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Re: Antimicrobial Stewardship (AS) as a Medicare Condition of Participation (CoP)

Dear CDR Cooper,

The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) are writing to present the Centers for Medicare & Medicaid Services (CMS) with the supportive evidence and rationale to adopt Antimicrobial Stewardship (AS) as a Medicare Condition of Participation (CoP). The IDSA represents over 10,000 infectious diseases physicians and scientists devoted to patient care, prevention, public health, education, and research in the area of infectious diseases (ID). IDSA's members focus on the epidemiology, diagnosis, investigation, prevention and treatment of infectious diseases in the U.S. and abroad. SHEA is a professional society representing more than 2,000 physicians and other healthcare professionals globally that have expertise in and passion for healthcare epidemiology and infection prevention. SHEA's mission is to prevent and control healthcare-associated infections and advance the field of healthcare epidemiology. The society promotes science and research, develops expert guidelines and guidance for healthcare workers, provides high-quality education, promotes antimicrobial stewardship, encourages transparency in public reporting related to hospital-acquired infections (HAIs), works to ensure a safe healthcare environment, and facilitates the exchange of knowledge. SHEA upholds the value and critical contributions of healthcare epidemiology to improving patient care and healthcare worker safety in all healthcare settings.

In October 2012, IDSA formed a work group with the objective of promoting the expansion of AS programs, through quality measure development and alternative system-level opportunities. SHEA having aligned interests and broad experience relating to AS, was invited to collaborate with IDSA on this work group. With extensive experience in developing training and educational content, policy statements, and clinical practice guidelines to promote and enhance stewardship activities among a diverse group of healthcare professionals and at varying healthcare facilities, our organizations would jointly like to offer the justification and supportive evidence to demonstrate how adopting AS as a CoP would better patient care, improve outcomes, and lower the healthcare costs associated with antibiotic overuse (i.e. expenditures on antibiotics) as well as costs associated with infections and antimicrobial resistance.
Rationale

Over the last several decades there has been a dramatic increase in antibiotic use in hospitals, consequently increasing the prevalence of antimicrobial-resistant pathogens.\textsuperscript{1,2} Adding to this increase in resistant pathogens, antibiotics are often prescribed sub-optimally or inappropriately.\textsuperscript{3} Antibiotics are often administered needlessly, continued when they are no longer necessary, or prescribed at the wrong dose. Broad-spectrum agents may be administered unnecessarily against bacteria that are very susceptible to narrow-spectrum antibiotics or an ineffective antibiotic may be used to treat a particular infection. As a consequence, this inappropriate and sub-optimal use of antibiotics has led to increased rates of serious diseases such as \textit{Clostridium difficile} (\textit{C. diff}).\textsuperscript{4} Moreover, the misuse of antibiotics can also result in preventable adverse events.

The overuse of antibiotics, in particular, leads to resistance among pathogens and this resistance leads to adverse outcomes, including mortality. The healthcare sector has seen bacteria that are resistant to first-line treatments or extensively resistant to multiple drugs spread widely among patients in all healthcare settings. In some cases these pathogens have been pan-resistant, meaning that they are resistant to all available antibiotics. The unique nature of antibiotics, in which the use of the drugs in one patient can impact the effectiveness of the drug in a different patient, makes antibiotic overuse a serious patient safety issue and public health threat. In fact, the World Health Organization has characterized antibiotic resistance as “a crisis that has been building up over decades, so that today common and life-threatening infections are becoming difficult or even impossible to treat.”\textsuperscript{5} Resistant infections not only result in increased morbidity and mortality, but increased economic burdens.\textsuperscript{6,7,8} For example, studies have shown that antibiotic-resistant infections are associated with longer lengths of stay and increased mortality, both in the hospital and in intensive care units (ICUs). Combined with a dramatic drop in the development and approval of new antibacterial agents over the last 20 years and a rapidly dwindling antimicrobial armamentarium, it is becoming increasingly difficult to treat what were recently “routine” infections.

AS is the optimal use of antimicrobials to achieve the best clinical outcomes while minimizing adverse events, limiting factors that lead to antimicrobial resistance, and reducing excessive costs

\textsuperscript{5} The evolving threat of antimicrobial resistance - Options for action, The World Health Organization
attributable to suboptimal antimicrobial use. Fortunately, AS and related interventions to ensure effective prescribing can minimize antimicrobial resistance and HAIs and improve clinical outcomes. Multiple published studies have indicated that AS programs provide significant cost savings or at least offset the cost of AS programs through reduction in drug acquisition costs, correlating with improved clinical outcomes. AS has significance across the continuum of care and relies heavily on multi-disciplinary and collaborative approaches to care, which are high priorities for both the public and private sector. It also coincides with the Department of Health and Human Services’ Action Plan to Prevent HAIs and aligns with the National Quality Strategy’s three-part aim of better care, affordable care, and healthy people in healthy communities.

As you are well aware, the purpose of the Hospital CoP process is to protect patient health and safety and to ensure that quality care is furnished to all patients in Medicare-participating hospitals. The IDSA and SHEA view the Hospital CoP process as an excellent opportunity to promote AS interventions in facilities across the nation, reduce costs, and most importantly, improve the quality of care received by our patients.

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Evidence

AS programs vary in terms of design/composition and can be customized according to the facility’s needs, practices, and availability of resources. AS interventions have been shown to provide cost savings associated with antibiotic use and acquisition for varying types of hospital facilities that include academic teaching, community, long term acute care (LTAC), intensive care, and pediatric hospitals with patient bed capacities ranging from 60 to 880.11,12

Numerous studies have quantified the cost savings at various hospital facility types, as well as demonstrated beneficial patient outcomes to dispel the notion that only large scale hospitals with ample financial support can sustain the personnel to operate an effective AS program.

