use of "low-risk" antibiotics and decrease the use of broad-spectrum "high-risk" antibiotics to decrease rates of *C. difficile* infection	Decreased use of fluoroquinolones by 105.33 DDDs/1000 occupied bed–days/mo (p<0.001) and cephalosporins by 45.93 DDDs/1000 occupied bed–days/mo (p<0.0001); decreased rates of *C. difficile* infection after the intervention (p<0.0001)

ADVISE = Antibiotic Decision Support for the Victorian Infectious Diseases Service; CI = confidence interval; CPIS: clinical pulmonary infection score; DDD = defined daily dose; ESBL = extended-spectrum β-lactamase; ICU = intensive care unit; ID = infectious diseases; IRR = incidence rate ratio; MICU = medical intensive care unit; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; rPCR = rapid polymerase chain reaction; URI = upper respiratory infection; UTI = urinary tract infection; VAP = ventilator-associated pneumonia; VRE = vancomycin-resistant *Enterococcus*.

Table 3. Impact of Antimicrobial Stewardship and the Use of Process Measures Alone

Antimicrobial Stewardship Team and Setting	Strategy and Intervention	Impact
ID M.D.; 500-bed hospital[44]	Formulary restriction: targeted agents that required ID consultation	Immediate decrease in level of use by 17,238 g/yr (p=0.007), but no significant sustained change in slope (+948 g/yr, p=0.398)
Multidisciplinary team; 460-bed hospital[45]	Education: parenteral antibiotic order form supported by educational sessions and reminders (written "advertisements" mailed to all physicians and posters displayed on wards)	Inappropriate dosing of cefazolin (60%), clindamycin (90%), and metronidazole (75%) virtually eliminated within 3 mo; annual cost savings of $44,500 for cefazolin, $9400 for clindamycin, $5400 for metronidazole, and $17,000 for consumables and labor saved by less frequent dosing of all three drugs
ID fellow; academic medical center[46]	Rapid processing and reporting of antimicrobial susceptibility tests compared with routine methods	Changes to therapy recommended in 64% of study group vs 45% of control group and resulted in 93% vs 78% compliance with recommendations in study group vs control group (p<0.05); most frequent recommendation was change to less expensive therapy (34% vs 18%, study group vs control group)
Department leaders; hospital size not specified[47]	Educational guidelines; cefoxitin removed from supply shelf in labor and delivery area and cefazolin recommended for prophylaxis on an educational antibiotic order form	Almost complete substitution of cefazolin for cefoxitin for women undergoing cesarean sections receiving < 5 g of either drug; annual savings in drug costs of $26,711
M.D.; 720-bed hospital[48]	Restriction: computerized order requiring providers to indicate rationale for initiating vancomycin at time of order entry and additional reminder after 72 hrs of therapy for continued use	Intervention group had 11.3 vancomycin orders vs 16.7 in control group (p=0.04); 28% fewer patients received vancomycin therapy in intervention group (p=0.02); duration of vancomycin therapy 36% shorter in intervention group (p=0.05)
ID M.D., ID Pharm.D.; multi-center[49]	Education: academic detailing to prescribers if cefotaxime use did not meet the guideline (randomized prescriptions to study vs control groups)	Study vs control groups: 75% vs 69% of prescriptions met guidelines (p=0.24); indication appropriate for 81% vs 80%; dosage appropriate for 94% vs 86% (p=0.018); mean duration of therapy 4.3 days vs 4.6 days (p=0.28); mean cost of therapy $198 vs $245 (p=0.32)
Pharmacy and therapeutics committee; 2 hospitals[50]	Restriction of cephalosporins; electronic antimicrobial approval system to monitor use and provide feedback to staff	Immediate decrease in use of cefotaxime or ceftriaxone by 32.54 DDDs/1000 bed-days (p<0.0001) and increase in gentamicin use by 13.91 DDDs/1000 bed-days (p=0.03); no sustained change in slope for either drug after the intervention
ID Pharm.D.; 900-bed hospital[51]	Concurrent review and feedback; "alert antibiotics" policy implemented that targeted carbapenems, glycopeptides, i.v. amphotericin, i.v. ciprofloxacin, linezolid, piperacillin-tazobactam, third-generation cephalosporins.	Overall use of all "alert antibiotics" decreased by 0.27 DDDs/100 bed-days/mo (95% CI 0.19–0.34, p<0.0001); reduction in cost of "alert antibiotics" by £1908/mo in the 2 yrs after the intervention (95% CI £1238–2578, p<0.0001); cost of program was £20,133 over 2 yrs
ID M.D., ID Pharm.D.; 175-bed hospital[52]	Restriction by use of clinical decision support system	11.6% reduction in the number of dispensed doses; estimated cost savings of $370,069; user satisfaction increased by 46% among prescribers and 56% among pharmacists; 21% reduction in number of prescriber reports of missed doses and 32% reduction in delayed doses; 37% reduction in number of pharmacist reports of delayed approvals; measured dispensing times were unchanged; 40% fewer restricted-antimicrobial–related phone calls noted by the pharmacy staff

