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REVIEW ARTICLE

A Baker's Dozen of Top Antimicrobial Stewardship Intervention Publications in 2019

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Staying current on literature related to antimicrobial stewardship can be challenging given the ever-increasing number of published articles. The Southeastern Research Group Endeavor (SERGE-45) identified antimicrobial stewardship–related peer-reviewed literature that detailed an actionable intervention for 2019. The top 13 publications were selected using a modified Delphi technique. These manuscripts were reviewed to highlight the actionable intervention used by antimicrobial stewardship programs to provide key stewardship literature for teaching and training and to identify potential intervention opportunities within one's institution.

Keywords: antibiotics; antimicrobial stewardship; infectious diseases; metrics; resistance.

Antimicrobial stewards and infectious diseases (ID) clinicians experienced important advances throughout 2019. Included among the new antimicrobial approvals by the Food and Drug Administration were new agents to combat multidrug-resistant (MDR) gram-negative infections (cefiderocol and imipenem/cilastatin/relebactam), community-acquired pneumonia with a novel mechanism of action (lefamulin), and MDR tuberculosis (pretomanid) [1]. While the advent of new agents brings hope in managing difficult-to-treat infections, positioning these new drugs on formularies and in treatment decisions remains a constant challenge for stewardship teams. Additionally, several pharmaceutical companies continue to struggle with or abandon the antimicrobial market as sales of new agents flounder, which calls into question the future of novel antimicrobial approvals [2, 3].

The year brought mixed news regarding antimicrobial resistance rates. As reported by the Centers for Disease Control and Prevention (CDC) in the 2019 edition of the Antibiotic Resistance Threats report, proportions of traditional hospital-acquired infections such as MDR *Pseudomonas aeruginosa* and *Acinetobacter baumannii* declined, perhaps owing to the impact of acute care stewardship teams meeting CDC core elements [4–6]. In contrast, the proportion of extended-spectrum beta-lactamase (ESBL)–producing *Escherichia coli* increased, emphasizing the need for focused stewardship efforts outside the hospital walls [4]. Reducing unnecessary antimicrobial prescriptions and overall antimicrobial utilization remain valued metrics and pillars for successful antimicrobial stewardship teams to combat the untoward effects of antimicrobials [7].

The body of literature continues to grow, offering new ideas and strategies along with supporting data reinforcing traditional interventions for antimicrobial stewardship teams. Since 2016, members of the Southeastern Research Group Endeavor (SERGE-45), an interprofessional research network primarily composed of expert pharmacist stewards in the Southeastern United States, has systematically compiled and reviewed publications involving an antimicrobial stewardship intervention annually [8–11]. The top 13 selected articles from 2019 are detailed herein and briefly reviewed in Table 1 [12–24].

METHODS

Using a modified Delphi technique (detailed previously), members of the SERGE-45 network identified antimicrobial stewardship publications from 2019 considered to be significant using the following inclusion criteria: (1) published in 2019, including electronic, "early-release" publications, and (2) included an actionable intervention [25]. An actionable intervention was defined as a stewardship strategy that was implemented in

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Table 1. Summary of Top 13 Antimicrobial Stewardship Intervention Papers, 2019

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Brotherton et al. J Antimicrob Chemother 2020; 75:1054–60 [12].	Single-center, retrospective quasi-experimental study in a large academic medical center comparing adherence to an institutional SAB management bundle	Upon isolating *Staphylococcus aureus* from blood cultures, clinical decision support software triggered an automated, hard-stop alert in the electronic health record prompting providers to use a 6-component SAB bundle, which consisted of (1) infectious diseases consultation, (2) source control, (3) echocardiogram, (4) repeat blood cultures, (5) antimicrobial therapy, and (6) appropriate duration.	Primary outcome: -Adherence to all 6 components of SAB bundle: 29.7% vs 56.9%; $P < .001$ Secondary outcomes: -ID consult within 5 days of positive culture: 76.6% vs 88.8%; $P = .021$ -Source control: 54.1% vs 79.3%; $P < .001$ -Repeat blood cultures within 72 hours of initial positive: 98.2% vs 100%; $P = .238$ -Echocardiogram: 76.6% vs 83.6%; $P = .244$ -Antimicrobial therapy: 94.6% vs 96.6%; $P = .532$ -Appropriate duration: 80.2% vs 83.6%; $P = .605$ -30-day all-cause mortality: 12.6% vs 6%; $P = .110$ -90-day readmission due to SAB complications: 14.3% vs 8.3%; $P = .256$
Erickson et al. Open Forum Infect Dis 2019; 6:XXX–XX [13].	Retrospective, single-center cohort study comparing a pre-antimicrobial stewardship period with a postantimicrobial stewardship period	Antimicrobial stewardship bundle in conjunction with rapid diagnostic testing for uncomplicated gram-negative bacteremia: promoting IV-to-PO switches, 7-day antibiotic durations, advising against repeat blood cultures. This is compared with a pre-antimicrobial stewardship period with only rapid diagnostic testing available.	Primary outcome: -Shorter median treatment duration in the ASP bundle group (10 vs 14 days; $P < .001$) Secondary outcomes: -Earlier switch to PO therapy (day 4 vs day 5; $P = .046$) -Lower 30-day all-cause readmission (23.3% vs 39.2%; $P = .047$) -Lower incidence of repeat blood cultures (44.2% vs 66.7%; $P = .01$) -No difference in 30-day mortality (0 vs 2.3%; $P = .27$)
Peñalva et al. Lancet Infect Dis 2019; 20:199–207 [14].	Quasi-experimental, interrupted time-series study across 214 primary health centers in 4 primary health care districts	Education that focused on 5 aspects: 1. Central and local dissemination of program information 2. Open online courses focused on appropriate antibiotics for common infections 3. Regular in-person clinical protocol updates 4. Educational interviews 5. Quarterly reports with analysis	Primary outcomes: -Inappropriate antibiotic prescribing had an annual change of 3.2% (36.5% in 2014 to 26.9% in 2017; $P = .001$) Incidence density of ESBL-producing *E coli* in urine cultures: RR –65.6% 4 years after start of program: -Pre-intervention (2012–2013) increase: 0.004 cases per 1000 inhabitants; $P < .0001$ -Intervention (2014–2017) decrease: –0.006 cases per 1000 inhabitants; $P < .0001$
Christensen et al. Infect Control Hosp Epidemiol 2019; 40:269–75 [15].	Retrospective, single-center, quasi-experimental	A *C. difficile* NAAT ASP preauthorization and chart review was initiated in October 2016. A preimplementation period of January 2014 to September 2016 was compared with a postimplementation period of October 2016 to April 2018. The ASP pharmacist prospectively reviewed all weekday *C. difficile* NAAT orders and provided recommendations for canceling those that did not meet testing criteria.	Primary outcome: pre-implementation vs postimplementation -Mean monthly NAAT, 15.4 vs 12.4; $P = .018$ Secondary outcomes: pre-implementation vs postimplementation -HO-CDI-IR, 8.5 vs 6.4 per 10 000 patient days; $P = .0036$ -SIR, 0.97 vs 0.78; $P = .015$ -Mean vancomycin consumption,10.8 vs 10.7 DOT/1000 DP; $P = .91$
Seddon et al. Clin Infect Dis 2019; 69:414–20 [16].	Retrospective, multicenter cohort study	Risk of CDI was examined in adults hospitalized for >48 hours for the treatment of Enterobacterales bloodstream infections.	Primary outcome: -Higher incidence of CDI in patients who received >48 hours of APBL: 7.0% (95% CI, 4.2% to 9.8%) vs 1.8% (95% CI, 0.4% to 3.2%) in patients who received ≤48 hours of APBL; log-rank $P = .002$ Secondary outcomes: - Receipt of >48 hours of APBL was associated with an HR of developing CDI of 3.56 (95% CI, 1.48 to 9.92); $P = .004$ -End-stage renal disease was associated with an HR of developing CDI of 4.27 (95% CI, 1.89 to 9.11); $P = .001$