Evidence: Cost Savings and Antimicrobial Stewardship Program Personnel

Several studies show the effectiveness of AS programs in achieving significant cost savings.

Summary of Antimicrobial Stewardship Program Cost Savings Evidence

<table>
<thead>
<tr>
<th>Location/Type of Facility</th>
<th>Number of Beds</th>
<th>Cost Savings / Reductions</th>
<th>AS Team Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monroe, Louisiana Community Hospital</td>
<td>120</td>
<td>$177,000/ 1 Year13</td>
<td>ID Specialist, Clinical Pharmacist</td>
</tr>
<tr>
<td>Dallas, Texas LTAC Hospital</td>
<td>60</td>
<td>$159,580/ 15 Months11</td>
<td>ID Specialist, Director of Pharmacy</td>
</tr>
<tr>
<td>Dorchester, Massachusetts Community Teaching Hospital</td>
<td>159</td>
<td>$200,000-250,000/ 1 Year14</td>
<td>ID Specialist, ID-trained Pharmacist</td>
</tr>
<tr>
<td>Baltimore, MD Large tertiary care, teaching medical center</td>
<td>800</td>
<td>$2,949,705 / 3 Years15</td>
<td>ID Specialist, Clinical Pharmacist</td>
</tr>
<tr>
<td>Winston-Salem, NC Academic Medical Center</td>
<td>880</td>
<td>$920,070 to $2,064,441 per year over 11 years12</td>
<td>2 ID Specialists, 3 Clinical Pharmacists</td>
</tr>
</tbody>
</table>

For more details on the cost savings achieved by the institutions listed in the table above, see Appendix A.

11 Pate G Perry, et al. Implementation of an Antimicrobial Stewardship Program at a 60-Bed Long-Term Acute Care Hospital. Infection Control and Hospital Epidemiology. 2012 Apr; 33(4): 405-408
Evidence: Stewardship is Associated with Reduced Resistance

The principles of AS have been shown to counteract the commonplace medical practices, antibiotic overuse\(^1\) and inappropriate use\(^2\), that have been associated with the increased prevalence of antimicrobial-resistant pathogens.\(^{16}\) Several studies have shown the effectiveness of AS programs in reducing resistance rates:

### Summary of Antimicrobial Stewardship Program Reduction in Resistance Rates

<table>
<thead>
<tr>
<th>Location/Type of Facility</th>
<th>No. of Beds</th>
<th>Resistance Reduction</th>
<th>AS Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Houston, TX Urban Teaching Hospital</td>
<td>575</td>
<td><em>E. coli</em> isolates 20% increase in susceptibility to ticarcillin/clavulanate; ICU(^{17})</td>
<td>Antibiotic restriction, prior approval required for use of for intravenous amikacin, ceftazidime, ciprofloxacin, fluconazole, ofloxacin, and ticarcillin/clavulanate</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> isolates 22% increase in susceptibility to ceftazidime; ICU(^{17})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>K. pneumonia</em> isolates 14% increase in susceptibility to imipenem; Inpatient setting(^{17})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pittsburgh, PA Veterans Affairs Medical Center and University of Pittsburgh Medical and Surgical ICUs</td>
<td>108</td>
<td>Antimicrobial resistance and/or superinfection was documented in 15% of the patients in the AS intervention group compared to 35% of the patients in the control group(^{18})</td>
<td>Development and use of operational criteria for decision-making regarding appropriate antibiotic therapy</td>
</tr>
<tr>
<td>Nashville, TN Vanderbilt University Hospital Surgical and Trauma ICUs</td>
<td>82</td>
<td>Proportion of healthcare-acquired infections caused by multi-drug-resistant (MDR) gram-negative pathogens decreased from 37.4% (2001) to 8.5% (2008)(^{19})</td>
<td>AS program consisted of: (1) protocol-specific empiric and therapeutic antibiotics for healthcare-acquired infections; (2) surgical antibiotic prophylaxis protocols; and (3) quarterly rotation/limitation of dual antibiotic classes</td>
</tr>
<tr>
<td>The observed rate of healthcare-acquired infections per 1,000 patient days attributable to specific MDR gram-negative pathogens decreased over time: <em>Pseudomonas</em> −0.14 per year, <em>Acinetobacter</em> −0.49 per year, and <em>Enterobacteriaceae</em> −0.14 per year(^{19})</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
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| Hospital A (HA): Academic Tertiary Care Medical Center | HA: Prevalence of *Escherichia coli* and *Klebsiella* species (ESBL-EK) decreased by 45%, 0.42 isolates per 1,000 patients-days (preintervention period) to 0.23 isolates per 1,000 patients-days (postintervention period)\(^\text{20}\) | Antibiotic restriction, prior approval required for use of ceftazidime and ceftriaxone |
| Hospital B (HB): Urban Community Hospital | HB: Prevalence of ESBL-EK decreased by 22%, from 0.45 isolates per 1,000 patient-days (preintervention period) to 0.35 isolates per 1,000 patient-days (postintervention period)\(^\text{20}\) |
| Queens, NY University-Affiliated Community Hospital | An 80.1% reduction in hospital-wide cephalosporin use led to a 44.0% reduction in the incidence of ceftazidime-resistant *Klebsiella* infection and colonization throughout the medical center, a 70.9% reduction within all intensive care units, and an 87.5% reduction within the surgical intensive care unit\(^\text{21}\) | Antibiotic restriction, prior approval required from ID Physician for use of cephalosporin |
| Toronto, Ontario Sunnybrook Health Sciences Centre 3 Level III ICUs | Significant increase in overall gram-negative susceptibility to meropenem in the postintervention period, compared with the preintervention period (83.4% vs 78.2%; P = .03)\(^\text{22}\) | Prospective audits and feedback |

For more details on the reduction of resistance rates achieved by the institutions listed in the table above, see Appendix B.

