6-1-2018

The Hospital Antimicrobial Use Process: From Beginning to End.

William R Truong
Department of Pharmacy, St. Joseph Hospital, Orange, California

Jason Yamaki

Open Forum Infectious Diseases

PERSPECTIVES

The Hospital Antimicrobial Use Process: From Beginning to End

William R. Truong[1] and Jason Yamaki[2,3]

[1]Department of Pharmacy, St. Joseph Hospital, Orange, California; [2]Department of Pharmacy Practice, Chapman University School of Pharmacy, Irvine, California; and [3]Department of Pharmacy, Hoag Memorial Hospital Presbyterian, Newport Beach, California

Hospital antimicrobial stewardship (AMS) programs are responsible for ensuring that all antimicrobials are utilized in the most appropriate and safe manner to improve patient outcomes, prevent adverse drug reactions, and prevent the development of antimicrobial resistance. This Perspectives article outlines the hospital antimicrobial use process (AUP), the foundational system that ensures that all antimicrobials are utilized in the most appropriate and safe manner. The AUP consists of the following steps: antimicrobial ordering, order verification, preparation and delivery, administration, monitoring, and discharge prescribing. AMS programs should determine how each step contributes to how an antimicrobial is used appropriately or inappropriately at their institution. Through this understanding, AMS programs can integrate stewardship activities at each step to ensure that every opportunity is taken to optimize antimicrobial use during a patient's treatment course. Hence, approaching AMS through the framework of a hospital's AUP is essential to improving appropriate antimicrobial use.

Keywords. antibiotics; antimicrobial resistance; antibiotic stewardship; antimicrobial stewardship program; antimicrobial use process.

Antimicrobial stewardship (AMS) is predicated on ensuring appropriate and optimal antimicrobial use to improve patient outcomes, prevent adverse drug reactions, and prevent the development of antimicrobial resistance [1, 2]. Although there is no universal definition of appropriate antimicrobial use, expert societies consider the "selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration" as an indicator of appropriate use [3]. Hospital-based AMS programs are tasked with developing, implementing, and monitoring interventions to meet the goal of improving appropriate antimicrobial use. As AMS is by virtue an endeavor to improve pharmaceutical drug use in patients, stewards need to appreciate and approach AMS within the framework of their hospital's antimicrobial use process (AUP) to comprehensively integrate effective stewardship practices. The AUP is the foundational system that ensures all antimicrobials are utilized in the most appropriate and safe manner across all settings. Despite being a foundational element for appropriate antimicrobial usage, it may not be thoroughly reviewed as a whole by specifically looking at each step of the process and how it relates to antimicrobial usage, and how each step can be improved. The AUP is based broadly on the medication use process, which traditionally consists of 5 principal steps: prescribing, transcribing, dispensing, administration, and monitoring [4]. The AUP within the context of a hospital can be adapted to include the following steps: antimicrobial ordering, order verification, preparation and delivery, administration, monitoring, and discharge prescribing (Figure 1). Optimal execution of each step ensures that the patient receives the right drug, at the right dose, at the right time, for the right duration, and with the narrowest spectrum of activity required to treat the infection. Therefore, AMS practices and processes need to be integrated at each of these steps to ensure this outcome. This can be achieved by having a holistic understanding of the antimicrobial use process. In this article, each step of the AUP is presented, their importance is explained, and examples of AMS activities are given that occur at each step to optimize the process.

PRESCRIBER ORDERING

Prescribing of antimicrobials during physician order entry is the first step of the AUP, and for this reason, it is a critical focus of AMS interventions as it is ideal to have the optimal antimicrobial entered at the beginning of the process. In hospitals that utilize computerized physician order entry systems, electronic behavioral change interventions have been shown to be effective in driving appropriate antimicrobial use [5, 6]. Implementation of antimicrobial order sets that incorporate syndrome-specific clinical pathways to "guide" prescribers toward guideline-concordant and institutional best practice

Received 13 March 2018; editorial decision 23 April 2018; accepted 27 April 2018.

Correspondence: W. R. Truong, PharmD, Department of Pharmacy, St. Joseph Hospital, 1100 West Stewart Drive, Orange, CA 92868 (william.truong2@stjoe.org).