Table 1. Continued

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Depuy et al. Open Forum Infect Dis 2019; 6:XXX–XX [17].	Retrospective, single-center cohort study evaluating impact of an ARV stewardship team on identification and correction of ARV medication errors	Medication reconciliation and daily review of ARV medications throughout inpatient admission by an interdisciplinary pharmacist–physician ARV stewardship team. Included contact with outpatient HIV providers for regimen confirmation and standardized communication with the primary team via documentation in the EHR.	Primary outcome: -336 interventions made by ARV stewardship team over 12-month period; drug interaction (45.2%), incorrect regimen (17.9%), and OI prophylaxis (10.1%) errors occurred most frequently Secondary outcomes: -43.2% of hospitalizations with ARV orders required at least 1 intervention -96.4% intervention acceptance rate -$263 428 estimated associated cost savings -Multivariable analysis identified multitablet inpatient regimen ($P = .009$), ICU admission ($P = .01$), surgical care ($P = .02$), days reviewed ($P = .02$), and noninstitutional HIV provider ($P = .07$) as risk factors for ARV medication errors
Langford et al. Infect Control Hosp Epidemiol 2019; 40:1344–47 [18].	Pre/post design over a 4-year period examining impact of a high-intensity, interdisciplinary, round-based PAF compared with a low-intensity PAF on antimicrobial use measured in DDD per 1000 PD on internal medicine wards in a 400-bed community hospital	Pre-intervention: low-intensity phase 24 months before the intervention -ASP pharmacists provided PAF to prescribers on 5 internal medicine units; focus on patients receiving targeted antibiotics -1-on-1 recommendation to the internal medicine physician performed for each patient requiring intervention Postintervention: high-intensity phase 24 months -Structured, twice-weekly ASP rounds -Interdisciplinary team (ward pharmacist, internal medicine physician, ASP pharmacist, and ASP physician) rounded for 30 minutes per unit -Internal medicine physician made final decision after PAF recommendation	Primary outcomes: -Low-intensity phase antimicrobial use: 483 DDD/1000PD vs 442 DDD/1000PD in high intensity (difference, –42; 95% CI, –74 to –9) -Adjusted analysis to account for seasonality (difference, –93 DDD/1000PD; 95% CI, –169 to –20) Secondary outcomes: Adjusted analysis to account for seasonality: postintervention period: -Months 1–12, 483.3 DDD/1000PD in low-intensity group vs 458.3 DDD/1000PD in high-intensity group (difference, –75.3; 95% CI, –145.9 to –5.9) -Months 13–24 in low-intensity group 483.3 DDD/1000PD vs high-intensity group 415.5 DDD/1000PD (difference, –121.5; 95% CI, –217 to –28.3) Targeted antibiotics: -153.1 DDD/1000PD in low-intensity vs high-intensity group 141 DDD/1000 PD (difference, –50.1; 95% CI, –71.7 to –28) -No changes in clinical outcomes of CDI, readmission rate, or mortality after the switch to high-intensity PAF
Bolten et al. Am J Health Syst Pharm 2019; 76:S85–90 [19].	Retrospective study evaluating antibiotic usage comparing traditional ASP PAF with implementation of an ADAP	Implemented an automatic antibiotic discontinuation policy of antibiotics authorizing ASP team to stop antibiotics therapy in cases with inappropriate duplicate antimicrobial coverage (atypical, anaerobic, dual-β-lactam without documented rational) or excess duration of therapy in specified disease states/or antibiotics >48 hours and no documented infection	Primary outcome: -Mean total antibiotic days per patient (7.6 days vs 6.6 days; $P < .05$) Secondary outcome: -Mean excess days of antibiotics (2.3 days vs 1.5 day; $P < .05$) -Patients prescribed antibiotics at discharge (18.5% vs 8%; $P < .05$) -30-day readmission (12.3% vs 14.2%; NS) -CDI (1 vs 2 cases; NS) -Multidrug-resistant infection (4.3% vs 2.5%; NS)
Shively et al. Clin Infect Dis 2020; 71:539–45 [20].	Multicenter, quasi-experimental, pre- and postintervention study	Review of patients on broad-spectrum antimicrobials and those admitted with lower respiratory tract infections and skin and soft tissue infections by remote ID physicians and local pharmacists	Primary outcomes: -A total of 1419 recommendations were made, of which 1262 (88.9%) were accepted -Decrease in tier 1 antimicrobial use (DOT/1000 PD): 10.6 during the intervention period vs 16.3 in historical control; $P = .04$ -Decrease in tier 2 antimicrobial use (DOT/1000 PD): 248.2 during the intervention period vs 325.9 in historical control; $P < .001$ -Numerical decrease in total antimicrobial use (DOT/1000 PD): 820.7 during the intervention period vs 777.1 in historical control; $P = .18$ -Increase in ID consultations/1000 PD: 21.5 during the intervention period vs 15.4 in historical control; $P = .001$ -Estimated annual cost-savings: $104 087.34 on tier 1 antimicrobials and $56 239.05 on tier 2 antimicrobials vs increase of $17 696.55 on nontiered antimicrobials (difference, $142 629.83)

