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

Ashley H. Marx,1,2,3 David Cluck,2,4 Sarah B. Green,3 Daniel T. Anderson,4 Kayla R. Stover,5,6 Daniel B. Chastain,6 Elizabeth W. Covington,7 Bruce M. Jones,8 Evan Lantz,9 Ethan Rausch,10 Patrick J. Y. Tu,11 Jamie L. Wagner,12,13 Cyle White,14 Christopher M. Bland,12,13 and P. Brandon Bookstaver14

1Department of Pharmacy, UNC Medical Center, Chapel Hill, North Carolina, USA, 2Department of Pharmacy Practice, East Tennessee State University Bill Gatton College of Pharmacy, Johnson City, Tennessee, USA, 3Department of Pharmacy, Emory University Hospital, Atlanta, Georgia, USA, 4Department of Pharmacy, Augusta University Medical Center, Augusta, Georgia, USA, 5Department of Pharmacy Practice, University of Mississippi School of Pharmacy, Jackson, Mississippi, USA, 6Department of Clinical and Administrative Pharmacy, University of Georgia College of Pharmacy, Athens, Georgia, USA, 7Department of Pharmacy Practice, Samford University McWhorter School of Pharmacy, Birmingham, Alabama, USA, 8Department of Pharmacy, St. Joseph’s/Candler Health System, Inc., Savannah, Georgia, USA, 9Department of Pharmacy, Spartanburg Regional Healthcare System, Spartanburg, South Carolina, USA, 10Department of Pharmacy, UNC Medical Center, Chapel Hill, North Carolina, USA, 11Department of Pharmacy, Charlie Norwood VA Medical Center, Augusta, Georgia, USA, 12Department of Pharmacy, Erlanger Health System, Chattanooga, Tennessee, USA, 13University of Georgia College of Pharmacy, Clinical and Administrative Pharmacy, Savannah, Georgia, USA, and 14Department of Clinical Pharmacy and Outcomes Sciences, University of South Carolina College of Pharmacy, Columbia, South Carolina, USA

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, 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.
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;
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.

---

*Figure 1. Flow diagram of the article selection process for the 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 - In-patient 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. | Primary: - Change in the probability of cephalosporin use among patients with a penicillin allergy at the intervention site after the removal of the warning (IRROR, 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 55% PI vs 55% PE (P = .005; PI vs PI = .0005; PI vs PDI = .0009; PDI vs PE = .93). Secondary: - Median length of antimicrobial therapy (d): 5.75 PI vs 2.18 PDI vs 4.45 PE (P = .035; PI vs PDI = .0001; PDI vs PE = .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+ or 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. Post-intervention 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. |
| 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 7–11) 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 000 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. Alasaimy 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 (PRE) vs 3.6 (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 |
| 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 cefazidime use (PRE; RR, 0.994; 95% CI, 0.992–0.995; P < .0001); rate of cefazidime 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 cefazidime (PRE; RR, 1.09; 95% CI, 0.997–1.192; P = .06); rate of Pseudomonas aeruginosa nonsusceptible to cefazidime (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 cefazidime (PRE; RR, 1.116; 95% CI, 1.078–1.154; P < .0001); rate of Enterobacter cloacae nonsusceptible to cefazidime (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: 4.5% (23/512) vs 4.8% (22/446) -Mortality: 7.7% (44/512) 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 -Recurrence fever: 34.7% (233/672) vs 41.6% (289/695); P = .009 -LOS, median (range): 27 (10–101) d vs 27 (12–79) d
| 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: e0029-21. | 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. |
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 postdiagnostic 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 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 pre-intervention 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 upfront 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.

**Acknowledgments**

**Financial support.** No funding supported this work.

**Potential conflicts of interest.** All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**Author contributions.** A.H.M., S.B.G., C.M.B., and P.R.B. all supported idea and content development. All authors provided written content and edits for the manuscript.