DOI: 10.1093/ofid/ofy098

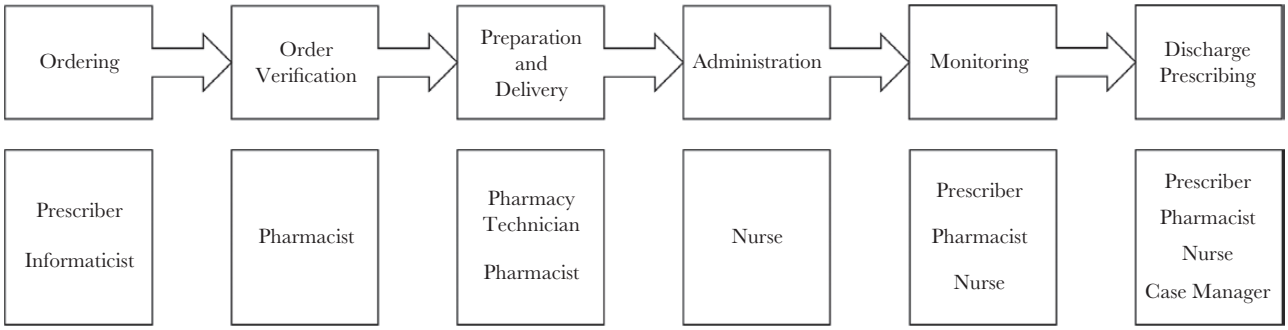

Figure 1. Diagram of the antimicrobial use process and the possible health care professionals who are involved at each step.

therapy are widely used by AMS programs to improve antimicrobial use [7–9]. Best practice alerts (ie, "pop-ups") utilizing clinical decision support mechanisms can be used to notify prescribers of which agents may or may not be appropriate based on computed clinical data, local susceptibilities, hospital formulary, and restriction criteria. Requiring the prescriber to input a clinical indication during electronic order entry has also been shown to be effective in reducing antimicrobial use in the outpatient setting and can be used in the inpatient setting to promote judicious use [10]. In institutions that lack robust electronic medical record (EMR) capabilities where best practice alerts, computerized order entry, and order sets cannot be utilized, hard copy best practice and institutional guidelines that are easily accessible can provide guidance to prescribers during order entry [1].

PHARMACIST ORDER VERIFICATION

An important juncture in the AUP is the step following prescriber ordering: pharmacist order verification. During this step, the prescriber has already entered an order for a patient and requires verification by a pharmacist. Order verification pharmacists are responsible for ensuring that drug interactions and allergies are assessed, dosing is adjusted for organ dysfunction, and duplications of therapy are reconciled. Many hospitals have pharmacist-driven automatic renal dosing protocols that allow for timely adjustment of dosing [11]. Duplications in therapy (eg, double beta-lactam or double anaerobic coverage) ideally should be intervened on at this stage by contacting the prescriber to inquire about the need for duplication. In institutions that utilize pharmacist-driven pharmacokinetic dosing protocols, the pharmacist at this step is typically responsible for initiating the dosing and monitoring of vancomycin and/or aminoglycosides to ensure attainment of target serum concentrations to optimize efficacy and reduce toxicity [12–14]. In hospitals where preauthorization of restricted antimicrobials is required for ordering, order verification pharmacists ensure that each restricted agent has met the hospital's policy for use [15].

PREPARATION AND DELIVERY

Once an antimicrobial order is verified and processed by the order verification pharmacist, pharmacy personnel are tasked with the preparation and compounding of each drug. Accurate preparation and timely delivery of the antimicrobial to the patient's unit is critical for the treatment of severe infections manifesting in sepsis. As studies have demonstrated increasing mortality when time elapses to the first administration of broad-spectrum antimicrobials [16, 17], pharmacy workflow and delivery methods need to be optimized to ensure that the time between drug preparation and delivery to the patient's unit is reduced. Additionally, accurate preparation is necessary to ensure that the patient receives the correct dose and a product that is safe for use. The clinical ramifications of accurate and safe preparation are emphasized by adverse events and deaths that have occurred with compounded medications. According to Pew Charitable Trusts, during the period of 2001–2017, there were 1416 adverse events and 115 deaths associated with compounded or repackaged medications [18]. Automated drug dispensing cabinets containing premixed antibiotics in patient care units have been shown to reduce time to intravenous antibiotic administration [19]. Also important is the need to educate pharmacy technicians on the importance of their role in the AUP and how their compounding and delivery efforts have an impact on patient care. Lastly, considered a "low-hanging fruit" intervention, antimicrobial batching during preparation is a method employed at this step to reduce waste and expenditures for certain high-cost drugs such as daptomycin and caspofungin [20].