**Evidence: Stewardship is Associated with Reduced Incidence of Clostridium difficile**

*Clostridium difficile* infection (CDI) has become one of the most prevalent conditions to affect the hospital patient population\(^\text{23}\) and more recently, has been reported more frequently in previously low risk populations, including young adults, pregnant females, and children.\(^\text{23,24}\) The combination of increased antibiotic use, the emergence of a hypervirulent strain of *C. difficile*, increased awareness amongst healthcare providers, and the development of detection methodologies with increased sensitivity\(^\text{24}\) has elevated CDI to a level that is tremendously concerning and needs immediate attention to reduce patient morbidity and mortality as well as economic burden. Additionally, cases of CDI have contributed to ever increasing healthcare costs, with recent literature estimating the per-case cost of CDI to be $11,285 (95% CI, $9118-$13,574).\(^\text{25}\)

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\(^\text{22}\) Elligsen, et al. Audit and feedback to reduce broad-spectrum antibiotic use among intensive care unit patients: a controlled interrupted time series analysis. ICHE 2012; 33:354


### Summary of Antimicrobial Stewardship Program Reduction in C. diff Rates

<table>
<thead>
<tr>
<th>Location/Type of Facility</th>
<th>No. of Beds</th>
<th>C. diff Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ann Arbor, MI</td>
<td>537</td>
<td>Prospective audits of 510 antimicrobial orders yielded an approximate 50% reduction in the odds of developing CDI²⁶</td>
</tr>
<tr>
<td>Saint Joseph Mercy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community Hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston, MA</td>
<td>159</td>
<td>Prior authorization and prospective audit interventions led to reduced incidence of nosocomial C. difficile from 2.2 cases per 1,000 PD to 1.4 cases per 1,000 PD in a span of three years¹⁴</td>
</tr>
<tr>
<td>Carney Hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community Teaching Hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>450</td>
<td>Antibiotic restriction of ceftriaxone and ciprofloxacin reduced hospital-acquisition rates for C. difficile by 77%, for MRSA by 25%, and ESBL-producing coliforms by 17%²⁷</td>
</tr>
<tr>
<td>District General Hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>78</td>
<td>Narrow-spectrum antibiotic use policy reinforced by an audit and feedback program lead to a reduced CDI incidence rate ratio of 0.35²⁸</td>
</tr>
<tr>
<td>3 acute-care wards for the elderly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>233</td>
<td>The restriction of high-risk antibiotics (second-generation cephalosporins, third-generation cephalosporins, fluoroquinolones and clindamycin) was associated with a significant change in the incidence trend of CDI; decreased by 0.0047/100 bed-days per month²⁹</td>
</tr>
<tr>
<td>Causeway Hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute care hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>341</td>
<td>Retrospective case-control study examining an outbreak of Clostridium difficile PCR ribotype 027 identified use of cephalosporins and fluoroquinolones as major risk factors for developing CDI; the outbreak ended only after implementation of restricted use of cephalosporins and complete ban of fluoroquinolones in addition to other stewardship and infection control interventions³⁰</td>
</tr>
<tr>
<td>Community Hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quebec, Canada</td>
<td>683</td>
<td>AS interventions markedly decreased total antibiotic and targeted antibiotic consumption by 23% and 54% respectively, and decreased nosocomial-CDAD incidence by 60%²⁴</td>
</tr>
<tr>
<td>Secondary/Tertiary-care Hospital</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For more details on the reduction of C. diff rates achieved by the institutions listed in the table above, see Appendix C.  

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### Evidence: Stewardship Improves Infection Cure Rates

<table>
<thead>
<tr>
<th>Location/Type of Facility</th>
<th>No. of Beds</th>
<th>Infection Cure Rates</th>
</tr>
</thead>
</table>
| Philadelphia, PA          | 772         | Cases managed by the Antimicrobial Management Team (AMT) had better a cure rate than those managed by ID fellows; 64% AMT cure rate vs. 42% ID fellows cure rate \( P = .007 \)\(^{31}\)  
Additionally, AMT managed cases had fewer treatment failures compared to ID fellows managed cases; 15% vs. 28%, respectively \( P = .03 \)\(^{31}\) |
| Detroit, MI               | 802         | Phase I: Retrospective baseline period; Patients diagnosed with MRSA bacteremia who were treated with vancomycin therapy with blood MRSA isolates exhibiting vancomycin minimum inhibitory concentrations (MICs) greater than 1 mg/L  
Phase II: Intervention period; Patients diagnosed with MRSA bacteremia who were initially treated with vancomycin but were switched to daptomycin if blood MRSA isolates exhibited a vancomycin MICs greater than 1 mg/L  
Phase II patients were more likely to achieve clinical success compared to Phase I patients (75.0% vs 41.4% \( p < 0.001 \)). Phase II patients also demonstrated a shorter total hospital length of stay and shorter duration of inpatient therapy, fever, and bacteremia\(^{32}\) |
| Hartford, CT              | 867         | Utilizing AS principles, this open-label controlled study compared the effectiveness of continuous versus intermittent administration of piperacillin-tazobactam  
The study resulted in clinical success rates of 94% for the continuous-infusion group and 82% for the intermittent-infusion group \( p = 0.081 \).\(^{33}\)  
Also, days to normalization of fever were significantly lower \( p = 0.012 \) in the continuous-infusion group (1.2 +/- 0.8 days) than in the intermittent-infusion group (2.4 +/- 1.5 days)\(^{33}\) |

For more details on the cure rates achieved by the institutions listed in the table above, see Appendix D.