Table 1. Continued

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Anderson et al. JAMA Netw Open 2019; 2:e199369 [21].	Multicenter, historically controlled, prospective, nonrandomized clinical trial with crossover design	Modified PA by pharmacists and PPR by the stewardship team targeting vancomycin, piperacillin-tazobactam, and the antipseudomonal carbapenems on formulary	Primary outcomes: -Intervention approval processes took a median of 95 days -Pharmacists performed 1456 interventions (median per hospital, 350) during PA and 1236 interventions (median per hospital, 298) during PPR -Recommendations were accepted by clinicians in 79.2% of cases during PA and 69.0% during PPR -More study antibiotics were determined to be inappropriate during PPR: 41.0% during PPR vs 20.4% during PA; $P < .001$ -Pharmacists recommended de-escalation more during PPR: 29.1% during PPR vs 13.0% during PA; $P < .001$ -Pharmacists recommended dose change more during PA: 15.9% during PA vs 9.6% during PPR; $P < .001$ -The median time dedicated to the stewardship interventions varied by hospital (range of median hours per week, 5–19) Secondary outcomes: -No decrease in antibiotic use (DOT/1000 PD) during PA: 931.0 vs 926.6 during matched historical control (difference, 4.4; 95% CI, –55.8 to 64.7) -Decrease in antibiotic use (DOT/1000 PD) during PPR: 925.2 vs 965.3 during matched historical control (difference, –40.1; 95% CI, –71.7 to –8.6) -Same median length of hospitalization per admission for PA, PPR, matched historical control
Gross et al. Open Forum Infect Dis 2019; 6:XXX–XX [22].	Implementation of antimicrobial stewardship in an academic dental practice using the CDC Core Elements of Outpatient Antimicrobial Stewardship	Multimodal intervention consisting of standardizing antimicrobial therapy for acute dentoalveolar conditions, educational interventions, and patient-facing educational posters focusing on the necessity of antibiotics and potential harms	Primary outcome: -72.9% decrease in antibiotic prescribing rate per urgent care visit (pre-intervention urgent care prescribing rate, 8.5% [24/283]; postintervention, 2.3% [8/352]; $P < .001$)
Webb et al. Clin Infect Dis 2019; 68:498–500 [23].	Retrospective quasi-experimental pre- and postimplementation of 2 antimicrobial stewardship interventions in an inpatient hematological malignancy treatment unit	Utilized monthly antibiotic cycling with either piperacillin-tazobactam or cefepime (with or without metronidazole) and a previously described clinical prediction tool to guide empiric VRE therapy when managing febrile neutropenia	Primary outcomes: -Carbapenem use decreased by 230 DOT/1000 PD (95% CI, –290 to –180; $P < .001$) -Unadjusted antipseudomonal carbapenem use decreased after intervention (396.5 vs 123.4 DOT/1000 PD; $P < .001$) -Daptomycin prescribing (–160 DOT/1000 PD; 95% CI, –200 to –120; $P < .001$) -VRE clinical prediction score (–30 DOT/1000 PD; 95% CI, –50 to 0; $P = .08$) Secondary outcomes: -VRE colonization (OR, 0.64; 95% CI, 0.51 to 0.81; $P < .001$) and infection decreased after intervention (2.38 vs 1.08 infections/1000 PD; $P = .006$) -Infection due to ESBL-producing Enterobacteriaceae increased (0.14 to 0.81/1000 PD; $P = .01$) postintervention -No impact on inpatient mortality (OR, 0.91; 95% CI, 0.6 to 1.5; $P = .72$)
Graber et al. Clin Infect Dis 2020; 71:1168–76 [24].	Pre/post quasi-experimental study evaluating impact of novel antimicrobial use visualization tools on antimicrobial usage at 8 VA inpatient facilities	Development of interactive graphic tools for dissemination of in-depth facility-level antimicrobial usage data to facility stewards. The tools were optimized based on collaborative feedback from the 8 volunteer facilities and ultimately provided dashboards that could be filtered by antimicrobial use decision point, antimicrobial agent type, unit, disease state, or SAAR category and compared with similar or all VA facilities. Change in antimicrobial use was assessed pre-intervention (January 2014–January 2016) and postintervention (July 2016–January 2018).	Average change in DOT/1000 DP at intervention vs nonintervention sites Primary outcome: -Total inpatient antimicrobial use: –2.1% (95% CI, –5.7% to 1.6%; $P = .2529$) vs +2.5% (95% CI, 0.8% to 4.1%; $P = .0026$); absolute difference, 4.6% ($P = .025$) Secondary outcomes: -Total inpatient use of anti-MRSA agents: –11.3% (95% CI, –16.0% to –6.3%; $P < .0001$) vs –6.6% (95% CI, –9.1% to –3.9%; $P < .0001$); absolute difference, 4.7% ($P = .092$) -Total inpatient use of antipseudomonal agents: –3.4% (95% CI, –8.2% to 1.7%; $P = .185$) vs +3.6% (95% CI, 0.8% to 6.5%; $P = .011$); absolute difference, 7.0% ($P = .018$)