ID = infectious diseases; DDD = defined daily dose; CI = confidence interval.

There are both strengths and weaknesses to using process measures, such as amount used or cost, as a means of measuring the impact of ASPs. Measuring the change in amount of antimicrobial use as a process measure is easy to understand and interpret. Theoretically, remedial action is clear and simple, and merely requires an increase or decrease in use to produce the desired change. Process measures can be beneficial, as they may serve as direct measures of the quality of care, assuming that a link between a given process and desired outcome is present.[53] For example, if increased antimicrobial exposure is associated with increased rates of CDI, then it would be logical to target ASP interventions at decreasing antimicrobial exposure and subsequently measure this process by showing a decrease in the amount of antimicrobial used. However, the process measures of amount used and cost are not always direct measures of quality of care. If antimicrobial use is decreased to zero, CDI rates may decrease significantly, but the initial infection that prompted the use of antimicrobials would not be adequately treated. In this case, decreasing antimicrobial exposure by decreasing the amount used would not be reflective of the best quality of care. Therefore, amount used should be further delineated into whether use was appropriate. In the previous example, where the goal is to decrease rates of CDI by decreasing antimicrobial exposure, ASP interventions should specifically target decreasing amount of unnecessary or inappropriate use rather than total use.

As antimicrobial resistance rates rose over the last several years, and research and development programs for novel antimicrobial agents dwindled, the focus of antimicrobial management expanded beyond limiting the quantity of antimicrobial use and began to target the quality and appropriateness of antimicrobial use. A recent randomized, controlled intervention trial demonstrated this by measuring the proportion of appropriate empiric, definitive (therapeutic), and end (overall) antimicrobial usage in relation to the presence or absence of ASP services.[37] This study included patients on internal medicine wards who were given piperacillin-tazobactam, levofloxacin, or vancomycin. Every month for 10 months, internal medicine teams were randomly assigned to either an intervention or control group. Teams in the intervention group received academic detailing by the antimicrobial utilization team, whereas teams in the control group were given indication-based guidelines for prescription of broad-spectrum antimicrobials that were considered standard of care. The proportion of appropriate antimicrobial orders written by the intervention teams was significantly higher than the proportion of appropriate prescriptions written by control teams for empiric (82% vs 73%; risk ratio [RR] 1.14, 95% confidence interval [CI] 1.04–1.24), definitive (82% vs 43%; RR 1.89, 95% CI 1.53–2.33), and end antimicrobial use (94% vs 70%; adjusted RR 1.34; 95% CI 1.25–1.43). In the multivariate analysis, intervention by the antimicrobial utilization team and infectious diseases consultation were independent predictors for appropriate end antimicrobial use with significant interaction between these two factors. Teams that received feedback from the antimicrobial utilization team alone were significantly more likely to prescribe end antimicrobial use appropriately comparable with control teams (adjusted RR 1.37, 95% CI 1.27–1.48). An even greater effect was seen when teams received feedback from both the antimicrobial utilization team and infectious diseases consultation service compared with control teams (adjusted RR 2.28, 95% CI 1.64–3.19). There were no differences in the in-hospital mortality rates among patients cared for by the intervention teams or control teams. Patients treated by the intervention team also had a shorter median length of stay (7 days, range 1–50 days) compared with patients treated by the control group (8 days, range 2–86 days, p=0.03). The authors of this study concluded that a multidisciplinary antimicrobial utilization team that provides feedback to prescribing physicians was an effective method for improving antimicrobial use.