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### Evidence: Stewardship Improves Renal Dosing

<table>
<thead>
<tr>
<th>Location/Type of Facility</th>
<th>No. of Beds</th>
<th>Improvement of Renal Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer-Sheva, Israel</td>
<td>1000</td>
<td>A prospective controlled trial examined the effect of pharmacokinetic dosing and fixed once-daily dosing on patients with gram-negative sepsis. The two study groups were similar in age, sex, and indications for therapy. The pharmacokinetic group received significantly greater doses of aminoglycosides compared to the once-daily group, however incidence of nephrotoxicity was significantly lower in the pharmacokinetic group (5% [2/43] vs. 21% [8/38], P = 0.03). Results suggest that individualized pharmacokinetic dosing of aminoglycosides reduces the incidence of nephrotoxicity and allows the use of greater doses of aminoglycosides.</td>
</tr>
<tr>
<td>Sacramento, CA</td>
<td>619</td>
<td>Prospective study investigated the treatment impact of aminoglycoside pharmacokinetics on patients receiving intermittent hemodialysis (IHD). Outcomes measured were pharmacokinetic parameters in stage 5 chronic kidney disease (CKD) and acute renal failure (ARF) patients, impact of the dialysis prescription, and treatment results of individualized dosing regimens lasting more than four days. 167 consecutive patients who received 216 courses of aminoglycosides were evaluated; 91% treatment success rate was observed in 117 individualized treatment courses in 100 patients receiving ≥ 5 days of aminoglycoside therapy. Individualized regimens using serum concentrations drawn in patients requiring treatment (non-synergistic) targeting peak concentrations of 7-10 mg/L and pre-hemodialysis serum concentrations of 3.5-5 mg/L appears successful for eradicating infections.</td>
</tr>
</tbody>
</table>

For more details on the AS interventions utilized by the institutions to improve renal dosing listed in the table above, see Appendix E.

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## Evidence: Stewardship Improves Surgical Prophylaxis

<table>
<thead>
<tr>
<th>Location/Type of Facility</th>
<th>No. of Beds</th>
<th>Improvement of Surgical Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston, MA Teaching Hospital Tertiary-Care Hospital Beth Israel Deaconess Medical Center</td>
<td>320</td>
<td>Observational 4-year cohort study compared the effect of short (&lt;48 hours) antibiotic prophylaxis (ABP) with prolonged (&gt;48 hours) ABP on surgical site infections (SSIs) and acquired antimicrobial resistance after coronary artery bypass graft (CABG) surgery. 1502 procedures using short ABP, 131 SSIs were recorded, compared with 100 SSIs after 1139 operations with prolonged ABP (crude OR, 1.0; CI, 0.8 to 1.3)(^{36}). Prolonged ABP was not associated with a decreased risk of SSI (adjusted OR, 1.2; CI, 0.8 to 1.6) and was correlated with an increased risk of acquired antibiotic resistance (adjusted OR, 1.6; CI, 1.1 to 2.6)(^{36}).</td>
</tr>
<tr>
<td>Valladolid, Spain Valladolid University Hospital</td>
<td>900</td>
<td>Randomized prospective clinical study compared the effectiveness of single dose cefazolin (2g) versus a 24-hour treatment of cefazolin (2g initial dose, followed by 1g every 8 hours) against SSIs on patients undergoing CABG and/or valve operations. A total of 419 patients received single-dose cefazolin and another 419 received 24-hour treatment. SSI occurred in 35 (8.3%) patients receiving single doses and 15 (3.6%) patients administered the 24-hour treatment ((P = .004))(^{37}). Single-dose cefazolin used as antibiotic prophylaxis in cardiac surgery was associated with a higher SSI rate than the 24-hour, multiple-dose cefazolin regimen(^{37}).</td>
</tr>
<tr>
<td>Nashville, TN Vanderbilt University Medical Center Surgical and Trauma Intensive Care Units</td>
<td>21 Surgical Critical Care Beds</td>
<td>Implementation of an AS program in the surgical and trauma intensive care units (ICUs) resulted in:  - The proportion of healthcare-acquired infections (HAIs) caused by MDR gram-negative pathogens decreased from 37.4% (2001) to 8.5% (2008)(^{19}).  - Rate of total HAIs per 1,000 patient-days that were caused by MDR gram-negative pathogens declined by –0.78 per year (95% confidence interval [CI] –1.28, –0.27)(^{19}).  - Observed rate of HAIs per 1,000 patient days attributable to specific MDR gram-negative pathogens decreased over time: <em>Pseudomonas</em> –0.14 per year (95% CI –0.20, –0.08), <em>Acinetobacter</em> –0.49 per year (95% CI –0.77, –0.22), and <em>Enterobacteriaceae</em> –0.14 per year (95% CI –0.26, –0.03)(^{19}).</td>
</tr>
</tbody>
</table>

Additional data on the effectiveness of AS in surgical prophylaxis can be found in the supporting literature for the NQF Endorsed Measure 0128 - Duration of Antibiotic Prophylaxis for Cardiac Surgery Patients. For more details on the AS interventions utilized by the institutions to improve surgical prophylaxis listed in the table above, see Appendix F.

