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ANTIMICROBIAL DEVELOPMENT AND DRUG RESISTANCE (K CLAEYS AND A VEGA, SECTION EDITORS)

Antimicrobial Stewardship Interventions to Combat Antibiotic Resistance: an Update on Targeted Strategies

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Abstract

Purpose of Review Overutilization of antimicrobials is a known contributor to the development of antimicrobial resistance, which is a threat to global health. The goal of antimicrobial stewardship programs (ASPs) is to implement targeted interventions to reduce inappropriate antimicrobial prescribing and prevent development of antimicrobial resistance. We aim to review recently published literature focused on five categories of ASP interventions that have demonstrated success in optimizing appropriate antimicrobial use, improving patient outcomes, and fighting antimicrobial resistance.

Recent Findings In the past year, ASP interventions in the published literature have focused on minimizing duration of antimicrobial therapy for infectious syndromes, implementing novel methods for performing prospective audit and feedback, utilizing microbiology laboratory or rapid diagnostic tests to expedite diagnosis, leveraging clinical decision support and electronic medical record tools, and performing penicillin allergy assessment. While the majority of studies assessing ASP interventions do not assess changes in antimicrobial resistance, outcomes demonstrating improved appropriate antibiotic use have been used as a surrogate.

Summary Successful ASPs should seek to implement and evaluate novel interventions targeting improvement in antimicrobial prescribing. Such interventions are of critical importance to prevent further growth of antimicrobial resistance.

Keywords Antimicrobial stewardship · Antibiotic resistance · Intervention

Introduction

Antibiotics are a critical resource, having saved millions of lives over the past century. Unfortunately, the overuse and misuse of antibiotics have led to the development of antimicrobial resistance, which is currently one of the most serious public health concerns across the globe [1]. In a report by the Centers for Disease Control and Prevention (CDC), multidrug-resistant organisms (MDROs) are responsible for more than 2 million infections and result in approximately 23,000 deaths annually in the USA [2]. A 2018 report by Burnham and colleagues estimated that these numbers may actually be much higher with over 150,000 deaths due to MDROs annually [3]. If the trend of increasing resistance continues at its current rate, by the year 2050, annual deaths attributable to antimicrobial-resistant organisms are expected to reach 10 million patients world-wide and cost over 100 trillion dollars annually [4].

In order to combat the growing threat of bacterial resistance, immediate action is needed. Antimicrobial stewardship

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Summary This article reviews literature published over the past year (2018–present) that address antimicrobial stewardship interventions aimed at combating antibiotic resistance.

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programs (ASPs) have repeatedly demonstrated improvement in antimicrobial prescribing practices, which can stem the tide of antimicrobial resistance and preserve current antimicrobial therapies [5]. The CDC as well as the Joint Commission have published recommendations and standards for conducting antimicrobial stewardship in both inpatient and outpatient settings [6–8, 9••]. While the practice and main principles of antimicrobial stewardship have been established for more than a decade, ASPs are continuously evolving, looking to increase program efficiency, reach, and implement novel approaches to patient care. Despite being one of the main goals of antimicrobial stewardship, the direct effects of ASP interventions on reducing antimicrobial resistance are often not able to be measured and are confounded by many factors [5, 6]. Therefore, interventions aimed at minimizing inappropriate antibiotic use, including unnecessary and suboptimal use, are often used as surrogate markers to measure the impact of ASPs on resistance [10]. In this paper, we review antimicrobial stewardship literature from the year 2018, focusing on five main categories of interventions that can be implemented by ASPs to improve antimicrobial use, patient outcomes, and fight antibiotic resistance.

Minimizing Durations of Therapy

A paradigm shift in infectious diseases pharmacotherapy in recent years has involved defining the shortest appropriate duration of therapy for different infection types. In a sample of over 7000 patients in a single ICU, Teshome and colleagues demonstrated that each additional day of antipseudomonal beta lactam therapy was associated with an increased risk for developing new beta lactam resistance with an adjusted hazard ratio (aHR) of 1.04 (95% confidence interval [CI], 1.04–1.05) [11••]. Prescribing antibiotic treatment for the shortest duration possible is likely the most important method of achieving clinical success while reducing antibiotic resistance; however, durations of therapy studies have been lacking for many disease states and most courses are likely prescribed for much longer than needed [12, 13, 14].