Defining and measuring the appropriateness of antimicrobial use rather than measuring total quantity of use brings ASPs closer to determining the effect on clinical outcomes by creating a stronger link between the process and outcome. As discussed previously, process measures can serve as a direct measure of the change in process (i.e., the intervention) and are useful in determining the effectiveness of ASPs. They do not, however, replace the use of outcome measures when determining the effect of ASPs on clinical outcomes.

Antimicrobial use as a process measure is being increasingly used to evaluate the quality of care as ASPs continue to expand their scope of responsibilities to other areas, such as surgical prophylaxis interventions.[54] Application of antimicrobial use as a quality metric has become

standardized and nationally reported by key stakeholders, including the Joint Commission and the Centers for Medicare and Medicaid Services (CMS), two organizations responsible for establishing the Surgical Care Improvement Program (SCIP). This program standardizes evidence-based practices into measurable processes to improve perioperative care. Of the seven SCIP infection prevention measures, three include the selection, timing, and discontinuation of perioperative antibiotic prophylaxis. The goal of these measures is to reduce surgical infection–related morbidity and mortality by 25%. The CMS has incorporated these metrics into their core measures assuming that process standardization will improve outcome.[55] However, benchmarks for the SCIP prophylaxis metrics were established on the basis of methodology for achievable benchmarks based on current use and not on outcomes data. Without outcomes data, it is difficult to assess the relative importance of the process of standardizing antimicrobial use; therefore, antimicrobial use as a process measure should be used with caution.[54]

Decreasing time to appropriate therapy may also be a useful process measure for determining the effectiveness of ASPs, particularly when initiating new therapy or deescalating therapy to minimize unnecessary exposure to broad-spectrum antimicrobials.[56–59] Time to appropriate antimicrobial therapy has been tied to positive effects on overall mortality for a variety of infections. Of interest, only one of the studies included in Tables 1–3 measures time to appropriate therapy.[38] The investigators evaluated both clinical and economic outcomes of a rapid polymerase chain reaction methicillin-resistant *Staphylococcus aureus* (MRSA)/*S. aureus* blood culture test (rPCR). Outcomes were compared during two time frames: before rPCR testing was implemented (pre-rPCR) and after rPCR testing was implemented (post-rPCR). Mean time to switch from empiric vancomycin to cefazolin or nafcillin in patients with methicillin-susceptible *S. aureus* (MSSA) bacteremia was 1.7 days shorter in the post-rPCR group (p=0.002). Compared with the pre-rPCR group, the mean length of stay was shorter by 6.2 days (p=0.07), and mean hospital costs were $21,387 lower (p=0.02) in the post-rPCR MSSA and MRSA groups. In conclusion, the addition of rPCR allowed for rapid differentiation between MSSA and MRSA bacteremia, and subsequently decreased time to appropriate therapy, which was associated with decreased length of stay and lower health care costs. Of note, however, the use of rPCR was in addition to antimicrobial stewardship intervention, and this must be taken into consideration when evaluating the overall clinical effect. Nevertheless, this study illustrates how measuring the impact of a process change, that is, a change in the process of antimicrobial prescribing by technology, can be useful in determining its effect on clinical outcomes.