ADMINISTRATION

Antimicrobial administration is performed by bedside nurses, and hence nursing serves a critical role in the AUP [21, 22]. Timely antimicrobial administration is a crucial factor during this step, and nurses should accurately record the dose and time of each administration. Precise administration at scheduled frequency intervals ensures that consistent serum drug concentration levels are achieved. If cultures are ordered, every effort

should be made to administer the antibiotics after cultures are taken, so long as it does not extensively prolong the time to antibiotic administration. This ensures optimal microbiological yield of each culture, which provides critical organism identification and susceptibility information during the treatment course. In hospitals where extended infusion beta-lactam administration is utilized, nurses are responsible for ensuring that these antibiotics are programmed to be administered at the correct infusion duration and that any residual antibiotic in the intravenous lines is infused into the patient. Furthermore, coordinating the administration of vancomycin or aminoglycosides relative to serum level draws prevents any aberrated serum level results, potentially leading to suboptimal therapy. Ensuring compatibility of intravenous antibiotics with other drugs during infusion is also important to maximize therapeutic effect and avoid adverse events.

MONITORING

Antimicrobials should be monitored for efficacy and toxicity daily. Certain interventions can be implemented at this stage to ensure that antimicrobials are appropriately managed. One intervention outlined in the Centers for Disease Control and Prevention's (CDC's) Core Elements of Hospital Antibiotic Stewardship Programs, and now required by The Joint Commission as an accreditation standard, is implementation of an antibiotic timeout. An antibiotic timeout requires the treating team to assess their patient's antibiotics 48 hours after they are initiated to determine if they still need to be continued or if any adjustments need to be made [2]. After 48 hours, more diagnostic and microbiological data (ie, culture results) are available to guide the treating team in modifying antibiotics (eg, de-escalation). If technologically feasible, computerized best practice alerts can be utilized to notify the prescriber that a timeout assessment is due and acknowledge that an assessment has been conducted. Institutions utilizing pharmacist-driven timeout assessments have demonstrated improved antibiotic use [23, 24]. Bedside nurses, as central communicators throughout an inpatient stay, can also be involved in the timeout process by prompting the treating team to assess antimicrobials and duration of therapy.

A principal component of monitoring that should be performed is daily prospective audit and feedback. This is conducted by a clinical infectious diseases pharmacist or physician and is one of the core activities undertaken by an antimicrobial stewardship program [25–27]. Hospitals can invest in pharmacosurveillance and data-mining software applications to readily identify patient cases that are candidates for stewardship interventions. This allows the stewardship team to review and provide interventions on an expanded scope of patients as identification of intervention opportunities is automated [28]. Alternatively, if these software applications are not available, manual antimicrobial reports can be generated to identify patient cases for stewardship interventions.

Additionally, during this stage of the AUP, patient-level assessments should occur through labs and physical examination to monitor for development of adverse drug reactions. For example, physicians and nurses should monitor for cutaneous reactions and/or diarrhea to determine if there are any signs of hypersensitivity reaction or possible *Clostridium difficile* infection among other medication-specific monitoring parameters. Furthermore, the treating and antimicrobial stewardship team should identify patients who are candidates for intravenous to oral conversion and intervene to switch the patient to oral therapy [29]. The CDC recommends that hospitals have in place intravenous-to-oral antimicrobial conversion programs where conversion is done automatically, typically by a clinical pharmacist, when the patient meets specified inclusion and exclusion criteria [2]. Good communication between clinicians is critical in institutions that utilize rapid diagnostics. Rapid diagnostics are only beneficial if results are rapidly translated into appropriate modifications of the patient's antimicrobial regimen. In many institutions, critical culture results, whether obtained via rapid diagnostics or traditional culture methods, are communicated from the microbiology laboratory to the bedside nurse, who then communicates them to the physician. This process must be made efficient to ensure that the patient benefits from a rapid diagnostic result. Alternative approaches have also included notification directly to the team physician, as well as the patient's nurse. In some institutions, results of rapid cultures are provided to a clinical pharmacist, who then communicates the information to the physician with a recommendation for therapy modification [30]. The mechanism by which the physician is notified will depend on the resources available at the institution.

DISCHARGE PRESCRIBING

The final step in the AUP is the prescribing of antimicrobials for the transition from inpatient to outpatient. Once patients are clinically stable, they often are discharged on oral step-down antimicrobials to complete their treatment course [31]. When this occurs, it is typically with an outpatient prescription, and at many hospitals, it may not be prescribed through the computerized physician order entry system. Therefore, these antimicrobial prescriptions may not be subjected to the stewardship oversight and detailing described in the earlier AUP stages. This is an important gap as oral step-down therapy often involves a different class of antimicrobial (ie, beta-lactam to fluoroquinolone) or a different agent within the same class (ie, cefazolin to cephalexin). Hence, spectrum of activity, dosing, contraindications, hypersensitivity potential, and pharmacokinetic/pharmacodynamic properties may be different than the inpatient intravenous antimicrobial that a patient was receiving. This can lead to inappropriate antimicrobial prescribing at patient discharge [31, 32].