Three studies were published in the past year evaluating short-course therapy for Gram-negative bacteremia in the inpatient setting. The first, by Chotiprasitsakul and colleagues, was a retrospective, multi-center, cohort examining 30-day mortality in patients with monomicrobial Enterobacteriaceae bacteremia [15•]. Patients were stratified for comparison based on the receipt of short-course (6–10 days therapy) vs. prolonged-course (11–16 days) therapy. The majority of bacteremias were caused by *Escherichia coli* (46.9%), *Klebsiella* (32.6%), and *Enterobacter* species (10.4%). Urinary (37.9%) and intra-abdominal (34.2%) were the most common sources of infection. Out of the 385 propensity score-matched pairs, no difference in mortality was observed between groups (aHR, 1.00; 95% CI, 0.62–1.63) despite the short-course group receiving a median (interquartile range [IQR]) of 7 days fewer treatment (8 days [7–9 days] vs. 15 days [13–15 days]). There was also no difference in recurrence of bacteremia between groups (odds ratio [OR], 1.32; 95% CI, 0.48–3.41). Furthermore, the authors examined new Gram-negative resistance, not previously identified within a year prior to index blood culture date. While there were numerically more cases of new-onset antimicrobial resistance in the prolonged-course group (7.3% vs. 4.4%), this was not statistically significant (OR, 0.59; 95% CI, 0.32–1.09). Another multi-center, prospective, open-label, randomized study by Yahav and colleagues demonstrated similar results [16•]. Six hundred four patients with monomicrobial Gram-negative bloodstream infections achieving source control were eligible for 1:1 parallel group randomization to receive either 7-day (intervention group) or 14-day (control group) treatment. The majority of bacteremias were caused by *E. coli* (62.9%) followed by *Klebsiella* species (13.2%). *Pseudomonas* species accounted for 7.9% of cases, while 18% of all included organisms were considered multi-drug resistant. Urinary tract (68%) and intra-abdominal (11.8%) infections were the most common source of bacteremia. No difference was observed in the primary composite outcome of 90-day all-cause mortality, infection relapse, extended hospitalization (> 14 days), or readmission (intervention group 45.8% vs. control group 48.3%; risk difference − 2.6% [95% CI, − 10.5–5.3]). Finally, a third study by Fabre and colleagues examined the impact of short-course (7–11 days) vs. long-course (12–20 days) antibiotic therapy on 30-day mortality and recurrent infection in patients with *Pseudomonas aeruginosa* bacteremia [17••]. This retrospective, multi-center, observational, propensity-score-weighted cohort included 249 adult patients. The median (IQR) duration of therapy was 9 days (8–10 days) in the short-course group vs. 16 days (14–17 days) in the long-course group. There was no difference in the composite primary endpoint of 30-day mortality or reinfection between groups (OR, 1.06; 95% CI, 0.42–2.68), including in those who were switched to oral fluoroquinolone therapy (13% for both groups). Additionally, patients who received short-course therapy spent a median of 4.04 fewer days in the hospital compared with patients who received long-course therapy ($p = 0.005$). Overall, these studies demonstrated that short-course therapy for Gram-negative bacteremia appears to be safe and effective. These findings support

ASPs in pursuing interventions to reduce durations of therapy for Gram-negative bloodstream infections. In addition, it gives stewardship leaders further ammunition when discussing durations of therapy for other less severe infections in advocating for shorter courses.

The New Prospective Audit and Feedback: Handshake Stewardship

Prospective audit-with-feedback (PAF) remains a core strategy of inpatient ASPs; however, performing PAF in the outpatient setting is challenging as limited resources are available for successful implementation and sustainability [5, 18–21, 22, 23]. The most success has been seen when incorporating concepts of behavioral science such as peer comparison, accountable justification, and public commitment [7, 19–21, 22•, 23–25].