Time to first antibiotic dose for community-acquired pneumonia is another example of a process measure commonly used as a quality metric.[54] Based on the 2003 IDSA community-acquired pneumonia guidelines and the Medicare National Pneumonia project, the CMS and the Joint Commission advocated for the use of time to first antibiotic dose within 4 hours of presentation as a core quality measure.[60] Although this core quality measure was based on two before-and-after studies showing improved outcomes (decreased mortality and/or length of stay),[61, 62] adherence to a desired process does not always result in positive outcomes. In fact, patients without pneumonia frequently received unnecessary antibiotics, and community-acquired pneumonia was less accurately diagnosed as a consequence of trying to meet this core quality measure. As a result, the IDSA and the American Thoracic Society community-acquired pneumonia guidelines did not specify a time to first antibiotic dose in the latest update.[63] The CMS and Joint Commission did not eliminate time to first antibiotic dose as a core quality measure, but rather extended it to 6 hours instead of 4 hours. Furthermore, as of January 2012 this measure has been retired as noted in the Joint Commission Specifications Manual for National Hospital Inpatient Quality Measures.[64]

Impact of Antimicrobial Stewardship Programs and Clinical Outcome Measures: Resistance, *Clostridium difficile* Infection, Adverse Events, and Clinical Success

Although there is obvious financial incentive to decrease antimicrobial consumption, the cost savings associated with preventing resistant infections is less discernible. This was demonstrated by a recent study that measured the medical and societal cost attributable to antimicrobial-resistant infection in high-risk patients in an urban public teaching hospital in Chicago.[65] Medical costs attributable to antimi-

crobial-resistant infection ranged from $18,588–29,069/patient. Length of stay was 6.4–12.7 days longer for patients with an antimicrobial-resistant infection, and attributable mortality was 6.5%. Societal costs were $10.7–15.0 million. Despite several limitations, the authors concluded that the findings of their study suggest the need for further evaluation of the cost of resistance, which may result in potential economic benefits produced by prevention programs. This may help provide further incentive for ASPs to focus their efforts on measuring clinical outcomes and not rely so heavily on measuring change in antimicrobial use.

Although the relationship between antimicrobial use and resistance is complex, it is widely accepted that increased broad-spectrum antimicrobial use is associated with the emergence of resistance. Limiting unnecessary broad-spectrum antibiotic exposure is a practical and logical strategy to counter the emergence of resistance. In a prospective cohort study, improved susceptibility of gram-negative bacteria in an intensive care unit was demonstrated after implementation of a comprehensive computerized antibiotic decision support system.[14] This study was contingent on results published in an earlier study conducted at the same institution, which evaluated the effectiveness of the Antibiotic Decision Support for the Victorian Infectious Diseases Service (ADVISE) program in a prospective before-and-after cohort study.[29] The ADVISE program was a computerized decision support system developed to aid in the prescribing of antimicrobials in the intensive care unit. It provided antibiotic recommendations by integrating data on local antibiotic susceptibility profiles with patient-specific clinical information, including site of bacterial isolation and patient allergies. In addition, the ADVISE program provided tailored advice as susceptibility reports became available. Furthermore, the program was linked to the hospital pathology system and provided real-time microbiology results. These printed summaries were often used during patient rounds.

After adjustment for potential confounders and risk factors for antibiotic use, implementation of the ADVISE program was associated with a significant reduction in the proportion of patients prescribed carbapenems (OR 0.61, 95% CI 0.39–0.97, p=0.04), third-generation cephalosporins (OR 0.58, 95% CI 0.42–0.79, p=0.001), and vancomycin (OR 0.67, 95% CI 0.45–1.00, p=0.05). These changes were observed over two 6-month periods in 2001 and 2002. A total of 2838 gram-negative organisms were isolated over a 7-year period between January 2000 and December 2006 (before and after implementation of the ADVISE program) in order to assess changes in gram-negative susceptibilities. Compared with preintervention susceptibility trends, there were significant improvements in susceptibility of *Pseudomonas* to imipenem (18.3%/year, 95% CI 4.9–31.6%, p=0.009) and gentamicin (11.6%/year, 95% CI 1.8–21.5%, p=0.02).[16] Although deemed less clinically significant, statistically significant changes among the rates of gentamicin and ciprofloxacin susceptibility were observed in the inducible Enterobacteriaceae group. As opposed to other studies that measured resistance rates (Tables 1 and 2), this study was distinct in that it first demonstrated reduction in consumption of broad-spectrum antibiotics (process measure) followed by sustained reductions in resistance rates.