**References**

1. Pierce J, Stevens MP. COVID-19 and antimicrobial stewardship: lessons learned, best practices, and future directions. Int J Infect Dis 2021; 113:103–8.
2. Mazdaeyan H, Nori P, Patel P, et al. Antimicrobial stewardship at the core of COVID-19 response efforts: implications for sustaining and building programs. Curr Infect Dis Rep 2020; 22:23.
3. Winders HR, Bailey P, Kohn J, et al. Change in antimicrobial use during COVID-19 pandemic in South Carolina hospitals: a multicenter observational cohort study. Int J Antimicrob Agents 2021; 58:106453.
4. Khan S, Hasan SS, Bond SE, O’Day BR, Aldeyab MA. Antimicrobial consumption in patients with COVID-19: a systematic review and meta-analysis. Expert Rev Anti Infect Ther 2022; 20:74–79.
5. Centers for Disease Control and Prevention. COVID-19 U.S. impact on antimicrobial resistance. 2022 special report. Available at: https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf. Accessed April 8, 2022.
6. Antimicrobial Stewardship & Healthcare Epidemiology. Available at: https://www.cdc.gov/healthcare-safety/antimicrobial-stewardship-and-healthcare-epidemiology. Accessed August 6, 2022.
7. Journal of Antimicrobial Chemotherapy. Antimicrobial resistance. Available at: https://academic.oup.com/jacarrow. Accessed August 6, 2022.
8. Chastain DB, Cluck DB, Stover KR, et al. A baker’s dozen of top antimicrobial stewardship intervention publications in 2017. Open Forum Infect Dis 2019; 6. https://doi.org/10.1093/ofid/ofz133
9. Chahine EB, Durham SH, Medwala KN, et al. A baker’s dozen of top antimicrobial stewardship intervention publications in 2018. Open Forum Infect Dis 2019; 6. https://doi.org/10.1093/ofid/ofz450
10. Stover KR, Chahine EB, Cluck D, et al. A baker’s dozen of top antimicrobial stewardship intervention publications in 2019. Open Forum Infect Dis 2020; 7. https://doi.org/10.1093/ofid/ofaa402
11. Green SB, Stover KR, Barbieri A. A baker’s dozen of top antimicrobial stewardship intervention publications in 2020. Open Forum Infect Dis 2021; 8. https://doi.org/10.1093/ofid/ofab422
12. Green SB, Mars AM, Chahine EB, et al. A baker’s dozen of top antimicrobial stewardship intervention publications in non-hospital care settings in 2021. Open Forum Inf Dis 2022; 9. https://doi.org/10.1093/ofid/ofac599
13. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin “allergy” in hospitalized patients: a cohort study. J Allergy Clin Immunol 2014; 133:790–6.
14. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. JAMA 2019; 321:188–99.
15. DePestel DD, Benninger MS, Danziger L, et al. Cephalosporin use in treatment of penicillin allergies. J Am Pharm Assoc 2008; 48:530–40.
16. Collins CD, Bookal RS, Malani AN, et al. 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. Open Forum Infect Dis 2022; 9. https://doi.org/10.1093/ofid/ofab544
17. Blumenthal KG, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES. The impact of a reported penicillin allergy on surgical site infection risk. Clin Infect Dis 2018; 66:329–36.
18. Rice AD, Rehm SJ, Dalovisio JR, et al. Practice guidelines for outpatient parenteral antimicrobial therapy. IDSA guidelines. Clin Infect Dis 2004; 38:1651–71.
Baxter R, Ray GT, Fireman BH. Case-control study of antibiotic use and subsequent *Clostridium difficile*-associated diarrhea in hospitalized patients. Infect Control Hosp Epidemiol 2008; 29:44–50.

West RM, Smith CJ, Pavitt SH, et al. "Warning allergic to penicillin": association between penicillin allergy status in 2.3 million NHS general practice electronic health records, antibiotic prescribing and health outcomes. J Antimicrob Chemother 2019; 74:2075–82.

Jefres MN, Narayanan PP, Shuster JE, Schramm GE. Consequences of avoiding β-lactams in patients with β-lactam allergies. J Allergy Clin Immunol 2016; 137: 1148–53.

Macy E, McCormick TA, Adams JL, et al. Association between removal of a warning against cephalosporin use in patients with penicillin allergy and antibiotic prescribing. JAMA Netw Open 2021; 4:e218367.

Chowdhury F, Sarkar K, Branche A, et al. Preventing the inappropriate treatment of asymptomatic bacteriuria at a community teaching hospital. J Community Hosp Intern Med Perspect 2012; 2:17814.

Liu J, Kaye K, Mercure N, et al. It is time to define antimicrobial never events. Infect Control Hosp Epidemiol 2019; 40:206–7.

Advani S, Polage C, Fakih M. Deconstructing the urinalysis: a novel approach to diagnostic and antimicrobial stewardship. Antimicrob Steward Healthe Epidemiol 2021; 1:86.

Rico M, Sulaiman R, MacLeod R. Asymptomatic bacteriuria: impact of an antimicrobial stewardship bundle to reduce unnecessary antibiotics in patients without urinary catheters. Am J Health Syst Pharm 2021; 78(Suppl 3):S83–7.

McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018; 66:e1–48.

