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

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REVIEW ARTICLE FIDSA

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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