Previous studies evaluating resistance rates reported increases or no significant changes in prevalence of resistant organisms or no significant sustained reduction in resistance rates.[22, 23, 28] A decrease in broad-spectrum antibiotic use by 28% was demonstrated without having a corresponding significant effect on the local hospital antibiogram.[28] This further illustrates the limitations of outcome measures as performance indicators since they are not a direct measure of quality of health care in the same way process measures are.[53] Outcome measures reflect all aspects of the process of care, not just the ones that are measurable. In other words, antimicrobial resistance rates are not solely affected by antibiotic use. Their measurement may be subject to multiple confounders such as comorbidities, secular trends, resistance outbreaks, and concomitant infection prevention strategies. Therefore, when using outcome measures, if differences in outcomes are observed, alternative explanations should be considered before one can conclude that the difference reflects true variations in the quality of care.[53]

As noted previously, the relationship between antimicrobial exposure and resistance is complex and may be difficult to illustrate. Antibiotic restriction is often employed in an effort to prevent the selection of resistant organisms, although this does not always produce the desired effect. This challenge is exemplified in a study where restriction of cephalosporin use and subsequent decrease in the incidence of

ceftazidime-resistant *Klebsiella* was replaced by an increased use of imipenem and increased incidence of imipenem-resistant *Pseudomonas aeruginosa*.[10] This unintended effect known as "squeezing the balloon" must be considered when implementing restrictive interventions. On the other hand, the association between antimicrobial exposure and CDI seems to be more apparent, as demonstrated by a retrospective cohort study.[66] Specifically, the results showed dose-dependent increases in the risk of CDI associated with increasing cumulative dose, number of antibiotics, and days of antibiotic exposure. Compared with patients who received one antibiotic, the adjusted hazard ratios for patients who received two, three or four, or five or more antibiotics were 2.5 (95% CI 1.6–4.0), 3.3 (95% CI 2.2–5.2), and 9.6 (95% CI 6.1–15.1), respectively. The authors concluded that these findings support the overall principles of antimicrobial stewardship. Decreasing inappropriate and excessive use of antibiotics by optimizing antimicrobial selection, dosing, and duration will decrease cumulative antibiotic exposure, ultimately minimizing CDI as an unintended consequence of antimicrobial use. Although some studies have shown decreased rates of CDI after implementation of ASPs, most were short-term reductions. It is inherently difficult to show sustained effects on both rates of CDI and resistance due to the prolonged time period required for preferred study designs (i.e., interrupted time series with segmented regression).[67] However, another study illustrated the use of appropriate methods to examine the effect of infection prevention and antibiotic stewardship on CDI. In this study, CDI decreased by 60% from 2003–2004 and 2005–2006.[15] Furthermore, interrupted time series analysis revealed differences in levels and slopes sustained over time for both infection prevention and stewardship interventions. The authors concluded that antimicrobial stewardship independently and significantly reduced the incidence of CDI.