Gould CV, Edwards JR, Cohen J, et al. Effect of nucleic acid amplification testing on population-based incidence rates of *Clostridium difficile* infection. Clin Infect Dis 2013; 57:1304–7.

Herman DJ, Sarabia A, Chan H, Graham C. Changing results to change results: nudging antimicrobial prescribing for *Clostridium difficile*. Open Forum Infect Dis 2021; 8. https://doi.org/10.1093/ofid/ofab605

Schweitzer VA, et al. 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. Lancet Infect Dis 2021; 21:e81.

Yahav D, Francheshini E, Koppel F, et al. Seven versus fourteen days of antibiotic therapy for uncomplicated gram-negative bacteremia: a non-inferiority randomised controlled trial. Clin Infect Dis 2019; 69:1091–8.

von Dach E, Albrich WC, Brunel AS, et al. Effect of C-reactive protein-guided anti-bacterial treatment duration, 7-day treatment, or 14-day treatment on 30-day clinical failure rate in patients with uncomplicated gram-negative bacteremia: a randomized clinical trial. JAMA 2020; 323:2160–9.

Molina J, Montero-Matos E, Praena-Segovia J, et al. Seven versus 14-days course of antibiotics for the treatment of bloodstream infections by Enterobacteriales. A randomised, controlled trial. Clin Microbiol Infect 2022; 28:550–7.

 Fukuda T, Tanuma K, Iio S, et al. 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. Cureus 2021; 13: e14635.

Kumar A, Ellis P, Arabi Y, et al. Initiation of inappropriate antimicrobial therapy results in a five-fold reduction of survival in human septic shock. Chest 2009; 136: 1237–48.

Kang GI, Kim SH, Park WB, et al. Bloodstream infections caused by carbapenem-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. Antimicrob Agents Chemother 2005; 49:760–6.

Cain SE, Kohn J, Bookstaver PB, Albrecht H, Al-Hasan MN. Stratification of the impact of inappropriate empirical antimicrobial therapy for gram-negative bloodstream infections by predicted prognosis. Antimicrob Agents Chemother 2015; 59:245–50.

Banerjee R, Komarow L, Virk A, et al. Randomized trial evaluating clinical impact of rapid identification and susceptibility testing for gram-negative bacteremia: RAPIDS-GN. Clin Infect Dis 2021; 73:e39–46.

Dare RK, Lusardi K, Pearson C, et al. Clinical impact of accelerate pheno rapid blood culture detection system in bacteremic patients. Clin Infect Dis 2021; 73: e4616–26.

Ehren K, Meilinner A, Jazzmatz N, et al. Clinical impact of rapid species identification from positive blood cultures with same-day phenotypic antimicrobial susceptibility testing on the management and outcome of bloodstream infections. Clin Infect Dis 2020; 70:1285–93.

Robinson ED, Sülwoll AM, Attai AE, et al. Implementation of a rapid phenotypic susceptibility platform for gram-negative bloodstream infections with paired antimicrobial stewardship intervention: is the juice worth the squeeze? Clin Infect Dis 2021; 73:783–92.

Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. Infect Control Hosp Epidemiol 2005; 26:166–74.

Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States and Prevention; 2019. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf. Accessed August 3, 2022.

Davis JS, Sud A, O’Sullivan MVN, et al. Combination of vancomycin and β-lactam therapy for methicillin-resistant *Staphylococcus aureus* bacteremia: a pilot multicentered randomized controlled trial. Clin Infect Dis 2016; 62: 173–80.

Tong SYC, Lye DC, Yahav D, et al. Effect of vancomycin or daptomycin with vs without an anti-staphyloococcal β-lactam on mortality, bacteremia, relapse, or treatment failure in patients with MRSA bacteremia: a randomized clinical trial. JAMA 2020; 323:527–37.

Geria M, Haddad F, Ruzvi K, et al. Clinical data on daptomycin plus cefetamor versus standard of care monotherapy in the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother 2019; 63: e02483-18.

Paulsen J, Solligård E, Damås JK, Dewan A, Åsvold BO, Bracken MB. The impact of infectious disease specialist consultation for *Staphylococcus aureus* bloodstream infections: a systematic review. Open Forum Infect Dis 2016; 3. https://doi.org/10.1093/ofid/ofw048

Goto M, Jones MP, Schweizer ML, et al. Association of infectious diseases consultation with long-term postdischarge outcomes among patients with *Staphylococcus aureus* bacteremia. JAMA Netw Open 2020; 3:e1921048.

Alosaimy S, Lagnf AM, Morrisette T, et al. Standardized treatment and assessment pathway improves mortality in adults with methicillin-resistant *Staphylococcus aureus* bacteremia: STAPH study. Open Forum Infect Dis 2021; 8. https://doi.org/10.1093/ofid/ofab621

Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016; 62: e51–77.