Abbreviations: ADAP, automatic discontinuation of antibiotics policy; APBL, antipseudomonal β-lactam; ARV, antiretroviral; ASP, antimicrobial stewardship programs; CDC, Centers for Disease Control and Prevention; CDI, *Clostridioides difficile* infection; DDD, defined daily dose; DOT, days of therapy; DP, days present; EHR, electronic health record; HO, hospital-onset; HR, hazard ratio; ICU, intensive care unit; ID, infectious diseases; IQR, interquartile range; IR, incident rate; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; NAAT, nucleic acid amplification tests; NS, nonsignificant; OI, opportunistic infection; OR, odds ratio; PA, preauthorization; PAF, prospective audit and feedback; PD, patient-days; PO, per oral; PPR, postprescription audit and review; RR, relative reduction; SAAR, standardized antimicrobial administration ratios; SAB, *Staphylococcus aureus* bacteremia; SIR, standardized infection ratio; VA, Veterans Affairs; VRE, vancomycin-resistant *Enterococcus*.

practice and resulted in measurable outcomes. Clinical practice guidelines, official statements, review articles, and articles without an actionable intervention were excluded.

A PubMed search using "antimicrobial stewardship" for 2019 revealed 1293 potential publications. P.B.B. screened abstracts to ensure that all relevant articles were considered. In addition, 79 author-identified publications (most duplicated from the literature search) were submitted for potential inclusion. C.M.B., K.R.S., and P.B.B. screened these to ensure that articles met inclusion criteria. During the first round of reviews, a total of 60 articles were distributed to the SERGE-45 network (65 members) for ranking using SurveyMonkey based on contribution and/or application to antimicrobial stewardship programs (ASPs); 21 participants (32%) ranked their top 13 based on clinical judgment [26]. During the second round, 12 authors (100%) ranked their top 13 based on clinical judgment. Finally, in a teleconference C.M.B., K.R.S., and P.B.B. reviewed the group ranks and established final consensus on the top 13 articles based on number of votes received for each article, described herein. Figure 1 is a flowchart of the database and article selection process, and Table 1 is a summary of the selected articles.

RESULTS

Automated Stewardship Intervention for *Staphylococcus aureus* Bloodstream Infection

Management of *Staphylococcus aureus* (SA) bloodstream infection (BSI) remains challenging, with mortality rates around 20% [27]. Furthermore, adherence to evidence-based recommendations for managing SABSI continues to be suboptimal. Brotherton and colleagues conducted a single-center, retrospective quasi-experimental study to evaluate rates of adherence and clinical outcomes after implementing an SABSI management bundle [12]. The intervention used an automatic, hard-stop alert in the electronic health record directing providers to use an electronic order set after detection of SABSI. Providers were required to utilize the order set or provide a reason for dismissing the alert. In addition, brief educational sessions regarding guideline location and bundle elements were provided before implementation.

In total, 227 patients were included (111 in the preintervention group compared with 116 in the postintervention group), of which almost all were complicated SABSI (97.3% vs 92.2%, respectively; $P = .136$). Adherence to all components of the bundle occurred significantly more often in the postintervention group (Table 1). In the postintervention group, the median time to repeat blood cultures and sterilization of blood cultures was significantly shorter, and the median time from SABSI identification to alert activation was 0.5 hours. Despite alert activation occurring in 95.7% of cases in the postintervention group, the order set was utilized in only 57.8%. No differences in hospital length of stay, 30-day mortality, or 90-day readmission for SABSI complications were observed between groups.

As opposed to other SABSI management bundles requiring prospective audit with intervention and feedback, this study reinforces the possibility of utilizing an automated antimicrobial stewardship intervention to improve management. Although high rates of adherence to individual components of the bundle were observed, adherence to all components remained low.

Impact of a Stewardship Bundle on Gram-Negative Bacteremia

The literature for gram-negative BSI has significantly changed treatment recommendations by supporting shorter treatment durations [28], early switch to oral antibiotics [29], and demonstrating lack of benefit of repeat blood cultures [30]. Using an approach that is well described in gram-positive infections, Erickson and colleagues conducted a single-center, retrospective cohort evaluation of an antimicrobial stewardship bundle coupled with rapid diagnostic tests (RDTs) for uncomplicated gram-negative bacteremia [13]. The prestewardship group did not have an active stewardship intervention, whereas the poststewardship group had 0.5 full-time equivalent (FTE) physicians and 1 FTE pharmacist to implement the bundle, which included intravenous-to-oral (IV-to-PO) antibiotic switches, 7-day antibiotic durations, and avoidance of repeat blood cultures. Patients with uncomplicated gram-negative bacteremia (monomicrobial, with source control, and no immunosuppression or indications for longer duration of therapy) managed with active therapy within the first 24 hours were eligible for inclusion.