Discharge oral prescriptions are typically filled at outside pharmacies, which do not have access to the patient's hospital

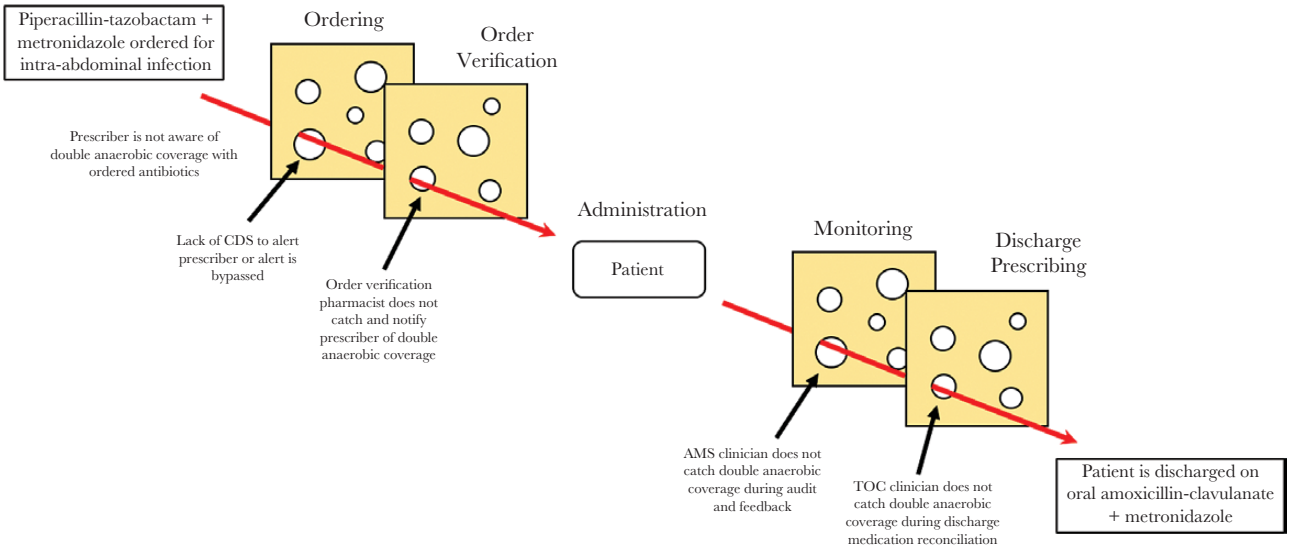

Figure 2. A scenario in which a patient with an intra-abdominal infection, without *Clostridium difficile* infection, is unnecessarily prescribed double anaerobic coverage with piperacillin-tazobactam and metronidazole while hospitalized. This Swiss cheese model depicts a series of failures within the antimicrobial use process ultimately resulting in discharge prescribing of double anaerobic coverage for the entire treatment course. Abbreviations: AMS, antimicrobial stewardship; CDS, clinical decision support; TOC, transitions of care.

medical record or details on their inpatient clinical course. Furthermore, patients may be discharged when cultures are preliminary, and final results may not be available until after the patient leaves the hospital, potentially leaving the patient on inappropriate therapy (eg, resistant organism) [33]. Discharge prescribing is an important step in the AUP that stewardship programs can intervene on. Reviewing discharge prescriptions for appropriateness and their duration of therapy can ensure that the patient completes their therapy on the right drug, at the right dose, for the right duration, and one with the narrowest spectrum of activity. Hospitals can implement transition of care programs that consist of a coordinated team of pharmacists, physicians, nurses, and care coordinators to improve the patient discharge process. Transition of care pharmacists can be integral members of AMS programs by providing stewardship services during the discharge prescribing process as well as conducting medication reconciliation and reviews, and counseling patients on newly initiated medications. For patients being discharged on intravenous antibiotics, an outpatient parenteral antimicrobial therapy (OPAT) program can improve patient outcomes by reducing hospital readmissions [34].

