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A Baker's Dozen of Top Antimicrobial Stewardship Intervention Publications in 2017

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With an increasing number of antimicrobial stewardship–related articles published each year, attempting to stay current is challenging. The Southeastern Research Group Endeavor (SERGE-45) identified antimicrobial stewardship-related peer-reviewed literature that detailed an "actionable" intervention for 2017. 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 training and teaching and identify potential intervention opportunities within their institutions.

Keywords. antibiotics; antimicrobial stewardship; infectious diseases; intervention.

Fueled by concerns over antimicrobial resistance and heightened emphasis on optimizing antimicrobial use, stewardship programs have populated facilities for over a decade [1, 2]. Regulatory agencies including the Joint Commission (TJC) and the Centers for Disease Control and Prevention (CDC) have provided blueprints for antimicrobial stewardship programs (ASPs), which serve as guidelines for institutions certified by TJC [3, 4]. Stewardship expansion across the continuum of care is vital to curbing antimicrobial resistance. Successful ASPs are interprofessional, including infectious diseases (ID) pharmacists, physicians, and microbiologists collaborating with stewardship extenders or non-ID-trained specialists [1, 5].

To achieve stewardship goals, ASPs must maintain knowledge of evidence-based ASP interventions and newly approved antimicrobials [6]. From 2016 to 2017, there were 40% and 46% increases in peer-reviewed publications using the search terms "antibiotic stewardship" and "antimicrobial stewardship," respectively (Medline searches, accessed September 7, 2018), with noted growth in international stewardship and rapid diagnostic technology (RDTs) scholarship [7–9]. Members of the Southeastern Research Group Endeavor (SERGE-45) systematically compiled the top peer-reviewed publications from 2017 involving an ASP intervention. Table 1 provides a brief review and commentary. A previous publication by these authors, using similar criteria, reviewed top publications from 2016 [21]. We anticipate that this will be a key resource for ASPs for both implementation strategies and to mentor learners on key peer reviewed literature.

METHODS

Using a modified Delphi technique, members of the SERGE-45 network identified antimicrobial stewardship publications from 2017 considered to be significant [22]. SERGE-45 is a network of infectious diseases practitioners, primarily pharmacists, who are clinician-educators and scholars. Eligible articles met the following inclusion criteria: (1) published in 2017, including electronic, "early-release" publications, and (2) must include an "actionable" intervention. Guideline manuscripts or those without an actionable intervention were excluded.

All coauthors nominated publications from 2017 and provided comments via a REDCap Survey [23]. A PubMed search using "antimicrobial stewardship" for the time period of 2017 revealed 934 potential publications. DBC and PBB screened abstracts to ensure that all relevant articles were considered. Three manuscripts were added to the original list from the survey results. The included articles were distributed to the SERGE-45 network for individual ranking based on contribution and/or application to ASP. A web-based teleconference with the co-authors established consensus on the top 13 articles (Table 1) described herein.

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Table 1. Summary of Included Studies

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Wenzler et al. 2017 [10]	Retrospective, single-center quasi-experimental	Implementation of scoring tool and subsequent prepopulated progress note embedded with EMR triggered by positive results of Verigene gram-positive blood culture assay. Adherence to quality components (primary) and associated clinical outcomes were assessed.	Improved adherence to quality-of-care components • Pre-intervention: 68.9% vs postintervention: 92.3%; *P* = .008 Increased proportion of ID consults obtained • Pre-intervention: 75.6% vs postintervention: 94.9%; *P* = .015 Increased timeliness of initiation of targeted therapy • Pre-intervention: 91.8 hours vs postintervention: 54.3 hours; *P* = .079
Smith et al. 2017 [11]	Retrospective, single-center study	ASP education provided prestudy on the clinical utility of the MRSA nasal PCR to predict the involvement of MRSA in nosocomial pneumonia. ASP provided recommendations to discontinue anti-MRSA therapy based on the PCR screening.	Diagnostic performance of the MRSA nasal PCR panel for detecting MRSA pneumonia Respiratory culture (n = 400): • NPV: 99.03% • PPV: 37.36% • Sensitivity: 91.89% • Specificity: 84.3% Respiratory culture (n = 164): • NPV: 96.83% • Median 7.4 days from PCR to time to culture Respiratory culture (n = 68): • NPV: 100% • Median 13.4 days from PCR to time to culture Respiratory culture (n = 23): • NPV: 87.5% • Median 21.9 days from PCR to time to culture Vancomycin de-escalation • 45.3% (n = 169) with negative PCR result (n = 309) • No difference in AKI • Cost reductions in laboratory monitoring and medication
Mullin et al. 2017 [12]	Quasi-experimental study with an initial intervention, followed by an observation phase, followed by another intervention, followed by another observation phase	First intervention, implemented in 2013: optimizing Foley catheter insertion, maintenance, and removal with periodic audits in ICUs. Second intervention, implemented in 2014: adopting the ACCCM/IDSA recommendations for evaluating new fever in critically ill patients, which emphasized that urine cultures should only be evaluated in patients at high risk of invasive infections. Interventions targeted a reduction in NHSN-reported CAUTI and HABSI.	Reduction in the rate of CAUTIs per 1000 catheter-days • 3.0 in 2013 vs 1.9 in 2014: RR, 0.6291; 95% CI, 0.49–0.81; *P* = .0003 Nonsignificant reduction in the rate of HABSIs per 1000 patient-days • 2.8 in 2013 vs 2.4 in 2014; *P* = .15 Nonsignificant reduction in the rate of HABSIs secondary to Enterobacteriaceae per 1000 patient-days • 0.71 in 2013 to 0.66 in 2014: RR, 1.1; 95% CI, 0.73–1.60; *P* = .72
Shea et al. 2017 [13]	Multicenter, quasi-experimental study	Following development of a health care system–wide respiratory fluoroquinolone restriction policy, the impact of the following interventions was measured at 4 adult hospitals: 1.Educational campaigns, including pharmacist competency and prescriber presentations and emails delivered over a 3-month period. 2.Prospective audit and feedback on respiratory fluoroquinolone orders performed by pharmacists.	Reduction in fluoroquinolone utilization (DOT/1000 PD) • Pre: 41.0 vs education: 21.5; *P* = .023; vs postrestriction: 4.8; *P* < .001 Reduction in CDI cases/10 000 PD • Pre: 4.0 vs education: 3.43 (*P* = .044) vs postrestriction: 2.2; *P* = .044 Increased appropriate use of a respiratory fluoroquinolone in patients receiving 1 or more doses • Pre: 74/232 (32%) vs postrestriction: 74/130 (57%); *P* < .001 Increased appropriate use of a respiratory fluoroquinolone in patients receiving 2 or more doses • Pre: 67/191 (35%) vs postrestriction: 47/65 (72%); *P* < .001 Decline in moxifloxacin annual acquisition cost • Pre: $123 273 vs postrestriction: $12 273; *P* < .002
Broyles et al. 2017 [5]	Singe-center, retrospective pre- and post-intervention study	Introduction of a pharmacist-driven PCT algorithm, allowing pharmacists to order PCT and recommend antibiotic changes. Patients were included based on DRGs for sepsis, COPD, pneumonia, and respiratory infections. Pharmacists could order PCT and could encourage or discourage antibiotic usage based on PCT changes, in accordance with PCT algorithm.	Decrease in median antibiotic DOT • Pre-intervention: 17 (IQR, 8.5–22.5) vs postintervention: 9 (IQR, 6.5–12); *P* < .001 Decline in hospital mortality • Pre-intervention: 7.6% vs postintervention: 2.9%; *P* < .001 Decrease in 30-day readmissions • Pre-intervention: 22.4% vs postintervention: 11.1%; *P* < .001 Decrease in antibiotic-associated ADEs • Pre-intervention: 16.2% vs postintervention: 8.1%; *P* < .001 Decrease in CDI incidence • Pre-intervention: 2.5% vs postintervention: 0.9%; *P* < .001
Eljaaly et al. 2018 [14]	Retrospective, single-center, pre- and post-intervention study	Additional authorization of restricted antibiotics required on day 3 of treatment. ASP team provided feedback directly to ordering provider if agent was considered suboptimal. Changes in antibiotic DOT and associated clinical outcomes (LOS and hospital mortality) were assessed.	Decrease in overall restricted antibiotic median DOT • Pre-intervention: 5 vs postintervention: 4; *P* < .001 Reduced LOS • Pre-intervention: 8 days vs postintervention: 6 days; *P* < .001

Table 1. Continued

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Yogo et al. 2017 [15]	Quasi-experimental retrospective study	Dissemination of institutional guidelines detailing the selection and duration of oral step-down antibiotic recommendations at discharge, coupled with prospective audit and feedback of discharge prescriptions by pharmacists.	Nonsignificant reduction in antibiotic median total DOT • Pre-intervention: 10 (IQR, 7–13) days vs postintervention: 9 (IQR, 6–13) days; *P* = .13 Reduced antibiotic median DOT prescribed at discharge • Pre-intervention: 6 (IQR, 4–10) days vs postintervention: 5 (IQR, 3–7) days; *P* = .003 Reduced antibiotic median inpatient DOT • Pre-intervention period: 3 (IQR, 3–5) days vs postintervention: 4 (IQR, 3–5) days; *P* = .01 Decreased use of antibiotics with broad activity against gram-negative bacteria • Pre-intervention period: 51% vs postintervention: 40%; *P* = .02 No significant differences in treatment failure, readmission, CDI, or adverse events
Bookstaver et al. 2017 [8]	Quasi-experimental cohort study	Implementation of an antimicrobial stewardship bundle for GNBSIs: 1) GNBSI management institutional guidelines. 2) Prospective audit and feedback on all positive blood cultures. 3) Sequential introduction of 2 RDTs, MALDI-TOF and FilmArray BCID panel.	Improved appropriateness of empirical therapy improved overall • Pre-intervention: 91% vs postintervention: 95%; *P* = .02 Improved appropriateness of empirical therapy in patients with BSI due to *P. aeruginosa*/chromosomally mediated AmpC-producing Enterobacteriaceae • Pre-intervention: 87% vs postintervention: 97%; *P* = .02 Improved appropriateness of empirical therapy in critically ill with a Pitt bacteremia score of ≥4 • Pre-intervention: 89% vs postintervention: 97%; *P* = 0.06 Improved time to de-escalation from combination antimicrobial therapy • Overall, pre-intervention: 2.8 days vs postintervention: 1.5 days; *P* < .001 • APBLs, pre-intervention: 4.0 days vs postintervention: 2.5 days; *P* < .001 • Carbapenems, pre-intervention: 4.0 days vs postintervention: 2.5 days; *P* < .001 • Two-thirds of all de-escalation occurred before return of susceptibilities in the postintervention period
Leis et al. 2017 [16]	Multicenter, prospective evaluation	ASP pharmacists and physicians were trained to perform and interpret BLAST in collaboration with allergy specialists. A structured allergy history, followed by pharmacist-performed BLAST when needed, was implemented for patients with reported β-lactam allergies who needed β-lactam therapy.	Increased utilization of preferred β-lactam therapy in patients with reported β-lactam allergies • Baseline: n = 124/246 (50%) vs intervention period: n = 313/386 (81%) • No reported increase in adverse effects • The intervention required an average of 1 hour of pharmacist time per patient
Lowe et al. 2017 [17]	Quasi-experimental pre- and post-intervention study	Audit with real-time feedback of adult inpatients based on findings from microbiologic samples and chest imaging.	Decrease in mean antibiotic DOT • Pre-intervention: 4.1 days vs postintervention: 2.8 days; 95% CI, 0.3–2.3; *P* < .01
Dumkow et al. 2017 [18]	Retrospective, descriptive study	Three pharmacists (ID pharmacist, ED pharmacist, and pharmacy resident) located off campus from an urgent care center affiliated with main hospital reviewed positive cultures and intervened when required under a CPA over the course of a calendar year.	Follow-up intervention was required in 320 of 1461 (22%) isolates • The most common cultures requiring intervention were urine (25%) and STIs (25%), requiring approximately 15 minutes per intervention • Most patients did not require a new/changed antimicrobial prescription upon follow-up for 2 primary reasons: Sexually transmitted infection cultures had been treated appropriate (only notification of results required) or patients were asymptomatic upon follow-up (unique to center's CPA) • The average time for all aspects of intervention including documentation was 15 minutes Treatment outcomes of these interventions were not evaluated
Rac et al. 2018 [19]	Single-center, quasi-experimental, pre- and post-intervention study	Antifungal susceptibility testing and real-time culture alerts, leading to a single phone call from the ASP pharmacist to the primary team with recommendations for antifungal therapy and other candidemia management strategies (infectious diseases consult, remove lines, ophthalmology examination, repeated blood cultures).	No difference in time to adequate therapy in business hours population • Pre-intervention: 2h 57min vs postintervention: 2h 15min; *P* = .094 Decrease in time to adequate therapy in total population • Pre-intervention: 3h 30min vs postintervention: 2h 9min; *P* = .021 Decrease in time to adequate therapy order in total population • Pre-intervention: 1h 35min vs postintervention: 24min; *P* = .017 Increase proportion of ID consults obtained • Pre-intervention: 36% vs postintervention: 75%; *P* < .001 Increase in proportion of ophthalmology consults obtained • Pre-intervention: 35% vs postintervention: 69%; *P* < .001 Increase in streamlining of IV to PO antifungals • Pre-intervention: 18% vs postintervention: 39%; *P* = .015

Table 1. Continued

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Wilson et al. 2017 [20]	Pre- and post-intervention surveys	A free 6-module online course was made available to nurses. Pre-/postintervention surveys assessed demographics, perceptions, and knowledge.	Increase in nursing knowledge scores • Precourse: 75% vs postcourse: 86%; $P < .001$ Nurses had increased agreement that their role influences whether long-term care residents receive antibiotics ($P < .001$)

Abbreviations: ACCCM, American College of Critical Care Medicine; ADE, adverse drug event; AKI, acute kidney injury; APBLs, antipseudomonal β-lactams; ASP, antimicrobial stewardship program; BCID, blood culture identification; BLAST, β-lactam allergy skin testing; CAUTIs, catheter-associated urinary tract infections; CDI, *Clostridioides difficile* infection; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPA, collaborative practice agreement; DOT, days of therapy; DRG, diagnosis-related groups; ED, emergency department; EMR, electronic medical record; GNBSIs; gram-negative bloodstream infections; HABSIs, hospital-acquired bloodstream infections; ICUs, intensive care units; ID, infectious diseases; IDSA, Infectious Diseases Society of America; IQR, interquartile range; IV, intravenous; LOS, length of stay; MALDI-TOF, matrix assisted laser desorption ionization-time of flight mass spectrometry; MRSA, methicillin resistant *Staphylococcus aureus*; NHSN, National Healthcare Safety Network; NPV, negative predictive value; PCR, polymerase chain reaction; PCT, procalcitonin; PD, patient-days; PO, oral; PPV, positive predictive value; RDT, rapid diagnostic technology; RR, rate ratio; STIs, sexually transmitted infections.

RESULTS

Health Informatics and *Staphylococcus aureus* Bacteremia

The correlation between infectious diseases consultation and improved patient outcomes in *Staphylococcus aureus* bacteremia (SAB) has been well described [24]. The use of health informatics (HI), including electronic medical records (EMRs) and clinical decision support software, has the potential to augment patient care in institutions with limited ID and/or ASP resources.

Wenzler and colleagues conducted a retrospective quasi-experimental study of hospitalized patients with SAB [10]. Patients who were incarcerated, who received an ID consult before identification of SAB, or who were transferred from an outside hospital or discharged against medical advice were excluded. The objective was to evaluate the impact of incorporating HI into SAB management via a pharmacist-driven initiative. The primary outcome was overall compliance with quality-of-care components, which consisted of ID consult, repeat blood cultures, echocardiogram, and initiation of SAB-targeted therapy. Secondary outcomes included time to pharmacist intervention, duration of bacteremia, length of hospital stay (LOS), infection-related LOS, 30-day readmission, and 30-day mortality. The study used a 3-month pre- and postintervention study design.

Of 123 patients screened, 84 patients were included. Most patients were excluded due to ID consult before SAB. Over half of the isolates displayed methicillin resistance. In the postintervention arm, targeted treatment was initiated significantly more often (100% vs 84%; $P = .013$), at a median of 40 hours sooner. The incidence of ID consult increased significantly, by approximately 20%. All-cause mortality was lower in the postintervention arm (15.6% vs 2.6%; $P = .063$), although this difference was not statistically significant.

The findings of this study are limited by the small sample size and retrospective study design in a single center, as well as the use of RDT, as not all centers may have access. However, utilization of HI, development of institutional guidelines for management of SAB, and intervention by non-ID pharmacists should be broadly applicable to optimizing patient care.

Utility of MRSA Nasal PCR Assays in ICU Patients With Nosocomial Pneumonia

The American Thoracic Society and Infectious Diseases Society of America (IDSA) nosocomial pneumonia guidelines recommend empiric methicillin-resistant *S. aureus* (MRSA) coverage in at-risk patients; however, no guidance is provided for de-escalation of therapy before respiratory culture results [25]. Consequently, empiric anti-MRSA therapy is continued, contributing to antimicrobial overuse. MRSA nasal polymerase chain reaction (PCR) assays demonstrate high negative predictive values (NPVs) in ruling out MRSA as the causative pneumonia pathogen and supporting de-escalation of therapy before or in absence of culture results [26].

Smith and colleagues evaluated the clinical utility and diagnostic performance of the rapid MRSA nasal PCR assay in adult intensive care unit (ICU) patients with nosocomial pneumonia [11]. Eligible patients underwent MRSA nasal PCR assay screening before or within 48 hours of ICU admission, and an initial respiratory culture was collected within 7 days of screening. Before the study, the ASP team educated ICU prescribers about the utility of the assay for anti-MRSA therapy de-escalation, and during the study period, they provided de-escalation recommendations based on screening results. Changes in NPV over time, acute kidney injury (AKI) incidence, and medication and laboratory cost avoidance were evaluated.

The prevalence of culture-confirmed MRSA pneumonia was 9.3%. The diagnostic performance of the assay for detecting MRSA pneumonia from initial culture was as follows: NPV, 99.03%; positive predictive value (PPV), 37.36%; sensitivity, 91.89%; specificity, 84.3%. Vancomycin de-escalation occurred in 45.3% of patients with a negative PCR. Early vancomycin discontinuation yielded medication and laboratory cost avoidances but did not impact the AKI rate.

This analysis reinforces the high NPV of MRSA nasal PCR assay for predicting MRSA as the causative pathogen in nosocomial pneumonia. The external validity of this study is limited, as use of the assay was pre-established, pneumonia diagnosis was based on EMR documentation, MRSA pneumonia prevalence was low, and the ASP team performed rounds daily to provide de-escalation recommendations.

Reducing ICU CAUTIs

Catheter-associated urinary tract infections (CAUTIs) represent approximately 75% of all hospital-acquired UTIs [27]. Risk factors include duration of catheterization, female sex, older age, and failure to maintain a closed drainage system. Treatment of CAUTIs involves administration of antibiotics and catheter removal when possible [28]. However, asymptomatic bacteriuria (ASB) associated with indwelling urinary catheters is not diagnostic of CAUTIs and should not be treated in most patients [27, 28].

Mullin and colleagues report a multifaceted multidisciplinary approach to reducing the incidence of CAUTIs in adult and pediatric ICUs [12]. In 2013, they implemented interventions targeted at optimizing Foley catheter use. In 2014, they adopted best-practice recommendations for evaluating new fever in critically ill patients. Throughout 2013 and 2014, results of CAUTIs and hospital-acquired bloodstream infections (HABSIs) surveillance were recorded prospectively, and device utilization ratios (DURs) and rates of CAUTIs and HABSIs were calculated. The primary outcome was the rate of CAUTIs. Between 2013 and 2014, the number of ICU patient-days (PDs) and DURs were comparable (74 705 vs 75 569 and 0.7 vs 0.68, respectively), whereas the number of urine cultures decreased from 4749 to 2479. The rate of CAUTIs per 1000 catheter-days was significantly reduced. Reductions in the rates of HABSIs and HABSIs secondary to Enterobacteriaceae were also observed.

This study's multifaceted approach focusing on the appropriate use of Foley catheters and the "stewardship of culturing" successfully reduced the rate of CAUTIs by 33%, along with a reduction in overall rates of HABSIs or HABSIs secondary to Enterobacteriaceae. The authors report aggregate data rather than patient-specific data and did not report antibiotic days of therapy (DOT), resistance rates, *Clostridioides difficile* infection (CDI) rates, LOS, or resource utilization. In addition, the analysis suffered from a lack of interrupted time-series analysis, did not report the extent of adherence to the interventions, and did not have a control group.

Respiratory Fluoroquinolone Restriction Program

Fluoroquinolones are among the most commonly prescribed antibiotics in the United States [13]. In addition to increased rates of resistance and significant adverse drug events (ADEs), fluoroquinolones adversely impact CDI rates.

In a multicenter, quasi-experimental design, Shea and colleagues evaluated 4 hospitals restriction of moxifloxacin, their formulary respiratory fluoroquinolone [13]. Pre-approved criteria for use included ID consultation or approval; endophthalmitis or ophthalmic surgery; or community-acquired pneumonia (CAP) or severe acute exacerbation of chronic obstructive pulmonary disease (COPD) plus 1 of the following: severe β-lactam allergy, receipt of a cephalosporin in the prior 3 months, or culture-proven ceftriaxone-resistant or penicillin-intermediate or -resistant *Streptococcus pneumoniae*. Pharmacists performed prospective audit and feedback (PAF) of moxifloxacin orders when criteria for use were not met. Educational interventions included implementing a pharmacist-driven β-lactam allergy assessment tool, presentations to clinicians conducted by ID pharmacists, and emails to key stakeholders.

Outcomes of interest included monthly use (DOT/1000 PD) of moxifloxacin for 5 months pre-intervention, during a 3-month education period, and for 12 months postintervention; moxifloxacin acquisition costs; usage of other antimicrobials that could influence CDI rates; and appropriateness of moxifloxacin prescriptions. In segmented regression analysis, each hospital achieved average reductions of 48% to 88% in moxifloxacin usage $P < .001$. Usage rates of other key antimicrobial agents were unaffected. CDI rates decreased by approximately 50% from baseline ($P = .044$).

The strengths of this intervention were its multicenter design, measurement of off-target antimicrobials, and evaluation of appropriateness during pre- and postintervention periods. The authors noted major reductions in usage, and CDI rates were achieved despite maximal "appropriate use" rates of approximately 70% in the first 6 months of the intervention. ASPs interested in implementing a similar strategy must consider the resources necessary to build consensus around specific criteria, staffing to perform PAF, and decision support to increase adoption of the criteria.

Impact of Procalcitonin on Antibiotic Exposure

Procalcitonin (PCT), a biomarker produced in response to bacterial infections, is Food and Drug Administration (FDA) approved for use in and respiratory infections and is increasingly used by ASPs to impact antibiotic consumption [29].

Broyles performed a single-center, pre–post, retrospective cohort study to assess the impact of a local pharmacist-driven PCT algorithm (PCT-A) [5]. Outcomes included median antibiotic DOT, in-hospital mortality, 30-day readmission, CDI, and ADE. This study compared 4 years before (2006–2009) and 4 years after (2011–2014), with the PCT implementation year (2010) as a washout period. Patients who received nonprophylactic intravenous (IV) antibiotics were included based on diagnosis-related groups (DRGs). ASP workflow before PCT-A included patient review for antibiotic use. After introduction of PCT-A, PCT could be ordered and used to recommend antibiotic changes to clinicians as indicated in the algorithm.

There were 985 pre-PCT-A patients and 1167 post-PCT-A patients included. The groups were comparable, except the post-cohort had more patients with sepsis (1.3% vs 7.7%; $P < .001$) and COPD (16.9% vs 18.8%; $P < .001$) and fewer with pneumonia (59.8% vs 54.9%; $P = .02$). There was a 47% reduction in median DOT in the post-PCT-A cohort ($P < .001$). Hospital mortality ($P < .001$), 30-day readmission ($P < .001$), antibiotic ADE ($P < .001$), and CDI ($P = .002$) were all lower in the post-PCT-A cohort. Pharmacist recommendations were highly accepted (95%) by the end of the study period.

The addition of a pharmacist-driven PCT-A impacted antibiotic consumption and patient outcomes at a small, rural hospital. Limitations include the applicability to larger health care settings with a higher pharmacist-to-patient ratio. The DOT calculation example provided in the paper used a half-DOT, which is not consistent with the current CDC–National Healthcare Safety Network guidelines [30]. Other limitations acknowledged by the author include LOS variations, lack of protocol adherence capture, and physician staffing model changes in 2012, which may have influenced the results.

Prescription Reauthorization With Feedback

Antimicrobial preauthorization (PA) and PAF are considered critical support elements of ASPs, and inclusion of 1 or both is recommended by current guidelines [29]. Both interventions are associated with reductions in overall antimicrobial use, resistance, and CDI rates. However, recent studies suggest a more rapid benefit with PA, at the risk of sacrificing the sustained effects of PAF correlated with relationship-building and direct provision of education [29].

Eljaaly and colleagues retrospectively examined the effect of combining both PA and PAF via prescription reauthorization on appropriate use of intravenous acyclovir, aztreonam, cefepime, ciprofloxacin, daptomycin, ertapenem, fluconazole, linezolid, voriconazole, meropenem, micafungin, piperacillin/tazobactam, oral vancomycin, fluconazole, linezolid, and voriconazole [14]. The ASP team re-reviewed restricted antimicrobial orders on day 3, and if considered suboptimal, the ASP team discussed the case directly with the ordering provider. Outcomes included restricted antimicrobial DOT per patient and per agent, hospital LOS, in-hospital mortality, and proportion of patients on antimicrobial therapy for >4 days before and after implementation of the required reauthorization. Statistically significant decreases in all end points except in-hospital mortality were observed.

The authors note that required reauthorization at day 3 allows for incorporation of culture and clinical data into assessment of antimicrobial appropriateness and facilitates additional discussion of de-escalation, IV to oral (PO) conversion, and duration of therapy. Limitations of the study include assessment of only restricted antimicrobial agents, not overall use, and the pre–post study design. Further research is needed to assess the sustainability of the intervention, long-term impact, ability to expand beyond restricted antimicrobials, and provider satisfaction with the process.

Reducing Prescription of Broad-Spectrum Antibiotics and Treatment Duration at Hospital Discharge

Antimicrobial use at hospital discharge is often overlooked, although up to 70% of treatment durations are completed in the outpatient setting [31]. Few published studies discuss interventions that reduce the duration and use of broad-spectrum antibiotics postdischarge [32, 33].

Yogo and colleagues evaluated syndrome-specific antibiotic therapy prescribed at discharge [15]. The intervention comprised 2 parts: (1) dissemination of institutional guidelines via laminated pocket-size cards, intranet resources, and a smartphone app on de-escalating to PO antibiotics for CAP, UTIs, skin and soft tissue infections (SSTIs), health care–associated pneumonia (HCAP), nosocomial pneumonia HAP, COPD, CDI, and *Helicobacter pylori* for an appropriate duration at discharge; and (2) PAF of discharge prescriptions by pharmacists. Three hundred patients in the pre-intervention group were compared with 200 in the postintervention group to determine the effect on DOTs, and number of patients receiving broad-spectrum gram-negative (GN) antibiotics, fluoroquinolones, or amoxicillin/clavulanate at discharge.