In the pediatric population, PAF is commonly implemented as part of "handshake stewardship", which entails review of prescribed antimicrobials and provision of in-person feedback by the ASP team. Handshake stewardship was first described by Hurst et al., which found a 10.3% decrease in antibacterial days of therapy (DOT) per 1000 patient-days over the 4-year study period [26•]. In 2019, Hurst et al. published an expanded report detailing the types of interventions performed during handshake stewardship. In the 19-month study period, 3078 interventions were made, with an 86% acceptance rate [27]. The majority of interventions focused on de-escalation/discontinuation (49%), education (24%), or escalation (18%). Interventions often targeted vancomycin (17%) and antipseudomonal beta lactams (16%); however, narrow-spectrum antimicrobials were targeted in 28% of interventions, emphasizing the importance of evaluating all antimicrobial use. This study also demonstrated the value of infectious diseases (ID) physician participation in PAF, as the rate of intervention increased significantly when an ID physician was present (9.6% vs. 5.4%, $p < 0.0001$). A similar intervention was implemented in a pediatric intensive care unit (PICU) in Tokyo, Japan. PAF was performed daily via joint ID/PICU rounds where all patients prescribed antimicrobials were discussed. Antimicrobial pre-authorization was required for five antipseudomonal antibiotics. Together, these interventions resulted in a 24% decrease in antipseudomonal DOT/1000 patient-days (288 vs. 215, $p = 0.026$) in an interrupted time-series analysis [28]. There was no change in non-antipseudomonal DOT/1000 patient-days over the same time period, indicating that the ASP interventions did not merely shift antimicrobial use to more narrow-spectrum agents. Clinical outcomes such as PICU length of stay, infection-related deaths per 1000 patient-days, and PICU readmission rates did not change, suggesting no harm to patients secondary to decreased antimicrobial utilization.

Unfortunately, implementation of handshake stewardship can be challenging in institutions where ASP resources are limited or are a shared resource. In these settings, "stewardship extenders" can be utilized to perform PAF via handshake stewardship. Klatte and colleagues describe their implementation of handshake stewardship within a non-freestanding pediatric hospital, noting that pediatric patients were not commonly targeted by the adult-focused ASP team [29]. Thus, a pediatric ASP team comprised of pediatric-trained clinical pharmacists and ID physicians was established to perform thrice weekly PAF on patients actively prescribed a targeted antimicrobial. Over an 18-month time period, 882 ASP reviews were performed with an action rate of 37.1% and acceptance rate of 74.6%. Gentamicin and ceftriaxone were the most common antimicrobials reviewed; however, vancomycin (OR, 2.08; 95% CI, 1.74–2.48) and clindamycin (OR, 1.37; 95% CI, 1.05–1.77) reviews were most likely to generate a recommendation. While the most common intervention performed was recommending antibiotic discontinuation (45%), targeted antimicrobial DOT/1000 patient-days did not significantly change (247.3 vs. 222.5).

At their 2018 Leading Practices in Antimicrobial Stewardship key stakeholder meeting, the Joint Commission declared handshake stewardship to be an emerging practice, emphasizing the value of active engagement of frontline prescribers [30]. Handshake stewardship is a growing trend in PAF interventions and is supported by literature demonstrating high intervention acceptance rates and significant decreases in antimicrobial consumption. Based on these data, ASPs may consider implementing handshake stewardship for additional populations beyond pediatric patients.

Rapid Diagnostic Technology Interventions

Fostering a collaborative relationship between the microbiology and antimicrobial stewardship teams is of critical importance. The positive impact of implementing rapid diagnostic tests (RDT) for blood stream infections in conjunction with real-time antimicrobial stewardship team notification in the inpatient setting has been well-described in the literature [31–33, 34••]. In contrast to these findings, a study by Bukowski and colleagues studied the implementation of an RDT for bacteremia caused by Gram-positive cocci (GPC) in clusters in a community teaching hospital with limited stewardship resources [35•]. The GeneXpert MRSA/SA (Cepheid, Sunnyvale, CA) blood culture RDT was used for organism identification which is able to discern *Staphylococcus aureus* species as well as coagulase-negative staphylococcus (CoNS). A microbiology laboratory staff member notified the patient's bedside nurse with both the positive Gram-stain result and final result of the RDT who was then responsible for notifying the patient's primary inpatient provider. The RDT

significantly decreased the median time to appropriate therapy (15 vs. 0 h, $p < 0.001$) and length of stay (10.5 vs. 7.7 days, $p = 0.015$) for patients with CoNS blood cultures even without real-time antimicrobial stewardship team notification. The author's concluded that the test's easy-to-interpret results allowed for quick and appropriate interpretation by clinicians and for the hospital's limited ASP resources to be directed toward other interventions. These findings are similar to those by Avdic and colleagues who demonstrated that blood cultures positive for GPC in clusters identified by the Verigene nucleic acid microarray assay resulted in significantly decreased time to appropriate therapy even after ASP intervention was removed [36]. In all, these data demonstrate that while the majority of RDT require real-time ASP notification for successful implementation, there may be less complex tests that can be successfully used without ASP shepherding which may help hospitals with limited ASP resources in choosing which RDT to implement.