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Conclusion

We have presented the justification and supportive evidence to demonstrate how adopting Antimicrobial Stewardship as a Condition of Participation would better patient care, improve outcomes, and lower the healthcare costs associated with antibiotic overuse (i.e., expenditures on antibiotics) as well as costs associated with infections and antimicrobial resistance. Our hope is that this document serves as a useful reference for you to consider as you assess changes to Medicare Conditions of Participation in future rulemaking.

Request

The IDSA and SHEA thank CMS for taking the time to consider this important issue. We value CMS’s guidance and insight, and would greatly appreciate the opportunity to have a follow-up discussion with you to determine the best path forward for antimicrobial stewardship to be adopted as a Medicare Condition of Participation. To further discuss this issue, please contact Andres Rodriguez, IDSA Director for Practice & Payment Policy at 703-299-5146 or arodriguez@idsociety.org.

Sincerely,

Barbara E. Murray, M.D., F.I.D.S.A.
President, IDSA

Daniel Diekema, M.D., F.S.H.E.A. F.I.D.S.A.
President, SHEA
Appendix A

Demonstrating the adaptability of AS according to the resources available, the Glenwood Regional Medical Center, located in rural Louisiana, is a 120-bed community hospital that implemented an antibiotic review program to obtain cost savings related to antibiotic use. With an AS team consisting of an infectious diseases (ID) specialist, a clinical pharmacist, and representatives from the infection control department and microbiology laboratory, approximately 128 recommendations to discontinue one or more antibiotics due to duplicate coverage, inappropriate use, or excessive duration; 111 recommendations to change from intravenous to oral administration; 77 recommendations to substitute or add an antibiotic to therapy; and twenty recommendations to change dosage were provided. An estimated 8-12 hours per week of the ID specialist’s time were required to collaborate with the AS team to decrease antibiotic costs from $18.21 to $14.77 per patient-day – a reduction of 19% and a total estimated yearly savings of $177,000.

Utilizing similar interventions, a resource limited 60-bed LTAC facility in Dallas, Texas employed an ID physician, who had a dual role as the medical director for infection control, and the director of pharmacy of the LTAC, who had no specialized infectious diseases training, to implement a facility-tailored AS program. The AS team of two provided a 28% reduction in mean monthly cost per 1,000 patient-day and pharmaceutical cost savings of $159,580 over a period of 15 months. The cost savings resulted from a dedicated AS program schedule of approximately 10 hours per month and 5 hours per week for the ID physician and pharmacists respectively.

Carney Hospital, situated in Dorchester, Massachusetts, is a 159-bed community teaching hospital that evaluated an interventional multidisciplinary antibiotic management program over the course of seven years. The Carney Hospital AS program utilized both prior authorization and prospective audit interventions that led to individualized therapeutic recommendations. Under the management and efforts of an ID specialist, contracted for one-quarter-time, and a full-time ID-trained clinical pharmacist, the program saved an estimated $200,000 to $250,000 in antibiotic costs in the span of a year after deduction of expenditures to support the program, which was approximated to be $43,000 per year or $860 per 1,000 patient-days.

Significant cost savings were also observed at the 800-bed University of Maryland Medical Center (UMMC) in Baltimore, Maryland. With an Antimicrobial Management Team (AMT) that consisted of an ID physician and a clinical pharmacist with ID training, active computer-assisted real-time reviews of antimicrobial orders for the designated restricted antimicrobials were provided as well as active AS interventions whenever necessary. During the first 3 years after implementation of the AS program, a reduction of $2,949,705 was observed in all 3 major areas of the medical center: the cancer center, the shock trauma center, and the main hospital. To further evaluate the financial impact of the AS program by way of contrast, the study discontinued the AS program and observed an immediate increase in cost of $1 million during the first year after discontinuation and an additional increase of $873,184 during the second year, which resulted in a 41.2% cost increase (FY 2008; P = .025).

Furthermore, the 880-bed Wake Forest Baptist Medical Center implemented an AS program, which was staffed by 2 ID physicians and 3 ID-trained pharmacists, to evaluate the financial
impact on hospital expenditures over an 11-year period. Utilizing AS interventions that included prior authorization for use of restricted antimicrobials and adherence to antimicrobial dosing guidelines, the program was associated with average cost savings of $920,070 to $2,064,441 per year. The cost savings figures were calculated with the subtraction of AS program labor costs.
Appendix B

The Houston, Texas-based Ben Taub General Hospital is a 575-bed urban teaching hospital that implemented a prior authorization AS program that resulted in the increased susceptibilities to restricted and unrestricted antibiotics as well as lowering antibiotic expenditures. With the implementation of restrictive interventions, susceptibilities to all quinolone and β-lactam antibiotics increased, significantly in the ICU, where an 18% increase in susceptibility of *Pseudomonas aeruginosa* isolates to imipenem was observed.

With aims to reduce antimicrobial resistance, the University of Pittsburgh affiliated Veterans Affairs Medical Center performed a randomized trial within their 108-bed medical and surgical intensive care units (ICUs) to observe the effects of AS interventions that curtailed excessive, inappropriate use of antibiotics to treat patients infected with nosocomial pneumonia. Utilizing operational criteria for decision-making regarding antibiotic therapy, patients diagnosed with a low likelihood of pneumonia were randomized into standard and experimental therapy groups. The standard therapy group was treated with a 10 to 21 day course of antibiotics that was chosen by the treating physician while the experimental group received ciprofloxacin for 3 days then reevaluated for either continuation or discontinuation of therapy. Antimicrobial resistance and/or superinfections were present in both therapy groups, but the experimental therapy group had a 20% lower rate of antimicrobial resistance/superinfections, 15% (5 of 37) of the patients in the experimental versus 35% (14 of 37) of the patients in the standard therapy group (p=0.017).