One of the goals of antimicrobial stewardship according to the IDSA-SHEA guidelines is to minimize unintended consequences of antimicrobial use, including toxicity.[3] An expert review on interventions and associated outcomes of ASPs found that only two of 36 studies showed the impact of stewardship intervention on antimicrobial-related adverse events.[68] Changes in the rates of adverse events were expressed as a relative change between the preintervention and postintervention time periods. One of these studies evaluated the effect of an antimicrobial cycling protocol in two community hospitals of a health system where fluoroquinolones and β-lactams cycled alternatively every 3 months for empiric therapy of all infections except meningitis, endocarditis, sexually transmitted infections, or infections with presumed resistant pathogens.[69] Results of this study demonstrated no increase in the observation of adverse events. Although the primary intent of this study was to reduce bacterial resistance, the second study used adverse events as the primary outcome. That study demonstrated a reduction in the rate of aminoglycoside-related nephrotoxicity over 1 year in a 960-bed, university-affiliated teaching hospital through the use of education, guideline development, and review with feedback carried out by a team of infectious diseases physicians.[70] Recommendations on aminoglycoside use were updated, including dosing regimens, indications, and timing of drug level monitoring. These updates were disseminated to all staff and junior physicians through educational sessions on each ward. In addition, each aminoglycoside order was reviewed, and interventions were provided through counseling to the prescriber when appropriate.

With regard to antimicrobial stewardship, outcomes research has primarily focused on measuring outcomes of collateral damage—that is, the emergence of antimicrobial resistance and CDI, rather than measuring other relevant outcomes such as clinical success and failure of antimicrobial therapy. This may be, in part, due to the subjective nature of defining these terms and also the difficulties in attributing these outcomes to an ASP, particularly in the presence of confounders. Acknowledging these challenges, it is still imperative for ASPs to focus efforts on understanding how to optimize care by evaluating clinical outcomes such as clinical success, length of stay, and infection-related morbidity and mortality. Disease state management approaches can be applied to evaluate outcomes of specific infections. Different disease-oriented guidelines provide individualized tests of cure that may be extrapolated into distinct definitions of clinical success. This is important to consider when evaluating clinical success as an outcome measure due to the need for separate definitions for various infectious diseases. For example, defining clinical response for osteomyelitis is different from that of bacteremia. This may be inconvenient and challenging when trying to

evaluate the impact of an ASP, but it is necessary to more accurately demonstrate the effect of ASP interventions and determine whether ASPs are achieving their primary goal of optimizing clinical outcomes. Unfortunately, like other outcome measures, clinical response is highly dependent on all aspects of care and not just one change in process (e.g., providing more appropriate antimicrobial coverage). If a patient with an MRSA abscess receives an antibiotic with adequate MRSA coverage based on an ASP intervention but does not receive adequate source control (incision and drainage of the abscess) for whatever reason independent of the ASP, then clinical response may not be truly reflective of the ASP intervention. A practical solution to this may include defining clinical response with regard to both the intervention and disease state. For example, clinical failure of treatment for bacteremia secondary to intraabdominal abscess may be a useful outcome measure if defined as "failure in the presence of adequate source control." Of course there may be other factors that affect clinical response separate from adequate source control, and these may be considered when defining an outcome measure.

Methodologic Issues and Limitations

In 2005, a Cochrane review of the efficacy of ASPs identified 643 studies from 1980–2003, of which only about 66 met the rigorous inclusion criteria.[71] The majority of excluded studies were rejected because of methodologic limitations including inadequate study design. The use of outcome measures in uncontrolled before-and-after studies or retrospective drug utilization evaluation–type analyses are subject to inherent confounding issues such as secular trends, patient comorbidities, resistance outbreaks, and concomitant infection prevention strategies. Randomized controlled trials are generally considered the highest level of evidence but are not frequently used to measure the impact of ASPs secondary to resource and logistical restraints and ethical considerations of control groups in process improvement initiatives. Interrupted time series studies and controlled before-and-after studies are common alternatives but may require extended periods of time to collect enough data before and after interventions to prevent bias due to external secular trends unrelated to the intervention.[54]

Given that most antimicrobial stewardship studies are conducted in a single center and are often not funded, it may be particularly difficult to obtain an adequately powered sample size to detect statistically significant differences in clinical outcomes, such as mortality and length of stay. Some logistical limitations not previously mentioned include the difficulty in assessing clinical response due to limitations of documentation and issues with follow-up. Clinical response is determined by the provider, and failure to adequately document this in the medical record may prevent antimicrobial stewardship specialists from evaluating the effectiveness of their interventions. Furthermore, for patients discharged from the hospital with treatment for an infectious disease, there is the potential for loss to follow-up or inappropriate duration of follow-up. Clinical response to antimicrobial treatment is dependent on the type of infection; therefore, duration of follow-up will vary depending on type of infection (e.g., duration of follow-up for osteomyelitis would be longer than that for bacteremia).