The main infection source was the urinary tract, and the most common organism was *E. coli*. The poststewardship group had a shorter median duration of antibiotic therapy, and patients were switched to oral antibiotics sooner, had fewer repeat cultures obtained, and had a lower 30-day readmission rate. Mortality and bacteremia recurrence were similar between the groups. This study demonstrated the efficacy of an antimicrobial stewardship bundled approach coupled with rapid diagnostic testing for management of uncomplicated gram-negative bacteremia and further supports the safety of shorter durations of antibiotics in these patients.

Impact of Education in Primary Care on ESBL *Escherichia coli* in the Community

Education alone is noted to be a low-effectiveness stewardship strategy, unless it is combined with real-time intervention(s) [31]. Peñalva and colleagues evaluated the impact of structured and consistent educational efforts on rates of ESBL *E. coli* in Spain [14]. The study spanned from January 2012 to December 2017 (pre-intervention 2012–2013, intervention 2014–2017) and included 5 interventions (shown in Table 1). The educational interview was the core strategy. A patient who received

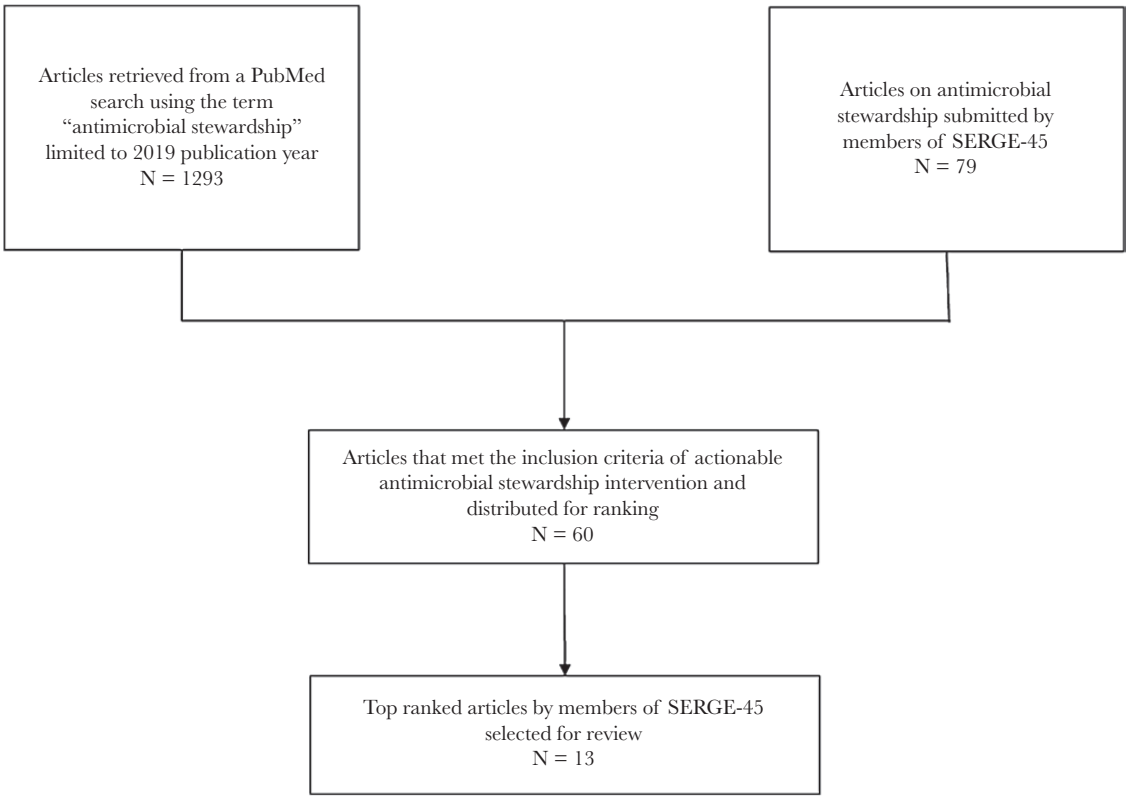

Figure 1. Flowchart of the database search and article selection process.

antibiotics was randomly selected, then the diagnosis and antibiotic course were reviewed with the prescriber and determined to be appropriate or inappropriate. Prescribers received an average of 5 interviews annually. Antibiotic consumption and ESBL incidence were assessed quarterly.

The study included 1 937 512 individuals seen by 1387 prescribers, who underwent 24 150 educational interviews. Each year of the intervention period saw an 11% increase in interviews conducted and a 3.2% decrease in inappropriate prescribing ($P = .001$). The most common causes for an "inappropriate" prescription were agent selection (36.9%) and duration (34.5%). Decreases in use were identified for ciprofloxacin and cefuroxime, but not for third-generation cephalosporins. No changes were noted for levofloxacin and amoxicillin-clavulanate, and increases were identified for amoxicillin and fosfomycin.

Susceptibilities were performed on 67 428 *E. coli* isolates during the 6 years, with a significant change in the rate correlating to the start of the intervention. Pre-intervention, the proportion of ESBL-producing *E. coli* was 7.1%, and by the end of the intervention period it was 5.5% ($P = .0001$).

This study was supported and funded by the Spanish government, marking high commitment within the European Union for antimicrobial stewardship. This study showed that consistent educational contact impacts prescribing and decreases resistance, especially in the primary care environment where the majority of antibiotic prescribing occurs. Additionally, it took an important step toward linking decreased antibiotic consumption to a meaningful outcome.