UTIs, CAP, and SSTIs were the most common indications in both groups, but COPD exacerbations occurred more often in the postintervention group (18% vs 8%; P = .001), increasing azithromycin use (12% vs 20%; P = .03). Approximately three-fourths of patients had at least 1 culture obtained, whereas only 30% were positive in both groups. *Escherichia coli*, *Streptococcus* spp., and *S. aureus* were isolated most commonly. Significantly fewer patients in the postintervention group received broad-spectrum GN antibiotics (P = .02), attributed to a reduction in fluoroquinolone use (38% vs 25%; P = .002). Total DOTs were comparable between groups, whereas DOT postdischarge was significantly decreased postintervention (P = .003). However, inpatient DOT was significantly higher during the postintervention period (P = .01). Of the 40% of discharge prescriptions reviewed, pharmacists contacted prescribers with recommendations in 27% of cases, with a 67% success rate. No difference in treatment failure, readmission for the same indication, CDI, or ADEs was observed.

Development and dissemination of institutional syndrome-specific guidelines may assist providers with selecting the appropriate antibiotic for an appropriate duration at discharge, a frequent shortcoming of inpatient ASP. Significant improvements in selection of discharge antibiotics and treatment duration occurred despite few cases being reviewed by pharmacists, which may allow an intervention of this nature to be developed regardless of institutional limitations.

Early Streamlining (Without Susceptibilities) Possible in Gram-Negative BSIs Using RDT and ASP Bundle

RDT, specifically used in bloodstream infections (BSIs), shortens time to organism identification, leading to earlier appropriate therapy [9]. Several ASPs use RDT for de-escalation purposes, although this is primarily demonstrated with vancomycin [34]. Few data exist exploring the impact of RDTs, specifically using multiple RDTs, on early de-escalation in GN BSIs, where combinations of antipseudomonal β-lactams (APBLs) are commonly employed.

Bookstaver and colleagues conducted a quasi-experimental cohort study at 2 hospitals measuring the impact of ASP bundle on both appropriate empirical therapy and time to de-escalation [8]. The intervention included (1) a BSI guideline and treatment algorithm, (2) stewardship team PAF for BSIs, (3) introduction of MALDI-TOF for all positive blood cultures, and (4) subsequent introduction of FilmArray BCID. Outcomes were compared between pre- and postintervention periods, including 2 independent postintervention period phases (Phase 1: MALDI-TOF alone; Phase 2: MALDI-TOF plus FilmArray BCID).

Among 1163 unique patients (830 pre-intervention and 333 postintervention), a urinary source (53%) was the most common, and *E. coli* was most frequently isolated. The average time to de-escalation was 2.5 days, approximately 1.5 days sooner in the postintervention period, and was further reduced to 2.2 days in Phase 2 of the postintervention period. Appropriate therapy within 48 hours of BSI improved from 91% to 95% between periods, despite the significant reduction in APBL and combination therapy. The greatest improvement was observed in ICU patients with Pitt bacteremia scores ≥4 (97% post- vs 89% pre-intervention period). Nearly two-thirds of all de-escalation occurred before susceptibility reporting.

Although retrospective in nature, this study supports an active ASP bundling of RDTs with local guidelines to reduce antibiotic utilization and improve empirical therapy and time to de-escalation. This stewardship group also utilizes prediction models in their guidelines, helping to facilitate early de-escalation. Two additional takeaways related to these data: (1) Pharmacist education on proper use of RDTs is critical to ensure maximum utility [35], and (2) patient-specific assessments of drug resistance risk factors should be a focus.

Point-of-Care β-Lactam Allergy Skin Testing by ASPs

The IDSA and Society for Healthcare Epidemiology of America 2016 antimicrobial stewardship guidelines recommend allergy assessment and β-lactam allergy skin testing (BLAST) when clinically appropriate [29]. However, many institutions lack the dedicated allergy and immunology specialty services required for inpatient drug allergy testing.

Leis and colleagues conducted a multicenter prospective study evaluating implementation of ASP-run BLAST services [16]. ASP pharmacists and at least 1 ID physician from each hospital completed BLAST training with an allergist. The ASP pharmacist conducted a structured allergy history and, to eligible patients, offered, performed, and interpreted BLAST. If BLAST was negative, the β-lactam antibiotic was prescribed, the EMR was updated, and patients received a letter explaining the BLAST results. Outcomes included the proportion of patients receiving preferred β-lactam therapy, ADEs, hospital LOS, and 30-day readmission or death.

At baseline, 246 patients reported a β-lactam allergy and had an infection where a β-lactam was the preferred therapy; 50% (124/246) received a β-lactam. In the intervention phase, 386 patients met criteria and 81% (313/386) received a β-lactam after structured allergy assessment and possible provision of BLAST ($P < .001$). The odds of receiving preferred β-lactam therapy were higher in the intervention period (odds ratio, 4.5; 95% CI, 2.4–8.2; $P < .0001$). No significant differences were observed among the secondary outcomes, including ADEs. Only 1 patient tested had a positive BLAST. The authors noted that BLAST required up to 1 hour of pharmacist time at the patient bedside.

This study demonstrates that ASPs can increase β-lactam utilization rates in patients reporting β-lactam allergies utilizing a structured allergy assessment followed by pharmacist-administered BLAST. When considering the implementation of this approach, the protocol should be institution-specific and developed in collaboration with allergy specialists. The ASP should consider the pharmacist and physician time involved when allocating and requesting resources.

Improving Management of Hospitalized Patients With Viral Respiratory Tract Infections

Often, patients presenting with respiratory tract infections (RTIs) are started on empiric antibiotics because the infectious etiology is unclear. Recent developments of real-time multiplex PCR testing allow for improved identification of causative respiratory viruses, but implementation alone may not improve unnecessary antibiotic therapy [36].

Lowe and colleagues performed a quasi-experimental pre-/postintervention study to evaluate the impact of ASP recommendations on antibiotic DOT in patients admitted with viral RTIs [17]. The intervention consisted of PAF and targeted patients with a positive PCR result for influenza A or B, respiratory syncytial virus, parainfluenza 1, 2, or 3, adenovirus, or human metapneumovirus, obtained from upper or lower respiratory tract samples. An ASP consultation was obtained in patients with no positive bacterial cultures and absence of radiographic findings. Similar numbers of patients were on antibiotics in the both groups (pre-intervention: 70/92; vs postintervention: 98/118; $P = .21$). Integrating virologic PCR testing decreased antibiotic DOT by a mean of 1.3 days ($P < .01$). ASP recommendations were accepted in 77% of cases postintervention. Among patients with positive influenza PCR, oseltamivir was started in significantly more patients in the postintervention group (31/43 vs 21/22; $P = .03$). No difference in LOS, ICU admission, receipt of mechanical ventilation within 14 days, restarting antibiotics within 14 days, CDI, or readmission within 30 days was observed between groups.

Implementation of syndrome-specific RDT may limit unnecessary antibiotic use in hospitalized patients with viral RTIs. Additionally, identification of influenza may lead to more appropriate oseltamivir use. However, optimizing RDTs relies on communicating results and recommendations to prescribers.

Urgent Care Antimicrobial Stewardship Through Pharmacist-Led Culture Follow-up

The CDC has published core elements for outpatient settings, including urgent care facilities, where significant antimicrobial prescribing occurs [37].

Dumkow and colleagues evaluated the feasibility of a pharmacist-led culture follow-up program at urgent care centers [18]. All positive cultures from any source except blood, synovial, and cerebrospinal fluid were evaluated over the course of a year by either an emergency department (ED) or ID pharmacist or pharmacy practice resident located off-site under a collaborative practice agreement (CPA). Of 1461 positive cultures reviewed, 320 (22%) required intervention, with the most common being urine, sexually transmitted infections (STIs), and throat (Streptococcal species), respectively. The majority of the STI patients did not require further treatment, only notification of results and counseling. Most patients were contacted with 1 phone call and required an average of 15 minutes for all interventions including documentation.

Of interest, the CPA in this study recommended no additional antibiotics prescribed if patients were asymptomatic at the time of the call (60% of patients). The strengths of the study include meaningful stewardship intervention, with minimal increase in workload/time due to involvement of 3 different pharmacists including a resident, all occurring in a community setting. CPAs may not be available in some areas, and the authors did not delineate how many interventions were performed by the resident, which, depending on resources, could limit generalizability. Additionally, further assessment of not only interventions but outcomes is needed for comprehensive evaluation of this service.

Syndrome-Specific Intervention: Candidemia

Candida species are the fourth leading reported cause of nosocomial BSIs, with hospital mortality rates approaching 40% [38]. Shortening the time to appropriate therapy improves outcomes, including mortality [39, 40].

Rac and colleagues conducted a single-center, pre–post, quasi-experimental study evaluating a 1-time antifungal stewardship intervention consisting of antifungal susceptibility testing paired with real-time culture alerts to the ASP pharmacist, who then would review results and convey recommendations related to antifungal therapy and ancillary care recommendations (ID consult, remove lines, ophthalmology examination, repeated blood cultures) to the primary team [19]. The ASP pharmacist intervened 24 hours/day, with most activity occurring during business hours (Monday–Friday from 6 AM to 6 PM). The primary outcome was time to adequate antifungal therapy in the business hours population, and secondary outcomes included infection-related LOS, compliance with quality indicators, and time to adequate and appropriate antifungal therapy in the total population. Therapy was considered adequate if it had documented or expected in vitro susceptibility and appropriate if it was the narrowest spectrum. There was no significant difference in the primary end point between groups, but time to adequate therapy and adequate therapy order in the total population were both statistically shorter in the postintervention period. Time to appropriate therapy was not different between groups in either population. The intervention was associated with a statistically significant increase in the number of ID and ophthalmology consults and the number of patients switched to oral therapy.

The authors hypothesized that similarities in the primary outcome were due to the large percentage of *C. glabrata* at this institution, which may have resulted in more empiric echinocandin usage in both periods. The limitations include a single-center design, small study population, and heavy reliance on the ID consult team to follow up on recommendations. Further research at hospitals without specific ID-trained physicians or consult teams would be beneficial.

Antimicrobial Stewardship in Nursing Homes

Interest in ASPs has been pivoting from a focus on hospitals to other health care workers and settings, as evidenced by TJC's standard on ASP applicable to nursing homes [41], the American Nurses Association/CDC White Paper on the role of registered nurses in ASPs [42], and the National Quality Forum's Playbook on ASPs in postacute and long-term care [43].

Wilson and colleagues investigated nurses' awareness of their role as antimicrobial stewards in nursing homes through pre– and post–online course surveys [20]. The course was free of charge, consisted of six 30-minute interactive modules, and provided 3.0 nursing contact hours. Assessing data from 71 registered nurses and 32 licensed practical nurses who completed both pre and post surveys, a statistical improvement in knowledge scores was identified (75% to 86%; $P < .0001$). After taking the course, respondents had heightened awareness that their role influences whether residents receive antimicrobials (3.8 to 4.5 on a 5-point Likert scale; $P < .001$).

The limitations include a limited sample size with a high attrition rate (103/200 nurses completed both surveys) and the absence of an assessment on the long-term impact of the intervention. Future research is warranted to further elucidate effective mechanisms for educating nurses and engaging them in ASP activities especially in non-acute care settings.

DISCUSSION

Regulation mandating ASPs is increasingly occurring across the health care spectrum. Although there is exponential growth in the number of ASP publications, most do not detail specific interventions with subsequent effects on patient outcomes. Documentation of both positive and negative outcomes with specific interventions is imperative to aid ASPs in selecting appropriate actions for their practice sites, especially for new or resource-limited programs. With few antimicrobials with novel mechanisms of action scheduled for FDA approval in the near future, processes that optimize antimicrobials are vital [44].

Several major themes are evident within the chosen manuscripts. First, integration of RDTs into stewardship activities improves outcomes [5, 8, 10, 11, 17]. Previous data describe a lack of benefit of RDTs when not acted upon by the ASP [36]. Facilities must inventory resources to determine if these outcomes are reproducible within their patient population and determine appropriate integration strategies.

Second, a growing literature supports shortening the duration of therapy for several diseases, as evidenced by our literature review, which found several articles shortening treatment duration within the inpatient setting and at the time of discharge [14, 15]. Implementation of prescription reauthorization with feedback on restricted antimicrobials decreased DOT and overall LOS.

Third, data are emerging regarding ASPs in community hospitals and health systems [5, 14, 18]. This is encouraging, considering that these locations represent most facilities, and many may not have significant resources to perform the CDC core elements [4]. Further research will help determine the best interventions for these patient populations.

As research focusing on specific, actionable stewardship interventions continues to increase, clinicians should work to stay familiar with key impactful interventions. Analyzing and implementing these strategies will help promote ASP activities and ultimately attain what we are all after, better patient outcomes.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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MAJOR ARTICLE

A Baker's Dozen of Top Antimicrobial Stewardship Intervention Publications in 2018

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With an increasing number of antimicrobial stewardship–related articles published each year, attempting to stay current is challenging. The Southeastern Research Group Endeavor (SERGE-45) identified antimicrobial stewardship–related peer-reviewed literature that detailed an actionable intervention for 2018. 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 as well as to identify potential intervention opportunities within one's institution.

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

Antimicrobial stewardship has become a common term in acute care facilities, sparking significant interest among physicians, pharmacists, and other health care professionals. Antimicrobial stewardship program (ASP) foundations, including leadership by infectious diseases (ID) pharmacists and physicians, have long been established and directed by clinical practice guidelines and regulatory bodies [1–3]. The focus of antimicrobial stewardship activities continues to move beyond the walls of inpatient institutions. Certificate programs targeting ID physicians and clinicians working in ambulatory or long-term care stewardship are now being offered [4–8]. In addition, formal recommendations and guidance for outpatient and nursing home ASP activities from the Centers for Disease Control and Prevention (CDC) and regulatory agencies are available [9–11]. In January 2020, new Joint Commission (TJC) standards for ambulatory care facilities that routinely prescribe antibiotics will go into effect [12]. Many questions on the optimal execution of antimicrobial stewardship activities still remain. Given the variability in institutional settings, local epidemiologic patterns, patient mix, and available resources, continued research on successful and optimal ASP interventions is needed [13].

The most successful work in antimicrobial stewardship has been the result of strong interprofessional collaborations, with research and scholarship being no exception. Members of the Southeastern Research Group Endeavor (SERGE-45), an interprofessional research network primarily composed of expert pharmacist stewards in the Southeastern United States, systematically compiled the top peer-reviewed publications from 2018 involving an ASP intervention. Table 1 provides a brief overview of the 13 selected articles (aka "Baker's Dozen"), which are detailed herein [14–26]. Annual reviews using similar criteria have been previously published since 2016 [27, 28].

METHODS

Using a modified Delphi technique (detailed previously), members of the SERGE-45 network identified antimicrobial stewardship publications from 2018 considered to be significant using the following inclusion criteria: (1) published in 2018, including electronic, "early-release" publications, and (2) must include an actionable intervention [29]. An actionable intervention was defined as a stewardship strategy that was implemented in 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 2018 revealed 916 potential publications. EBC and PBB screened abstracts to ensure that all relevant articles were considered. In addition, a total of 61 publications were also submitted by authors for potential inclusion, and comments were provided electronically to E.B.C., C.M.B., and P.B.B. A total of 117 articles

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Table 1. Summary of Included Studies

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Yadav et al. 2018 [14]	Single-center, quasi-experimental study of incorporation of institutional EP for duration of therapy into preexisting ASP rounds	Institutional EP for duration of antimicrobial therapy developed and approved by hospital committees. EP reinforced on ASP rounds. Preexisting ASP rounds included prospective audit and feedback, restriction program, and de-escalation rounds.	Primary outcomes: mean antimicrobial DOTs administered inpatient and prescribed outpatient for patients discharged with ICD-10 codes for UTI, SSTI, PNA, VAP in 12 months before and 12 months after implementation of EP • Change in mean DOTs: UTI, –1.4 (–2.3 to –0.6; *P* = .001); SSTI, –2.2 (–3.3 to –1.0; *P* < .001); PNA, –2.0 (–3.2 to –0.9; *P* = .001); VAP, –9.6 (–16.0 to –3.3; *P* = .003) Secondary outcomes: total antibiotic exposure (sum of total milligrams of antibiotics administered inpatient plus prescribed outpatient) • Change in antibiotic exposure: UTI, –3718 (–5185 to –2252; *P* < .001); SSTI, –5404 (–8227 to –2582; *P* < .001); PNA, –9430 (–12 028 to –6833; *P* < .001); VAP, –34 246 (–57 507 to –10 986; *P* = .004)
Thom et al. 2019 [15]	Multicenter, quasi-experimental, pre- and postintervention study	Provider-driven ATOs were implemented across 11 units located in 6 hospitals. Providers were prompted to complete paper ATO tool on antibiotic days 3–5 without study or stewardship input.	No difference between hospital DOT per admission or total DOT per admission before or after controlling for study unit and season • Average hospital DOT 12.7 vs 12.2 and total DOT 18.9 vs 18.2 • Multivariable analysis showed no association between intervention and number of times regimen was modified or discontinued on antibiotic days 3–5 (OR, 1.0; 95% CI, 0.85–1.19) • Multivariable analysis showed that the ATO was inversely associated with receipt of inappropriate antibiotics on antibiotic days 3–5 (OR, 0.58; 95% CI, 0.48–0.69), as was having undergone a surgical procedure (OR, 0.70; 95% CI, 0.54–0.90)
Foolad et al. 2018 [16]	Multicenter, quasi-experimental study	1) Update and dissemination of institution-specific CAP guidelines via pocket cards and hospital intranet sites. 2) Multiple educational sessions to prescribers and pharmacists regarding appropriate management of CAP, focusing on DOT, updates to the institution-specific guidelines, and the stewardship initiative. 3) Targeted prospective audit with feedback and intervention by ID pharmacists Monday–Friday.	Decrease in median antibiotic DOT • Historical 9 (IQR, 7–10) days vs intervention 6 (IQR, 5–7) days; *P* < .001 Improvement in guideline-concordant therapy • Historical 5.6 % vs intervention 42%; *P* < .001 Decrease in median excess antibiotic days • Historical 3 (IQR 2–5) days vs intervention 1 (IQR 0–2) days; *P* < .001 No significant difference in clinical outcomes 30 days postdischarge, No. (%) • CDI: historical 0 (0) vs intervention 0 (0); *P* = not reported • Re-presented to emergency center or clinic with pneumonia: historical 20 (6.8) vs intervention 13 (4.4); *P* = .22 • Readmission with pneumonia: historical 21 (7.1) vs intervention 11 (3.8); *P* = .075 • Mortality: historical 7 (2.3) vs intervention 3 (1); *P* = .233
Musgrove et al. 2018 [17]	Multicenter, single pre- and postintervention, quasi-experimental study	Clinical microbiology laboratory changed wording in reports on non-pathogen-containing respiratory cultures to emphasize no *Staphylococcus aureus*, MRSA, or *Pseudomonas aeruginosa.*	Primary outcome • De-escalation: 39% vs 73%; *P* < .001 Secondary outcomes • Discontinuation of anti-MRSA therapy: 37% vs 71%; *P* < .001 • Discontinuation of antipseudomonal therapy: 32% vs 70%; *P* < .001 • Acute kidney injury: 31% vs 14%; *P* = .003 • In-hospital, all-cause mortality: 30% vs 18%; *P* = .52
García-Rodríguez et al. 2019 [18]	Single-center, quasi-experimental, pre- and postintervention study	A multidisciplinary antimicrobial stewardship team was implemented with prospective follow-up of meropenem use. An ID physician reviewed the EMR for each case and provided antibiotic treatment recommendations to the prescribers, with adherence to or rejection of the recommendations from the ID physician assessed at 24–48 hours postrecommendation.	Improved rates in appropriate justification of meropenem use • Pre-intervention (2014) 47.3% vs postintervention (2017) 76.8%; *P* = .001 • Reduction in meropenem consumption (DDD/100 OBDs) • During 2015–2017, meropenem consumption decreased compared with 2012–2014 (RR, 0.67; 95% CI, 0.58–0.77; *P* < .001)
Kulwicki et al. 2019 [19]	Retrospective, single-center cohort analysis	Addition of an emergency medicine pharmacist into the ED to provide antimicrobial stewardship. Adherence to empiric treatment recommendations for CAP and community-acquired IAIs was examined pre-EMP and post-EMP. A secondary analysis was undertaken to examine adherence to these same guidelines in the early phases of implementation of an ASP compared with the established program.	Significant difference in total appropriate empiric antibiotic selection with the EMP vs without the EMP • 78% vs 61%; *P* = .001 Significant difference in CAP treatment with the EMP vs without the EMP • 95% vs 79%; *P* = .005 Significant difference in community-acquired IAIs treatment with the EMP vs without the EMP • 62% vs 44%; *P* = .025 Significant difference in guideline-directed antibiotic prescribing in the established ASP period compared with the pre-ASP period • 82.5% vs 60%; *P* < .001

Table 1. Continued

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Sacco et al. 2019 [20]	Single-center, quasi-experimental pre- and postintervention study	Following development of a validated risk stratification algorithm to guide testing and antibiotic use in patients with penicillin allergy. Health care professionals were educated on its use. The algorithm was intended to guide patient assessment and antibiotic selection. Data were assessed pre– and post–educational initiative.	Antibiotic use • Cephalosporins +121.2%; *P* = .03 • Penicillins +256%; *P* = .04 • Vancomycin –67.2%; *P* = .04 • Fluoroquinolones –33.3%; *P* = .31 • Carbapenems –81.9%; *P* = .08 • Aztreonam –73.8%; *P* = .18 EMR documentation of type of adverse reaction to penicillin in the admission note • Pre 4.8% vs education 64.9%; *P* < .001 Use of the test-dose procedure • 8/27 patients Occurrence of adverse drug reactions • None Length of hospital stay • Pre 2.33 days vs education 2.07 days
Lee et al. 2018 [21]	Retrospective, single-center quasi-experimental cohort analysis	A fluoroquinolone restriction policy was implemented in 2005. Fluoroquinolone susceptibility was analyzed in a pre-implementation period (1998–2004) and a postimplementation period (2006–2016). Five Gram-negative organisms were included in the analysis: *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *P. aeruginosa*, and *Acinetobacter* species.	Fluoroquinolone use decreased from 173 DOT in the pre-implementation period to <60 DOT in the postimplementation period Fluoroquinolone susceptibility increased for: • *Acinetobacter* species (RR, 1.038; 95% CI, 1.005–1.072) • *E. cloacae* (RR, 1.028; 95% CI, 1.013–1.044) • *P. aeruginosa* (RR, 1.013; 95% CI, 1.006–1.020) Susceptibility did not change significantly for *K. pneumoniae* (RR, 1.002; 95% CI, 0.996–1.008) *E. coli* susceptibility continued to decline postimplementation (RR, 0.981; 95% CI, 0.975–0.987)
Keller et al. 2018 [22]	Single-center, prospective time series analysis	To reduce the ordering of urinalyses and urine cultures in patients without symptoms of a UTI, a series of interventions including the distribution of educational materials and implementation of CDS alerts in the EMR was implemented. CDS alerts were placed on all orders for urinalyses, urine cultures, and for antibiotics commonly used for treating UTIs (nitrofurantoin, trimethoprim-sulfamethoxazole, ciprofloxacin, cefazolin, cephalexin, and ceftriaxone).	Primary outcome: Urinalysis orders did not significantly decrease • –10.2%; *P* = .24 Secondary outcome: Orders for urine cultures did significantly decrease • –6.3%; *P* < .001 Other results • Decrease in simultaneously ordering urinalyses and urine cultures (–5.8%; *P* < .001) • Decrease in urinalysis orders followed by antibiotic orders within 1–24 hours (–0.56%; *P* = .021) • Decrease in urine culture results followed by an antibiotic order within 24 hours (–0.24%; *P* = .036)
Lee et al. 2018 [23]	Prospective, multicenter pre/post chart audit	15-minute education session to clinical staff focusing on the appropriate management of UTI and ASB, complimented by awareness posters and pocket cards summarizing UTI diagnostic criteria.	Reduction in antibiotic prescriptions for ASB • Pre-intervention 45 of 50 (90%) vs postintervention 22 of 35 (63%); *P* = .003 Increase in proportion of residents presenting with localizing UTI symptoms • Pre-intervention 21 of 62 (34%) vs postintervention 22 of 50 (44%); *P* = .273 Reduction in health care costs • 64% reduction for pharmacy • 30% reduction for laboratory
Porter et al. 2018 [24]	Retrospective, single-center, before-and-after study	Conventional microbiology communication vs mRDT plus pharmacist-driven reporting protocol for positive blood cultures.	Significant decrease in time to change in optimal therapy (50 vs 160 minutes; *P* = .0081) • Significant increase in percent changed to optimal therapy (41.4% vs 15.6%; *P* = .013) • Nonsignificant change in percent changed to effective therapy (17.2% vs 24.4%; *P* = .462) • Multivariate regression analysis showed that the intervention group was significantly less likely to have greater time-to-change value and more likely to be changed to optimal therapy (*P* < .01 for both)
Menichetti et al. 2018 [25]	Retrospective cohort comparing those who received ID consult plus intervention vs intervention alone	Restricted use of voriconazole, posaconazole, caspofungin, anidulafungin, micafungin, liposomal amphotericin B, and lipid complex amphotericin B to ID, intensive care, and hematology, plus ID consultation.	Primary outcomes • In-hospital, 30-day mortality 20% with ID consult vs 37% without; *P* = .011 Secondary outcomes • Antibiotic consumption (DDD/100 bed-days): increases in fluconazole (3.1 to 4.3), echinocandins (0.22 to 0.35); decreases in voriconazole (0.25 to 0.18), and amphotericin (0.06 to 0.04) • Antibiotic cost: increased by €207 000 during study period

Table 1. Continued

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Claeys et al. 2018 [26]	Retrospective, single-center, observational study	Validation of a theoretical Verigene GNB treatment algorithm based on institutional antibiogram data, evidence-based management, and ASP practice.	Significant theoretical decrease in cases receiving appropriate antibiotic therapy vs standard care (88.4% vs 78.1%; $P = .014$) • Strong level of agreement between reviewers regarding algorithm recommendations ($\kappa = .855$) • 14.4% appropriate de-escalation and 5.3% appropriate escalation • 4.8% inappropriate de-escalation and 16% unnecessary escalation

Abbreviations: ASB, asymptomatic bacteriuria; ASP, antimicrobial stewardship program; ATO, antibiotic time-out; CAP, community-acquired pneumonia; CDI, *Clostridioides difficile* infection; CDS, clinical decision support; CI, confidence interval; DDD, defined daily dose; DOT, days of therapy; ED, emergency department; EMP, emergency medicine pharmacist; EMR, electronic medical record; EP, expected practice; GNB, Gram-negative bacteremia; IAI, intra-abdominal infection; ICD-10, International Classification of Diseases, Tenth Revision; ID, infectious diseases; IQR, interquartile range; mRDT, molecular rapid diagnostic technology; MRSA, methicillin-resistant *Staphylococcus aureus*; OBD, occupied bed-days; OR, odds ratio; PNA, pneumonia; RR, rate ratio; SSTI, skin and soft tissue infection; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

were distributed to the SERGE-45 network for ranking using SurveyMonkey based on contribution and/or application to ASP [30]. A teleconference among E.B.C., C.M.B., and P.B.B. reviewed the final ranking and established final consensus on the top 13 articles based on number of votes received for each article; all articles are described herein. Figure 1 depicts the flowchart of database and article selection, and Table 1 is a summary of the selected articles.