Lee RA, Scully MC, Camins BC, et al. Improvement of gram-negative susceptibility to fluoroquinolones after implementation of a preauthorization policy for fluoroquinolone use: a decade-long experience. Infect Control Hosp Epidemiol 2018; 39:1419–24.

Idgo AJ, Brown ML, Wiener HW, et al. How fluoroquinolone preauthorization affects third- and fourth-generation cephalosporin use and resistance in a large academic hospital. Infect Control Hosp Epidemiol 2022; 43:848–59.

Verlinden A, Mikulska M, Knelange NS, Averbuch D, Styczynski J; Infectious Diseases Working Party (IDWP) of the European Group for Blood and Marrow Transplantation Group (EBMT). Current antimicrobial practice in febrile neutropenia across Europe and Asia: the EBMT Infectious Disease Working Party survey. Bone Marrow Transplant 2020; 55:1588–94.

Verlinden A, Janssen H, Goossens H, et al. Safety and efficacy of antibiotic deescalation and discontinuation in high-risk hematological patients with febrile neutropenia: a single-center experience. Open Forum Infect Dis 2022; 9. https://doi.org/10.1093/ofid/ofab624

Pal M. Morbidity and mortality due to fungal infections. J App Microbiol 2021; 7. https://doi.org/10.1177/2576-1412.100002

Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. Clin Infect Dis 2006; 43:25–31.

Apsisranthanarak A, Yatsares T, Mundy LM, et al. Impact of education and an antifungal stewardship program for candidiasis at a Thai tertiary care center. Infect Control Hosp Epidemiol 2010; 31:722–7.

Sutepvorn A, Apsisranthanarak A, Camins R, et al. Inappropriate use of antifungal medication in a tertiary care center in Thailand: a prospective study. Infect Control Hosp Epidemiol 2008; 29:370–3.

Nivoix Y, Launoy A, Lutun P, et al. Adherence to recommendations for the use of antifungal agents in a tertiary care hospital. J Antimicrob Chemother 2012; 67; 2506–13.

Jacobs DM, Dilworth TJ, Beyda ND, Casapao AM, Bowers DR. Overtreatment of asymptomatic candiduria among hospitalized patients: a multi-institutional study. Antimicrob Agents Chemother 2018; 62:e01464–517.

Delit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for...
developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007; 44:159–77.

62. Kara E, Metan G, Bayraktar-Ekincioglu A, et al. Implementation of pharmacist-driven antifungal stewardship program in a tertiary care hospital. Antimicrob Agents Chemother 2021; 65:e0062921.

63. Joint Commission on Hospital Accreditation. APPROVED: new antimicrobial stewardship standard. Jt Comm Perspect 2016; 36:1, 3–4, 8.

64. Duke Antimicrobial Stewardship Outreach Network website. Available at: http://dason.medicine.duke.edu/home. Accessed June 15, 2022.

65. Moehring RW, Yarrington ME, Davis AE, et al. Effects of a collaborative, community hospital network for antimicrobial stewardship program implementation. Clin Infect Dis 2021; 73:1656–63.

66. O’Leary EN, Edwards JR, Srinivasan A, et al. National Healthcare Safety Network Standardized Antimicrobial Administration Ratios (SAARs): a progress report and risk modeling update using 2017 data. Clin Infect Dis 2020; 71:e702–9.

67. Patel SJ, Saiman L, Duchon JM, Evans D, Ferri YH, Larson E. Development of an antimicrobial stewardship intervention using a model of actionable feedback. Interdiscip Perspect Infect Dis 2012; 2012:150367.

68. Shealy S, Kohn J, Yongue E, et al. Application of standardized antimicrobial administration ratio as a motivational tool within a multi-hospital healthcare system. Pharmacy (Basel) 2021; 9:32.

69. Barlam TF, Al Mohajer MA, Al-Tawfiq JA, et al. SHEA statement on antibiotic stewardship in hospitals during public health emergencies. Inf Control Hosp Epidemiol 2022; 43:1541–52.

70. Buckel WR, Stenehjem EA, Hersh AL, Hyun DY, Zetts RM. Harnessing the power of health systems and networks for antimicrobial stewardship. Clin Infect Dis. 2022. https://doi.org/10.1093/cid/ciac515

71. Verlinden A, Janssens H, Goossens H, et al. Clinical and microbiological impact of discontinuation of fluoroquinolone prophylaxis in patients with prolonged profound neutropenia. Eur J Haematol 2014; 93:302–8.