Over an eight year period, Vanderbilt University Hospital implemented an infection reduction program, which included AS interventions, in the surgical and trauma ICUs to reduce multi-drug-resistant (MDR) gram-negative healthcare-associated infections (HAIs). The program consisted of protocol for use of specific empiric and therapeutic antibiotics to treat HAIs, surgical antibiotic prophylaxis protocols, and quarterly rotation/limitation of dual antibiotic classes. With HAI surveillance conducted according to the National Health Safety Network criteria, HAIs caused by MDR gram-negative pathogens decreased from 37.4% (2001) to 8.5% (2008), whereas the proportion of HAIs caused by pan-sensitive pathogens increased from 34.1% to 53.2%. The rate of total HAIs per 1,000 patient-days that were caused by MDR gram-negative pathogens declined by -0.78 per year (95% confidence interval [CI] -1.28, -0.27). The observed rate of HAIs per 1,000 patient days attributable to specific MDR gram-negative pathogens decreased over time: *Pseudomonas* -0.14 per year (95% CI -0.20, -0.08), *Acinetobacter* -0.49 per year (95% CI -0.77, -0.22), and *Enterobacteriaceae* -0.14 per year (95% CI -0.26, -0.03).

Lipworth et al. conducted a 5-year quasi-experimental study comparing two hospitals within the same health system to examine the effects of AS interventions to control the emergence of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* species (ESBL-EK). Restricting the use of ceftriaxone and ceftazidime, the prevalence of ESBL-EK at Hospital A (625-bed academic medical center) decreased by 45% (P < .001), compared to a 22% decrease (P = .36) at Hospital B (344-bed urban community hospital). While decreases in prevalence were observed at both hospitals, variability in the epidemiological profiles of ESBL-EK isolates at different hospitals must be considered when designing interventions to respond to these pathogens.
Restricting the use of cephalosporin without prior approval from an infectious diseases specialists, a 500-bed university-affiliated community hospital in Queens, NY examined the outcomes regarding the incidence of patient infection and colonization by cephalosporin-resistant *Klebsiella*. Encompassing all adult medical and surgical inpatients in the span of one year, a 44.0% reduction in the incidence of ceftazidime-resistant *Klebsiella* infection and colonization throughout the medical center was observed (P < .01), more specifically a 70.9% reduction within all intensive care units (P < .001), and an 87.5% reduction within the surgical intensive care unit (P < .001).²¹

Further evaluating the impact of AS interventions on critical care patients, the Sunnybrook Health Sciences Centre in Toronto, Ontario, Canada conducted a controlled interrupted time series analysis across three level III ICUs, a 20-bed general critical care unit (CRCU), a 14-bed cardiovascular ICU (CVICU), and the 14-bed Ross Tilley Burn Centre (RTBC).²² Comparison of the susceptibilities of pre-intervention and post-intervention gram-negative bacterial isolates indicated an increased susceptibility of 5.2% to meropenem.²² The prospective audits and feedback interventions provided a reduction in the use of antimicrobial agents, subsequently decreasing antibiotic expenditures and resistance in a vulnerable and complex patient population.²²
APPENDIX C

Saint Joseph Mercy Ann Arbor Hospital, a 537-bed community hospital, initiated an audit and feedback AS program comprised of two infectious diseases specialists and three ICU pharmacists to evaluate patient outcomes that included death within 30-days of hospitalization, readmission within 30-days of discharge, and development of CDI. One year after initiation of the AS program, 510 antimicrobial orders were reviewed, resulting in an approximate 50% reduction in the odds of developing CDI (odds ratio, 0.46; 95% confidence interval, 0.25-0.82).26 While the AS interventions were not associated with decreased mortality at 30-days after discharge and readmission rates, antimicrobial use, pharmacy costs, and CDI rates were all significantly reduced.26

In addition to obtaining cost savings, Carney Hospital was able to reduce the incidence of nosocomial \textit{C. difficile} from 2.2 cases per 1,000 PD to 1.4 cases per 1,000 PD in a span of three years, with the decrease strongly attributable to the AS interventions.14 The reduction in \textit{C. difficile} incidences was achieved despite an increase in the acuity of patient care.14 Following suit, the abovementioned Sunnybrook Health Sciences Centre (Appendix B) was able to reduce antimicrobial resistance within varying types of ICUs and decrease the number of monthly nosocomial \textit{C. difficile} infections by 31%, 16 to 11 reported cases, in comparison to the control non-ICU wards that increased by 33%, 87 to 116 reported cases.14

A 450-bed British general district hospital implemented a restrictive antibiotic policy on the use of ceftriazone and ciprofloxacin to assess its effects on hospital-acquired \textit{Clostridium difficile}, extended-spectrum beta-lactamase (ESBL)-producing coliforms, and methicillin-resistant \textit{Staphylococcus aureus} (MRSA). Comparing the rates of \textit{C. difficile}, MRSA, and ESBL-producing coliforms 9-months prior to the AS program to 10-months after implementation of the AS program, hospital-acquisition rates for \textit{C. difficile} reduced by 77% (2.398 to 0.549 cases/1000 patient-bed days (pt-bds)), for MRSA by 25% (1.187 to 0.894 cases/1000 pt-bds), and for ESBL-producing coliforms by 17% (1.480 to 1.224 cases/1000 pt-bds).27 An audit performed 3 years after the policy showed sustained reduction in \textit{C. difficile} rates (0.259 cases/1000 pt-bds), with additional decreases for MRSA (0.409 cases/1000 pt-bds) and ESBL-producing coliforms (0.809 cases/1000 pt-bds).27