RESULTS

Expected Practice and Duration of Therapy

Yadav and colleagues sought to determine the impact of an institutional "expected practice" (EP) for antimicrobial duration of therapy on total days of therapy (DOT) administered inpatient and prescribed at discharge for common infections at a large academic medical center in Los Angeles, California [14]. The EP document, developed by a interdisciplinary group, listed many common infections seen in the inpatient and outpatient settings and referenced shorter courses of therapy with supporting evidence. The EP was endorsed by the Pharmacy & Therapeutics Committee and Medical Executive Committee. Providers were asked to explicitly justify longer antimicrobial durations in the medical record when deemed necessary for optimal patient care.

Implementation included a memo to clinicians and incorporation of EP into ASP rounds. Total DOTs and total antimicrobial exposure (defined as total mg of antibiotic administered + antibiotic prescribed at discharge) were compared among patients discharged from the facility in the 12 months before and after implementation of the EP, modeled as a function of the ASP. Patients were included if International Classification of Diseases, Tenth Revision (ICD-10), codes corresponding to targeted infectious

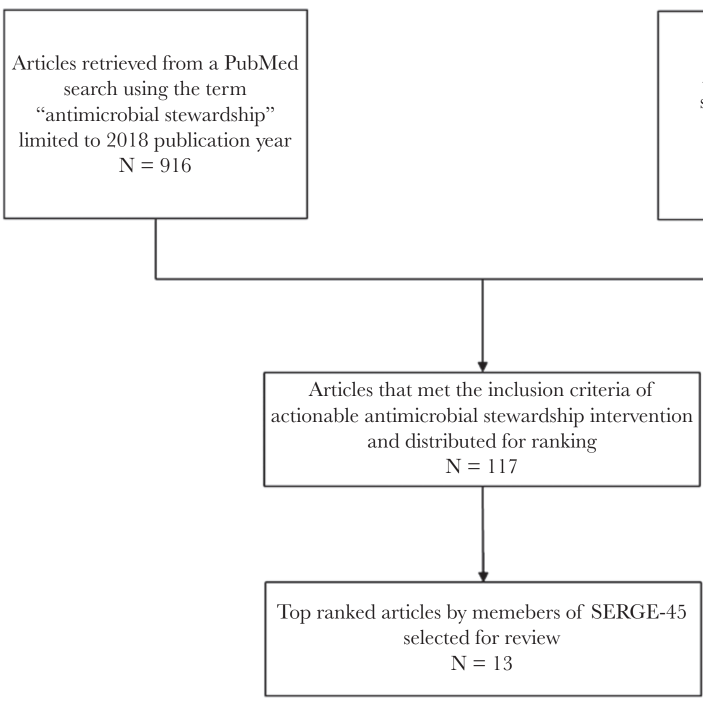

Figure 1. Strategy for identification of top antimicrobial stewardship publications.

processes were within the top 20 discharge diagnoses. Covariates in the model included age, gender, insurance status, in-hospital and expected mortality, and severity of illness. Significant decreases were observed in average DOT and antimicrobial exposure for all infection types. Mortality was assessed as a measure of safety for shorter courses of therapy and was similar across both time periods for each infection type. Use of the procalcitonin assay, which was implemented at the same time as the EP, was associated with longer durations of therapy. The authors attributed this to confounding by indication, as clinicians likely ordered procalcitonin for cases of greater complexity.

ASPs may consider EP an effective way to translate shorter durations of therapy into new institutional standards of care.

Antibiotic Time-outs and Duration of Therapy

The CDC and TJC recommend the use of interventions such as antibiotic time-outs (ATOs) or prospective audit and feedback (PAF) to improve antibiotic prescribing [3, 11]. ATOs may occur as part of standard practice without ASP involvement, prompting providers to have a structured conversations regarding the appropriateness of antibiotic regimens and durations.

Thom and colleagues performed a quasi-experimental study pre- and postimplementation of an ATO across 11 units (including adult and pediatric general and intensive care wards) located in 6 different hospitals in Maryland to measure the impact of a provider-driven ATO [15]. Pre-intervention data were collected during a 6-month baseline period, and postintervention data were collected for 9 months after implementation of the paper ATO tool that prompted care teams on antibiotic days 3–5 without input from the study or stewardship team. Primary outcomes were hospital antibiotic DOT per patient admission and total antibiotic DOT per patient admission, including antibiotic prescriptions at discharge. Secondary outcomes included antibiotic appropriateness and proportion of cases in which there was a modification or discontinuation of the regimen within 3–5 calendar days of onset. There was no difference between hospital DOT per admission or total DOT per admission in the pre- vs postimplementation groups, before and after controlling for unit and seasonal differences. Multivariable analysis showed no association between ATO intervention and number of times antibiotic regimens were modified or discontinued on days 3–5.

The findings of this study contribute to growing evidence supporting the impact of ASP input on improving antimicrobial utilization and overall patient outcomes. Further studies are needed to investigate the impact of additional adjunctive methods with ASP feedback on antibiotic use.

Optimizing the Treatment of Community-Acquired Pneumonia

The 2007 Infectious Diseaes Society of America (IDSA)/American Thoracic Society (ATS) guidelines for community-acquired pneumonia (CAP) recommend that patients be treated for a minimum of 5 days, afebrile for 48–72 hours, and have no more than 1 CAP-associated sign of clinical instability before discontinuation of therapy [31]. Despite these recommendations, patients continue to receive longer courses of therapy, increasing the risk of adverse events and antimicrobial resistance.

Foolad and colleagues conducted a multicenter, pre–post quasi-experimental study assessing the impact of a multifaceted prospective stewardship intervention on antimicrobial DOT and clinical outcomes in patients admitted with CAP to the medicine service at 3 large academic medical centers in Ann Arbor, Michigan, Milwaukee, Wisconsin, and New Orleans, Louisiana [16]. Interventions included (1) dissemination of institution-specific CAP guidelines and pocket cards, (2) educational sessions to prescribers and pharmacists on the appropriate management of CAP, focusing on DOT, and (3) targeted PAF and intervention by ID pharmacists Monday–Friday. Notably, patients admitted to the ICU were excluded. The primary objective was CAP antimicrobial DOT pre- and postintervention. Secondary clinical outcomes evaluated included mortality, readmission or presentation to a health care facility for pneumonia, and incidence of *Clostridioides difficile* infection, all at 30 days postdischarge. Six hundred patients were included in the study, 307 in the historical group and 293 in the intervention group. Decreases in median antibiotic DOT and improvement in guideline-concordant therapy were demonstrated postintervention. There were no significant differences in secondary clinical outcomes within 30 days of discharge.

The authors note that this was the largest study to date assessing the impact of ASP interventions on antibiotic DOT and clinical outcomes in patients with CAP. It was conducted at 3 large academic institutions and required dedicated ASP pharmacist time and resources to perform PAF, which may limit generalizability. It is also difficult to assess which intervention had the greatest impact, as they were implemented concurrently, and the number of interventions performed by the ASP pharmacists was not reported.

Microbiology Reports and Antibiotic Prescribing for Pneumonia

Antimicrobial prescribing patterns are directly influenced by clinicians' interpretation of microbiology results and reports [32]. Musgrove and colleagues conducted a quasi-experimental study to compare de-escalation rates before and after changing respiratory culture reports across a 4-hospital health system in Detroit, Michigan [17]. The intervention, in combination with previously established antimicrobial stewardship practices (eg, syndrome-specific treatment guidelines, PAF), modified wording on non-pathogen-containing respiratory cultures to specifically note absence of *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), or *Pseudomonas aeruginosa*. In addition, in-person education was provided to intensive care unit providers and pharmacists, which was supplemented by a 1-page educational handout. One hundred five patients receiving inpatient treatment with anti-MRSA (vancomycin or linezolid) and antipseudomonal (cefepime, piperacillin/tazobactam, meropenem, or aztreonam) therapy for respiratory infections were included in both the 6-month pre- and postintervention groups. De-escalation and discontinuation of unnecessary anti-MRSA and antipseudomonal therapy occurred significantly more often in the postintervention group, resulting in an average decrease of 2 DOTs. After adjusting for disease severity, the revised wording on respiratory cultures was associated with 5.5-fold increased odds of de-escalation. Fewer patients in the postintervention group experienced acute kidney injury, but no difference was observed in intensive care unit or hospital length of stay (LOS), or in-hospital, all-cause-mortality.

This study reinforces the importance of microbiology reports in achieving ASP goals. In addition, the results of this study demonstrate that simple ASP interventions can result in significant improvements in antimicrobial prescribing.

Optimizing the Use of Meropenem

García-Rodríguez and colleagues performed a quasi-experimental pre/postintervention study to evaluate the impact of meropenem ASP recommendations on rates of appropriate justification of treatment, antibiotic consumption measures, infection-related and all-cause mortality, and incidence of multidrug-resistant hospital-acquired bloodstream infections [18]. Additional clinical and economical comparisons were described between the groups of patients with and without acceptance of ASP recommendations when meropenem did not fulfill justification criteria.

This study describes a resource-limited approach by a multidisciplinary team to improve meropenem utilization at a single 350-bed teaching hospital in Spain from 2015 to 2017. Local guidelines for empiric antibiotic treatment were developed and made accessible on every hospital desktop computer. In addition, active surveillance was performed 6 hours weekly by an ID physician who reviewed each case and provided recommendations to prescribers in 1 of the following ways: face to face, telephone, or through the electronic medical record (EMR). During the last 4 months of 2014, patient cases with meropenem were reviewed retrospectively as the pre-intervention study group for comparison. Overall, in the pre-intervention period, 47.3% of the 150 patients receiving meropenem were considered justified based on study criteria for appropriate treatment, which included severe sepsis, history of extended spectrum beta-lactamase (ESBL) colonization, or hospital-acquired infection in which broad-spectrum antibiotics were necessary. There were 852 patients who received meropenem treatment during the intervention period, with 61% of cases considered justified or appropriate. Of the 330 cases that were not considered justified, the prescribers accepted 82% of the ID physician recommendations. Acceptance of intervention was associated with shorter duration of antibiotic treatment and inpatient days. The study further compared patients with and without acceptance of ASP recommendations and found that pulmonary and abdominal infections were associated with lower acceptance rates. Overall, there was a 33% decrease in meropenem consumption when comparing the pre-intervention years (2012–2014) with the intervention years (2015–2017).

The strength of this study is that it can be replicated in settings where targeting a specific antibiotic is needed and an ID physician is available for intervention. Despite these results, it remains important to consider syndrome-specific interventions that may result in advantageous declines in antibiotic utilization and avoid compensatory increases in other broad-spectrum antibiotics.

Emergency Medicine Pharmacist and Antibiotic Prescribing for CAP and Intra-abdominal Infections

In the United States, approximately 16% of all patients who visit the emergency department (ED) each year receive an antibiotic, but many are either inappropriate or unnecessary [33, 34]. ASPs can help improve antibiotic prescribing practices, including in the ED, and pharmacists play an important role in the provision of ASPs [35].

Kulwicki and colleagues conducted a retrospective cohort analysis to determine the effect of an emergency medicine pharmacist (EMP) on the selection of appropriate empiric antibiotics for the treatment of CAP and community-acquired intra-abdominal infections (IAIs) in the ED, compared with having no EMP, in Grand Rapids, Michigan [19]. Determination of appropriate antibiotics was based on following institutional protocols derived from IDSA guidelines, in conjunction with local antimicrobial resistance patterns. A secondary objective was to examine empiric antibiotic prescribing for these 2 disease states in the ED during a period of early ASP (2014) compared with an established ASP (2016). Three-hundred twenty patients were included (185 in the EMP group and 135 in the no-EMP group). Appropriate empiric prescribing occurred more often in the EMP group compared with the no-EMP group. Treatment of both CAP and community-acquired IAIs was more likely to be appropriate in the EMP group compared with the non-EMP group. Further, guideline-directed antibiotic prescribing significantly improved from the early ASP period to the established ASP period.

Overall, the results of this study demonstrate the positive impact of having an EMP as a steward extender for ASPs.

Use of an Inpatient Penicillin Allergy Assessment Protocol

Allergy to penicillin is one of the most frequently reported and documented allergies. Over 30 million patients have reported an allergy to penicillin, and as many as 90% of these allergies are inaccurate [36]. Carrying this label has an impact on ASP, as it leads to increased prescribing of broad-spectrum or second-line agents, as well as increased LOS and overall costs [36]. One intervention used to assess patients with a history of IgE-mediated allergy is penicillin skin testing (PST); however, logistics and access to PST can be limited [37].

Sacco and colleagues performed a single-center, quasi-experimental pre- and postintervention study in Jacksonville, Florida, to assess the effects on antibiotic prescribing after education and implementation of a validated algorithm that categorizes patients based on risk stratification [20]. Providers were educated by an allergist on penicillin allergies and given a standardized algorithm to help with taking a proper history and antibiotic selection. In the pre- and postintervention cohort of patients admitted to the general medicine ward with a reported penicillin allergy, there were 42 and 57 patients, respectively. Documentation of allergy reaction history on admission improved from 4.8% pre-intervention to 64.9% postintervention ($P < .001$). Penicillin and cephalosporin usage increased by 256% and 121%, respectively, whereas vancomycin, fluoroquinolone, carbapenem, and aztreonam usage decreased.

Although only a single center with limited sample size, this study demonstrated that education and standardization of prescribing can affect antibiotic selection in patients who present with a penicillin allergy to facilities with limited resources to routinely perform PST.

Fluoroquinolone Use and Pre-authorization Policy

Fluoroquinolone use in the United States has steadily increased in the past decade, with a concomitant increase in resistance, particularly among Gram-negative organisms [38, 39]. ASPs can improve fluoroquinolone use and lead to improvements in susceptibility.

Lee and colleagues conducted a retrospective, quasi-experimental study to examine fluoroquinolone susceptibility before (pre-intervention period 1998–2005) and after (postintervention period 2006–2016) implementation of a policy that required ASP approval for empiric fluoroquinolone use at a large academic medical center in Birmingham, Alabama [21]. Susceptibility patterns of 5 Gram-negative organisms were analyzed: *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *P. aeruginosa*, and *Acinetobacter* species. Inpatient use of fluoroquinolones increased steadily beginning in 1998, peaking in 2004 with 173 DOT per 1000 patient-days. The fluoroquinolone prior authorization policy was implemented in October 2005 and was successful in reducing fluoroquinolone use. Between 2006 and 2016, fluoroquinolone use was <60 DOT per 1000 patient-days. In the postintervention period, fluoroquinolone susceptibility significantly increased ($P < .0001$) for *Acinetobacter* species, *E. cloacae*, and *P. aeruginosa*. No significant change was noted for *K. pneumoniae*. The susceptibility for *E. coli* continued to decline, albeit not as dramatically as in the pre-intervention period. Both *E. coli* and *K. pneumoniae* are often community-onset pathogens, and unrestricted fluoroquinolone use in the community setting would likely contribute to the lack of significant impact on susceptibilities.

One limitation of this study was that the data were from a single academic center. In addition, a control unit or hospital could not be used for comparison because the fluoroquinolone restriction was universally applied. The results of this study demonstrate the effectiveness of a fluoroquinolone restriction policy in decreasing overall use and improvement in susceptibility of hospital-acquired Gram-negative organisms.

Asymptomatic Bacteriuria and Clinical Decision Support

Asymptomatic bacteriuria (ASB) is a common medical condition that seldom requires treatment [40]. Obtaining urinalyses and urine cultures in patients without signs or symptoms of a urinary tract infection (UTI) can lead to unnecessary antibiotics, which in turn leads to increasing resistance [41, 42].

Keller and colleagues implemented a combination of interventions to reduce urine testing for ASB that included provider education and clinical decision support (CDS) alerts in the EMR at a large academic medical center in Baltimore, Maryland [22]. In August 2015, educational materials were placed on hospital-wide screen savers and disseminated through a newsletter email. The CDS tools included informational messages recommending not to test for UTIs in patients without symptoms and recommending against treating ASB. These messages appeared on all EMR orders for urinalysis, urine culture, and for antibiotics commonly used for treating UTIs. The authors performed a prospective time series analysis utilizing a pre-intervention phase (September 2014–June 2015) and a postintervention phase (September 2015–June 2016). Orders for urinalyses did not decrease significantly but orders for urine cultures significantly decreased. Additionally, in the postintervention phase, there was a decrease in simultaneously ordering urinalyses and urine cultures (–5.8%), a decrease in urinalysis orders followed by antibiotic orders within 1–24 hours (–0.56%), and a decrease in urine culture results followed by an antibiotic order within 24 hours (–0.24%).

This study has a number of limitations, including short duration (<1 year) and a single center, and appropriateness of each antibiotic-based documentation of symptoms was not assessed. Overall, this study demonstrated that the use of educational materials and CDS may reduce the number of urine cultures ordered and antibiotics prescribed for the treatment of ASB.

Asymptomatic Bacteriuria and Antibiotic Use in the Long-term Care Setting

Unnecessary antimicrobial use in long-term care (LTC) residents related to ASB has been identified as a major area of opportunity for improvement and has led to efforts such as the "Symptom-Free Pee, Let It Be" campaign [43]. The best approach to increasing appropriate ASB management in the LTC setting is not known, and great interest exists in identifying viable methods for tackling the problem, particularly in resource-limited organizations.

Lee and colleagues undertook an evaluation of an educational intervention related to ASB in patients at 7 LTC facilities in Regina, Saskatchewan, Canada, with the primary outcome of percentage of residents who received inappropriate antibiotic treatment for ASB [23]. There was a pre-assessment period and a postassessment period of 5 weeks each, and the intervention took place during the 2 weeks in between. The intervention was designed to include feedback and monitoring, shaping knowledge, natural consequences, and comparison of behavior. The intervention included educational sessions that incorporated information on ASB treatment guidelines, local findings from the pre-intervention audit, and diagnostic criteria for UTIs. Educational posters were displayed after the 15-minute sessions, and pocket cards were distributed. Educational efforts were focused toward clinical staff, which was primarily made up of nursing staff. Intervention demonstrated a decrease in ABS antibiotic prescribing from 90% to 63%

One important limitation to this study is that only 15% of the clinical staff were present for an educational session and physicians were not included. Additionally, the study period was relatively short, with long-term impact unknown. However, this resource- and time-limited effort was effective in improving ASB management at 7 different LTC facilities.

Multiplex Polymerase Chain Reaction Blood Culture Results vs Conventional Microbiology Methods

Rapid identification of organisms and timely optimization of therapy are important to limit morbidity and mortality, decrease use of broad-spectrum agents, and improve clinical response [44–47]. With recent advancements in molecular rapid diagnostic technology (mRDT), organisms can be identified faster than the conventional 48–72 hours. Pharmacists are optimally placed to aid in correct interpretation and application of these results.

Porter and colleagues performed a single-center, retrospective, before-and-after study comparing time with change in antimicrobial therapy between a conventional microbiology protocol (December 2014–November 2015) and multiplex polymerase chain reaction with pharmacist-driven reporting protocol (April 2016–March 2017) at a community hospital in Savannah, Georgia [24]. Conventional protocol included results being communicated to a nurse, who would then notify the provider. The intervention group consisted of pharmacists utilizing a protocol developed and approved by the ASP subcommittee to notify the team, make recommendations, and enter accepted orders into the EMR. The primary outcome of time to change in antimicrobial therapy was measured from time of call with results to time of antimicrobial change, with only changes within 24 hours and initial calls being included. Secondary outcomes further divided results by time to change from suboptimal to optimal therapy or from ineffective to effective therapy. Change to optimal therapy included escalation to vancomycin for MRSA and discontinuation of vancomycin when clinically unnecessary. Patients in the intervention group (77/118) had decreased median time-to-change values for effective therapy (50 vs 160 minutes; $P = .0081$), and a higher percentage were changed to optimal therapy (41.4% vs 15.6%; $P = .013$). Additionally, there was a significant decrease in vancomycin utilization for coagulase-negative *Staphylococcus* spp. in the intervention group (69.3% vs 10%; $P < .01$).

Lack of improvement in clinical outcomes with mRDT without ASP intervention has been previously established. This study provides evidence for clinical benefits with mRDT and pharmacist involvement in resource-limited institutions, enabling front-line pharmacists to provide direct recommendations, with additional backup by ASP pharmacists through approved protocols. Additionally, analysis of immediate changes only may more closely represent the impact of ASP and the protocol.

ASP With or Without ID Consults and Candidemia

With the persistently high rates of associated mortality, programs have been targeting candidemia for antifungal stewardship interventions [48–51]. Menichetti and colleagues conducted a single-center retrospective study evaluating patients receiving an ID consultation in combination with an antifungal stewardship program vs those who did not at a large academic medical center in Italy [25]. The intervention consisted of antifungal restriction for most agents outside of fluconazole, requiring authorization via ID consult. ID consults were at the discretion of the primary provider and were completed within 24–36 hours of the request by 2 senior ID physicians. Education regarding awareness and appropriate treatment of candidemia based on published guidelines was additionally provided during the study period. The primary outcome was impact of the antifungal stewardship program with or without ID consultation on in-hospital 30-day mortality associated with candidemia. Secondary outcomes included mortality risk factors, antifungal consumption, and cost. From 2012 to 2014, 276 patients were included (76 with ID consult, 200 without). In-hospital 30-day mortality was 20% for patients with an ID consult and 37% for those without ($P = .011$). Of note, 26% of patients in the group without ID consult received no antifungal treatment. On univariate analysis, age >65 years and admission to an internal medicine ward were associated with higher risk of death, whereas ID consult, late-onset candidemia, and nonalbicans *Candida* species were protective. In multivariate analysis, ID consult, nonalbicans *Candida* species, and age remained significant. During the study period, fluconazole and echinocandin use increased, whereas voriconazole and amphotericin decreased.

Limitations include the small sample size, retrospective single-center design, and lack of information on source control. Further study on the impact of antifungal stewardship on patient outcome metrics would be beneficial in extrapolating these data to other institutions.

mRDT for Gram-Negative Bacteremia

Timely, appropriate antibiotic therapy is key for improved morbidity and mortality in Gram-negative bacteremia (GNB). The Verigene Blood Culture Gram-Negative (BC-GN) rapid diagnostic test can quickly identify 8 common target organisms and 6 resistance determinants with 97.1% sensitivity and 99.5% specificity [52, 53]. It is important to pair these with ASP involvement.

In a retrospective, single-center, observational study at a large academic medical center in Baltimore, Maryland, Claeys and colleagues developed a GNB treatment algorithm based on institution-specific antibiogram data and evidence-based practice [26]. A cutoff value of at least 88% susceptible, based on the reported susceptibility of piperacillin/tazobactam, was utilized for Gram-negative organisms without a resistance mechanism identified by Verigene BC-GN. Empiric therapy with meropenem was utilized in immunocompromised or critically ill patients where the antibiogram data showed higher rates of third-generation cephalosporin resistance with *E. coli* and *Klebsiella* spp. ASP pharmacists determined definitions for standard care (empiric) vs algorithm-based (optimal and targeted) antibiotic therapy and independently evaluated the appropriateness of standard care vs theoretical receipt of algorithm-based therapy. Allergy history or reconciliation was not considered for this assessment. Out of 144 patients with Verigene BC-GN target organisms, there was a moderate level of agreement between the reviewers regarding the appropriateness of standard care antibiotics and a strong level of agreement for algorithm recommendations. In vitro susceptibility was higher with algorithm-recommended therapy (92.1% vs 77.8%), and significantly more cases would have received appropriate therapy (88.4% vs 78.1%). Although 14.4% of cases were appropriately de-escalated, 4.8% were inappropriately de-escalated; related risk factors included polymicrobial GNB, central line source, *Acinetobacter* spp., *Enterobacter* spp., and/or OXA+ resistance determinants.

The strengths of this study include validation of a GNB treatment algorithm based on institution-specific antibiogram data, Verigene BC-GN results, and ASP input. This combination showed the potential for increase in patients receiving timely, appropriate therapy with theoretical, retrospective validation. ASPs interested in this implementation strategy must note that 100% adherence to the algorithm may cause unnecessary escalation or inappropriate de-escalation and should customize their algorithm according to their institutional data and practices.

DISCUSSION

Novel antimicrobial stewardship interventions continue to move practice and research forward for clinicians and ASP stakeholders. The scholarship highlighted in this review demonstrates a continued commitment to novel models of stewardship interventions, value assessment of mRDT implementation, and integration of stewardship into areas outside the traditional inpatient walls of an academic medical center (eg, community hospitals, LTC facilities). As the quantity of stewardship publications increases, it is important that the quality and scientific rigor of research increases as well [13]. For many inpatient institutions, antimicrobial stewardship is not a new concept; thus scholarship demonstrating sustainability is important. Clinicians and scholars should ensure that stewardship training includes skills development on research study design, methods, and data analysis. Mentoring by and collaboration with established scholars will aid new stewards in executing high-quality scholarship and promote generalizability of results. Prospective, interventional stewardship studies conducted across multiple centers outside the umbrella of a single health system would provide the quality evidence needed to establish best practices and efficient models to optimize antimicrobial therapy.

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Open Forum Infectious Diseases
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 pre-intervention 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

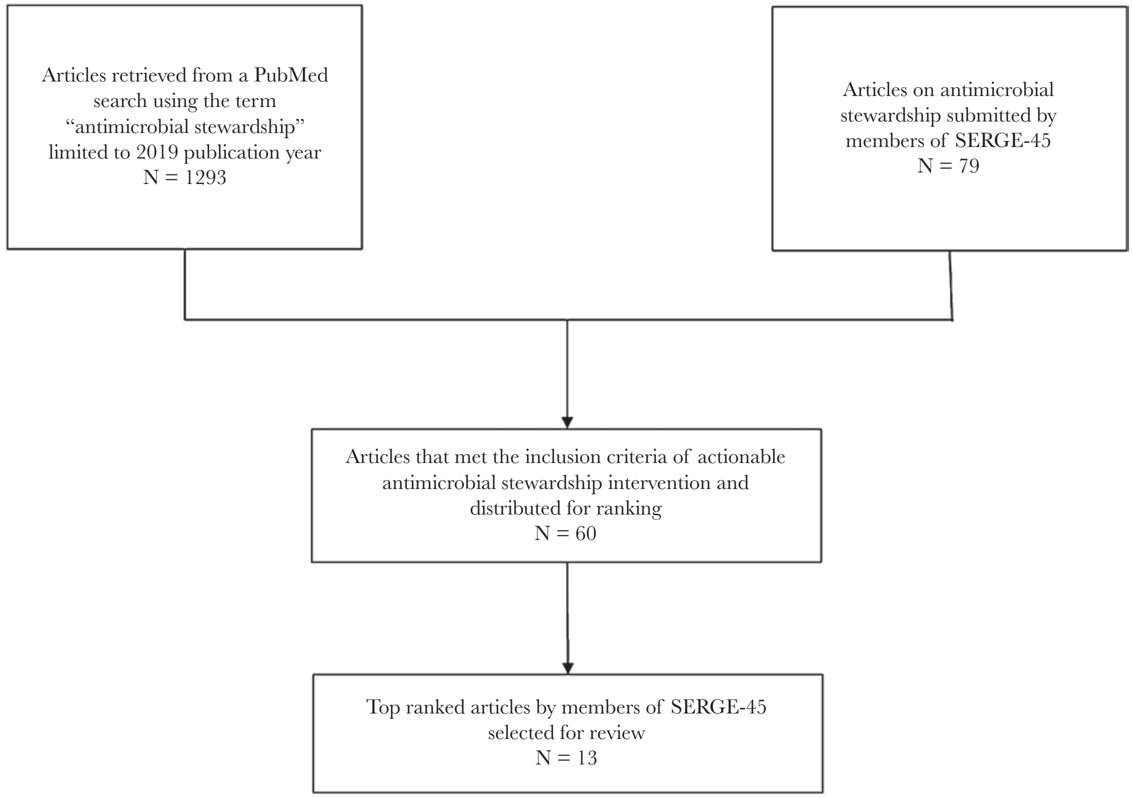

Figure 1. Flowchart of the database search and article selection process.