Diagnostic Stewardship and *Clostridioides difficile* Testing

RDTs are important tools for ASPs. The 2017 Infectious Diseases Society of America (IDSA) and Society for Healthcare and Epidemiology of America guidelines for *Clostridioides difficile* infections (CDIs) have specific recommendations for the use of nucleic acid amplification tests (NAATs) [32]. These include the use of either a multistep test involving NAAT, glutamate dehydrogenase (GDH), and/or toxins with NAAT, or NAAT alone with established testing criteria. However, inappropriate use of *C. difficile* RDTs may lead to false-positive results and the treatment of asymptomatic patients.

Christensen and colleagues performed a quasi-experimental retrospective, single-center study evaluating ASP-led education and prior authorization on *C. difficile* NAATs [15]. The study had a pre-intervention period from January 2014 to September 2016 and a postintervention period from October 2016 to April 2018. During the postintervention period, an ASP pharmacist reviewed all weekday NAATs ordered on hospital day ≥4. Of note, this study used NAAT testing alone, not multistep testing. The ASP pharmacist evaluated clinical signs and symptoms

of CDI, recent NAAT results, administration of tube feeds, laxatives, stool softeners, or contrast dye in the preceding 24 hours as well as imaging studies. Providers were contacted on all NAATs that did not meet preauthorization criteria and recommended to cancel the test. Of note, patients in the stem cell transplant unit were excluded.

The postintervention group had statistically significant improvement compared with the pre-intervention group with regards to the mean hospital-onset CDI (HO-CDI), incident rate of HO-CDI, and standardized infection ratio. Interestingly, the consumption of oral vancomycin did not differ between the 2 intervention periods. Overall, this study confirms that RDTs for CDI must be used in conjunction with ASP to be an effective patient care tool.

Early De-escalation of Antibiotic Therapy and Risk of *Clostridioides difficile* Infection

The association between use of broad-spectrum antibiotics and risk of CDI is well established [33]. Seddon and colleagues sought to determine the impact of early de-escalation of antipseudomonal β-lactam (APBL) antibiotics on the risk of CDI within 90 days in patients hospitalized for the treatment of Enterobacterales BSI in South Carolina [16]. Patients 18 years and older who had a first episode of monomicrobial BSI due to Enterobacterales from January 1, 2011, to June 30, 2015, who were identified through microbiology laboratory databases and who had a full 48-hour window for de-escalation of antibiotics were included. Patients who had a CDI within 1 year of BSI and those with concurrent CDI and BSI were excluded. A total of 808 patients were included (414 received >48 hours of APBL, 394 received ≤48 hours). *E. coli* was the most common bloodstream isolate (56%), followed by *Klebsiella* species (21%). The median time to CDI (interquartile range) was 11 (4–27) days. The overall incidence of CDI was 4.4% (95% CI, 2.8% to 6.0%), with significantly higher incidence of CDI in patients who received >48 hours of APBL than in those who received ≤48 hours of APBL. After adjustments for the propensity to receive >48 hours of APBL, end-stage renal disease and receipt of >48 hours of APBL remained independently associated with higher risk of CDI. This study showed that end-stage renal disease and receipt of APBL for >48 hours are associated with CDI in adults hospitalized for the treatment of Enterobacterales BSI. Therefore, appropriate empiric antibiotic selection and early de-escalation of APBL using clinical risk assessment tools or molecular RDT are likely to reduce the incidence of CDI in patients with Enterobacterales BSI.

Impact of an Inpatient Antiretroviral Stewardship Team

Errors in antiretroviral (ARV) medication prescribing, particularly at transitions of care, remain a prevalent patient safety issue, with reported rates as high as 86% [34]. DePuy and colleagues sought to determine if an ARV stewardship program (ARVSP) composed primarily of an HIV pharmacist specialist and ID physician would be able to identify and correct inpatient ARV medication errors [17]. The team reviewed ARV orders within 24 hours of admission and confirmed regimens with outpatient HIV providers as needed. A standardized communication was entered within the electronic health record (EHR) containing medication reconciliation notes and additional recommendations. A daily profile review was completed for all patients throughout admission.

The overall 12-month error rate, medication error types, and subsequent intervention acceptance rate were consistent with other reports in the literature. However, there were several innovative ARVSP components to highlight in this study. This was the first published report of cost avoidance associated with an ARVSP. The interdisciplinary structure of the ARVSP was unique and mimicked the established model for robust ASPs. Daily profile review and standardized communication in the EHR facilitated ongoing error monitoring, expanded capture of intervention outcomes, and enhanced financial impact estimation. Additionally, this study identified novel risk factors for ARV medication errors that can be applied to future ARVSP development and research.

High- vs Low-Intensity Prospective Audit and Feedback

A major core ASP strategy supported by the IDSA and CDC is prospective audit and feedback (PAF). While effective, PAF is typically labor-intensive, difficult to implement in resource- and/or workforce-limited settings, and relies on provider acceptance of recommendations [31, 35]. The current literature describes a wide variation in PAF designs that have attempted to overcome these disadvantages.

Langford and colleagues examined the impact of a high-intensity, twice-weekly interdisciplinary rounds-based PAF compared with low-intensity (weekly review, 1-on-1 education) PAF on antimicrobial use in internal medicine wards in a 400-bed community hospital over a 4-year period [18]. A reduction in the primary outcome of antimicrobial use was seen in the high-intensity phase as compared with the low-intensity phase, with a greater reduction in usage seen in the latter half of the high-intensity period. No change was seen in clinical outcomes of CDI, readmission rate, or mortality. The findings of this study highlight the benefit of "handshake stewardship," a term first coined by Hurst and colleagues [36]. Although face-to-face rounds have proven impactful on antimicrobial use, the time requirements can be rate-limiting. Further studies are needed to evaluate the impact of workload requirements associated with high-intensity PAF to ensure appropriate return on investment for the time-intensive approach.