Rapid diagnostic tests may also be a powerful tool to aid ASPs in the treatment of respiratory tract infections. The MRSA nasal PCR has been identified as a helpful real-time tool in de-escalation of antimicrobial therapy [37, 38]. With a turn-around time of approximately 60 min and a negative predictive value over 99%, it can help ASPs to quickly rule out MRSA pneumonia [39••, 40]. A study by Dunaway and colleagues evaluated the implementation of a pharmacist-initiated MRSA nasal PCR protocol on the duration of antimicrobial therapy in patients with pneumonia [41]. Notably, their protocol allowed pharmacists to independently stop vancomycin therapy following negative PCR results. The median duration of vancomycin therapy was shortened from 49 h in the pre-PCR group to 18 h in the PCR group ($p < 0.001$). The authors reported no negative impact on patient outcomes; however, they did not report on protocol compliance or if any patients had vancomycin reinitiated following discontinuation by the pharmacy team.

The use of PCR-based platforms to detect respiratory viruses also has the potential to improve antimicrobial stewardship-related outcomes, as identification of a virus as the causative pathogen of illness may lead to discontinuation of empiric antibiotics. However, data supporting utilization of respiratory pathogen panels (RPPs) to improve antimicrobial stewardship outcomes is conflicting. In a matched cohort study by Srinivas et al., a clinical decision support (CDS)-based antimicrobial stewardship alert was created to identify patients who tested positive for a respiratory virus and were prescribed antimicrobial therapy commonly used for bacterial pneumonia [42]. The CDS alerts were monitored by antimicrobial stewardship pharmacists and PAF was performed to recommend antibiotic de-escalation or discontinuation. Post-intervention, 172 CDS alerts were reviewed with a 32% action rate. Antibiotic use metrics were evaluated 3 months before ($n = 77$) and after ($n = 86$) the CDS with PAF was implemented and found no change in time to antibiotic de-escalation (median 2.7 days vs. 2.3 days, $p = 0.088$). Time to discontinuation of piperacillin-tazobactam (4 vs. 1.9 days, $p = 0.057$), ceftriaxone (2.7 vs. 1.8 days, $p = 0.75$), and levofloxacin (3.6 vs. 2 days, $p = 0.4$) was numerically lower but did not reach statistical significance. These findings may be limited due to the small sample size and short period of evaluation, but suggest there is opportunity to encourage antibiotic de-escalation in the setting of respiratory illness caused by a viral pathogen.

In the outpatient setting, the use of RDT has a similar potential to improve antimicrobial use by providing real-time, diagnostic information by which more informed prescribing can be made. Most of the literature to date has centered around the diagnosis of upper respiratory tract infections (URIs) where the use of rapid antigen tests for group A streptococcus and influenza-like illnesses have led to improved prescribing and overall reductions in unnecessary antimicrobial use [43, 44, 45••, 46, 47, 48–50, 51, 52, 53, 54]. A pre/post study assessed implementation of an RPP in pediatric patients diagnosed with uncomplicated URIs in the inpatient and emergency department (ED) setting. While mean inpatient DOT and percentage of ED discharge prescriptions remained unchanged, inpatients who were RPP-positive ($n = 81$) had fewer antibiotic DOT compared with RPP-negative patients ($n = 27$) [2.99 vs. 4.30, $p = 0.032$] [55]. In the ED group, 100% (34/34) of the patients tested using the RPP had a positive result and of them, only 3 (8.8%) were prescribed an antibiotic at discharge compared with 178/433 (41.4%) of patients who were not tested with the RPP ($p < 0.001$). Low ED utilization of the RPP was likely because the RPP result was not available at the time of ED discharge and the cost of the test is often not covered by medical insurance. These data suggest there is a role for ASPs to leverage respiratory viral diagnostic technology to decrease antimicrobial consumption. However, until reliable, affordable, point-of-care tests with good sensitivity and specificity are available; further data are needed to identify the optimal mechanism by which these tests should be incorporated. Additionally, collaborative models to enhance access to this intervention should be considered.