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.

Acknowledgments

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REVIEW ARTICLE

A Baker's Dozen of Top Antimicrobial Stewardship Intervention Publications in 2020

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The number of articles related to antimicrobial stewardship published each year has increased significantly over the last decade. Keeping up with the literature, particularly the most innovative, well-designed, or applicable to one's own practice area, can be challenging. The Southeastern Research Group Endeavor (SERGE-45) network reviewed antimicrobial stewardship–related, peer-reviewed literature from 2020 that detailed actionable interventions. The top 13 publications were summarized following identification using a modified Delphi technique. This article highlights the selected interventions and may serve as a key resource for teaching and training, and to identify novel or optimized stewardship opportunities within one's institution.

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

More than a decade since the release of national guidelines for establishing antimicrobial stewardship programs (ASPs), there continues to be an emphasis on evidence-based approaches to optimizing stewardship in the literature. The lack of strong evidence supporting antimicrobial stewardship (AS) guideline recommendations is well documented, and many stewards report not measuring the impact of common tools such as rapid diagnostics that support many ASPs [1]. From 2010 to 2020, there has been a nearly 3000% increase in PubMed-indexed papers with a mention of AS (Figure 1) [2]. Efforts to bolster research within ASPs also continues to garner attention as experts in the field and leading infectious diseases (ID) organizations have published recommendations or provided programming to enhance scholarly efforts [3–7].

A recent white paper released from a Society of Healthcare Epidemiology of America working group identified 4 key research gaps in the AS literature. The most important but resource-intensive of these is the need for advanced study designs and optimal analytical methods to answer questions regarding optimal stewardship delivery and measurement of impact [4]. Over the past year, funded studies to support ID therapeutic research and the use of advanced study designs, including randomized controlled trials, have become more common [8, 9]. Perhaps as a tangible result, leading ID journals have published several high-impact articles focused on AS interventions. The Southeastern Research Group Endeavor (SERGE-45) network is one of several supporting mentored, collaborative research in ID and AS and has methodically selected the top AS articles for the previous 4 years [10–14]. Detailed in this article are the top AS intervention publications from 2020 as determined by the SERGE-45 network [8, 9, 15–25].

METHODS

Using a modified Delphi technique (detailed previously), members of the SERGE-45 network identified AS publications from 2020 considered to be significant using the following inclusion criteria: (1) published in 2020, including electronic, "early-release" publications, and (2) included an actionable intervention [26]. An actionable intervention was defined as an AS strategy that was implemented in practice and resulted in measurable outcomes. Clinical practice guidelines, official statements, review articles, and articles without an actionable intervention were excluded.

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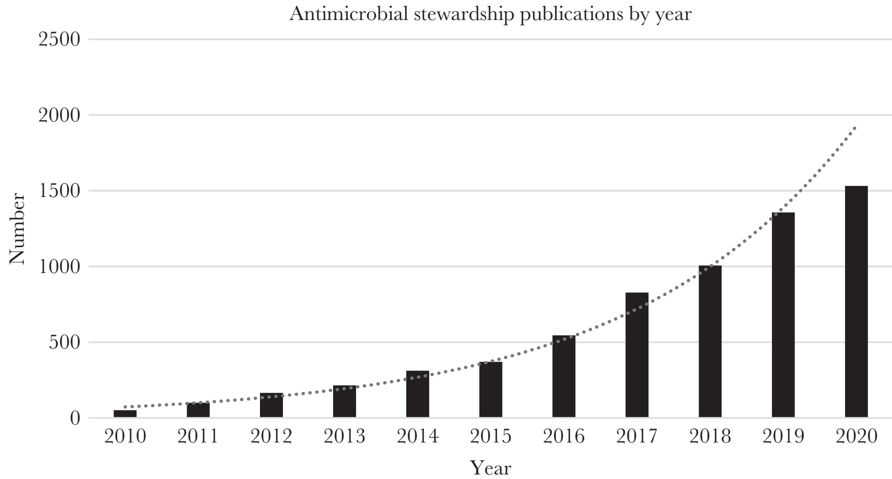

Figure 1. Number of publications indexed in PubMed by the term "antimicrobial stewardship" each year from 2010 to 2020.

A PubMed search using "antimicrobial stewardship" for 2020 revealed 1501 potential publications. Abstracts were screened to ensure that all relevant articles were considered. Seventy publications were submitted by the network for evaluation and those meeting criteria not previously identified were also included for consideration. A total of 121 article citations and abstracts were distributed to the SERGE-45 network for ranking via REDCap survey of the top 13 articles based on contribution and/or application to ASPs [27]. Follow-up email reminders were sent to encourage participation in the voting process. Of note, no conflict of interest disclosure was required of participating voters.

Of the 84 network members at the time of survey, 30 rank lists (36% participation) were submitted. Article ranks from the group were averaged and the top-scoring articles were reviewed by S. B. G., B. J. F., P. B. B., and C. M. B. via teleconference. This group discussed rankings and settled disputes on article rankings based on inclusion criteria and diversity of topics included, and a final consensus on the top 13 articles was established. Included articles are presented in the discussion in a random order and should not be considered to be ranked according to placement. Figure 2 is a flowsheet of the article selection process, and Table 1 provides a summary of the selected articles.

RESULTS

Peer Comparison–Based Stewardship Intervention in the Emergency Department

The focus of AS activities has expanded to include outpatient primary care offices and emergency departments (EDs). Traditional inpatient stewardship strategies such as prospective audit and feedback (PAF) are not always feasible in the ED's fast-paced environment. Using an adapted framework based on a successful ASP in their Veterans Affairs (VA) primary care clinics [28], Buehrle and colleagues implemented an ED ASP [15]. A prospective observational study was conducted to evaluate the impact of peer comparison on antibiotic prescribing by ED physicians at patient discharge.

An ID physician presented a 30-minute educational module on antibiotic overuse, diagnosis, and treatment of commonly seen infections in the ED. Following the presentation, ED physicians received monthly emails with de-identified bar graphs comparing their antibiotic prescribing to that of their peers. Upon initiation of the peer comparison emails, prescriptions decreased at a monthly rate of 10.4 per 1000 ED visits. The rate of antibiotics prescribed without an indication also decreased. This study illustrates the effectiveness of de-identified peer feedback in a new setting with unique challenges to traditional stewardship intervention implementation. There were no *Clostridioides difficile* infection (CDI) tests ordered during the 90 days after prescriptions were reviewed; readmissions and other adverse events were not reported. Limitations to this study include its retrospective nature and lack of control group. Development of the educational module and scheduling ED staff to attend may represent challenges to implementing this type of intervention in addition to time needed to create de-identified feedback on a monthly basis.

Multidisciplinary Penicillin Allergy Delabeling

Many hospitals have initiated programs to evaluate medication allergies given the abundance of data reflecting the benefits of accurate allergy assessments [29–31]. In particular, rates of true allergic reactions to penicillins have been shown to be far less than previously reported [32]. Chua and colleagues conducted a multicenter, prospective study to evaluate rate of penicillin allergy delabeling following review by trained nursing, pharmacy, or medical staff using a validated assessment tool [16]. Based on risk stratification, patients were directly delabeled, offered oral penicillin challenge, or referred for outpatient allergy assessment.

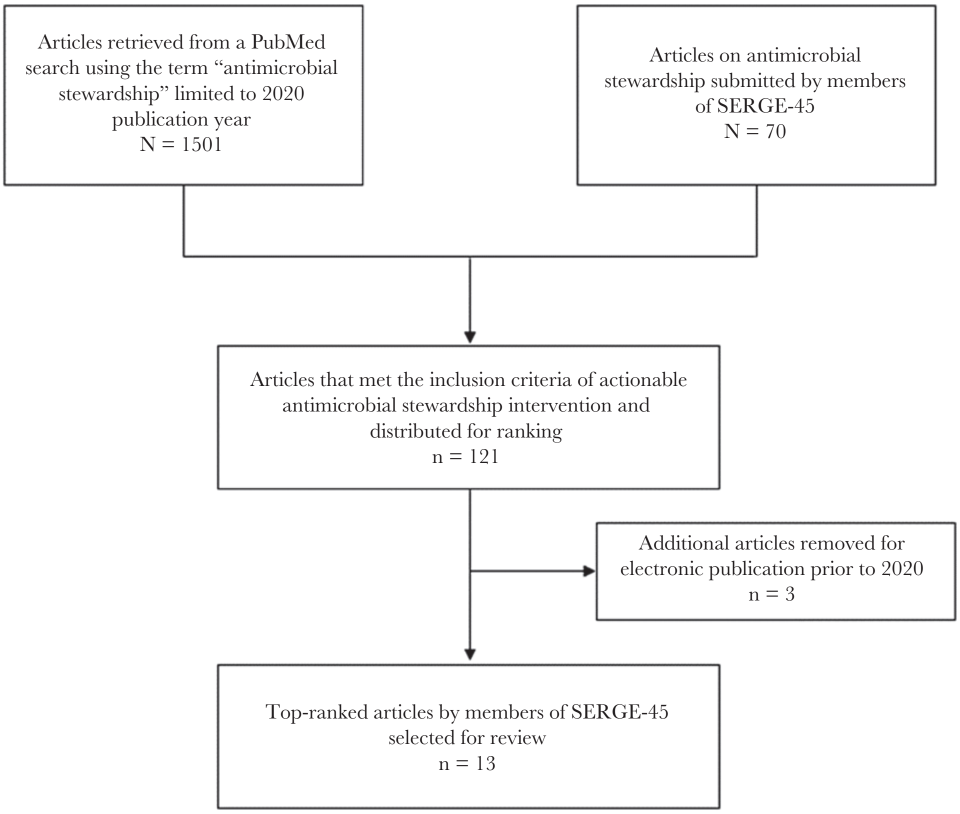

Figure 2. Flowchart of the database search and article selection process. Abbreviation: SERGE-45, Southeastern Research Group Endeavor.

A total of 1225 patients with 1264 reported penicillin allergies were included in the analysis. Of these, 558 (45.6%) patients were determined to be low risk. Approximately 30% of patients were delabeled (355/1225) following the allergy assessment, the majority in the low-risk group. Estimated costs of delabeling for the 355 patients were $6825 in the inpatient setting compared to $60 447 for the same group if referred for outpatient assessment: $21 125 for direct delabeling and $39 322 for oral challenge. Limitations included lack of diversity of patient acuity and inability to generalize across healthcare centers. This study demonstrated efficacy and potential cost savings of a multidisciplinary, inpatient penicillin allergy delabeling protocol without negative impact on readmission, length of stay (LOS), or mortality.

Clinical Impact of Rapid Identification and Susceptibility Testing for Gram-Negative Bacteremia

Gram-negative bloodstream infections (BSIs) represent a serious infection process associated with high mortality rates [33]. With increasing antimicrobial resistance rates, the need for prompt, appropriate therapy is imperative [34]. Banerjee and colleagues conducted a prospective, multicenter, randomized controlled trial assessing the clinical impact of the Accelerate Pheno system compared to standard of care (SOC) for patients with gram-negative bacteremia (GNB) [9]. Both groups received PAF from the ASP, using scenario-based standardized recommendations.

In total, 497 patients were included with *Escherichia coli*, the most frequently identified organism in blood cultures. The primary outcome, time to first antibiotic change from randomization, was faster in the intervention group compared to the SOC group with a median difference of 6.3 hours ($P = .02$). Similarly, time to gram-negative antibiotic change was faster by nearly 25 hours ($P < .001$). Third-generation cephalosporin– and carbapenem-resistant Enterobacterales occurred in roughly 20% and 3% of cases, respectively. Antibiotic escalations occurred 43.3 hours faster in the intervention group compared to the SOC group ($P = .01$). Thirty-day mortality occurred in 25 (11%) patients in the intervention group and 18 (8%) patients in the SOC group ($P = .27$). Of note, 10% of the organisms identified were not on the Accelerate Pheno panel, thus representing a limitation for infections caused by rare organisms. This study provides prospective data in gram-negative BSI supporting rapid diagnostics in conjunction with ASP intervention for faster time to appropriate therapy.

Ambulatory Care Pharmacist-Led Interventions Effect on Antimicrobial Prescribing

Approximately 30%–50% of outpatient antibiotic prescriptions are either unnecessary or inappropriate [35]. Education alone may be an insufficient AS strategy in this setting [36]. Westerhof and colleagues evaluated the impact of a multifaceted, outpatient ASP led by 2 ambulatory care pharmacists (AMCPs) on prescribing practices for upper respiratory infections (URIs), urinary tract infections (UTIs), and skin and soft tissue infections at a family medicine resident clinic [17]. The

Table 1. Summary of Top 13 Antimicrobial Stewardship Intervention Publications, 2020

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Buehrle et al, 2021 [15]	Prospective, observational cohort study to evaluate antibiotic prescribing by ED physicians for discharged patients and the impact of a peer-comparison stewardship intervention	Following an educational module given by an ID physician, ED physicians were emailed antibiotic de-identified prescribing information comparing their antibiotic prescribing to that of their peers	Primary outcomes: - Rate of antibiotic prescriptions for patients discharged from the ED - Overall monthly decrease of 10.4 prescriptions per 1000 ED visits (95% CI, –21.7 to 1.0; $P = .07$) - Relative decrease of 9.9 prescriptions per 1000 ED visits from established baseline through intervention period (95% CI, –20.9 to –1.0; $P = .07$). - Random review found rate of unnecessary antibiotic prescriptions to be 55.6% preintervention and 38.7% postintervention
Chua et al, 2020 [16]	Prospective, multicenter study evaluating impact of a detailed allergy assessment on penicillin allergy delabeling	Detailed allergy assessment by trained nursing, pharmacy, or medical staff in patients prospectively identified from 21 Jan 2019 through 31 Aug 2019. Assessments included evaluation and risk stratification using the validated antibiotic allergy assessment tool. Based on risk stratification, patients were directly delabeled, offered direct oral penicillin challenge, or referred for outpatient allergy assessment	Primary outcome: - 355/1225 (29%) had penicillin allergy delabeling - 161/355 patients (45%) had direct delabeling (150 low-risk allergy, 11 high-risk) - 194/355 patients (55%) had delabeling following oral penicillin challenge - 344/558 (62%) of low-risk allergies were delabeled Secondary outcomes: - Increased use of penicillins, reduced cephalosporins, and reduced restricted antibiotics (lincosamides, fluoroquinolones, vancomycin, carbapenems, 3rd- or 4th-generation cephalosporins) in delabeled patients posttesting - No difference in readmission rates, LOS, or mortality between delabeled and non-delabeled groups
Banerjee et al, 2020 [9]	Prospective, multicenter study evaluating clinical impact of rapid identification for GNB	GNB patients randomized Oct 2017–Oct 2018 to 2 groups: SOC culture and antimicrobial susceptibility testing vs rapid organism identification and phenotypic susceptibility testing with Accelerate Pheno system	Primary outcome: - Median time (hours) to first antibiotic change after randomization was decreased by 6.3 hours in Rapid vs SOC groups (8.6, IQR 2.6–27.6 vs 14.9, IQR 3.3–41.1; $P = .02$) Secondary outcomes: - Median time (hours) to first gram-negative antibiotic change was decreased by 24.8 hours in Rapid vs SOC groups (17.3, IQR 4.9–72 vs 42.1, IQR 10.1–72; $P < .001$). - No difference in 30-d mortality, LOS, readmission, ICU LOS, HO-CDI, or acquisition of MDRO
Westerhof et al, 2020 [17]	Retrospective, quasi-experimental study in a single family medicine resident clinic including adult and pediatric patients	3-pronged intervention: 1. Resident educational sessions 2. Local health system treatment guideline pocket cards 3. Biweekly AMCP audit and feedback	Primary outcome: - Total guideline-concordant antibiotic prescribing at baseline was 38.9% (URI, 53.3%; SSTI, 16.7%; UTI, 46.7%) and improved across all 3 infection types to 57.9% (URI, 61.2%; SSTI, 57.6%; UTI, 53.5%; $P = .001$). Secondary outcomes: - Significant improvements were seen in guideline-concordant antibiotic selection (68.9% vs 80.2%; $P = .018$), dose (76.7% vs 86.2%; $P = .023$), and duration of therapy (73.3% vs 86.2%; $P = .02$).
Watson et al, 2020 [18]	Multicenter, quasi-experimental, before-and-after intervention study of an electronic order set for urine studies	An electronic order set required providers to choose an indication for urine studies. CDS directed providers to order the appropriate urine study according to the indication.	Primary outcomes: - Number of UCs performed per 10 000 PD decreased by 40.4% (1175.8 vs 701.4; $P < .01$) - Antibiotic DOT/1000 PD for UTIs decreased by 15.2% (102.5 vs 86.9; $P < .01$) - CAUTI SIR decreased from 1.0 to 0.8 ($P = .21$) - Cost per 1000 PD decreased by US$2112 ($P < .01$), representing an annual total estimated cost savings of US$535 181
Nace et al, 2020 [19]	Multifaceted quality improvement intervention evaluation	1-hour introductory webinar, pocket-sized educational cards, tools for system change, and educational clinical vignettes addressing the diagnosis and treatment of suspected uncomplicated cystitis. Monthly web-based coaching calls were held for staff of intervention nursing homes. All facilities received quarterly feedback reports regarding the management of uncomplicated cystitis.	Primary outcome: - Lower incidence of AU for unlikely cystitis (AIRR, 0.73 [95% CI, .59–.91]; $P = .004$) Secondary outcomes: - Lower overall AU for any UTI (AIRR, 0.83 [95% CI, .70–.99]; $P = .04$) - Reduced adjusted rate of CDI (AIRR, 0.35 [95% CI, .19–.64]; $P < .001$) - No difference in incidence of UCs performed, all-cause hospitalization, or death

Table 1. Continued

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Coussement et al, 2021 [20]	Multicenter, randomized, open-label superiority trial in kidney transplant recipients who had ASB and were ≥2 months posttransplantation	Antibiotics or no therapy for kidney transplant recipients ≥2 months posttransplantation with ASB	Primary outcome: - No difference in the incidence of symptomatic UTI: 27% vs 31%; HR 0.83 (95% CI, .50–1.40) Secondary outcomes: - Death: 4% vs 3%; P = NS - Graft loss: 2% vs 3%; P = NS - Biopsy-proven graft rejection: 3% vs 2%; P = NS - Pyelonephritis: 17% vs 16%; P = NS - Number of participants in whom second episode of bacteriuria was caused by a more resistant bacteria than was their baseline episode of ASB: 18% vs 4%; P = .003
Elligsen et al, 2020 [8]	Quasi-experimental study evaluating impact of individualized predictive models on antibiotic prescribing in patients with monomicrobial GNB	Application of a retrospectively derived and validated logistic regression model was used to predict probability of susceptibility and guide subsequent, pharmacist-initiated antimicrobial recommendations for a predefined cascade of antimicrobials, from narrow to broad: ceftriaxone, ciprofloxacin, ceftazidime, piperacillin-tazobactam, and meropenem/ertapenem	Primary outcomes: - Antibiotic de-escalation: Intervention group was more likely to have their therapy de-escalated: 29% vs 21%; aOR, 1.77 (95% CI, 1.09–2.88) - Adequacy of therapy: No difference in the proportion of patients who were on adequate therapy at time of culture finalization: 96% vs 97% (P = .774) Secondary outcomes: - Proportion of patients on narrowest adequate therapy at time of culture finalization: 55% vs 44%; aOR, 2.04 (95% CI, 1.27–3.27) - Time to adequate therapy: 5 h vs 4 h (P = .95) - Mortality: 13% vs 13% (P = .99) - LOS: 9.7 vs 8.4 days (P = .50) - CDI: 4% vs 3% (P = .86) - Overall recommendation acceptance rate: 78%
Moghnieh et al, 2020 [21]	Single-center, retrospective interrupted time series analysis assessing formulary restriction vs handshake stewardship on antibiotic consumption, expenditures, nosocomial bacteremia, and patient outcomes	A "handshake"-based antimicrobial stewardship program using PAF plus education and local guideline dissemination was compared to a program consisting of an antimicrobial restriction policy for select agents only	No primary endpoint was identified. - Broad-spectrum antibiotic consumption: mean use density of imipenem and meropenem decreased by 13.7% (P = .017) with decreased rate of prescriptions (–24.83 defined daily dose per 1000 PD per month; P = .02) - Antibiotic expenditures: 24.6% cost reduction (P = .0001) - Incidence of nosocomial bacteremia caused by carbapenem-resistant GNB: 34.8% decrease (P = .13) - Patient outcomes: no change was detected for all-cause mortality, LOS, or 7-day readmissions
Claeys et al, 2021 [22]	Retrospective, quasi-experimental, nonrandomized, intervention study comparing rates of urine cultures before and after policy intervention for conditional urine reflex orders	Conditional urine reflex policies were implemented to allow for testing based only on specific criteria met on UA in adults admitted to acute-care beds. Three sites served as intervention sites and 3 as control. Two sites allowed culturing when WBC >10 cells/HPF (restrictive criteria) and 1 site allowed culturing when urine was positive for leukocyte esterase, nitrites, or had WBC >10 cells/HPF (permissive criteria)	Primary outcome: - Rate of UCs performed per 1000 PDs: 21% decrease in culture at intervention site relative to control sites ($P \leq .01$) - Control - Preintervention: 40.3 cultures/1000 PDs vs postintervention: 44.2 cultures/1000 PDs (P = .67) - Preintervention: 35.8 cultures/1000 PDs vs postintervention: 33.7 cultures/1000 PDs (P = .29) Secondary outcome - Rate of GNB per 1000 PDs postintervention: 0.8 cases/1000 PDs at intervention site vs 0.6 cases/1000 PDs at control site (P = .13)
Ridgway et al, 2020 [23]	Multicenter, randomized controlled trial with crossover design investigating the impact of WISCA on patient outcomes	Intervention consisted of ASP physician performing PAF on patients who were identified via the WISCA tool within 24 h of antibiotic start via page or phone call to primary provider and via written documentation in the EMR vs control of ASP physician–recorded antibiotic recommendations in the study base unless regimen caused concern for harm	Primary outcome: - Mean hospital LOS (4.54 d vs 4.50 d; P = .6899) Secondary outcomes: - 30-d readmission (344 vs 374; P = .8180) - 30-d mortality (178 vs 194; P = .8730) - Antibiotic charges ($546.75 vs $548.72; P = .8931) - CDI within 180 d (151 vs 165; P = .8717) - New-onset MDRO within 180 d (55 vs 52; P = .5950)

Table 1. Continued

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Howard-Anderson et al, 2020 [24]	Quasi-experimental analysis of HO-CDI testing 2 y before and after implementation of an EMR intervention leading to default CDI test cancellation	EMR intervention was an alert that prompted prescribers to consider CDI test cancellation as the default when patients were admitted >3 d and had documented laxative or stool softener administration within the prior 24 h	Primary outcome: - Median (IQR) monthly rates of total monthly HO-CDI orders per 1000 PD: 10.9 (10.5–11.6) vs 7.0 (6.4–7.6); $P < .001$ - Rate ratio for level change in total HO-CDI testing, 0.79 (95% CI, .73–.86) - Median (IQR) monthly rates of inappropriate monthly HO-CDI orders per 1000 PD: 0.8 (0.8–1.0) vs 0.4 (0.3–0.6); $P < .001$ - Rate ratio for level change in rate of inappropriate HO-CDI testing, 0.8 (.61–1.05) - Proportion of inappropriate tests decreased 8% to 6% ($P < .001$) Secondary outcome: - Change in rate of HO-CDI LabID events per 1000 PD before and after: rate ratio level change, 0.74 (95% CI, .60–.91). Note: rate decreased only in 1 of 4 hospitals
Sapozhnikov et al, 2021 [25]	Single-center, retrospective descriptive study at a health system including a 604-bed academic medical center and 2 community hospitals	The ASP team reviewed requests for additional AST with the multidisciplinary team during microbiology rounds. The ASP approach to AST requests focused on decreased treatment of culture contaminants, recommendations for narrow-spectrum, less toxic, and less costly treatment alternatives if appropriate. If approved by the AST team, the requested tests were released for viewing or performed if not already completed.	Primary outcome: - Of the susceptibility request (n = 67), 59.7% were from physicians and 34.3% were from ID providers. Of the requests from ID providers 65.2% ($P = .039$) were approved. - ASP pharmacist completed chart reviews for 92.5% of patients and contacted the requester or primary team 74.6% of the time - Interventions included approval of susceptibility in 47.8% of requests, education of providers in 43.4%, ASP referral in 7%, and ID consult referral in 1% - Potential benefits were prevention of unnecessary susceptibility testing (47.8%), opportunities for providing physician education (40.3%), discouraged treatment of contaminant (19.4%), optimized susceptibility request (16.4%), avoided need for parenteral therapy (10.4%), and additional workup performed (7.5%).

Abbreviations: AIRR, adjusted incidence rate ratio; AMCP, ambulatory care pharmacist; aOR, adjusted odds ratio; ASB, asymptomatic bacteriuria; ASP, antimicrobial stewardship program; AST, antimicrobial susceptibility testing; AU, antimicrobial use; CAUTI, catheter-associated urinary tract infection; CDI, *Clostridioides difficile* infection; CDS, clinical decision support; CI, confidence interval; DOT, days of therapy; ED, emergency department; EMR, electronic medical record; GNB, gram-negative bacteremia; HO-CDI, hospital-onset *Clostridioides difficile* infection; HPF, high-power field; HR, hazard ratio; ICU; intensive care unit; ID, infectious diseases; IQR, interquartile range; LOS, length of stay; MDRO, multidrug-resistant organism; NS, not significant; PAF, prospective audit and feedback; PD, patient-days; SIR, standardized infection ratio; SSTI, skin and soft tissue infection; SOC, standard of care; UA, urinalysis; UC, urine culture; URI, upper respiratory infection; UTI, urinary tract infection; WBC, white blood cell; WISCA, weighted incidence syndromic combination antibiogram.

study evaluated the effect of a 3-pronged ASP intervention on the rate of prescribing concordance with local guidelines. Based on their previous pilot study, biweekly AMCP feedback provided positive reinforcement of prudent prescribing with constructive and supportive comments highlighting better options when available [37].