Another methodologic limitation of studies that evaluate the impact of ASPs, and the topic of this review, is determining the ideal measures to use. As outlined in this review, process measures are useful for measuring the effectiveness of ASPs by confirming that interventions are fulfilling their purpose, whereas outcome measures are required to ensure the optimization of clinical outcomes. Therefore, when measuring the effect of a program or targeted intervention, the most robust analysis will include both strategies. Antimicrobial stewardship programs rely heavily on measuring antimicrobial utilization, where the unit of measurement varies widely from point prevalence of antimicrobial use and measuring the percentage of patients who are receiving a particular antimicrobial agent to average duration of therapy in days or defined daily doses/fixed number of patient-days. The persistent use of different measures of antibiotic consumption may be a limitation in comparing both process measures and outcomes with internal or external standards—that is, benchmarking.[72]

Although it may be perceived as slightly controversial, one of the reasons antimicrobial consumption and/or costs are so frequently used to measure the effect of ASPs may be a silo mentality. This is present particularly in acute care hospitals where ASP personnel are pressured to show direct cost savings to the pharmacy department rather than considering the total cost of

care. Unfortunately, this has become a barrier to evaluating treatment outcomes. Instead of measuring antibiotic consumption or cost of antimicrobials alone as a more immediate cost-minimization approach, ASPs can become more outcomes driven and measure the total quality of care by taking a disease-state management approach and evaluating outcomes of specific infections such as infection-related mortality, multidrug-resistant infection–related mortality, and length of stay. They can also measure resource utilization or costs of care that are more representative of downstream costs. Furthermore, if individual ASPs can evaluate outcome measures consistent with one another, health care systems will have the means to compare program effectiveness across institutions.

Implications for Practice

In 2007, the IDSA-SHEA guidelines recognized that there was a lack of well-designed studies demonstrating the relationship between antimicrobial stewardship interventions and patient outcomes.[3] Since then, more investigators have attempted to conduct well-designed, controlled, before-and-after studies and randomized controlled trials to determine the effect of ASPs. Unfortunately, this continues to be a challenging task. As demonstrated in this review, the majority of recent trials are still using process measures as primary end points (Table 2). Although the evidence, in relation to both ASPs and to other pertinent medical literature, highlights the validity of using process measures, clinical outcomes are theoretically the optimal measures of the effectiveness of an ASP. Showing improvement in clinical outcomes would likely garner the attention of a broader audience outside of infectious diseases specialists and key national stakeholders, and provide support for both the development of new ASPs and continued expansion of existing ASPs. Although antimicrobial stewardship interventions have demonstrated a clear benefit in patient outcomes, reduced the burden of resistance, and saved health care costs, ASPs have yet to become standard entities in United States hospitals. Cognizant of this, the Centers for Disease Control and Prevention launched Get Smart for Healthcare, a new campaign focused on improving antimicrobial use particularly in inpatient health care settings.[73]