Effects of Automatic Antibiotic Discontinuation

As described above, PAF is a fundamental strategy utilized by ASP that engages providers after an antibiotic is prescribed [31]. Bolten and colleagues evaluated antibiotic usage comparing

traditional ASP PAF with an ASP-led automatic discontinuation of antibiotics policy (ADAP) in an 800-bed, tertiary care academic teaching hospital [19]. The policy targeted duplicate therapy, defined as unnecessary double anaerobic, atypical, and/or β-lactam agents without documented rationale and excessive durations of therapy for prespecified disease states exceeding evidence-based recommendations. Antibiotics for >48 hours without a documented infection were also included in the ADAP. Education on the ADAP scope was provided via the pharmacy and therapeutics committee, and the ASP team documented ADAP interventions with written notes. An ID-trained physician and ID-trained pharmacist comprised the ASP team.

The most common diagnoses encountered in the pre- and post-ADAP groups were pneumonia, complicated cystitis, and chronic obstructive pulmonary disease exacerbation. Excess duration of therapy (73.5% vs 62.3%), followed by antibiotics without an indication (18.5% vs 22.2%), was the most frequent reason for ASP intervention. The mean total number of antibiotic days per patient and the percentage of patients discharged on antibiotics were reduced post-ADAP. There was a nonsignificant increase in 30-day readmission after ADAP; however, readmission rate due to an infectious diseases diagnosis was higher in the pre-ADAP group (65% vs 39%).

This single-center study demonstrated that an ASP-led ADAP can reduce overall in- and outpatient antibiotic use without increasing adverse patient outcomes. However, in settings where ID-trained personnel are not readily available, approval and implementation of this type of policy may be difficult to achieve.

Telehealth-Based ASP in Community Hospitals

Community hospitals often have less access to ID expertise and are less likely to have robust ASPs than academic medical centers [37]. Shively and colleagues sought to describe the practical implementation and assess the effectiveness of a telehealth-based ASP (TeleASP) in 2 community hospitals using the expertise of a large health network in Pennsylvania [20]. On-site hospitalists, advanced practice providers, and pharmacists were trained by ID physicians and ID/ASP pharmacists from within the large network. On-site providers were permitted to order tier 1 antimicrobials for 24 hours, after which they could be continued only with TeleASP or local ID approval. Tier 2 antimicrobials were not restricted but were monitored via PAF during weekdays. There was no restriction or audit and feedback on nontiered antimicrobials unless they were encountered by the TeleASP team in review of eligible patients. A review of patients on broad-spectrum antimicrobials and those admitted with select common infections was performed by remote ID physicians who discussed patients by telephone with local pharmacists. Following the call, local pharmacists communicated the interventions to primary teams. Antimicrobial use was collected for 12 months before TeleASP implementation and for 6 months after implementation. The majority of recommendations made were accepted by the local clinicians. The most frequent type of intervention was de-escalation of antimicrobial therapy. Tier 1 and tier 2 antimicrobial use decreased significantly during the intervention period compared with historical control, while nontiered antimicrobial use increased. Local ID consultations increased significantly during the intervention period compared with historical control. The program led to substantial cost-savings largely from an overall decrease in antimicrobial use. This study showed that a TeleASP in community hospitals is likely to result in reduction in broad-spectrum antimicrobial use, increase in ID consultations, and reduction in antimicrobial expenditures.

Core Antibiotic Stewardship Interventions in Community Hospitals

Antimicrobial stewardship guidelines recommend the implementation of preauthorization (PA) and/or PAF as the core components of any ASP [31]. Anderson and colleagues sought to determine the feasibility of implementing modified PA and postprescription audit and review (PPR) in 4 community hospitals in North Carolina [21, 38]. The modified PA consisted of a trained pharmacist reviewing all study antibiotic prescriptions for approval during weekday study hours, and PPR consisted of the stewardship team reviewing eligible prescriptions between 48 and 96 hours after order entry. Hospitals were paired based on size, and 1 hospital from each pair was assigned to a modified PA for 6 months, then transitioned to PPR for 6 months after a 1-month washout. The other 2 hospitals were assigned to PPR for 6 months, then transitioned to modified PA for 6 months after a 1-month washout. Antibiotics targeted were vancomycin, piperacillin-tazobactam, and the antipseudomonal carbapenems on formulary. Antibiotic use was collected for 12 months before ASP implementation. An ID physician was available for consultation at 2 participating hospitals. Eligible patients were identified using lists generated from pharmacy prescription databases. Implementing the 2 core stewardship strategies was feasible, as evidenced by (1) approval of administration and committees at all study hospitals; (2) completion of pharmacist training; (3) initiation and implementation of interventions; and (4) documentation of time required for interventions. The majority of pharmacist recommendations were accepted by clinicians. Study antibiotics were determined to be inappropriate 2 times more often during the PPR period than during the PA period. Pharmacists recommended a dose change more often in the PA period and de-escalation more often in the PPR period. Antibiotic use did not decrease during the PA period; however, it decreased significantly compared with matched historical control during the PPR period. Length of hospitalization did not change throughout the study. This trial showed that while strict PA is unlikely to be feasible in community hospitals with limited resources, PPR can be an effective stewardship strategy.

Implementing Antimicrobial Stewardship in an Academic Dental Practice

Dentists have become increasingly recognized as significant prescribers of antimicrobial therapy. It is estimated up to 10% of all outpatient antimicrobial prescriptions can be attributed to dentists, with clindamycin being most frequently prescribed [39]. However, best practices for antimicrobial stewardship in the area of dentistry are lacking.