Overall, 525 antibiotic prescriptions were audited. Guideline concordance at baseline was 38.9% and improved across all 3 infection types to 57.9%. Improvements were most notable in antibiotic selection, proper dose, and duration of therapy with no significant differences by indication. This novel study provides evidence that non-ID-trained AMCPs can be effective in ambulatory ASPs. The major limitation of the style of intervention is that it is not in "real time" and does not allow the AMCPs to intervene on the patient case, but rather allows the AMCP to teach and encourage change in prescribing habits for the future.

Impact of Clinical Decision Support for Urine Studies

Integration of clinical decision support (CDS) into the electronic medical record (EMR) is recommended to help ASPs meet targeted goals [36]. CDS may also be leveraged for diagnostic stewardship, which can improve the accuracy of infectious diagnoses and better inform decisions regarding antimicrobial therapy [38]. Watson and colleagues evaluated the impact of CDS embedded in an electronic order set intended to guide appropriate selection of urine studies [18]. The order set required providers to choose an indication for the urine study from 3 options: (1) suspected UTI, (2) noninfectious indications, or (3) screening purposes or neutropenic patients with urinary symptoms. Specific types of urine studies could then be ordered according to the indication. For suspected UTI, a hard stop also required the provider to document the signs or symptoms by selecting from a list of criteria established by the Infectious Diseases Society of America (IDSA) [39]. Urine cultures (UCs) could not be ordered for noninfectious indications.

Following implementation of the order set, there was a significant reduction in the number of UCs performed, antibiotic days of therapy for UTIs, and costs. A non–statistically significant reduction in the catheter-associated UTI standardized infection ratio was also observed. Implementation of CDS for urine studies requires adequate support from information technology resources and relies on accurate selection of the indication by the ordering clinician. Overall, this study highlights computerized CDS as an effective tool to improve outcomes that align with the goals of both AS and infection prevention programs.

A Multifaceted ASP for the Treatment of Uncomplicated Cystitis in Nursing Home Residents

UTIs are commonly diagnosed in nursing home residents. Age and inadequate communication in this population often lead to misdiagnosis and inappropriate antimicrobial use (AU). Nace and colleagues conducted a multifaceted quality improvement intervention to target uncomplicated and unlikely cystitis [19]. Unlikely cystitis was defined as asymptomatic bacteriuria, contaminated urinary specimens, or noninfectious conditions that can be confused with cystitis (eg, nonspecific symptoms in the absence of urinary-specific symptoms). The intervention nursing homes received an introductory webinar, pocket-sized educational cards, established guidelines, and educational clinical vignettes. They also received monthly web-based coaching calls and quarterly feedback reports for the management of uncomplicated cystitis.

At baseline, intervention facilities had higher rates of UTIs, unlikely cystitis treated with antimicrobials, and all-cause death at baseline; however, none were statistically significant. Postintervention, significant reductions were observed in AU for unlikely cystitis, overall AU for any UTI, and adjusted CDI rates with no differences in all-cause hospitalization or death. Limitations included lack of randomization by baseline antibiotic use and facility blinding, personnel staffing differences, and dedicated resources for education that may not be readily present at most institutions. However, this study provides additional support for education with feedback strategies in nursing home settings.

Treatment of Asymptomatic Bacteriuria in Kidney Transplant Recipients

Asymptomatic bacteriuria (ASB) is a common observation after kidney transplantation, occurring in roughly half of recipients [40]. Due to limited evidence in guiding management, the tendency to screen and treat ASB varies by institution and treating clinician. A recent European survey demonstrated that >70% of physicians always screen for ASB, and ASB is often treated among surveyed physicians [41].

Coussement and colleagues sought to evaluate the impact of ASB treatment on the incidence of symptomatic UTI during the 1-year transplant follow-up period [20]. There was no difference in the cumulative incidence of symptomatic UTI between the antibiotic and no-therapy groups. Additionally, withholding antibiotic therapy for ASB resulted in similar incidences of death, graft loss, biopsy-proven graft rejection, pyelonephritis, and BSI due to UTI compared to the antibiotic group. Not surprisingly, the antibiotic group (1) developed bacteriuria caused by a more resistant bacteria compared to the index bacteriuria episode at a higher rate and (2) had a lower rate of ASB at 12 months post–study inclusion, both of which were statistically significant.

Overall, a screen-and-treat strategy for ASB in kidney transplant recipients ≥1–2 months after transplantation increases AU, promotes antimicrobial resistance, and most importantly, does not seem to improve clinical outcomes. This study adds important evidence and further supports the 2019 IDSA guideline recommendation against the treatment of ASB in kidney transplant recipients >1 month posttransplantation; however, results of this study may not be generalizable to ASB in kidney transplant recipients during the immediate posttransplantation period.

Improving Decision Making in Empiric Antibiotic Selection for GNB

Selection of empiric antimicrobials requires balancing receipt of active therapy with avoidance of unnecessarily broad-spectrum agents [42, 43]. Tools to determine patient-specific risk for antimicrobial resistance or inadequate therapy may assist clinicians in decision making [44–46]. Elligsen and colleagues conducted a quasi-experimental evaluation of predictive, multivariable models to guide AU in the treatment of GNB [8]. The intervention group received pharmacist-initiated recommendations for patients with GNB when speciation was available with susceptibility results pending. Patients were identified via a local stewardship database thrice daily during working hours. The pharmacist used validated logistic regression models to recommend the lowest level of a predefined cascade of antimicrobials while maintaining a 90% probability of susceptibility for patients with quick Sequential Organ Failure Assessment score of 3 and 80% for those with scores <3 [47, 48].

Patients in the intervention group were more likely to undergo de-escalation, primarily driven by GNB caused by *E coli* and *Klebsiella* species. While time to adequate therapy was similar between groups, patients receiving the intervention were more likely to be on narrowest adequate therapy at time of culture finalization. There was no difference in mortality nor length of stay between groups. Overall suggestion acceptance was 78%. This study demonstrates that individualized predictive models for resistance can facilitate early de-escalation of antimicrobials while maintaining adequate activity in patients with GNB; however, replication of this study may be limited by resource requirements and necessity for a high level of prescriber engagement.

Effect of Handshake Stewardship Versus Formulary Restriction

"Handshake" stewardship has been described as the use of prospective antibiotic prescription audits with rounding-based feedback to prescribers, ideally in person, coupled with an absence of antimicrobial restriction [49]. It is a unique ASP strategy that accounts for the importance of human interaction and relationship building in impacting antimicrobial prescribing practices. While "handshake" stewardship appears a promising option for ASPs, there are limited publications on the topic and it can be resource-intensive. Moghnieh and colleagues analyzed AU, cost, nosocomial bacteremia, and patient outcomes in a comparison of a formulary restriction policy versus a "handshake" stewardship approach [21]. Practices during the period of restriction were based upon specialist approvals and driven by targeting broad-spectrum or expensive agents. Practice during the "handshake" period included feedback during daily rounds as well as education and dissemination of local guidelines and treatment pathways of common infectious syndromes.

The "handshake" stewardship approach was associated with significant decreases in broad-spectrum AU and nosocomial, carbapenem-resistant GNB. No change was detected for all-cause mortality, LOS, or 7-day readmission. For facilities that have the resources to support it, a "handshake" stewardship approach may have positive effects on broad-spectrum antibiotic consumption and expenditures without impacting patient outcomes.

Evaluation of a Practice-Based Research Network Diagnostic Stewardship Intervention

Indiscriminate ordering of UCs may lead to inappropriate ASB treatment [50, 51]. Diagnostic stewardship may be utilized in conjunction with AS to prevent unnecessary urine culturing and subsequent AU [52]. Claeys and colleagues evaluated the effectiveness of conditional urine reflex policies across hospitals within the VA-CDC Practice-Based Research Network [22]. Six VA sites, each with different conditional reflex policies, were included.

There were 224573 UCs performed during the study period. Trends in UC ordering did not differ between the pre- and postintervention periods for either the control group or the intervention group. Restrictive reflex criteria saw the largest reduction in UC orders (21.1 cultures/1000 patient-days vs 13.1 cultures/1000 patient-days, $P < .01$). Nine hundred cases of BSI were documented with no significant difference in the rate of gram-negative BSIs at the intervention sites. The implementation of conditional reflex policies during differing years and the variable populations between sites could have influenced the pre- and postintervention periods, leading to the lack of significance. Despite trends not differing within intervention sites, this study highlights a reduction in cultures between intervention and control without increasing the risk of bacteremia. With the incorporation of separate control sites, this study provides a unique design that emphasizes the importance of the role of research networks in conducting meaningful multicenter comparative studies.

Weighted Incidence Syndromic Combination Antibiogram Tool

Due to antimicrobial overuse and increased resistance, it is recommended that computerized decision tools be incorporated into ASP practices [53–56]. The weighted incidence syndromic combination antibiogram (WISCA) was previously developed to assess the likelihood for appropriate coverage based on individual real-time data [23, 57]. WISCA previously showed an increased likelihood of coverage [58], reduction in time to effective coverage, and identification of narrower choices than previously prescribed [59, 60]. This trial investigated WISCA impact during active ASP surveillance on LOS, mortality, readmission, adverse events, and costs. Inpatient microbiological data were collected over a 3-year period. The ASP physician reviewed WISCA-identified regimens that primarily included UTI and abdominal biliary infection (ABI), with 18 and 22 combinations, respectively. However, it was prespecified that all 6 clinical syndromes were part of the inclusion criteria, whereas previously only UTI and ABI were of focus. It is unclear if the subgroup syndromic analysis adjusted for multiple tests. Logistic regression models assessed regimen coverage for isolated organisms. The ASP physician contacted the primary provider within 24 hours of antibiotic start for intervention of identified patients. Control group patients had recommendations recorded in the study database only, unless a concern for harm was identified.

The enrolled 6849 patients received antibiotics for ABI (32.33%), UTI (24.88%), community-acquired pneumonia (CAP) (7.11%), and cellulitis (5.93%). Overall, WISCA was not associated with improved primary and most secondary outcomes. However, intervention for CAP diagnosis was associated with significantly decreased odds of 30-day mortality (adjusted odds ratio, 0.582 [95% confidence interval, .396–.854]; $P = .0204$), and cellulitis diagnosis was associated with significantly shorter LOS. Of note, the previous WISCA study discussed that certain infections may not be amenable with utilization of the WISCA tool due to syndromes, such as pneumonia, not allowing for a robust sample size. Thus, this finding may be a chance result achieved by increased testing. However, this study reinforces continued investigation into computerized methods to support ASP practices.

Impact of an EMR Nudge on Reduced Testing for Hospital-Onset CDI

In 2020, ASPs continued to publish results of efforts to reduce inappropriate testing for CDI. Howard-Anderson et al described an EMR intervention that prompted a warning screen for prescribers to cancel CDI tests when test orders were placed for patients admitted >3 days who had received laxatives or stool softeners in the prior 24 hours [24]. Prescribers were able to continue with the order if they selected a button to proceed.

This "nudge" approach was associated with decreases in both monthly total hospital-onset CDI (HO-CDI) testing and inappropriate testing rates. In segmented regression analysis designed to control for unmeasured variables, the rate ratio for monthly total HO-CDI orders per 1000 patient-days reflected a 21% decrease in testing for HO-CDI. The proportion of inappropriate HO-CDI tests, defined as tests ordered when a laxative or stool softener was administered within the previous 24 hours, also decreased significantly. The rate of inappropriate testing continued to decrease each month during the postintervention period, but implementation was not associated with an immediate level change. ASPs may consider this strategy to address testing in the HO-CDI population when other explanations for diarrhea exist.

Impact of an ASP Pharmacist During Microbiology Rounds

Successful ASPs typically use a multipronged approach to achieve its goals. One approach that has been previously described is the impact of adding an ASP pharmacist to microbiology plate rounds in the inpatient setting [60]. The impact of this effort in both the inpatient and outpatient settings has not been studied. Sapozhnikov and colleagues evaluated the impact of participation of an ASP pharmacist in review of antimicrobial susceptibility testing request from both inpatient and ambulatory adults at a large academic health system [25]. The institution utilized selective and cascade reporting to guide antimicrobial prescribing. The enhanced ASP team had various responsibilities, including participation in telephonic rounds with the microbiology laboratory, to provide further interpretation of microbiologic results.

Over a 6-month period, the team reviewed 67 susceptibility requests. The ASP pharmacist completed chart reviews for 92.5% of patients and contacted the requester or primary team 74.6% of the time. The interventions included approval of susceptibility in 47.8% of requests. While education of providers occurred in 43.4%, ASP referral occurred in 7% and ID consult referral in 1% of the requests. Benefits of ASP pharmacist involvement included prevention of unnecessary susceptibility testing, opportunity for education, decreased treatment of contaminants, optimized susceptibility request, evaluation of potential oral options, and additional workup recommendations. This was a single-center retrospective observational study at a large academic health system, with a robust ASP team, that shows the positive impact of an ASP pharmacist on microbiology rounds. However, a limitation of this study is the difficulty in duplicating at an underresourced institution with a limited ASP team.

DISCUSSION

ASPs continue to mature within traditional inpatient settings and expand into a number of outpatient settings, both for general and specialized populations. Stewardship responsibilities are often layered upon various existing responsibilities, making identification of best stewardship interventions paramount to maximize benefit with limited resources. Two important themes were identified within the 13 articles chosen for 2020: First, a number of articles demonstrated the importance of microbiology personnel within AS practices. Microbiology input historically has been minimal or absent within day-to-day stewardship activities at many sites despite clear recommendations from national stewardship guidelines [61]. From coordination of blood culture notification and management to unique opportunities within microbiology rounds, full integration of microbiology in ASP practice and patient care is important to ensure beneficial outcomes [9, 25].

Second, many successful ASP interventions incorporate diagnostic stewardship. This year's baker's dozen included diagnostic interventions using electronic decision support to decrease ordering of UCs and CDI testing, and rapid diagnostic technology for treating the sickest patient populations [9, 18, 24]. ASPs can examine all steps in the diagnostic process for opportunities to improve patients' management.

The trend toward higher-quality data supporting specific ASP interventions is encouraging. ASPs can use these data to evaluate and refine daily activities. As programs expand in scope and into new settings, literature documenting actionable and reproducible interventions will help advise future metrics and agendas.

Notes

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REVIEW ARTICLE

A Baker's Dozen of Top Antimicrobial Stewardship Intervention Publications for Hospitalized Patients in 2021

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Keeping abreast of the antimicrobial stewardship–related articles published each year is challenging. The Southeastern Research Group Endeavor (SERGE-45) identified antimicrobial stewardship–related, peer-reviewed literature that detailed an "actionable" intervention among hospitalized populations during 2021. The top 13 publications were selected using a modified Delphi technique. These manuscripts were reviewed to highlight "actionable" interventions used by antimicrobial stewardship programs in hospitalized populations to capture potentially effective strategies for local implementation.

Keywords. antibiotics; infection metrics; resistance; stewardship.

The coronavirus disease 2019 (COVID-19) pandemic has brought challenges and opportunities for antimicrobial stewardship programs (ASPs) across the globe [1]. In many instances, antimicrobial stewardship (AS) duties and resources were reallocated to COVID-19 patient care responsibilities. Telehealth initiatives led to care provided across a larger area with limited direct, in-person contact. While these initiatives brought new access points for rural or off-site providers and allowed a closer look at the contributions an ASP can make to pandemic response [2], traditional ASP activities took a backseat. As a result, most hospitalized patients with COVID-19 received broad-spectrum antibiotics despite the low likelihood of bacterial coinfection [3–5], and ASP follow-up was limited due to pandemic response. A recent report from the Centers for Disease Control and Prevention confirmed the concern of increasing drug-resistant bacteria during 2019 and 2020, many of which are encountered in hospitalized patients [5].

Despite these challenges, scholarship in the AS arena continued to grow. New journals emerging with a focus on antimicrobial resistance and stewardship created attractive options for original research [6, 7]. Continued interest in AS topics among top tier peer-reviewed journals has also maintained AS at the forefront of audiences' minds. For the fifth consecutive year, the Southeastern Research Group Endeavor (SERGE-45) network, an interprofessional, infectious diseases (ID) network of clinicians and scholars, has provided an annual critical review of the published literature on AS interventions [8–11]. The goal remains to highlight novel and valuable AS interventions across the spectrum of ID and associated therapeutic areas for the purpose of educating clinicians, guiding further research, and encouraging local discussion for implementation. In all past publications of the Baker's Dozen of Stewardship Interventions, the focus encompassed inpatient and outpatient settings. Because of the continued development of outpatient-focused AS interventions and the growing evidence for expanded inpatient services, the SERGE-45 network has decided to separate this endeavor into hospitalized and non-hospitalized focused reviews. This paper will focus on AS intervention publications for hospitalized patients.

METHODS

Using a previously detailed modified Delphi technique, members of the SERGE-45 network identified AS publications from 2021 considered to be significant using the following inclusion criteria: (1) published in 2021, including electronic, "early-release" publications, and (2) included an actionable intervention [8–11]. Due to the continually increasing numbers of eligible publications, a new criterion was adopted for 2021: (3) intervention was conducted among hospitalized patients.

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While many patients enter the hospital setting through the emergency department (ED), AS interventions conducted in the ED setting were placed in the nonhospitalized group of publications in recognition of their broader population base. An actionable intervention was defined as an AS strategy that was implemented in practice and resulted in measurable outcomes. Publications that met criteria 1 and 2 but were conducted in nonhospitalized populations were considered for the top AS publications for nonhospitalized patients in 2021 [11, 12]. Clinical practice guidelines, official statements, review articles, and articles without an actionable intervention were excluded.

A PubMed search using "antimicrobial stewardship" for 2021 revealed 1740 potential publications. Abstracts were screened to ensure that all relevant articles were considered, electronic publications before 2021 were removed, and publications were appropriately stratified between hospitalized and nonhospitalized populations. Fifty-three publications pertaining to hospitalized patients were submitted by the network, and those meeting criteria and not identified previously were also included for consideration. A total of 186 articles were distributed to the entire SERGE-45 network for ranking via electronic survey of the top 13 articles based on contribution and/or application to ASPs. Of the 84 network members at the time of the survey, 27 rank lists (32% participation) were submitted. The group ranks were reviewed by A.H.M, S.B.G., P.B.B., and C.M.B. via teleconference, and a final consensus on the top 13 articles is described herein. Figure 1 is a flowsheet of the manuscript selection process, and Table 1 provides a summary of the selected manuscripts. Manuscripts are presented below grouped by theme.

Patient Consent

The design of this study does not include factors necessitating patient consent.

RESULTS

Antibiotic Side Chain–Based Cross-Reactivity Chart Combined With Enhanced Allergy Assessment Can Increase Use of Beta-Lactams in Patients With Pneumonia

Patients with beta-lactam (BL) allergies are often treated with non-BL alternative therapies that may be associated with adverse events and clinical failure [13]. However, the risk of cross-reactivity among BLs has historically been overestimated, and rates of cross-reactivity are lower among BLs with dissimilar R-group side chains [14, 15]. Collins and colleagues sought to compare the incidence of BL use among adult patients with documented pneumonia and BL allergy pre- and postimplementation of a side chain cross-reactivity chart in 2014 created by a multidisciplinary team [16]. The chart provided information based on type and severity of allergy and likelihood of cross-reactivity based on side chains. A total of 964 patients were included, with 341 in the historical cohort (2013–2014) and 623 patients in the intervention cohort (2017–2018). The primary outcome, incidence of BL use, significantly increased in the intervention cohort (70.4% vs 89.3%; $P < .001$). The use of alternative antibiotics decreased, with a predicted avoidance of 568 fluoroquinolone (FQ) days of therapy (DOT). There was no difference in incidence of allergic reactions, 30-day readmission, inpatient costs, or antibiotic DOT (Table 1). A reduction in health care facility–onset *Clostridioides difficile* infection (CDI) was shown in the propensity score–adjusted analysis. Higher in-hospital mortality was seen in the intervention cohort, though no deaths were attributed to allergic reaction, and there was no difference in mortality when comparing patients who received BL vs alternative therapies. Limitations include the fact that antibiotic use may not have exclusively been for the treatment of pneumonia and an unknown proportion of patients with community- vs hospital-acquired pneumonia. Simultaneous AS initiatives during the time frame of the study, such as a pneumonia care bundle and initiatives to improve prescribing for pneumonia and urinary tract infections, could have confounded results. Nonetheless, this study describes a real-world intervention to increase BL use without an associated increase in allergic reactions.

Removing Cephalosporin Prescribing Warning in Penicillin Allergy Patients

Electronic health record (EHR) systems include basic clinical decision support, such as allergy checking; however, this functionality can inappropriately discourage the use of cephalosporins in patients with a documented penicillin (PCN) allergy. Prescribers often use second-line, non-BL agents in these patients, leading to worse clinical outcomes, decreased safety, and increased antimicrobial resistance [17–21]. Macy et al. [22] conducted a retrospective cohort of a natural experiment at 2 sites using a difference-in-differences design to assess the impact of removing an EHR warning to avoid prescribing cephalosporins to patients with a PCN allergy and without. A total of 4 206 480 patients were included, with 2 252 525 at the intervention site (warning removed) and 1 953 955 at the control site (warning kept). At the start of the study period, 9.4% of patients had a PCN allergy. The primary outcome of change in the probability of cephalosporin use among patients with a PCN allergy increased by 47% at the intervention site (Table 1). There was no significant difference in the rates of anaphylaxis between patients with PCN allergies at each site who used a cephalosporin. Additionally, patients with a PCN allergy at the intervention site who used a cephalosporin had a similar rate of newly documented cephalosporin allergies both pre– and post–warning removal (1% vs 0.9%), indicating no adverse harm from warning removal. The ratio of ratios of rate ratios was not significantly different for all-cause mortality (1.03; 95% CI, 0.94–1.13), hospital days (1.04; 95% CI, 0.99–1.10), or new infections (CDI: 1.02; 95% CI, 0.84–1.22; methicillin-resistant *Staphylococcus aureus* [MRSA]: 0.87; 95% CI, 0.75–1.00;

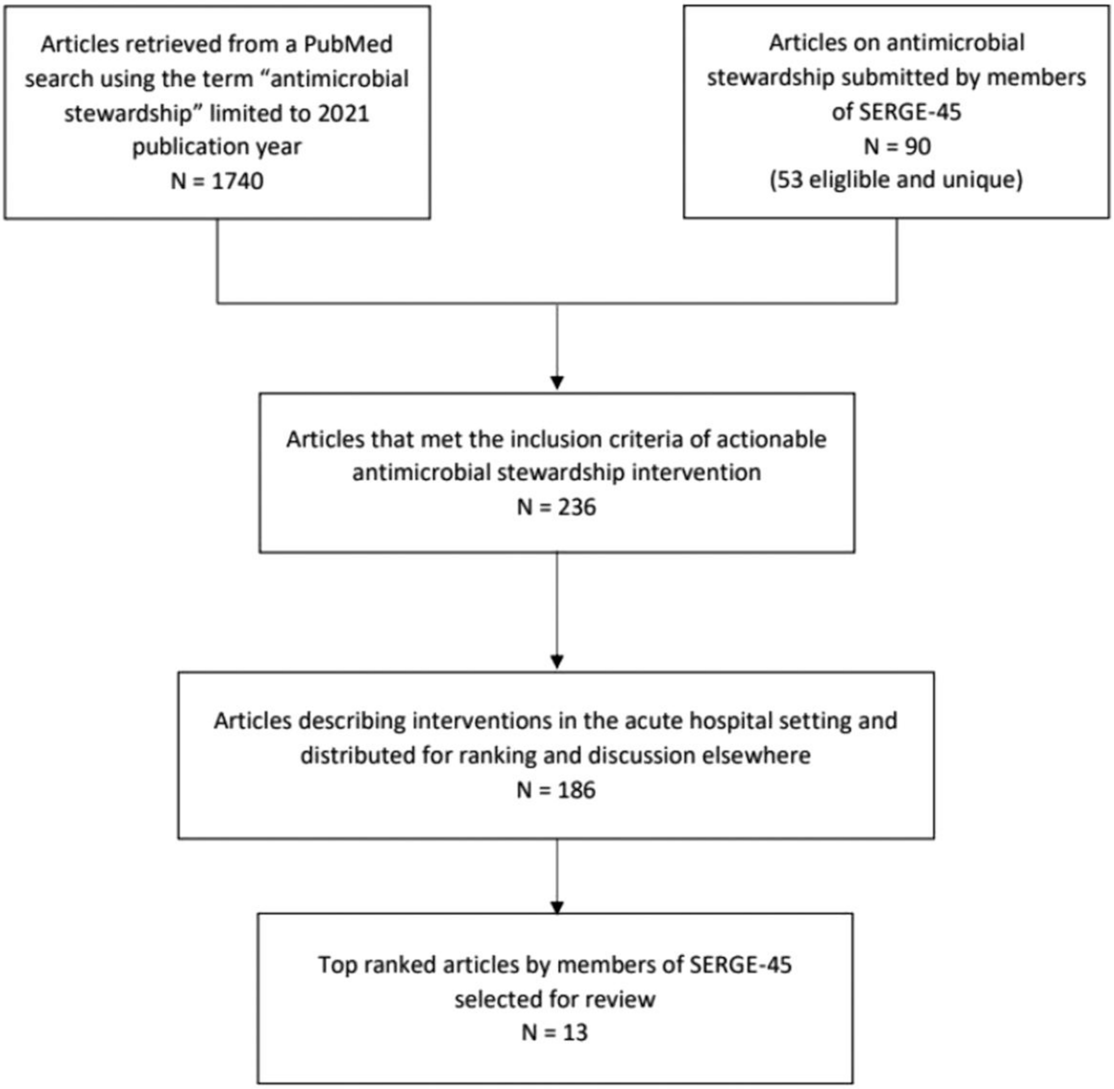

Figure 1. Flow diagram of the article selection process for the top 13 antimicrobial stewardship intervention papers for hospitalized patients, 2021.

vancomycin-resistant *Enterococcus* [VRE]: 0.82; 95% CI, 0.55–1.22). Limitations include inherent confounding and possible biases due to unmeasured patient characteristics, as well as the inability to rule out the lack of association between removing the warning and patient outcomes demonstrated by the wide confidence intervals. The study suggests that removal of the associated warning against prescribing cephalosporins in patients with a PCN allergy increases prescribing of cephalosporins without increasing harm.