Clinical Decision Support and Electronic Medical Record Interventions

Despite the efforts and time invested in developing clinical practice guidelines for different infectious disease states, simple dissemination and publication have had a variable impact on appropriate antimicrobial prescribing [56, 57, 58, 59, 60, 61, 62]. Thus, many initiatives aim to incorporate such guideline recommendations into the prescribing process, either by means of order sets and checklists or best practice alerts (BPAs) at the time of antimicrobial prescription [23,

63–66, 67, 68–73]. Inconsistent results have been seen with these strategies. In an open-label, two-arm, cluster randomized trial performed within general practices in the UK's Clinical Practice Research Datalink, sites were randomized 1:1 to either usual care or antimicrobial stewardship intervention, which consisted of three remotely delivered elements using electronic media targeting antimicrobial prescribing for URIs [74•]. These elements included a pre-recorded webinar, monthly antibiotic prescribing reports, and decision support tools that provided patient education and clinician guideline recommendations. Overall, the rate of antibiotic prescribing for URIs over the 12-month intervention period was lower in the intervention arm at 98.7 prescriptions per 1000 patient-years vs. 107.6 in the usual care arm (adjusted rate ratio 0.88; 95% CI, 0.78–0.99). Another study by Hansen et al., however, found that a real-time BPA reinforcing guideline recommendations for acute rhinosinusitis (ARS) was inffective in reducing inappropriate antimicrobial prescribing in 117 acute care, family medicine, and internal medicine clinics in an integrated health system [75]. The alert was generated when an antibiotic prescription was placed during a visit for ARS but could be dismissed without requiring justification by the provider. After introduction of the BPA, antibiotic prescription remained high (94.3% of visits vs. 94.8% pre-BPA), highlighting the need for alternative, potentially more intensive interventions. A final example of leveraging the electronic medical record (EMR) to improve antimicrobial prescribing comes from a patient safety initiative implemented in an outpatient VA health system that targeted fluoroquinolone (FQ) use [76]. The initiative required that, at the time of ordering a FQ, the provider documents [1] the antibiotic indication [2], patient education of the antibiotic risks, and [3] medication reconciliation to prescribe FQs. Despite an initial reduction in FQ prescribing immediately after initiative implementation (62% per week reduction; IRR 0.383; 95% CI, 0.271–0.538), this reduction was not sustained at the end of the 43-week intervention period. Ultimately, these studies demonstrate the need to identify strategies that promote the most robust and sustainable impact of EMR interventions, such as ongoing clinician education (i.e., academic detailing, communications training), provider feedback with peer comparison, or accountable justification.

EMR interventions may also be useful for inpatient and pediatric settings to improve antimicrobial stewardship outcomes. Unique EMR interventions to improve clarity in laboratory reporting may assist prescribers in choosing appropriate therapy. A quasi-experimental study by Musgrove and colleagues evaluated a stewardship intervention involving the clinical microbiology staff where a comment was inserted into reports for respiratory cultures in order to nudge prescribers to de-escalate therapy [77•]. For patients whose sputum cultures displayed no growth or no predominant pathogen, the microbiology staff would insert the comment, "commensal flora only, no *Staphylococcus aureus* or *Pseudomonas aeruginosa*". Prior to the intervention, no comments were made regarding *S. aureus* or *P. aeruginosa*. The intervention resulted in a 5.5-fold increase in odds of de-escalation (adjusted OR 5.5; 95% CI, 2.8–10.7). The authors concluded that working with the microbiology laboratory team to create and implement a simple behavioral nudge can significantly impact antibiotic de-escalation and improve antibiotic prescribing. Dassner et al. described their experience with implementing a second-sign process for restricted antimicrobials [78•]. During business hours, all restricted antimicrobial orders were reviewed prospectively in real-time by an ID physician and required ID physician co-signature to become active. Outside of normal business hours, pharmacists were authorized to approve an 18-h duration on the antimicrobial order, with subsequent use requiring ID approval. The author's found that the rate of appropriate restricted antibiotic use increased significantly, from 84.5 to 92.9% ($p = 0.01$). There was no change in median time from order entry to antibiotic administration pre- and post-intervention, suggesting that the need for co-signature did not impact timely antibiotic administration. The results of this study demonstrate that the EMR may be utilized to enforce antimicrobial restrictions and possibly assist with other antimicrobial stewardship activities.

Finally, as the use of medical applications on mobile devices becomes more prevalent, ASPs may also be able to expand their reach through the development of customizable smartphone CDS software [79, 80, 81]. Mobile device applications offer advantages over paper or intranet-based guidelines in that they can be readily accessed from any location, have easy to obtain utilization metrics, and allow for real-time updating, publishing, and dissemination [82]. In 2016, The University of Iowa Hospitals and Clinics replaced their printed antimicrobial pocket guidelines with a mobile CDS application [83•]. The development of the mobile tool occurred over 20 months and was accompanied by a web-based version of the application available on health system workstations. Tools available via the application included antibiograms and clinical guidelines such as disease-state specific, empiric therapy, and a renal dose-adjustment guideline. The authors found that the mobile application was downloaded over 3000 times in its first 14 months and accessed over 9000 times. The majority of downloads were by hospital clinicians (88%) and physicians (66%). They concluded that the implementation of a novel mobile device application supported the ASP and likely allowed them to influence more prescribers than previous methods of data and guideline

dissemination. Further research regarding the use of mobile applications for stewardship is needed to measure their impact on antimicrobial utilization, antimicrobial resistance, and patient outcomes.