In conjunction with an academic dental practice, Gross and colleagues sought to improve antimicrobial prescribing using the CDC Core Elements of Outpatient Antibiotic Stewardship [22, 40]. The University of Illinois at Chicago (UIC) College of Dentistry provides care for >30 000 patients annually. In addition, dentists in Illinois account for nearly 80 antibiotic prescriptions per 1000 patients, thus illustrating an opportunity for intervention [41]. Leadership from both the University of Illinois Hospital and Health Sciences System ASP and the UIC College of Dentistry met and ultimately made the development of a dental ASP a strategic initiative. Baseline prescribing data cross-referenced with patient visit and dental coding were reviewed, and potential areas for improvement were identified. One particular area of concern was the number of prescriptions for acute dentoalveolar conditions in the urgent care clinic. The first practice intervention was to standardize antibiotic use for dentoalveolar conditions given feasibility via educational intervention and subsequent impact. To support this intervention, an evidence-based clinical decision support tool was developed that provided drug selection and optimal duration of therapy. While this represents a single intervention, the successful outcome as shown in Table 1 will facilitate expansion of the dental ASP to other areas in the future.

This study provides a template for other programs to utilize simple interventions to affect the prescribing of antimicrobials in the dental setting. Moreover, this study also highlights the effectiveness of collaboration between key stakeholders in different arenas as it pertains to stewardship.

Antimicrobial Stewardship in Patients With Cancer or Undergoing Hematological Stem Cell Transplant

Antimicrobial stewardship in patients with hematologic malignancy is challenging, as the optimal approach is not well defined. Implementation of stewardship interventions in this patient population is prone to the same barriers of many ASPs and thus should seek to find a balance between curtailing overuse of broad-spectrum antimicrobial therapy while providing adequate therapy.

Webb and colleagues conducted a quasi-experimental pre- and postimplementation of 2 antimicrobial stewardship interventions in a hematological malignancy treatment unit [23]. The interventions consisted of monthly antibiotic cycling for empiric treatment of febrile neutropenia and use of a clinical prediction rule to guide empiric vancomycin-resistant *Enterococcus faecium* (VRE) therapy [42]. The primary outcome for the antimicrobial cycling intervention was antipseudomonal carbapenem consumption in days of therapy per 1000 patient-days. The primary outcome for the VRE therapy prediction score intervention was days of daptomycin therapy per 1000 patient-days. Both outcomes were analyzed using an interrupted time-series regression analysis. Secondary outcomes included VRE colonization per 1000 admissions, inpatient mortality, and clinical infections due to VRE, ESBL-producing Enterobacterales, phenotypically suspected AmpC-harboring Enterobacterales, methicillin-resistant *Staphylococcus aureus* (MRSA), and CDI.

As outlined in Table 1, the interventions resulted in a significant decrease in carbapenem use and improved susceptibility in *Pseudomonas aeruginosa* isolates postintervention. In turn, this intervention likely also resulted in a decrease in daptomycin use attributable to lower rates of VRE colonization and subsequent VRE infections. The study also examined community ecology data in order to determine if changes in infection rates pre- and postimplementation were due to the antibiotic cycling intervention vs changes in local microbiology. The findings of this study lend support to antibiotic cycling as it pertains to carbapenem and daptomycin usage while not adversely impacting clinical outcomes in the management of febrile neutropenic patients. It is notable that the success of the program was facilitated by an ASP pharmacist and close partnership with clinician leadership to advance the stewardship initiatives.

Implementation of Electronic Stewardship Tools

Reporting to the National Healthcare Safety Network (NHSN) Antimicrobial Use (AU) Option is specifically recommended to facilitate AU benchmarking [5]. However, Graber and colleagues note NHSN report limitations in the areas of facility matching, AU by infection diagnosis, and temporal assessment of antimicrobial prescribing [24].

The authors attempted to overcome these limitations through creation of AU visualization tools. The graphical displays were built on a foundation of both disease state and time frame. Pneumonia, urinary tract infection, and skin/soft tissue infection (PUS) were identified by ICD-9 and ICD-10 codes. Time frame was described as choice, change, and completion (CCC), representing the major AU decision points of empiric therapy, de-escalation, and definitive course, respectively. Based on collaborative feedback from 1 physician and 1 pharmacist steward at each of 8 Veterans Affairs (VA) facilities, the dashboards were updated to include data on antimicrobial type and unit and to allow for comparison across all or select VA sites. The stewards implemented ASP initiatives at their respective facilities based on needs identified by these individualized dashboards.

Reductions in total antimicrobial, anti-MRSA agent, and antipseudomonal agent utilization were noted at intervention facilities with statistically significant differences observed in total and antipseudomonal agent use. Despite the resource-intensive requirements for dashboard development, these

results suggest that this type of tool would be effective for individualized, targeted ASP work across large health systems or networks. Additionally, the novel CCC framework allows for a unique drilldown on suboptimal antimicrobial prescribing at precise points in the AU continuum. Overall, the dashboard visualization approach allows for targeted selection of ASP interventions from a robust data source across all ASP stages regardless of previously implemented interventions.

DISCUSSION

As antimicrobial resistance, health care costs, and demands on stewardship programs continue to increase, stewards are challenged to implement creative solutions for improving patient care and antimicrobial use. Included here are 13 examples of novel stewardship interventions, representing a wide range of therapeutic areas, stewardship metrics including process outcomes and antimicrobial use, and documentation of stewardship interventions in inpatients and outpatients and in nonacademic medical centers.

Because of the wide variety of stewardship practices, the development of "best practices" of specific interventions can be difficult to implement across the board. Although there are an increasing number of ASP publications yearly, including those focused on interventions and outcomes, it is important for stewards to continue to report their innovative interventions and solutions to health care problems. Familiarity with these key, impactful interventions can provide a blueprint for teaching or intervention opportunities for stewards across the spectrum of experience and practice sites.

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