Changing Urine Culture Practices to Decrease Treatment of Asymptomatic Bacteriuria

Asymptomatic bacteriuria (ASB) is a common finding in a variety of populations. Despite recommendations against treatment, up to 65% of patients with ASB receive antibiotic therapy [23]. Given the frequency with which antibiotics are prescribed for ASB and its designation as an "antibiotic-never event," ASPs have investigated which interventions might reduce this harmful practice [24, 25]. Rico and colleagues evaluated the impact of an AS bundle to reduce unnecessary antibiotics in patients with ASB [26]. Before the intervention, the institution utilized a urinalysis (UA) reflex-to-culture protocol in which the urine would reflex to a culture if the UA was found to have leukocyte esterase (positive), nitrites (positive), or white blood cells (11–25 white blood cells/high-power field). The diagnostic intervention included a transition from the UA reflex-to-culture protocol to UA collection and result without automatic reflex-to-culture. However, a urine culture could be added within 48 hours by the provider for suspected or confirmed urinary tract infection with a separate order. The diagnostic intervention was coupled with pharmacist education to providers on the new process and appropriate management

Table 1. Summary of Top 13 Antimicrobial Stewardship Intervention Papers for Hospitalized Patients, 2021

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Antibiotic Use in Patients With β-Lactam Allergies and Pneumonia: Impact of an Antibiotic Side Chain-Based Cross-Reactivity Chart Combined With Enhanced Allergy Assessment. Collins et al. Open Forum Infect Dis 2022; 9: XXX–XX.	Retrospective, single-center cohort study at a 548-bed community teaching hospital assessing the impact of implementing a β-lactam cross-reactivity chart in patients with pneumonia.	An antibiotic side chain–based cross-reactivity chart was developed in 2014 to provide guidance on antibiotic prescribing. In addition to the cross-reactivity chart, enhanced allergy assessment included: -pharmacist assessment of previous BL tolerance; -pharmacist evaluation of cross-reactivity chart compliance; -pharmacist communication with providers as necessary; -allergy/immunology consultation upon request.	Primary: -Incidence of BL use per patient encounter: 70.4% vs 89.3%; $P < .001$ Secondary: -Incidence of allergic reactions: 2.4% vs 1.6%; $P = .738$ -30-d readmission: 14.7% vs 16.4%; $P = .806$ -In-hospital mortality: 0% vs 6.4%; $P < .001$ -30-d mortality: 2.3% vs 14.3%; $P < .001$ -HO-CDI: 1.2% vs 0.2%; $P = .032$ -Inpatient costs: $7921 ($4611–$14 600) vs $7454 ($4624–$13 431); $P = .303$ -Antibiotic DOT: 8 (5–13) vs 8 (5–12); $P = .9$
Association Between Removal of a Warning Against Cephalosporin Use in Patients with Penicillin Allergy and Antibiotic Prescribing. Macy et al. JAMA Network Open 2021; 4:e218367.	Retrospective, multicenter cohort utilizing a difference-in-differences design to evaluate the changes in prescribing patterns and adverse effects after removal of an EHR alert that warns against prescribing cephalosporins to patients with a penicillin at 1 of 2 regions of a large, integrated health system.	Removal of allergy warning at 1 site. At each of the 2 sites, patients allergic to penicillin were compared with patients without a penicillin allergy regarding antibiotic prescribing patterns, incidence of antibiotic allergy, incidence of cephalosporin-associated anaphylaxis, and rate of penicillin allergy–associated morbidities in patients with a penicillin allergy.	Primary: -Change in the probability of cephalosporin use among patients with a penicillin allergy at the intervention site after the removal of the warning (RROR, 1.47; 95% CI, 1.38–1.56) Secondary: -Treatment-course level -Anaphylaxis (not significant) -New antibiotic allergies (OR, 1.62; 95% CI, 1.58–1.66) -Antibiotic treatment failure (OR, 1.10; 95% CI, 1.10–1.11) -Patient level -All-cause mortality (OR, 1.03; 95% CI, 1.01–1.06) -Hospital days (OR, 1.09; 95% CI, 1.08–1.11) -New CDI per person-year (OR, 1.23; 95% CI, 1.17–1.29) -New MRSA infections per person-year (OR, 1.06; 95% CI, 1.02–1.10) -New VRE infections per person-year (OR, 1.39; 95% CI, 1.26–1.53)
Asymptomatic Bacteriuria: Impact of an Antimicrobial Stewardship Bundle to Reduce Unnecessary Antibiotics in Patients Without Urinary Catheters. Rico et al. Am J Health Syst Pharm 2021; 78(Suppl 3):S83–7.	Quasi-experimental, retrospective, single-center, pre/post study evaluating the effect of an antimicrobial stewardship bundle on the management of ASB at a community teaching hospital.	Replacing UA reflex to culture with a new UA/urine culture method in which the UA was collected and not automatically reflexed based on the results. Urine sample was held for 48 h, and the provider could order a urine culture if there was suspicion or confirmed urinary tract infection. In addition, pharmacists provided education to providers on the new process and appropriate management of ASB.	Primary: -Inappropriate treatment of ASB, 88% PI vs 58% PDI vs 55% PE (PI vs PE $P = .005$; PI vs PDI $P = .0009$; PDI vs PE $P = .93$) Secondary: -Median length of antimicrobial therapy (d), 5.75 PI vs 2.18 PDI vs 4.45 PE (PI vs PE $P = .035$; PI vs PDI $P = .0001$; PDI vs PE $P = .037$) -UA, No. per 1000 d present, 370 PI vs 224 PDI ($P < .0001$) -Urine cultures, No. per 1000 d present, 131 PI vs 54 PDI ($P < .0001$) -No difference in LOS
Changing Results to Change Results: Nudging Antimicrobial Prescribing for *Clostridium difficile*. Herman et al. Open Forum Infect Dis 2021; 8:XXX–XX.	Retrospective, pre/post cohort study at a large tertiary care community hospital in Mississauga, Ontario, Canada, evaluating the effect of modification of laboratory reporting on treatment of *C. difficile*.	Pre-intervention time period (January 1, 2016–March 28, 2017): If *C. difficile* testing yielded a PCR+/toxin EIA– result, lab reported "*Clostridium difficile* cytotoxin B gene detected" and included treatment recommendations. Modification of *C. difficile* lab reporting was implemented on March 29, 2017. Postintervention phase (March 29, 2017–June 30, 2018): the same result would generate the following statement with no treatment recommendations: "*Clostridium difficile* organism present but toxin not detected by EIA. Consider *C. difficile* colonization or early infection."	Primary: -Mean total DOT for composite metronidazole, oral vancomycin, and fidaxomicin: 13.6 (PRE) vs 7.9 (POST), 95% CI, −3.9 to −7.6; $P < .0001$ Secondary: -Percentage of patients receiving no treatment: 6.5% (PRE) vs 23.6% (POST); OR, 4.5, 95% CI, 2.2–8.7; $P < .0001$ -Subsequent toxin positive disease: 9.0% (PRE) vs 6.7% (POST); $P = .40$ -Colectomy: 0% (PRE) vs 0.6% (POST); $P = .27$ -All-cause mortality: 7.5% (PRE) vs 12.1% (POST); $P = .14$; nonattributable to CDI -Hospital LOS: 19 d (PRE) vs 16 d (POST); $P = .14$

Table 1. Continued

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Narrow-Spectrum Antibiotics for Community-Acquired Pneumonia in Dutch Adults (CAP-PACT): A Cross-Sectional, Stepped-Wedge, Cluster-Randomised, Non-Inferiority, Antimicrobial Stewardship Intervention Trial. Schweitzer et al. Lancet Infect Dis 2022; 22:274–83.	Investigator-initiated, stepped-wedge, cluster-randomized, noninferiority, antimicrobial stewardship trial at 12 hospitals in Denmark (2 university, 7 teaching, and 3 nonteaching hospitals).	Implementation of antimicrobial stewardship bundle for moderately severe community-acquired pneumonia; outcomes compared during the control and intervention periods. Antimicrobial stewardship bundle: 1. education; 2. engaging local opinion leaders. Prospective audit & feedback of antimicrobial use.	Co-primary: 1. Broad-spectrum antimicrobial DOT per patient: median 6 (IQR 2–9) in the control period; 3 (IQR 0–8) in the intervention period 2. 90-d all-cause mortality 10.9% control; 10.8% intervention Key secondary: 1. Narrow-spectrum antimicrobial DOT: median 0 (IQR 0–6) control; 5 (IQR 0–8) intervention 2. Total antimicrobial DOT (d): median 8 (IQR 7–10) control; 8 (IQR 7–11) intervention 3. 30-d all-cause mortality: 154 (6.9%) control; 123 (6.7%) intervention 4. LOS (d): median 5 (IQR 3–8) control; 5 (IQR 3–8) intervention 5. 30-d readmission: 11.3% control; 11.4% intervention
Impact of a Pharmacist-Led Antimicrobial Stewardship Program on the Number of Days of Antimicrobial Therapy for Uncomplicated Gram-Negative Bacteremia in a Community Hospital. Fukuda et al. Cureus 2021; 13:e14635.	Retrospective, single-center cohort review in a community hospital with no ID specialist in Japan evaluating the impact of a pharmacist-led antimicrobial stewardship program on duration of therapy for GN BSI.	Pharmacists performed antibiotic time-out at 72 h after blood culture results in patients with GN BSI. Pharmacists discussed antimicrobial prescribing with the physician on days 3, 5, 7, and 10 in the intervention group.	Primary: -Antibiotic treatment duration (d): 8 vs 14 ($P < .01$) Secondary: -De-escalation: 32.4% (intervention) vs 12.5% (control; $P = .08$) -Clinical success: 94.1% vs 93.8% ($P = 1$) -Clinical failure: 5.9% vs 6.3% ($P = 1$) -CDI: 2.9% vs 0% ($P = 1$) -30-d mortality: 2.9% vs 3.1% ($P = 1$) -60-d mortality: 5.9% vs 6.3% ($P = 1$)
Implementation of a Rapid Phenotypic Susceptibility Platform for Gram-Negative Bloodstream Infections With Paired Antimicrobial Stewardship Intervention: Is the Juice Worth the Squeeze? Robinson et al. Clin Infect Dis 2021; 73:783–92.	Single-center pre/post study evaluating the impact of rapid phenotypic susceptibility results paired with antimicrobial stewardship intervention on the time to IPT at a tertiary care academic hospital.	The pre-intervention arm utilized VITEK MS or lyophilized Sensititre results emailed to an ID-trained member of the ASP team during business hours 5 d per week paired with ASP intervention. The postintervention arm utilized the Accelerate Pheno gram-negative platform, with results emailed to a member of the ASP team 24/7. The ASP member collaborated with the microbiology lab to determine which results should be released into clinical charts followed by ASP recommendations to providers.	Primary: -Time to IPT: pre- and postintervention (64.5 h vs 43.3 h; $P < .001$) Secondary: -DOT/1000 d present in the 8 d following culture collection for broad-spectrum GN-active agents primarily used for hospital-acquired infections: 655 vs 585; $P = .043$ -Cefepime utilization: 265 vs 206.2; $P = .008$ -Narrow-spectrum BL utilization: 69.1 vs 141.7; $P < .001$ -Ampicillin-sulbactam utilization: 15 vs 48.1; $P = .004$ -Ampicillin utilization: 7.5 vs 21.3; $P = .049$ -Percentage of patients requiring OPAT at discharge: 12% vs 5%; $P = .009$ -No difference in in-hospital or 30-d mortality, length of stay, CDI, readmission, or relapse of BSI
Standardized Treatment and Assessment Pathway Improves Mortality in Adults With Methicillin-Resistant *Staphylococcus Aureus* Bacteremia: STAPH Study. Alosaimy et al. Open Forum Infect Dis 2021; 8:XXX–XX.	Retrospective, pre/post study between 2013 and 2020 at a large health care system, evaluating the implementation of a clinical pathway algorithm for MRSA BSI.	Implementation of an MRSA BSI clinical algorithm, focusing on early beta-lactam combination therapy as initial therapy, ID consultation, and microbiological assessment.	Primary: -30-d mortality: 15.6% (PRE) vs 9.7% (POST); $P = .011$ Secondary: -90-d mortality: 19.0% (PRE) vs 12.2% (POST); $P = .007$ -60-d recurrence: 5.8% (PRE) vs 4.3% (POST); $P = .978$ -Prolonged bacteremia: 24.5% (PRE) vs 21.8% (POST); $P = .362$ -Duration of bacteremia: 4.2 d (PRE) vs 3.6 d (POST); $P < .001$ -Hospital LOS: 12 d (PRE) vs 11 d (POST); $P = .486$ -ID consults: 90.8% (PRE) vs 94.5% (POST); $P = .042$ -AKI: 9.6% (PRE) vs 7.2% (POST); $P = .282$

Table 1. Continued

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
How Fluoroquinolone Preauthorization Affects Third- and Fourth-Generation Cephalosporin Use and Resistance in a Large Academic Hospital. Idigo et al. Infect Control Hosp Epidemiol 2022; 43:848–59.	Retrospective, pre/post study between 1998 and 2016 that used interrupted time-series Poisson regression models to assess the impact of FQ restriction on monthly trends in third- and fourth-generation cephalosporin DOT per 1000 patient-days and yearly resistance in a large academic medical center.	FQ preauthorization implemented in 2005. Rates of use and nonsusceptibility among GN isolates compared during the 6 y before and 10 y after FQ restriction.	Outcome: Trends in third- and fourth-generation cephalosporin use relative to time of intervention -Rate of ceftriaxone use (PRE; RR, 0.973; 95% CI, 0.970–0.977; $P < .0001$); rate of ceftriaxone use (POST; RR, 1.002; 95% CI, 1.002–1.003; $P < .0001$) -Rate of ceftazidime use (PRE; RR, 0.994; 95% CI, 0.992–0.995; $P < .0001$); rate of ceftazidime use (POST; RR, 0.991; 95% CI, 0.990–0.992; $P < .0001$) -Rate of cefepime use (PRE; RR, 1.017; 95% CI, 1.000–1.035; $P = .051$); rate of cefepime use (POST; RR, 1.003; 95% CI, 1.001–1.004; $P = .0007$) Outcome: trends in yearly resistance relative to time of intervention -Rate of *Pseudomonas aeruginosa* nonsusceptible to ceftazidime (PRE; RR, 1.09; 95% CI, 0.997–1.192; $P = .06$); rate of *Pseudomonas aeruginosa* nonsusceptible to ceftazidime (POST; RR, 0.937; 95% CI, 0.910–0.965; $P < .0001$) -Rate of *Pseudomonas aeruginosa* nonsusceptible to cefepime (PRE; RR, 1.034; 95% CI, 0.958–1.117; $P = .392$); rate of *Pseudomonas aeruginosa* nonsusceptible to cefepime (POST; RR, 0.937; 95% CI, 0.912–0.963; $P < .0001$) -Rate of *Enterobacter cloacae* nonsusceptible to ceftazidime (PRE; RR, 1.116; 95% CI, 1.078–1.154; $P < .0001$); rate of *Enterobacter cloacae* nonsusceptible to ceftazidime (POST; RR, 0.987; 95% CI, 0.948–1.028; $P = .531$) -Rate of *Enterobacter cloacae* nonsusceptible to cefepime (PRE; RR, 1.198; 95% CI, 1.112–1.291; $P < .0001$); rate of *Enterobacter cloacae* nonsusceptible to cefepime (POST; RR, 0.99; 95% CI, 0.962–1.018; $P = .461$) -Rate of *Acinetobacter baumannii* nonsusceptible to cefepime (PRE; RR, 1.169; 95% CI, 1.081–1.263; $P < .0001$); rate of *Acinetobacter baumannii* nonsusceptible to cefepime (POST; RR, 0.972; 95% CI, 0.939–1.006; $P = .100$)
Safety and Efficacy of Antibiotic De-escalation and Discontinuation in High-Risk Hematological Patients With Febrile Neutropenia: A Single-Center Experience. Verlinden et al. Open Forum Infect Dis 2021; 9:XXX–XX.	Single-center, pre/post interventional study in a hematology ward of an academic medical center in Belgium comparing the safety and efficacy of implementing the Fourth European Conference on Infections in Leukaemia (ECIL-4) recommendations to a historical cohort.	Standard operating procedure, which was implemented via informal provider training, included ECIL-4 recommendations: -prophylaxis with fluconazole and acyclovir, but not fluoroquinolones based on previous data [71]; -increase the number of blood cultures obtained; -discontinue IV amikacin after 3 d if no MDR organisms are isolated; -initiate IV vancomycin in patients based on specific indications; -de-escalate EAT based on susceptibility results in patients with documented infections; continue therapy until microbiologic eradication, resolution of signs and symptoms, or ≥7 d, of which ≥4 d should be fever free; -discontinue EAT after ≥72 h if patient is stable and afebrile for ≥ 8 h regardless of ANC if no documented infection.	Primary: -Severe sepsis: 10% (51/512) vs 10.8% (48/446) -Septic shock: 4.5% (23/512) vs 4.7% (21/446) -Infection-related ICU admission: 4.1% (21/512) vs 4.9% (22/446) -Mortality: 2.7% (14/512) vs 0.7% (3/446); $P = .016$ Secondary: -BSI: 30.5% (156/512) vs 46.9% (209/446); $P < .001$ -EAT discontinuation before ANC recovery: 13.5% (91/512) vs 41.6% (289/446); $P < .001$ -Antimicrobial consumption, median (range): 14 (0–69) days vs 12 (0–60) days; $P = .001$ -Recurrent fever: 34.7% (233/672) vs 41.6% (289/695); $P = .009$ -LOS, median (range): 27 (10–101) d vs 27 (12–79) d

Table 1. Continued

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Implementation of Pharmacist-Driven Antifungal Stewardship Program in a Tertiary Care Hospital. Kara et al. Antimicrob Agents Chemother 2021; 65: e00629–21.	Prospective, pre/post study evaluating the effect of an AFSP on appropriateness of antifungal therapy at a tertiary care university hospital.	Implementation of an AFSP in 3 phases: -observation (OBS, 4 mo): baseline data collected; -FE (4 mo): general education provided by clinical pharmacists on appropriate use of antifungals to prescribers; -IMP (8 mo): daily evaluation and patient-level recommendations from a clinical pharmacist in collaboration with AFSP team on antifungal use. Potential drug–drug interactions were evaluated, and a scoring system for appropriateness (indication, antifungal choice, dose, duration, route, adjustment based on microbiology) was used to compare phases.	Primary and secondary outcomes not specified -Overall appropriateness of antifungal use, 30.5% OBS vs 26.6% FE vs 62.7% IMP ($P < .001$) -Appropriateness of antifungal prophylaxis, 30.8% OBS vs 17.9% FE vs 46.3% IMP ($P = .046$) -Appropriateness of antifungal treatment, 27.8% OBS vs 32.4% FE vs 71.9% IMP ($P < .001$) -Recommendation acceptance rate, overall, 151 of 157 (96.2%) -30-d mortality, 19% OBS vs 15.6% FE vs 27.5% IMP ($P = .050$) -Potential drug–drug interactions, 4.2 OBS vs 3.3 FE vs 2.18 IMP ($P = .035$) -No difference in duration of therapy or adverse effects
Effects of a Collaborative, Community Hospital Network for Antimicrobial Stewardship Program Implementation. Moehring et al. Clin Infect Dis 2021; 73:1656–63.	Retrospective, longitudinal analysis of antimicrobial use in centers enrolled in the DASON with 36 mo of data. 17 community hospitals were included.	Community hospitals enrolled in DASON worked closely with an ID-trained physician/pharmacist to implement stewardship programs, including an electronic data collection system, individualized goals, feedback and education, institutional-specific guidelines or protocols, and assessment of stewardship program outcomes. A 1-y period (1–12 mo) was allowed for implementation.	Primary and secondary outcomes not specified -All hospitals implemented all 7 Core Elements by year 3 -Antimicrobial use overall, median (IQR): 925 (839–1014) month 1; 867 (764–989) month 42; 5% decline from month 13 to 42 (RR, 0.95; 95% CI, 0.91–0.99) -FQ use significantly decreased in month 42 vs month 13 (RR, 0.65; 95% CI, 0.58–0.73) -Nonsignificant decrease month 42 vs month 13 for antifungals (RR, 0.83; 95% CI, 0.68–1.01) and carbapenems (RR, 0.82; 95% CI, 0.61–1.09) -No difference in HO-CDI month 42 vs month 13 (RR, 0.95; 95% CI, 0.73–1.24)
Application of Standardized Antimicrobial Administration Ratio as a Motivational Tool within a Multi-Hospital Healthcare System. Shealy et al. Pharmacy 2021; 9:32.	Multicenter, prospective, pre/post cohort study evaluating the use of SAAR interfacility hospital comparison within a health system as a motivational antimicrobial stewardship tool.	ASP team presented baseline SAAR data, including interfacility comparisons, for 3 community hospitals (A, B, and C) at system-wide antimicrobial subcommittee meetings. Plans with focused interventions targeting key drivers of outlier SAARs at Hospital B were developed. SAAR data continued to be shared quarterly at system-wide ASP meetings to share progress.	Primary: -Reduction in mean outlier SAARs at Hospital B -All agents, all locations pre and post: 1.09 vs 0.83 ($P < .001$) -Broad-spectrum agents for HO infections, ICU: 1.36 vs 0.81 ($P < .001$) -Agents for resistant GP infections, ICU: 1.27 vs 0.72 ($P < .001$) -Statistically significant reductions in broad-spectrum agents for HO infections, ICU for Hospitals A (0.67 vs 0.52; $P = .01$) and C (0.83 vs 0.54; $P = .007$) noted as well

Abbreviations: AFSP, antifungal stewardship program; ASB, asymptomatic bacteriuria; BL, beta-lactam; BSI, bloodstream infection; CDI, *C. difficile* infection; DASON, Duke Antimicrobial Stewardship Outreach Network; DOT, days of therapy; EAT, empiric antimicrobial therapy; EHR, electronic health record; FE, feedback and education; GN, gram negative; GP, gram positive; HO, hospital onset; ID, infectious diseases; IMP, implementation; IPT, institution-preferred therapy; LOS, length of stay; MDR, multidrug resistant; MRSA, methicillin-resistant *S. aureus*; OPAT, outpatient parenteral antimicrobial therapy; OR, odds ratio; PDI, postdiagnostic intervention; PE, posteducation; PI, postintervention; RR, relative risk; RROR, ratio of ratios of odds ratios; SAAR, standardized antimicrobial administration ratio; UA, urinalysis; VRE, vancomycin-resistant *Enterococcus*.

of ASB. A total of 120 patients were included in the study, with 50 patients in the pre-intervention group, 50 patients in the postdiagnostic intervention group, and 20 more patients in a group after receiving extensive education on management of ASB. A significant reduction was observed in the percentage of patients who received antimicrobials for ASB in the post-diagnostic and posteducation groups compared with the pre-intervention group (Table 1). Reductions in median length of therapy, orders for UA, and urine culture orders in the post-diagnostic intervention group were also demonstrated; however, cost savings were not calculated. While it appears that the diagnostic intervention had the greatest impact, concurrent education may also provide benefit in different settings. This study provides a valuable intervention to reduce inappropriate treatment of ASB but highlights the need for continued investigation of strategies to curtail this "antibiotic-never event."

Clostridioides difficile Test Reporting

Rates of CDI have increased dramatically in inpatient settings, corresponding with an increase in the use of molecular assays to aid diagnosis [27]. Use of polymerase chain reaction (PCR)–based testing increases CDI incidence by 46%–67% compared with toxin-based testing, suggesting that the sensitivity of the assay may contribute to this increase [28]. Herman and colleagues conducted a retrospective cohort to assess the impact of a new reporting method for *C. difficile* tests that preserves provider autonomy and encourages assessment of potential *C. difficile* colonization at a large community hospital [29]. During the pre-intervention period, all PCR-positive/toxin enzyme immunoassay (EIA)–negative (PCR+/EIA−) results yielded the following laboratory report: "*Clostridium difficile* cytotoxin B gene detected" with treatment recommendations. During the postintervention period, all PCR+/EIA results yielded a modified laboratory report: "*Clostridium difficile* organism present but toxin not detected by EIA. Consider *C. difficile* colonization or early infection," with no treatment recommendations. A total of 199 and 165 CDI episodes were included in the pre-intervention and postintervention groups, respectively. The primary outcome of total DOT of anti-CDI therapy (metronidazole, oral vancomycin, fidaxomicin) decreased significantly in the postintervention group, while the proportion of patients not prescribed anti-CDI therapy increased during the same period (Table 1). The authors did not appreciate any statistically significant difference in subsequent toxin-positive disease, colectomy, mortality, or length of stay. Based on these results, this study provides a safe and effective, low-maintenance AS "nudge" to improve diagnosis and prescribing for CDI.

Narrow-Spectrum Antibiotics for Community-Acquired Pneumonia in Dutch Adults (CAP-PACT)

Dutch guidelines for empiric treatment of moderately severe community-acquired pneumonia (CAP) recommend narrow-spectrum BL (amoxicillin or benzylPCN) ± a macrolide, or a respiratory FQ. However, broad-spectrum antimicrobials are often used, and high-quality evidence for equivalence in using more narrow agents is lacking. Schweitzer and colleagues sought to evaluate the use of formalized ASP strategies to decrease broad-spectrum antimicrobials in this population [30]. All Dutch hospitals have ASPs that consist of an ID specialist, pharmacist, and microbiologist. Hospitals transitioned from a control period to an intervention period that included an intervention bundle focused on (1) education with clinical lessons, electronic e-learning, and educational attributes, (2) engaging key local opinion leaders to encourage local guideline adherence, and (3) antimicrobial prospective audit and feedback.

For the 9 hospitals included in the analysis (4084 total patients, 2235 in the control and 1849 in the intervention), median broad-spectrum DOT and adjusted mean broad-spectrum per patient DOT were decreased, while median total DOT were unchanged; this reflects the protocol focus on de-escalation rather than duration of therapy. Mortality at 90 days was similar in the control and intervention periods. There were 330 AS recommendations, of which 197 (59.7%) were accepted. The biggest limitation to the study was due to this being a bundled intervention; the effect size of individual elements was not able to be directly measured. This study demonstrates that a formalized, focused ASP implementing a targeted bundle approach can reduce broad-spectrum antimicrobial use in moderately severe CAP.

Impact of Pharmacist-Led ASP on Duration of Therapy for Uncomplicated Gram-Negative Bloodstream Infections

Recent literature supports shorter treatment durations for gram-negative bloodstream infections (GN BSIs) [31–33]. In many community settings, access to ID physicians is limited. Fukuda and colleagues conducted a retrospective, single-center cohort evaluating the impact of a pharmacist-led ASP on treatment durations for uncomplicated GN BSIs in a hospital with no ID specialists [34]. One ID-trained pharmacist and 6 ward pharmacists participated in the intervention arm.

In total, 66 patients were included. A majority of patients in both groups had a urinary source in which *Escherichia coli* was most commonly isolated. The intervention group had antimicrobial time-outs, consisting of discussions regarding efficacy, duration, de-escalation, and adverse events with the primary team physician, performed on days 3, 5, 7, and 10. Patients in the control group were managed at the primary team physician discretion with no pharmacist intervention. The primary outcome, antibacterial duration, was shorter in the intervention group. There was also a higher rate of de-escalation in the intervention group (Table 1). There were no differences in other secondary safety or efficacy outcomes. Of note, this study only evaluated uncomplicated, non–critically ill patients from a single center with no multivariate analysis for confounding factors. This study provides evidence that pharmacists play a key role in AS by optimizing treatment duration and de-escalation of antimicrobials as appropriate, especially in hospitals with limited ID physician presence.

Impact of Rapid Phenotypic Susceptibility Results on Antimicrobial Utilization and Clinical Outcomes in Patients With Gram-Negative Bloodstream Infections

Previous data have demonstrated worse outcomes associated with delayed appropriate antimicrobial use in patients with GN BSI [35–37]. Rapid diagnostic tests (RDTs) and phenotypic susceptibility results using the Accelerate Pheno system have been associated with shorter time to optimal antibiotic therapy, but data on clinical outcomes and discrepancies are limited [38–40].