Investigating the effect of an audit and feedback program reinforcing a narrow-spectrum antibiotic policy on the use of ceftriazone and ciprofloxacin to assess its effects on hospital-acquired \textit{Clostridium difficile}, extended-spectrum beta-lactamase (ESBL)-producing coliforms, and methicillin-resistant \textit{Staphylococcus aureus} (MRSA). Comparing the rates of \textit{C. difficile}, MRSA, and ESBL-producing coliforms 9-months prior to the AS program to 10-months after implementation of the AS program, hospital-acquisition rates for \textit{C. difficile} reduced by 77% (2.398 to 0.549 cases/1000 patient-bed days (pt-bds)), for MRSA by 25% (1.187 to 0.894 cases/1000 pt-bds), and for ESBL-producing coliforms by 17% (1.480 to 1.224 cases/1000 pt-bds).27 An audit performed 3 years after the policy showed sustained reduction in \textit{C. difficile} rates (0.259 cases/1000 pt-bds), with additional decreases for MRSA (0.409 cases/1000 pt-bds) and ESBL-producing coliforms (0.809 cases/1000 pt-bds).27

Investigating the effect of an audit and feedback program reinforcing a narrow-spectrum antibiotic policy on CDI rates, a prospective controlled interrupted time-series study was conducted at three acute medical wards for elderly people in a British teaching hospital. For a duration of 42 months (pre- and post-intervention periods 21-months each), 6,129 consecutive unselected acute medical admissions age 80 years or older were observed.28 Using the Poisson regression, the study showed a significant fall in CDI associated with the intervention [Incidence Rate Ratios 0.35 (0.17, 0.73), P = 0.009], but not in MRSA (control outcome) [0.79 (0.49, 1.28); P = 0.32].28

Further supporting the correlation of AS interventions on reduced CDI rates, Aldeyab et al. observed reduction in the use of high-risk antibiotics was associated with a significant change in the incidence trend of CDI (P=0.0081), i.e. the CDI incidence rate decreased by 0.0047/100 bed-days per month.29 The restriction of the high-risk antibiotics (second-generation cephalosporins, third-generation cephalosporins, fluoroquinolones and clindamycin) contributed to both a
reduction in their use and a reduction in the incidence of CDI at the 233-bed acute care Causeway Hospital located in the United Kingdom.29

Following an outbreak of CDI due to PCR ribotype 027, a 341-bed community hospital in Harderwijk, the Netherlands performed a retrospective case-control study to identify the main risk factors for the outbreak. Using multiple logistic regression analysis, cephalosporins and fluoroquinolones use were identified as the major risk factors for development of CDI.30 The risk of developing CDI was particularly high in people receiving a combination of a cephalosporin and a fluoroquinolone (OR 57.5; 95% CI 6.8-483.6).30 Additionally, independent risk factors for CDI were: above the age of 65 years (OR 2.6; 95% CI 1.0-5.7), duration of hospitalization (OR 1.04 per additional day; 95% CI 1.0-1.1), and antibiotic use (OR 12.5; 95% CI 3.2-48.1). The outbreak ended only after implementation of restricted use of cephalosporins and a complete ban on fluoroquinolones, in addition to general hygienic measures, cohorting of patients in a separate ward, education of staff, and intensified environmental cleaning.30

Assessing the effectiveness of AS interventions to decrease the incidence of C. difficile associated disease (CDAD) in comparison to infection control practices, the Centre Hospitalier Universitaire de Sherbrooke (CHUS), located in Quebec, Canada, conducted an interrupted time-series analysis at the hospital’s 683-bed secondary/tertiary-care sites.24 CHUS initiated the first portion of the evaluation with only infection control practices in place, e.g. staff education, isolation for patients with diarrhea prior to lab test confirmation of C. difficile. The second portion of the study aimed to reduce the use of antibiotics often associated with CDAD by utilizing educational and feedback AS interventions. While infection control practices provided no measureable impact on the reduction of the CDAD incidence rate, AS interventions markedly decreased total antibiotic and targeted antibiotic consumption by 23% and 54% respectively, and decreased nosocomial-CDAD incidence by 60%.24 Although infection control practices did not impact CDAD incidence rates alone, it should not be dismissed and be utilized synergistically with AS interventions to control CDAD, as infection control practices were ongoing with AS interventions during the second portion of the interrupted time-series analysis.24
APPENDIX D

The Hospital of the University of Pennsylvania performed a quasi-experimental study comparing the effectiveness of an Antimicrobial Management Team (AMT) with that of ID fellows regarding antimicrobial recommendations, clinical, and economic outcomes. The AMT consisted of a clinical pharmacist with training in anti-infective therapy and an ID physician. Examining the outcomes on appropriateness, cure rates, and treatment failures, the AMT outperformed ID fellows on all parameters ([87% vs. 47%; P < .001], cure rate [64% vs. 42%; P = .007], and treatment failures [15% vs. 28%; P = .03]). Differences in economic outcomes between cases managed by the AMT and those managed by the ID fellows were not statistically significant.