Beta Lactam Allergy Assessment

Perhaps one of the most heavily trending topics in antimicrobial stewardship is that of beta lactam allergy assessment [84, 85, 86]. Although penicillin allergies are commonly reported, less than 1% of patients reporting an allergy to penicillin are truly allergic [87, 88]. Alternative antimicrobial therapies used in lieu of beta lactams tend to have more toxicities, increased cost, and are broader in spectrum which can lead to poor patient outcomes and significant antimicrobial resistance [89••, 90••, 91, 92, 93]. A matched cohort study by Al-Hasan and colleagues evaluated the impact of reported penicillin allergy on empiric carbapenem use for community-onset Gram-negative bacteremia [94]. An ASP intervention was implemented near the end of the study period to clarify penicillin allergy. Of the 280 patients evaluated, those with a reported penicillin allergy were significantly more likely to receive empiric carbapenem therapy (27% vs. 12%, $p = 0.002$). In multivariate logistic regression, penicillin allergy was an independent risk factor for empiric carbapenem utilization (OR 3.98; 95% CI, 1.98–8.45) while the ASP intervention was protective (OR 0.41; 95% CI, 0.16–0.94).

Penicillin skin testing (PST) has been described as an optimal way to rule out penicillin allergy; however, this method is time consuming and requires a trained staff member to perform. Sacco and colleagues describe their single-center experience with allergist-performed PST without a structured guideline for testing [95]. The authors found that 78% of patients were able to receive beta lactam antibiotics after PST. The median time to testing consultation was 5 days, delaying time to optimal therapy. The authors concluded that implementation of a hospital protocol could expedite patient identification and allergist consultation for PST, thereby improving the time to receipt of beta lactams. Pharmacists have been identified as key providers in conducting PST in settings where allergist consultation is unavailable [96]. Chen et al. implemented a CDS tool to identify patients with reported beta lactam allergy and performed pharmacist-administered PST which reduced the median time between admission and PST from 3.31 to 1.05 days ($p = 0.008$) [97]. A 58% increase in penicillin exposure was observed ($p = 0.046$) and aztreonam utilization decreased from 2.54 to 1.47 administrations per 1000 patient-days ($p = 0.016$). Average antibiotic costs per patient decreased by 53%. These findings support the use of a structured process for PST, administered by either an allergist or pharmacist provider, to reduce broad-spectrum antibiotic use. Performance of PST or allergy assessment also allows for allergy de-labeling when Type-1 hypersensitivity reaction is ruled out. A recent systematic review found that penicillin allergy de-labeling has the potential to reduce outpatient prescription cost by $14–$193/patient [98]. Thus, it is essential to adequately document PST/allergy assessment and remove the allergy label within the EMR to ensure continuity in all settings of patient care [99].

Another approach to penicillin allergy assessment is utilization of direct oral challenges. A retrospective observational study at Emory University demonstrated that direct oral amoxicillin challenge without PST was safe and efficacious in adult outpatients seen by a single allergist/immunologist [100••]. These findings were corroborated in a small study of 46 patients conducted by Trubiano and colleagues who were considered to have low-risk penicillin allergies (i.e., unknown allergy > 10 years prior, adverse event, or childhood rash). Half of the study participants had a cancer diagnosis and 100% of patients tolerated the oral challenge and subsequently had their penicillin allergy de-labeled [101]. Direct oral penicillin challenges may represent a safe, inexpensive, and less time-consuming method to clarify and de-label beta lactam allergies in patients considered to be at low-risk compared with PST [102, 103].

Conclusions

The overuse and misuse of antimicrobials continues to propagate antimicrobial resistance. Antimicrobial stewardship programs aim to improve antimicrobial prescribing, with recent literature demonstrating advancement in many key strategies used to achieve this aim. For complete optimization, a multi-faceted approach, incorporating complementary intervention strategies should be pursued. Further research focusing on long-term antimicrobial resistance outcomes is needed to elucidate those interventions that are most effective in minimizing antimicrobial resistance and optimizing patient care.

Compliance with Ethical Standards

Conflict of Interest Dr. Cole, Dr. Rivard, and Dr. Dumkow declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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