Robinson and colleagues conducted a single-center, pre-/postintervention study of 514 unique adult patients with GN BSIs [41]. The primary outcome of time to institutional-preferred antimicrobial therapy (IPT) was shorter in the postintervention group. The postintervention group also had a decrease in broad-spectrum GN active agents in DOT per 1000 days present in the 8 days following culture results accompanied by an increase in narrow-spectrum BL utilization (Table 1). Despite the shorter time to IPT, there was no difference in clinical outcomes such as in-hospital or 30-day mortality, LOS, CDI, readmission, or relapse of BSI. However, investigators found discrepancies in standard-of-care and RDT in 69 (28%) of 250 patients in the postintervention group. These discrepancies consisted of 9% false resistant, 5% false susceptible, 5% no susceptibility data, 4% no identification, 2% incorrect identification, and 2% missed polymicrobial infections. The authors concluded that RDT with ASP may shorten time to optimal antimicrobials, but discrepancy risk should be considered and requires further investigation.

Standardized Management Pathway for Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection

The current literature continues to highlight the impact MRSA BSIs have on patient outcomes and the health care system [42, 43]. Various interventions, such as combination therapies and ID consultation, have been associated with improved outcomes in MRSA BSIs [44–48]. Alosaimy and colleagues conducted a retrospective quasi-experiment to evaluate baseline characteristics and clinical outcomes in patients pre-/postimplementation of an MRSA BSI pathway in a large health care system [49]. The pathway mandated ID consultation and emphasized early initial combination therapy (CT) with a BL, preferably cefazolin. Based on the updated microbiological and clinical data, regimens were allowed to be modified on days 3–5 of therapy, then again on days 7–10.

Given the study design and period, multivariable logistic regression and interrupted time-series (ITS) analysis were performed. Of the 813 adults with MRSA BSI in the final analysis, the primary outcome, 30-day mortality, was reduced between the pre- and postintervention groups (15.6% vs 9.7%; $P = .011$). Similarly, 90-day mortality, ID consultations, and bacteremia duration were significantly improved. Prolonged bacteremia, hospital LOS, and incidence of acute kidney injury did not change significantly between groups. Due to the prolonged study period, other health care improvements may have contributed to the final outcomes. Additional analyses were performed to adjust for confounders, including ID consultation. The pathway was independently associated with a 30-day mortality reduction (adjusted odds ratio, 0.608; 95% CI, 0.375–0.986). The study illustrates potential benefits from a multimodal approach to the management of MRSA BSIs. The clinical value of early CT for MRSA bacteremia outcomes requires further elucidation.

Impact of Fluoroquinolone Preauthorization on Third- and Fourth-Generation Cephalosporin Use and Resistance

Preauthorization is one of the cornerstones of AS [50]. While several studies have demonstrated the feasibility of limiting consumption of a class or specific agent, no studies to date have evaluated the possible juxtaposition of FQ restriction with extended-spectrum cephalosporin consumption and subsequent resistance patterns.

The University of Alabama–Birmingham (UAB) Hospital restricted FQs in 2005, largely restoring susceptibility to the class over a 10-year period [51]. Using a quasi-experimental ITS, Idigo and colleagues investigated the impact of FQ preauthorization on DOT per 1000 patient-days (DOT/1000 PD) for third- and fourth-generation cephalosporins from January 1998 to December 2016 [52]. During this time period, investigators also examined changes in resistance patterns of clinically significant GN organisms including *Pseudomonas aeruginosa*, *Acinetobacter baumannii,* and Enterobacterales species. Piperacillin-tazobactam and tobramycin DOT were captured and used as a control to account for longitudinal changes in Clinical Laboratory and Standards Institute (CLSI) extended-spectrum beta-lactamase (ESBL) breakpoints during the study period. Poisson regression was performed to determine trends in monthly antibiotic use as well as yearly trends in resistance. Ceftriaxone and cefepime use increased after FQ restriction, but rates of ceftazidime- and cefepime-nonsusceptible *Pseudomonas* declined. Resistance among *Enterobacter cloacae* and *Acinetobacter* appeared stable after FQ restriction (Table 1).

This study highlights the impacts on prescribing habits and local ecological changes in the inpatient setting after implementing FQ restriction. The beneficial effects of decreasing FQ-mediated resistance on other drug classes in particular should also be recognized. The findings of this study are limited by the retrospective, single-center nature of the study.

Antibiotic De-escalation and Discontinuation in High-Risk Hematological Patients With Febrile Neutropenia

Early discontinuation of empiric antimicrobial therapy (EAT) in patients with neutropenic fever (NF) has been previously recommended but not widely implemented [53]. Verlinden and colleagues evaluated the safety and efficacy of EAT de-escalation and/or discontinuation in high-risk hematological patients admitted for induction or consolidation chemotherapy or hematopoietic cell transplantation compared with a historical cohort [54]. The intervention included creation of a standard operating procedure (SOP) to guide diagnostic workup and EAT and to provide specific criteria for EAT de-escalation and/or discontinuation (Table 1).

Over a 9-year period, 512 patients were included in the preintervention group and 446 in the postintervention group. NF occurred more often in the postintervention group (86% vs 91%; $P = .020$) due to a higher proportion of microbiologically and clinically documented infections (51% vs 59%), of which GN BSI was most common (45% vs 55%; $P = .038$). Despite higher rates of recurrent fever in the postintervention group, the incidence of infectious complications was similar between groups, and mortality was significantly higher in the pre-intervention group. SOP adherence occurred in >90% of patients with microbiologically or clinically documented infections. As such, discontinuation of EAT before neutrophil recovery occurred more often in the postintervention group, resulting in decreased antimicrobial consumption.

Though recommendations for duration of EAT are inconsistent across multiple guidelines, this study supports EAT de-escalation and/or discontinuation in high-risk hematological patients with NF. High rates of SOP adherence were observed in patients with documented infections, whereas adherence was lowest in those without an identifiable cause of fever.

Implementation of an Antifungal Stewardship Program

Empiric antifungal use is often inappropriate [55–60], and establishment of antifungal stewardship programs (AFSPs) is recommended by the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America [61]. Kara and colleagues conducted a prospective, quasi-experiment to evaluate the effects of implementing an AFSP on antifungal appropriateness [62]. The intervention included 3 phases: observation (OBS), feedback and education (FE), and implementation (IMP), in which a pharmacist collaborated with an AFSP to evaluate antifungal therapy (Table 1).

A total of 418 antifungal episodes (377 patients) included 105 (84 patients), 109 (101), and 204 (192) episodes in OBS, FE, and IMP, respectively. Baseline characteristics were similar, but numerically more patients were in the intensive care unit (ICU) in IMP than OBS or FE (47.1% vs 35.2% vs 35.8%, respectively). In addition, 20.3% of patients in IMP had COVID-19, with 92.3% of those in an ICU. A total of 157 recommendations were made, with most related to treatment (68.8%) and requesting additional labs or imaging (19.1%), therapeutic drug monitoring (15.9%), or treatment discontinuation (15.9%). The mortality rate increased during IMP, which the authors noted may have been confounded by COVID-19.

The study demonstrated that implementation of an AFSP, consisting of daily evaluation and patient-specific feedback by a pharmacist in collaboration with a multidisciplinary team, improves appropriateness of antifungal therapy. Study limitations include single-center nonrandomized design, lack of wash-out periods between phases, and confounders such as COVID-19 that could have impacted program assessment.

Implementation of an Antimicrobial Stewardship Support Network

As of January 1, 2017, The Joint Commission Standard MM.09.01.01 requires hospitals to have ASPs [63]. In order to support community hospitals in implementing ASPs, the Duke Antimicrobial Stewardship Outreach Network (DASON) was established by the Duke Center for Antimicrobial Stewardship and Infection Prevention [64]. Community hospitals can enroll in DASON for an annual fee that includes expert consultation and help with data collection, analysis, and education from a trained AS physician or pharmacist. Data from participants are benchmarked yearly, and the consultant works with participants to set individualized goals for the ASP and antimicrobial use (AU) yearly.

Moehring and colleagues conducted a retrospective, longitudinal analysis of AS practices and AU among DASON-participating hospitals that had at least 36 months of data between 2013 and 2018 [65]. The intervention included consultation of hospital participants with DASON personnel, implementation of ASPs at individual hospitals, and assessment of ASP implementation.

A total of 17 hospitals were included. The median (IQR) hospital size was 220 (148–289) beds, with 3580 (2500–5220) patient-days per hospital month. An ID consult or pharmacist was available at 76% and 59% of sites, respectively. Individual site performance varied widely, but improvements in AU were seen overall (Table 1). This study demonstrated that a stewardship network with expert consultants benefited ASPs and AU in community hospitals. Study limitations include inability to assess appropriateness of AU, lack of information on process outcomes, and limited inclusion of clinical outcomes. In addition, the majority of hospitals had access to an on-site ID consult or pharmacist, which may not be representative of all small or community hospitals.

Application of Standardized Antimicrobial Administration Ratio as a Motivational Tool Within a Multihospital Health Care System

The Standardized Antimicrobial Administration Ratio (SAAR) was created to facilitate comparison of antimicrobial consumption at the hospital, health system, and national levels while accounting for differences in population- and hospital-specific risk factors for increased antimicrobial utilization [66]. Similarly, interfacility peer comparison has been associated with improvements in antimicrobial prescribing [67]. Shealy and colleagues conducted a 2-year prospective study to evaluate the use of SAAR as a motivational AS tool for comparison of hospital-specific antimicrobial utilization within a single health system [68].

The intervention began in October 2017 with the presentation of detailed, hospital-specific SAAR data for all 3 hospitals (A, B, and C) at the systemwide AS meeting. The hospital representatives were encouraged to utilize the peer comparison data to develop targeted interventions at their facilities, including increased utilization of existing AS interventions such as internal clinical risk scores and interdisciplinary rounds. Updated SAAR data were presented quarterly for the remainder of the study period.

Hospital B was noted to have high use (SAAR > 1) of antimicrobials in all 3 targeted areas of study at baseline. Statistically significant reductions occurred in all 3 areas postintervention and were maintained throughout the 20-month postintervention period. Importantly, the authors noted that before SAAR, the increased antimicrobial consumption at Hospital B was thought only to be due to the unique patient populations at that facility. This study demonstrated the role of SAAR as a motivational tool to reinvigorate targeted AS efforts in addition to traditional metrics.

DISCUSSION

The COVID-19 pandemic has impacted ASPs internationally, and the contributions of ASPs in pandemic response have been recognized [69]. The challenges of the past 2 years have demonstrated the necessity of robust data to inform ASPs on the most efficient intervention strategies for local implementation. Encouragingly, several studies included in this edition of the Baker's Dozen series demonstrate significant impact and quality manuscripts without external funding or prohibitive up-front resource costs. Several of this year's manuscripts added depth to knowledge on perennial topics like allergy reconciliation, diagnostic stewardship, de-escalation, and duration of therapy—these manuscripts also highlighted the reproducibility of specific AS interventions. New information emerged on the organization of AFSPs and use of SAAR data to create change within health systems. This signals a new direction for AS in the coming years as we capitalize on the power of larger systems, networks, and data sets as suggested by Buckel and colleagues [70]. The interventions reviewed here provide opportunities for ASPs seeking to enhance local practices with evidence-based strategies. Consideration of these specific interventions within the context of the ASP to determine lowest-effort/highest-impact interventions may be particularly insightful.

Emerging from the pandemic, it is our hope that AS personnel and their initiatives will be reinvigorated to tackle current challenges. Use of technology to best inform diagnostics and treatment and standardized pathways to optimize patient care and reduce the unintended consequences of antimicrobial therapy remain key to sustainable and efficient AS. Only in the coming years will we be able to determine the full impact of pandemic response on ASPs and the most efficient AS interventions for COVID-19 patients.

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REVIEW ARTICLE

A Baker's Dozen of Top Antimicrobial Stewardship Intervention Publications in Non–Hospital Care Settings in 2021

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The scope of antimicrobial stewardship programs has expanded beyond the acute hospital setting. The need to optimize antimicrobial use in emergency departments, urgent, primary, and specialty care clinics, nursing homes, and long-term care facilities prompted the development of core elements of stewardship programs in these settings. Identifying the most innovative and well-designed stewardship literature in these novel stewardship areas can be challenging. The Southeastern Research Group Endeavor (SERGE-45) network evaluated antimicrobial stewardship–related, peer-reviewed literature published in 2021 that detailed actionable interventions specific to the nonhospital setting. The top 13 publications were summarized following identification using a modified Delphi technique. This article highlights the selected interventions and may serve as a key resource for expansion of antimicrobial stewardship programs beyond the acute hospital setting.

Keywords. antibiotics; antimicrobial stewardship; emergency department; nursing homes; outpatient.

The original Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) antimicrobial stewardship (AS) guidelines were published over 15 years ago [1]. These guidelines focused on the development of successful inpatient antimicrobial stewardship programs (ASPs) as few data at the time were available to inform best practices in other health care settings. The importance of AS beyond the hospital has been evident, with most antimicrobial use (AU), >60% in the United States, occurring in outpatient care settings [2]. Approximately 30% of antibiotics prescribed at outpatient visits are unnecessary, with 50% of those being prescribed inappropriately [2–4]. Similar estimates of inappropriate long-term care antibiotic prescribing are as high as 75% [5, 6]. Prescribing practices in these settings significantly influence antimicrobial resistance (AR) patterns of organisms regardless of patient care location. Non–hospital care AS challenges vary widely, however. For example, the Centers for Disease Control and Prevention (CDC) Core Elements of outpatient ASPs is intended for application to primary and urgent care settings, dental practices, specialty clinics, emergency departments (EDs), and transitions of care (TOC) between settings, while separate guidance supports ASPs in nursing homes (Figure 1) [2, 7]. Similar to early acute hospital ASPs, successful nonhospital AS interventions to date have included provider education, prescribing guidelines, and prescription audit with feedback [8–11]. Outpatient and nursing home ASPs have demonstrated improvements in antimicrobial prescribing; however, lack of enduring and dedicated resources may limit overall impact [12, 13]. In addition to the CDC Core Elements, other national organizations have focused on AS in non–hospital care settings, such as The Joint Commission and the Centers for Medicare & Medicaid Services [14, 15]. While these initiatives represent progress toward improved AS in non–hospital care settings, data detailing specific, actionable, high-quality interventions within these settings are in their infancy and slowly accumulating.

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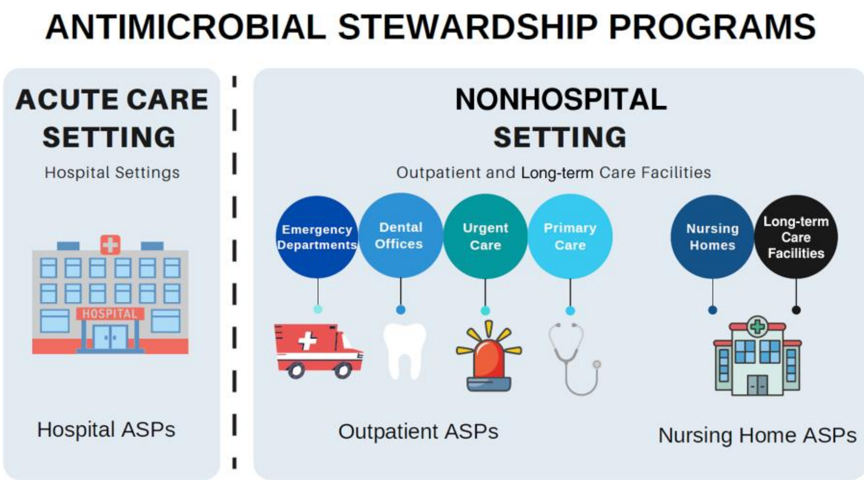

Figure 1. Patient care areas included in the SERGE-45 nonhospital definition based on inclusion in the CDC Core Elements for Outpatient and Nursing Home Antimicrobial Stewardship. Abbreviations: ASP, antimicrobial stewardship program; CDC, Centers for Disease Control and Prevention; SERGE, Southeastern Research Group Endeavor.

The Southeastern Research Group Endeavor (SERGE-45) has published the top overall AS interventions across all practice settings in recent years [16–21]. SERGE-45 is composed primarily of infectious diseases (ID) and AS clinical pharmacists, representing >50 individual health care institutions across all 13 Southeastern states and Washington DC, supporting a diverse mix of both community and academic medical centers. Each year, the number of AS intervention articles of interest outside of the acute hospital setting has grown, necessitating a separate evaluation of nonhospital interventions. This article highlights selected high-quality AS interventions specific to non–hospital care settings to assist newly formed or growing outpatient and nursing home ASPs in developing strategies to optimize antimicrobial use.

METHODS

Using a modified Delphi technique, members of the SERGE-45 network identified nonhospital AS publications from 2021 considered to be significant using the following inclusion criteria: (1) published in 2021, including electronic, "early-release" publications, and (2) included an actionable intervention [22]. An actionable intervention was defined as an AS strategy that was implemented in practice and resulted in measurable outcomes. Clinical practice guidelines, preprints, official statements, review articles, and articles without an actionable intervention were excluded.

A PubMed search using "antimicrobial stewardship" for 2021 revealed 1740 potential publications. Abstracts were screened to ensure that all relevant articles were considered, that electronic publications before 2021 were removed, and publications were appropriately stratified between acute hospital and non–hospital care settings. Thirty-seven nonhospital publications were submitted by the network, and those meeting criteria and not identified previously were also included for consideration. A total of 50 articles were distributed to the SERGE-45 network for ranking via a REDCap survey of the top 13 articles based on contribution and/or application to ASPs [23]. Follow-up email reminders were sent to encourage participation in the voting process. Of note, no conflict of interest disclosure was required of participating voters.

Of the 84 network members at the time of the survey, 27 rank lists (32% participation) were submitted. The group ranks were reviewed by C.M.B., P.B.B., A.H.M., and S.B.G. via teleconference. This group reviewed articles with the same ranking based on inclusion criteria and diversity of topics included, and a final consensus on the top 13 articles was established. Included articles are presented in the discussion in a random order and are not ranked according to placement. Figure 2 is a flowsheet of the article selection process, and Table 1 provides a summary of the selected articles.

RESULTS

Peer Feedback for Respiratory Tract Infection Prescribing in Primary Care

Inappropriate antibiotic prescribing for respiratory tract infections (RTIs) is common in primary care [37]. Dutcher and colleagues evaluated the impact of an education and feedback–based intervention to improve prescribing for respiratory tract diagnoses (RTDs) [24]. The first phase of the intervention consisted of an educational session on appropriate prescribing for common RTIs and effective patient communication strategies, particularly for when not prescribing an antibiotic. The second component consisted of monthly email reports of individual and peer comparison feedback on antibiotic prescribing for all RTDs and Tier 3 RTDs. Tier 1 and 2 diagnoses were defined as those for which an antibiotic is always and may be indicated,

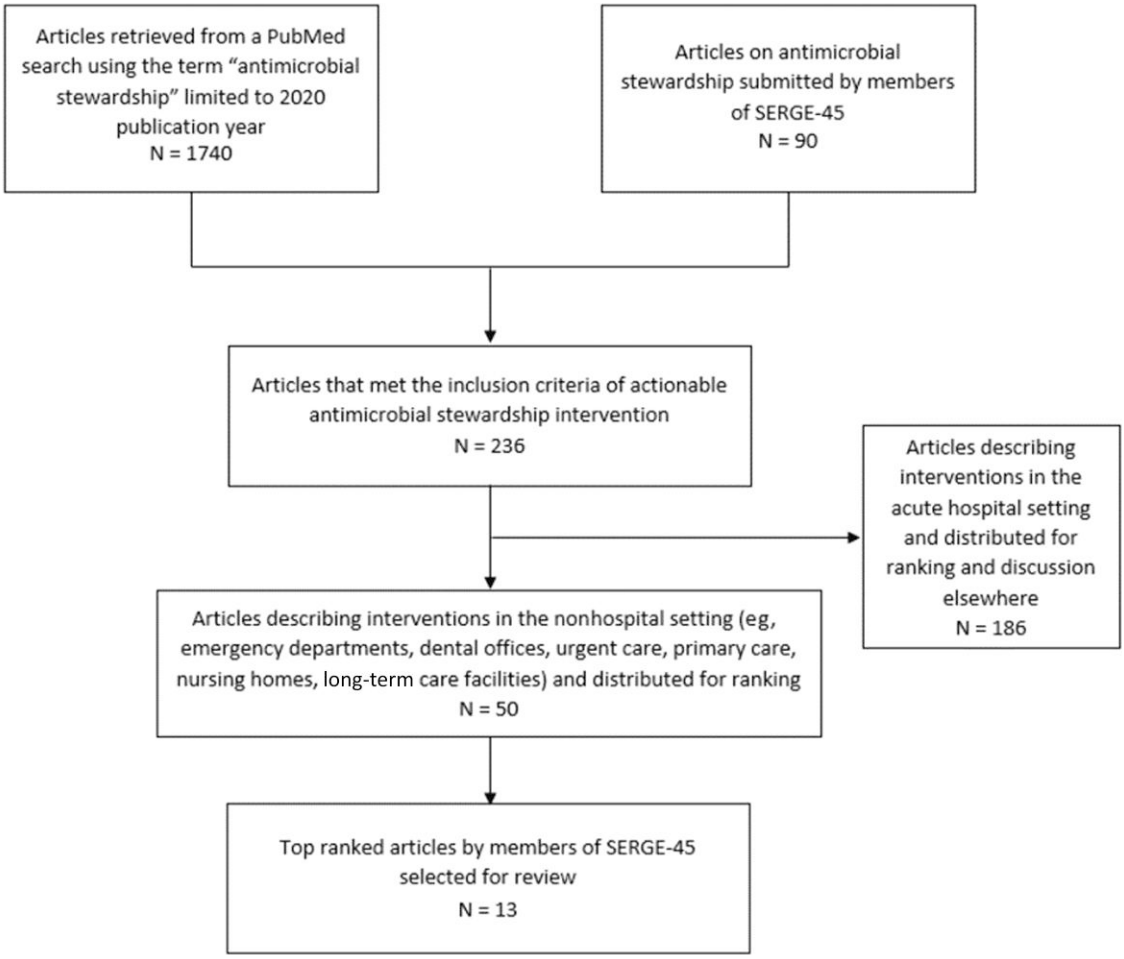

Figure 2. Flowchart of the database search and article selection process. Abbreviation: SERGE, Southeastern Research Group Endeavor.

respectively, while Tier 3 diagnoses included those for which an antibiotic is rarely indicated.

The study assessed 185 755 unique office visits for RTDs across 30 primary care offices in the University of Pennsylvania Healthcare System from July 2016 to October 2018. Overall antibiotic prescribing decreased in the postintervention period (35.2%–23.0%; $P < .001$), driven by decreases in antibiotic prescribing for Tier 2 and Tier 3 RTDs. This study demonstrates that an education and feedback–based intervention can significantly reduce overall antibiotic prescribing for RTDs without affecting the prescribing of RTIs in which antibiotics are always indicated.

Antimicrobial Stewardship at Hospital Discharge

Improvements in antimicrobial prescribing are needed at TOC [38–41]. Hospital ASPs are uniquely poised to impact antimicrobial prescribing at discharge; however, discharge prescribing is infrequently addressed by inpatient AS teams [3, 4, 37]. Parsels and colleagues evaluated the impact of infectious diseases (ID) pharmacist review of discharge prescriptions on drug-related problems (DRPs) [25].

A total of 803 discharge prescriptions were reviewed, most completed in <15 minutes (87.9%). The most common antimicrobial indications were prophylaxis (20.9%), skin and soft tissue infection (19.8%), cystitis/pyelonephritis (14.9%), and intra-abdominal infection (14.9%), and the medication was prescribed by adult medicine (58%) and general pediatric (15.2%) services. The most common DRPs were inappropriate duration (35.9%), typically due to excessive durations of therapy (88.4%). Upon acceptance of recommendations to reduce duration, the median number of antimicrobial days decreased from 8 to 4 ($P < .001$). This study demonstrated benefits of review of antimicrobial prescribing at time of discharge, but outpatient pharmacy infrastructure and adequate resources may limit its generalizability. Notably, hospital readmissions were not assessed.