Evaluating the effectiveness of daptomycin therapy in patients with methicillin-resistant Staphylococcus aureus (MRSA) bacteremia, the 802-bed tertiary care Henry Ford hospital located in Detroit, Michigan conducted a two-phase quasi-experimental study within their Level 1 trauma center. The study population consisted of 170 patients with MRSA bacteremia susceptible to vancomycin. Phase I included 70 patients who had initial blood MRSA isolates exhibiting a vancomycin minimum inhibitory concentrations (MICs) >1 mg/L and were treated with vancomycin. Phase II observed 100 patients who were administered vancomycin therapy initially then switched to daptomycin after MRSA isolates demonstrated vancomycin MICs greater than 1 mg/L. Phase II patients were observed to more likely achieve clinical success than phase I patients (75.0% vs 41.4% p<0.001) in addition to demonstrating shorter total hospital length of stay, shorter durations of inpatient therapy, fever, and bacteremia. Treatment during phase I was found to be independently associated with failure, with nine patients experiencing nephrotoxicity.

Further examining the association between AS and cure rates, the Hartford Hospital, a tertiary-care community teaching hospital, conducted an open-label controlled study comparing the effect of continuous and intermittent infusion of piperacillin-tazobactam on clinical and microbiological success rates as well as economic expenditures. A total of 98 patients were included in the study with the continuous-infusion group yielding clinical and microbiologic success rates of 94% (p=0.081) and 89% (p=0.092), respectively. Clinical and microbiologic success rates observed in the intermittent-infusion group were 82% (p=0.081) and 73% (p=0.092), respectively. Additionally, days to normalization of fever were significantly lower in the continuous-infusion group (1.2+/-. 0.8 days) than in the intermittent-infusion group (2.4 +/- 1.5 days) (p=0.081).
APPENDIX E

Evaluating the impact of individualized pharmacokinetic dosing, the Soroka University Medical Center located in Israel conducted a single-blind pseudo-randomized study comparing the effect of fixed, single daily dose and pharmacokinetic dosing on the reduction of nephrotoxicity and improvement of patients outcomes with gram-negative sepsis. Within the once-daily group (control), trough levels were determined every 2 to 3 days with no alterations being made in dosage or dosing interval, unless the trough level indicated aminoglycoside accumulation and potential kidney damage. The pharmacokinetic dosing group (intervention) had aminoglycoside levels determined daily 1 hour after initiation of infusion as well as 8 to 16 hours later for the first 3 days of therapy, and then once every 3 days. The study included 81 total patients, with 38 patients assigned to the fixed once-daily dose group and 43 in the pharmacokinetic group. Of the 43 patients in the pharmacokinetic group, 2 (5%) developed nephrotoxicity compared with 8 (21%) of the 38 patients in the fixed-dose group (P = 0.03). Although the intervention group had lower rates of nephrotoxicity, no significant differences were found between the study groups in mortality or cure rates.

The 619-bed University of California Davis Medical Center conducted a prospective study to investigate the optimal aminoglycoside dosing regimen for patients with acute renal failure (ARF) and chronic kidney disease (CKD) receiving intermittent hemodialysis (IHD) as well as the impact of patient-specific dosing regimens on treatment outcomes. A total of 167 consecutive patients receiving 216 courses of aminoglycoside antibiotics were included in the study. Of the 167 patients, 48 patients had ARF and 119 were diagnosed with stage 5 CKD. A treatment success rate of 91% was observed in patients who received treatment for 5 or more days, 106 treatment successes of 117 total treatment courses were observed in 110 patients. Multiple patient-specific factors that include dialysis prescription, fluid status, antibiotic requirements based on the infection location, organism cultured, minimum inhibitory concentration, and individual pharmacokinetic parameters may be necessary to provide optimal aminoglycoside therapy when prolonged treatment is necessary to eradicate infections.
APPENDIX F

In Boston, Massachusetts, the West Campus of Beth Israel Deaconess Medical Center performed a 4-year observational cohort study examining the effect of prolonged antibiotic prophylaxis (ABP) on the risk of surgical site infections (SSIs) and the selection of antibiotic-resistant microorganisms following coronary artery bypass graft (CABG) surgery. The main prophylactic practice being examined was the duration of ABP, less than or greater than 48 hours. Within the timeframe of the study, 2,641 CABG procedures were performed, with 2,180 patients receiving ABP. Of the 2,180 patients administered ABP, 1,502 received ABP for less than 48 hours and 1,130 received ABP for greater than 48 hours. Following statistical adjustment for independent risk factors for SSI, ABP greater than 48 hours was found not to be associated with a decreased risk of SSI (adjusted OR, 1.2; CI, 0.8 to 1.6). Regarding isolation of resistant organisms, prolonged ABP (> 48 hours) was associated with an increased risk of acquired antibiotic resistance (OR, 1.6; CI, 1.1 to 2.6). Harbarth et al. demonstrated that prolonged prophylaxis does not reduce the rate of SSI and is associated with an increased risk of acquired antibiotic resistance.

The 900-bed Valladolid University Hospital, located in Valladolid, Spain, conducted a random, prospective, clinical study testing the efficacy of single dose cefazolin compared to a 24-hour regimen of cefazolin in preventing SSIs in adult patients who underwent elective CABG, valve operations, or both. A total of 838 adult patients were randomly given a single dose of cefazolin (2g) or a 24-hour multiple dose treatment (2g initial dose, followed by 1g every 8 hours). An even split of 419 patients were randomly assigned to each dosage group, with SSI occurring in 35 (8.3%) patients within the single dose group and 15 (3.6%) patients in the 24-hour multiple dose group (P = .004). No differences were observed between the groups on outcomes of mortality or duration of hospitalization. Isolated microorganisms for SSIs had similar distributions in both groups, with 86% of the infections being gram-positive cocci. For cardiac surgery, single dose cefazolin was associated with higher rates of SSI than 24-hour multiple dose regimen of cefazolin.

For more information on the Dortch et al. Vanderbilt University Hospital (VUH) study, please see Appendix B.