In October 2011, the CMS Office of Clinical Standards and Quality/Survey and Certification Group summarized a memorandum stating that CMS was piloting three new surveyor worksheets for three hospital conditions of participation: discharge planning, infection control, and quality assessment and performance improvement.[74] The focus is assessing compliance with these conditions of participation as a means to reduce health care–acquired conditions by 40% and hospital readmissions by 20% by 2013. Included within the infection control worksheet draft is a section regarding systems to prevent transmission of multidrug-resistant organisms, promotion of antimicrobial stewardship, and surveillance. Among the elements to be assessed in this section are several strategies consistent with those recommended by the IDSA-SHEA antimicrobial stewardship guidelines, including both core and supplemental strategies. For example, one of the elements to be assessed includes whether the facility has a multidisciplinary process in place to review antimicrobial utilization, local susceptibility patterns, and antimicrobial agents in the formulary. Furthermore, part of the assessable element includes whether there is evidence that the process is followed. This would require the use of process measures to evaluate compliance with these processes while also suggesting the use of outcome measures to evaluate antimicrobial resistance patterns. The next element listed is whether systems are in place to prompt clinicians to use appropriate antimicrobials, consistent with the concept discussed previously in this review to delineate whether antimicrobial use is appropriate and not simply measuring total consumption. Also of note is an element listed to determine whether antibiotic orders include indication for use. Inadequate documentation is often a limitation in evaluating the effect of ASPs, including the lack of proper documentation of antibiotic indication. By requiring this quality metric as a part of the assessment tool used to assess compliance with the conditions of participation, this may assist ASPs in better defining appropriate antibiotic use. Through CMS' Survey and Certification program and their partners in the state survey agencies, there seems to be a stronger force to better define process and outcomes measures that have the potential to improve patient safety and quality of care.

Proposed initiatives such as the Centers for Disease Control and Prevention's antimicrobial stewardship campaign, combined with the evidence to support implementation of ASPs and attention from key stakeholders such as CMS,

have only strengthened the need for optimal quality measures to measure the impact of such programs. The IDSA-SHEA guidelines on ASPs recommend the use of both process and outcome measures to determine the impact of the programs on antimicrobial use and resistance, but they do not outline specific indicators of performance.[3] Recognizing that there is no standard approach to evaluating the impact of ASPs, a multidisciplinary panel of 10 experts recently convened and used a structured process to define quality improvement metrics for evaluating ASPs in hospital settings that also have the potential to be used as part of public reporting efforts.[75] After a thorough literature review, a final selection of four systematic reviews that included a total of 278 articles was referenced to create the initial list of measures. Using a multiphase modified Delphi technique, five final metrics were selected by the panel based on their usefulness for accountability purposes and potential to support quality improvement efforts. These five metrics are the following: days of therapy/1000 patient-days; number of patients with specific organisms that are drug resistant; mortality related to antimicrobial-resistant organisms; conservable days of therapy among patients with community-acquired pneumonia, skin and soft tissue infections, or sepsis and bloodstream infections; and unplanned hospital readmissions within 30 days after discharge from the hospital in which the most responsible diagnosis was one of community-acquired pneumonia, skin and soft tissue infections, sepsis, or bloodstream infections. The first two indicators were also identified as useful for accountability purposes, including public reporting. The panel agreed that the denominator for these indicators would be all hospitalized patients, and conservable days of therapy was defined as "unnecessary treatment days that were avoided based on widely accepted targets and benchmarks." This metric was chosen instead of length of stay to avoid the complexities of patient type and regional differences.

The five metrics identified consist of both process and outcome measures and include representation from three domains: antimicrobial consumption, antimicrobial resistance, and clinical effectiveness. As demonstrated by several of the studies reviewed by the expert panel, many of which are also included in this review, these metrics use data that are already commonly collected by hospitals and could feasibly be collected and reported on immediately. Considering the broad applicability of these metrics, the panel concluded that the proposed quality measures would help individual institutions monitor and evaluate ongoing ASP efforts and provide health care systems with a consistent means for comparing program effectiveness across institutions.

The utility of these proposed quality metrics may prove to be invaluable when measuring the impact of ASPs. Although the IDSA-SHEA guidelines provide ample description, justification, and advocacy of ASPs, the recommended optimal measures of effectiveness are lacking. As this review indicates, it is evident that the use of both process measures and outcome measures is ideal when measuring the impact of ASPs, and targeting both will result in the most robust analysis. Among the plethora of questions ASPs face include what is most important to target, and what are the recommended optimal measures of effectiveness? The ASPs may be able to take another step forward and begin to overcome this barrier with the newly proposed quality metrics.

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