Education and Data Feedback for Outpatient Urinary Tract Infections

Urinary tract infections (UTIs) are the most diagnosed infection in the outpatient setting [12, 42]. Funaro and colleagues

Table 1. Summary of Top 13 Antimicrobial Stewardship Intervention Papers in the Nonhospital Setting, 2021

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Improving Outpatient Antibiotic Prescribing for Respiratory Tract Infections in Primary Care: A Stepped-Wedge Cluster Randomized Trial. Dutcher et al. [24]	Stepped-wedge cluster randomized trial evaluating the impact of an education and feedback–based intervention to improve prescribing for RTDs	Educational session on RTI prescribing and patient communication strategies, followed by monthly electronic individual and peer comparison feedback	Primary outcome: • Overall antibiotic prescribing was reduced from 35.2% to 23.0% ($P<.001$) • Decreased odds of antibiotic prescribing by univariate analysis (OR, 0.47; 95% CI, 0.45–0.48) • Decreased odds of antibiotic prescription for Tiers 2 (OR, 0.57; 95% CI, 0.52–0.62) and 3 (OR, 0.57; 95% CI, 0.53–0.61) but not for Tier 1 (OR, 0.98; 95% CI, 0.83–1.16) in multivariate analysis
Hospital Discharge: An Opportune Time for Antimicrobial Stewardship. Parsels et al. [25]	Retrospective, descriptive, single-center study evaluating impact of ID pharmacist review of discharge prescriptions on DRPs	Oral, discharge antimicrobial prescriptions sent to the hospital's outpatient pharmacy were reviewed for appropriateness by an ID pharmacist	Primary outcome: • ≥1 DRP identified in 43.1% of prescriptions Secondary outcomes: • Most common DRP was inappropriate duration (35.9%) • 42.8% of discharge prescriptions required at least 1 intervention; 75.6% acceptance rate • 4-d reduction in antimicrobial days (8 vs 4; $P<.001$)
Impact of Education and Data Feedback on Guideline-Concordant Prescribing for Urinary Tract Infections in the Outpatient Setting. Funaro et al. [26]	2-phase, prospective, quasi-experimental study evaluating impact of a multifaceted AS intervention on guideline-concordant antibiotic prescribing for UTIs in an urgent care clinic and a primary care clinic	Phase I: development of clinic-specific antibiogram and guideline, education Phase II: education, provision of provider- and clinic-specific feedback	Primary outcome: • Guideline-concordant prescribing increased by 22% after Phase I, with 0.5% decrease every 2 wk thereafter • Phase II stabilized guideline-concordant prescribing Secondary outcomes: • UTI diagnoses decreased 21% after Phase I (RR, 0.79; 95% CI, 0.67–0.93) • 52.1% relative reduction in fluoroquinolone use • Encounters meeting 4-factor guideline concordance increased from 19% to 23.2% and 28% in Phase I and Phase II, respectively • Low rates of treatment failure and adverse effects
Retrospective Assessment of Antimicrobial Stewardship Initiative in Outpatient Use of Ertapenem for Uncomplicated Extended Spectrum Beta Lactamase Enterobacteriaceae Urinary Tract Infections. Wong et al. [27]	Quasi-experimental study assessing a stewardship initiative for outpatient usage of ertapenem or aminoglycosides for ESBL UTIs	Intervention consisted of interdisciplinary education for prescribers to enhance adherence to formulary restriction of ertapenem and encourage consideration of aminoglycosides as an alternative	Primary outcome: • No difference in recurrent UTIs ($P=.57$) or adverse effects in either treatment group Secondary outcomes: • Ertapenem utilization decreased from 0.0145 DOT/1000 APD to 0.0078 DOT/10 000 APD ($P<.01$) • Mean monthly ertapenem DOT declined 19% between the pre- and postintervention periods ($P<.01$)
Implementation of Veterans Affairs Primary Care Antimicrobial Stewardship Interventions for Asymptomatic Bacteriuria and Acute Respiratory Infections. Mortrude et al. [28]	Stepped-wedge trial evaluating the impact of multifaceted educational interventions on antibiotic prescribing for RTIs and ASB in 5 Veterans Affairs primary care clinics	Multifaceted ASP intervention including provider scorecard, peer comparisons, clinical decision support, patient-facing resources, and educational sessions to promote improvements in antimicrobial prescribing in RTIs and ASB	Primary outcome: • No difference in overall antibiotic prescription rate as a composite of prescriptions for RTIs and ASB (56% vs 49%) Secondary outcomes: • No difference in antibiotic prescription rate for ASB (3% vs 2%) • Decrease in antibiotic prescription rate for acute bronchitis (21% vs 13%; $P=.0003$) • No difference in antibiotic prescription rate for upper respiratory infections (9% vs 6%), uncomplicated sinusitis (17% vs 22%), uncomplicated pharyngitis (5% vs 5%) • No difference in the composite safety outcomes of related health care visits within 4 wk (9% vs 9%) • Improvement in appropriateness of prescriptions overall (2% vs 10%; $P=.0004$), uncomplicated sinusitis (OR, 4.96; 95% CI, 1.79–13.75; $P=.0021$), and uncomplicated pharyngitis (OR, 5.36; 95% CI, 1.93–14.90; $P=.0013$) • No difference in patient satisfaction scores (91/100 vs 89/100)

Table 1. Continued

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
Effectiveness of a Tailored Intervention to Reduce Antibiotics for Urinary Tract Infections in Nursing Home Residents: A Cluster, Randomised Controlled Trial. Arnold et al. [29]	Open-label, parallel-group, cluster randomized controlled trial evaluating a tailored intervention on UTIs in 22 nursing homes	Interactive 75-min educational sessions were conducted for nursing staff on how to distinguish between UTIs and ASB, how to evaluate symptoms, and how to use the dialogue tool A dialogue tool was provided for nursing staff and included a reflection tool based on the Loeb minimum criteria for ordering a urinary culture and questions for staff to reflect on the next step as well as a communication tool based on the ISBAR concept for diagnosing UTIs in nursing homes	Primary outcome: • Decrease in the number of antibiotic prescriptions for UTIs (134 vs 228), resulting in an adjusted RR of 0.42 (95% CI, 0.31–0.57) Secondary outcomes: • No change in the number of appropriate antibiotic treatments for UTIs (22 vs 24), resulting in an adjusted RR of 0.65 (95% CI, 0.41–1.06) • Decrease in the number of inappropriate antibiotic treatments for UTIs (32 vs 62), resulting in an adjusted RR of 0.33 (95% CI, 0.23–0.49) • A trend toward an increase in all-cause hospitalizations (246 vs 175), resulting in an adjusted RR of 1.28 (95% CI, 0.95–1.74) • No change in all-cause mortality (79 vs 75), resulting in an adjusted RR of 0.91 (95% CI, 0.62–1.33)
Improving Delayed Antibiotic Prescribing for Acute Otitis Media. Frost et al. [30]	Multisite, quasi-experimental, before-and-after intervention study evaluating the impact of a bundled antimicrobial stewardship intervention on rates of delayed prescribing for AOM	Practice sites received monthly education plus audit and feedback as well as access to online resources and content expertise, and monthly site-specific PDSA cycles were completed	Primary outcomes: • Percentage of delayed antibiotic prescriptions increased from 2% to 21% (RRR, 8.96; 95% CI, 4.68–17.17) • Improved rates of delayed antibiotic prescriptions were sustainable up to 6 mo postintervention (RRR, 6.69; 95% CI, 3.53–12.65) • 100% of practice site champions reported improved confidence in the use of QI methods and using PDSA cycles to implement change • Study participants highly valued the ability to earn CE credit from education, access to content expertise, and receipt of monthly data reports
A Pragmatic Randomized Trial of a Primary Care Antimicrobial Stewardship Intervention in Ontario, Canada. McIsaac et al. [31]	Pragmatic, randomized trial evaluating a primary care provider–focused antimicrobial stewardship intervention	A multifaceted initiative including an initial 1-hour educational session, provider education modules, clinical decision aids, patient information leaflets, local clinic ASP support, and financial incentives for providers aimed at reducing antimicrobial prescribing in 5 target disease states	Primary outcomes: • No difference in overall antibiotic prescribing between intervention and control clinics • 22% reduction in odds of antibiotic prescribing at intervention when adjusted for clinic differences Secondary outcomes: • Proportion of prescriptions issued as delayed antibiotic prescriptions increased in the intervention group 22.1% compared with 11.7% ($P \leq .01$) • Prescriptions for >7 d were reduced in the intervention group 21.3% compared with 29.3% ($P < .0001$) • First-line antibiotic of choice was higher in the intervention group (92.2% and 84.9%, respectively)
Impact of Pharmacist-Led Selective Audit and Feedback on Outpatient Antibiotic Prescribing for UTIs and SSTIs. Choi et al. [32]	Retrospective, quasi-experimental, before-and-after intervention study comparing appropriateness of antibiotic prescribing for UTIs and SSTIs at 2 outpatient clinics	An ambulatory care, pharmacist-led feedback and audit of antibiotics prescribed for UTIs and SSTIs were performed every 2 weeks at an internal medicine and family medicine clinic	Primary outcome: • Appropriateness composite (selection, dose, duration, and therapy indication per institutional empiric therapy guidelines): 27.5% vs 50.5% ($P < .0001$) Secondary outcomes: • ADR: 2% vs 2% ($P = .736$) • CDI: 0% vs 0% ($P > .999$) • Clinic revisit at 7 d: 12% vs 22% ($P = .005$) • Hospitalization at 30 d: 1% vs 0% ($P = .248$)
Population-Wide Peer Comparison Audit and Feedback to Reduce Antibiotic Initiation and Duration in Long-Term Care Facilities with Embedded Randomized Controlled Trial. Daneman et al. [33]	DD antibiotic utilization study on peer comparison audit and feedback for prescriptions in all long-term care facilities in Ontario	Peer comparison antibiotic prescribing metrics, including the percentage of initiated antibiotics and antibiotic durations over 7 d, were reported quarterly on a volunteer	Primary outcome: • DD analysis on average of quarterly proportion of residents initiated on antibiotics (0.10%; 95% CI, −0.51% to 0.67%; $P = .735$) • DD analysis on average of quarterly proportion of residents on antibiotic duration >7 d (−2.65%; 95% CI, −4.93% to −0.28%;

Table 1. Continued

Study Citation	Study Design	Intervention Summary	Primary and Key Secondary Outcomes
		basis for physicians treating residents in LTC facilities	$P = .026$) Secondary outcome: • Dynamic vs static reports: no differences in average of quarterly proportions of residents initiated on antibiotics or on antibiotic duration >7 d • Pre- vs postintervention: no significant differences in infection-related or all-cause ED visits, hospitalizations, or mortality
A Novel Program to Provide Drug Recovery Assistance and Outpatient Parenteral Antibiotic Therapy in People Who Inject Drugs. Gelman et al. [34]	Pre/post study design comparing clinical outcomes of a combined drug addiction and infection treatment program in a historical cohort	A multidisciplinary CCDAI team reviewed patients with serious bacterial infections and substance use disorder to determine eligibility for transition to a detoxification facility for simultaneous DRA-OPAT	Primary outcomes: • 40.2% (35/87) enrolled in DRA-OPAT program • 45.7% (16/35) completed the full prescribed OPAT duration Secondary outcomes: • Decreased median LOS 10.6 d vs 22.9 d ($P < .0001$) • Decreased median cost $27 592 vs $39 221 ($P < .0001$) • No difference in 30-d (12.6% vs 7.8%; $P = .09$) and 90-d readmission (24.1% vs 23.5%; $P = .8$) • No difference in 1-y all-cause mortality (1.2% vs 7.1%; $P = .06$)
Improving Urinary Tract Infection Treatment Through a Multifaceted Antimicrobial Stewardship Intervention in the Emergency Department. Zalmanovich et al. [35]	Quasi-experimental before-and-after study that compared adherence to a UTI treatment protocol in patients in the emergency department	A UTI treatment algorithm tailored for patients discharged from the ED was developed and implemented and maintained via monthly text message reminders	Primary outcomes: • Adherence to the overall treatment protocol increased significantly from 41% to 84% ($P < .001$) • Adherence remained high in the booster period at 41% vs 73.4% ($P < .001$) • Adherence to appropriate antibiotic agent selection increased significantly, from 76% to 95% ($P < .001$) and 92.6% in the booster period ($P < .001$) • Adherence to the appropriate duration improved significantly, from 42.4% to 85.9% ($P < .001$) and 74.5% in the booster period ($P < .001$) Secondary outcome: • Fluoroquinolone prescriptions decreased significantly from 19.1% to 5% ($P < .001$) and remained low at 7.4% ($P < .001$)
Reducing Expectations for Antibiotics in Patients With Upper Respiratory Tract Infections: A Primary Care Randomized Controlled Trial. Perera et al. [36]	3-arm randomized controlled trial evaluating the impact of viewing electronic tablet–based educational presentations on antibiotic treatment of upper RTIs on patient expectations for antibiotics and on family practitioners' antibiotic prescribing behavior	Participants were randomized to a 1-min presentation to view before their consultation on the futility of antibiotics in upper RTIs, adverse effects, or benefits of healthy diet and exercise (active control)	Primary outcome: • Mean reduction for antibiotic expectation of 1.1 (0.8–1.3) in the futility group, 0.7 (0.4–0.9) for the adverse effect group, and 0.1 (0–0.3) for the control group (Cohen d = 0.7; $P < .001$) Secondary outcomes: • Significant reduction in the belief "I think antibiotics are a helpful treatment for cold/flu" for futility or adverse effect groups vs control (Cohen d = 0.6; $P < .001$) • No significant differences in antibiotic prescribing, dispensing, or patient satisfaction

Abbreviations: ADR, adverse drug reaction; AOM, acute otitis media; ARI, acute respiratory infections; APD, adjusted patients days; AS, antimicrobial stewardship; ASB, asymptomatic bacteriuria; ASP, antimicrobial stewardship program; CCDAI, Comprehensive Care of Drug Addiction and Infection; CDI, *Clostridioides difficile* infection; CE, continuing education; DD, differences in differences; DOT, days of therapy; DRA-OPAT, drug recovery assistance and outpatient parenteral antibiotic therapy; DRP, drug-related problem; ESBL, extended-spectrum beta-lactamases; ID, infectious diseases; ISBAR, Identification, Situation, Background, Assessment, and Recommendation; LOS, length of stay; OR, odds ratio; PDSA, plan-do-study-act; QI, quality improvement; RR, rate ratio; RRR, relative risk reduction; RTD, respiratory tract diagnoses; RTI, respiratory tract infection; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

conducted a 2-phase, prospective, quasi-experimental study examining the impact of a multifaceted AS intervention on guideline-concordant antibiotic prescribing (GCAP) for UTIs in 2 outpatient clinics [26]. Phase I included provision of clinic-specific antibiograms, guidelines, and education. Phase II included education and provision of clinic- and provider-specific feedback. Patients were identified via diagnosis codes of acute cystitis or pyelonephritis. Patients were excluded if they experienced recurrent UTIs, received antibiotics within 30 days of diagnosis, reported allergies to guideline-preferred therapies (GPTs), presented with concomitant infection warranting antibiotics, warranted treatment of asymptomatic bacteriuria (ASB), or demonstrated culture results within 1 year that were resistant to all GPTs.

In Phase I, a 21.8% increase in GCAP occurred; this subsequently diminished by 0.5% per 2-week period postintervention. GCAP stabilized upon provision of feedback in Phase II. A decrease in diagnosis of UTIs was observed. Overall, there was a 52.1% relative reduction in fluoroquinolone use. Of note, there were low rates of treatment failure with GCAP. Inappropriate duration was the most common reason for guideline divergence. This study demonstrated that multifaceted AS in the outpatient setting can increase GCAP while limiting use of high-risk agents. However, implementation of 2-phase interventions may not be feasible at certain institutions.

Ertapenem Outpatient Parenteral Antibiotic Therapy Reduction Initiative

Ertapenem is frequently selected as an outpatient treatment agent due to its relative ease of administration [43, 44]. However, overuse of ertapenem can lead to carbapenem resistance [45]. Therefore, Wong and colleagues conducted a quasi-experimental study in adult female patients prescribed either ertapenem or an aminoglycoside for uncomplicated UTIs caused by extended-spectrum beta-lactamase (ESBL)–producing organisms in the outpatient parenteral antibiotic therapy (OPAT) setting [27].

A total of 183 patients were enrolled, with 101 in the preintervention group vs 83 in the postintervention group. The 90-day intervention period consisted of interdisciplinary educational presentations given to hospitalists, emergency medicine/urgent care physicians, intensivists, and pharmacists. The core strategy of the implementation, driven by pharmacists, included 3 items: (1) prospective audit and feedback, (2) formulary restriction/preauthorization, (3) clinical decision support for ASB. The goal was to assess the need for treatment and consider use of aminoglycosides when appropriate. The primary outcome of recurrent UTIs occurred in 28% treated with ertapenem vs 18% treated with aminoglycosides ($P = .57$). Acute kidney injury was not reported in any aminoglycoside-treated patients, and adverse effects did not differ between groups ($P = .99$). Additionally, monthly ertapenem DOT declined by 19% between the pre- and postintervention groups ($P < .01$). This study demonstrated that an AS intervention for UTIs in the OPAT setting can lead to reduced utilization of ertapenem without an effect on recurrent UTIs; there was reassuringly no observed increase in aminoglycoside-resistant isolates.

Educational Interventions for Common Bacterial Infections in Primary Care

Inappropriate antibiotic prescribing in the outpatient setting for treatment of RTIs and ASB has been associated with increases in both antibiotic expenditure and subsequent resistance [2, 46]. Mortrude and colleagues conducted a stepped-wedge trial to evaluate the impact of multifaceted educational interventions targeting providers on antibiotic prescribing for RTIs and ASB in 5 Veteran Affairs primary care clinics [28]. Individualized report cards featuring peer prescribing comparisons, pocket cards with local prescribing guidelines, symptomatic relief prescription pads, clinical decision support order sets, and local ASP patient brochures were implemented. Additionally, in-person educational sessions focused on guideline recommendations for antibiotic utilization, local antibiograms, and ASP resources were provided.

A total of 405 and 482 patients were included pre- and postintervention, respectively. There was no difference in the overall antibiotic prescription rate. However, decreases in prescriptions for acute bronchitis and improvements in the overall appropriateness of prescriptions, driven primarily by uncomplicated sinusitis and pharyngitis, were noted. The composite safety outcome of hospitalization, ED visit, or primary care visit within 4 weeks did not differ between groups. Lastly, patient satisfaction scores remained the same. This study showed that multifaceted educational interventions can improve antibiotic prescribing for acute bronchitis, which rarely requires antibiotics, in primary care clinics without adversely impacting related health care visits or patient satisfaction. Limitations include the retrospective study design and potential Hawthorne effect as providers were aware that their prescribing patterns were being monitored.

Nurse Education for Urinary Tract Infections in Long-term Care

Antibiotics are commonly prescribed inappropriately to treat ASB and UTIs in the LTC setting [7, 46]. Arnold and colleagues conducted an open-label, parallel-group, cluster randomized controlled trial to evaluate the impact of an educational intervention targeting nursing staff on antibiotic prescribing for UTIs in 22 nursing homes in Denmark [29].

In this study, a total of 11 nursing homes received interactive educational sessions and a dialogue tool for decision support, while 11 nursing homes continued standard practice. The primary outcome was the number of antibiotic prescriptions for UTIs per resident per days at risk, which were defined as the number of days the resident spent at the nursing home during the trial period. A total of 765 residents (84 035 days) and 705 residents (77 817 days) were assessed for the primary outcome for the intervention and control groups, respectively. There was a substantial decrease in the number of antibiotic prescriptions for UTIs per resident per days at risk in the number of inappropriate antibiotic treatments for UTIs for the intervention group. However, there was no change in the number of appropriate antibiotic treatments for UTIs. While there was a trend toward an increase in all-cause hospitalizations in the intervention group, there was no change in all-cause mortality. This study showed that a nurse-driven intervention can decrease antibiotic prescribing and inappropriate treatments for UTIs in nursing homes without significantly increasing all-cause hospitalizations and mortality. Limitations include the study location, which may limit the external validity of the study, the open-label design, which could have resulted in ascertainment bias, and the convenience sampling and voluntary participation of nursing homes.

Delayed Antibiotic Prescribing for Acute Otitis Media

Delayed antibiotic prescribing involves providing a prescription to fill in the event that symptoms worsen or fail to improve after 48–72 hours. This strategy is recommended for select patients with acute otitis media (AOM), including those 6 months and older with mild to moderate unilateral AOM [47]. Frost and colleagues performed a multisite, quasi-experimental, before-and-after intervention study evaluating the impact of bundled antimicrobial stewardship intervention on rates of delayed prescribing for AOM [30].

The bundled AS intervention included monthly education plus audit and feedback as well as access to online resources and content expertise. Practice site champions received guidance on suggested stewardship strategies, but they could tailor their approaches according to practice needs. After the 6-month intervention period, access to online resources and content expertise continued, but monthly education plus audit and feedback was stopped. The most commonly utilized stewardship strategies across all practices included provider and patient education, tracking rates of delayed prescribing, and reporting provider-level data to practitioners.

Delayed antibiotic prescriptions for AOM increased from 2% at baseline to 21% at intervention end. This improvement was sustainable up to 6 months postintervention. From this project, a free, publicly available resource package was developed to assist other practices with improving outpatient antibiotic prescribing for children [48]. Delayed antibiotic prescribing may reduce antibiotic use for AOM, but further research should investigate how often these prescriptions are filled. Overall, this study highlights a low-cost intervention to increase rates of delayed antibiotic prescribing for AOM across a diversity of settings.

Primary Care Provider Education Modules

Canada has shown minimal improvement in outpatient antibiotic prescribing over the past 10 years despite early ASP efforts, reporting 666 prescriptions dispensed per 1000 patient visits in 2012 compared with 658 prescriptions per 1000 patient visits in 2017 [49]. McIsaac and colleagues enrolled 6 Ontario-based family medicine clinics in a pragmatic, controlled trial of a primary care provider–focused AS initiative [31].

After an initial educational session on AS, resistance, and strategies for reducing antibiotic prescribing, providers were asked to complete education modules related to the 5 targeted disease states: RTIs, tonsillitis, pharyngitis, acute bronchitis, and acute uncomplicated cystitis. Additionally, providers were given clinical decision aids, patient information leaflets, local clinic ASP support, and financial incentives to support appropriate antimicrobial prescribing. At the end of the 5-month study period, there was no difference in overall antibiotic prescribing between control and intervention clinics. However, the number of delayed antibiotic prescriptions increased, and antibiotic prescriptions for durations >7 days decreased. Study limitations included lack of participation by all clinic providers at intervention clinics and heterogeneity among study clinics.

Ambulatory Care Pharmacist Prescription Audit and Feedback

Similar to inpatient ASPs, antibiotic prescription audit and feedback are recommended as core elements of outpatient ASPs [2]. Inpatient ASPs usually involve an infectious disease pharmacist or physician for these activities. However, ambulatory care pharmacists (ACPs) are uniquely situated to support this intervention at outpatient clinics.

Choi and colleagues performed a quasi-experimental, retrospective study at 2 primary care offices focusing on the ACP-led feedback and audit of antibiotic prescriptions [32]. Adults with documented International Classification of Diseases, Tenth Revision, codes for UTIs or skin and soft tissue infections (SSTIs) were included in the study. The ASP team provided education to providers and were available for consultation to the ACPs during the postintervention period. The ACPs provided audit and feedback to providers once every 2 weeks during that period.

The study's primary outcome was comparing antibiotic appropriateness before and after the process was implemented, defined as a composite of appropriate drug, dose, duration, and following local empiric therapy guidelines. There was a statistically significant increase in antibiotic appropriateness in the postintervention group. No differences in the secondary outcomes were found regarding rates of adverse drug reactions (ADRs), treatment failure, hospitalization within 30 days, or *Clostridioides difficile* infections. This study shows that even limited resources can have major impacts on antimicrobial prescribing in outpatient settings.

Peer Comparison via Antimicrobial Utilization Reporting in Long-term Care

Residents in LTC facilities are at greater risk for infection and antibiotic-associated adverse effects as compared with other health care settings, and according to some studies, the majority of antibiotic prescribing is inappropriate [5, 6, 50]. To improve prescription practices, Daneman and colleagues added 2 antibiotic variables, including the percentage of residents started on antibiotics and antibiotic prescriptions with a duration >7 days, to a province-wide, voluntary reporting system for quarterly peer comparison audit and feedback [33]. The authors included a randomized controlled trial component within the reporting system through comparing an online dynamic reporting system with the previously mentioned static method. Outcomes were compared between residents treated by physicians enrolled and not enrolled in the quarterly reports. A difference-in-differences (DD) analysis was utilized to compare prescription outcomes between the 4 quarters of the pre-intervention year (2018) with those of the intervention year (2019).

The DD analysis did not find a significant decline in antibiotic initiation, but did show a decline of 2.65% in extended antibiotic prescriptions associated with the audit and feedback. The authors estimated that the intervention reduced total antibiotic use by 335 912 days in 2019. Despite being limited by selection bias due to the voluntary enrollment of the reporting system and by practicality—as not all health care systems have similar large-scale reporting systems available—the use of peer comparison audit and feedback was shown to improve antibiotic prescribing practices in a complicated patient population.

Drug Recovery Assistance and Outpatient Parenteral Antibiotic Therapy

Management of serious bacterial infections in people who inject drugs (PWID) is complicated by concerns with utilizing OPAT. Gelman and colleagues describe a novel approach to managing drug recovery assistance and outpatient parenteral antibiotic therapy (DRA-OPAT) for PWID [34]. They established a multidisciplinary Comprehensive Care of Drug Addiction and Infection (CCDAI) team including an ID physician, hospitalist, psychiatrist, case manager, ID pharmacist, home health care nurse, and a representative from the partner detoxification facility. The CCDAI team met weekly to review management of infections in PWID and determine eligibility for patients to transfer to the detoxification facility for combined DRA-OPAT. Medications for opioid use disorder (MOUD) were offered during hospitalization when appropriate. The hospital system subsidized detoxification facility costs for the DRA-OPAT program.

Over a 1-year period, the team identified 87 patients as DRA-OPAT candidates. Thirty-five patients (40.2%) were successfully enrolled in the DRA-OPAT program. Of these 35 patients, 16 (45.7%) were able to complete the full course of OPAT. Medications for opioid use disorder were associated with successful OPAT completion. When compared with a historical cohort, there were observed reductions in median length of stay and median cost per patient. A limitation of this study is the difficulty in establishing a partnership with an outpatient drug recovery facility that will accommodate OPAT and enrolling all multidisciplinary stakeholders in the CCDAI team. Elements of this integrated program may be useful in management of infections in PWID, such as early provision of MOUD and hospital sponsorship of drug recovery facility costs for patients.

Text Messaging to Maintain Urinary Tract Infection Stewardship Efforts in the Emergency Department

In the ED, an estimated 15.7% of patients are discharged home with an antibiotic [51]. Zalmanovich and colleagues conducted a quasi-experimental before-and-after study to compare adherence to a UTI treatment protocol for patients discharged from the ED [35]. The primary objective was to improve overall adherence to the treatment protocol, with a specific focus on antibiotic selection and treatment duration; a secondary objective was to decrease fluoroquinolone prescribing.

The study design involved 3 different time periods: a 3-month pre-intervention period; a 3-month intensive intervention period, which involved disseminating guidelines, providing short lectures, incorporating order sets into the electronic ED charting system, and providing weekly personal audit and feedback; and an 11-month "booster" period in which monthly text messages of the treatment protocol were sent to ED providers. Adherence to the protocol was compared between the pre-intervention period and the last 2 months of the intensive intervention period, and compared with the last 2 months of the booster period. A total of 427 patients were included: 177 in the pre-intervention period, 156 in the intensive period, and 94 in the booster period. Adherence to the overall treatment protocol, selection of the appropriate antimicrobial agent, and appropriate treatment duration all increased significantly between the pre-intervention and intensive intervention periods and remained significantly increased in the booster period. Fluoroquinolone prescriptions also significantly decreased in the intensive and booster periods. Overall, this study supports that an ASP in the ED results in improved adherence to treatment protocols and uniquely demonstrates that a targeted monthly reminder can preserve the effects of the intervention over a prolonged period of time.

Rapid Patient Education to Reduce Antibiotic Expectations for Respiratory Tract Infections

Perera and colleagues evaluated the impact of providing a short, electronic tablet–based presentation about antibiotic treatment of upper RTIs on patients' expectations for antibiotics and subsequent antibiotic prescribing behavior [36]. Patients were randomized to view a 1-minute presentation immediately before their consultation highlighting either (1) the futility of antibiotics for upper RTIs, (2) potential adverse effects of antibiotics, or (3) healthy lifestyle choices (active control). Before and after the presentations, patients utilized a Likert scale to rate the strength of their belief that antibiotics are effective for treating upper RTIs and their desire to be prescribed an antibiotic.

Postpresentation, participants had a significant reduction in expectation to receive an antibiotic in those who viewed the futility and adverse effects presentations when compared with the control group. Additionally, there was a significant reduction in Likert scores for those who before consultation had agreed with the statement "I think antibiotics are a helpful treatment for cold/flu" in the futility presentation and adverse effect presentation groups than in those who viewed the control presentation.

However, there were no significant reductions in antibiotic prescribing, dispensing, or patient satisfaction. Overall, this study highlights an innovative approach to providing education that was well received and impactful to patients; however, we must also intervene upon prescriber practices as well. All stakeholders require engagement to affect sustainable change.

DISCUSSION

The majority of ASP interventions have been evaluated in inpatient settings, despite the vast majority of antimicrobial prescriptions being written and ultimately dispensed to patients in nonhospital settings [4]. Now that regulatory agencies require ASPs outside of acute care hospitals, data are emerging to inform ASP practice in these settings. Numerous research interventions have directed management of UTIs and RTIs [24, 26–29, 32, 35, 36]. This is not surprising considering that these are 2 of the top infectious syndromes for which excessive antimicrobial prescribing occurs, often due to colonization, lack of true infection (ASB), or viral etiology (upper RTIs). Interventions to improve prescribing within these diseases included education and feedback, specific guidelines and order sets, antibiogram development, and de-escalation of carbapenem usage for patients with UTIs. Some creative educational measures including text messages with protocol reminders and patient-facing rapid education videos were included [35, 36]. Interventions at the time of discharge also led to significant shortening of duration of therapy [25].

Higher-quality data will continue to help establish and grow robust nonhospital ASPs. As ASPs continue to mature in outpatient and nursing home settings, a focus on a greater variety of infectious diseases as well as technological interventions and implementation would be welcome.

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