Postdischarge antimicrobial therapy is often prolonged or may not be warranted at all. Thus, it is important at discharge planning to account for the number of days of effective antimicrobial therapy that a patient has already received in the hospital to avoid excess duration of total therapy. For patients being discharged to a skilled nursing or long-term care facility, documenting the duration of therapy is critical to ensuring that antimicrobials are discontinued on the appropriate date [35]. In some cases, the patient may have completed an adequate course of antimicrobial therapy, and utilizing their clinical response and biomarkers such as procalcitonin, discontinuation of therapy may be considered. This approach, particularly with the use of procalcitonin levels and other clinical parameters, would require education of clinicians, but there has been reported success in decreasing antimicrobial use with this approach [36, 37].

CONCLUSIONS

Various AMS activities and processes may lead to positive outcomes and occur at different steps of a continuum that can be termed the antimicrobial use process. Understanding all steps of the AUP from beginning to end will allow for institutions to better integrate AMS activities within the AUP. This integration reduces the opportunity for an inappropriate antimicrobial to be administered to a patient, and if administered, downstream AUP stewardship systems should identify and rectify the situation as soon as possible. Additionally, in the event that an inappropriate antimicrobial is administered to the patient, AMS programs can conduct a root cause analysis to identify the AUP stage in which it occurred and factors that allowed the inappropriate antimicrobial to proceed through and reach the patient (Figure 2). Conducting this analysis will provide insights on how to improve the AUP to prevent future inappropriate antimicrobial use. By understanding and optimizing a hospital's AUP, AMS programs can prevent or reduce inappropriate antimicrobial use.

Acknowledgments

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.

References

1. Barlam TF, Cosgrove SE, Abbo LM, et al. Executive summary: 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**; 62:1197–202.
2. Centers for Disease Control and Prevention. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: Centers for Disease Control and Prevention; **2014**.
3. Fishman N, Patterson J, Saiman L, et al. Policy statement on Antimicrobial Stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol **2012**; 33:322–7.
4. Moore SJ, Jenkins AT, Poppe LB, et al. Significant publications about the medication use process in 2012. J Pharm Pract **2015**; 28:387–97.
5. Charani E, Castro-Sánchez E, Holmes A. The role of behavior change in antimicrobial stewardship. Infect Dis Clin North Am **2014**; 28:169–75.
6. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev **2017**; 2:CD003543.
7. Fleming NS, Ogola G, Ballard DJ. Implementing a standardized order set for community-acquired pneumonia: impact on mortality and cost. Jt Comm J Qual Patient Saf **2009**; 35:414–21.
8. Paterson DL. The role of antimicrobial management programs in optimizing antibiotic prescribing within hospitals. Clin Infect Dis **2006**; 42(Suppl 2):S90–5.
9. Owens RC Jr. Antimicrobial stewardship: concepts and strategies in the 21st century. Diagn Microbiol Infect Dis **2008**; 61:110–28.
10. Meeker D, Linder JA, Fox CR, et al. Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices: a randomized clinical trial. JAMA **2016**; 315:562–70.
11. Hassan Y, Al-Ramahi RJ, Aziz NA, Ghazali R. Impact of a renal drug dosing service on dose adjustment in hospitalized patients with chronic kidney disease. Ann Pharmacother **2009**; 43:1598–605.
12. Streetman DS, Nafziger AN, Destache CJ, Bertino AS Jr. Individualized pharmacokinetic monitoring results in less aminoglycoside-associated nephrotoxicity and fewer associated costs. Pharmacotherapy **2001**; 21:443–51.
13. Bond CA, Raehl CL. Clinical and economic outcomes of pharmacist-managed aminoglycoside or vancomycin therapy. Am J Health Syst Pharm **2005**; 62:1596–605.
14. Welty TE, Copa AK. Impact of vancomycin therapeutic drug monitoring on patient care. Ann Pharmacother **1994**; 28:1335–9.
15. Mansouri MD, Cadle RM, Agbahiwe SO, Musher DM. Impact of an antibiotic restriction program on antibiotic utilization in the treatment of community-acquired pneumonia in a Veterans Affairs Medical Center. Infection **2011**; 39:53–8.
16. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med **2014**; 42:1749–55.
17. Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med **2010**; 38:1045–53.
18. U.S. illnesses and deaths associated with compounded medications or repackaged medications. Available at: http://www.pewhealth.org/other-resource/us-illnessesand-deaths-associated-with-compounded-medications85899468587. Accessed 11 April 2018.
19. Ward MJ, Boyd JS, Harger NJ, et al. An automated dispensing system for improving medication timing in the emergency department. World J Emerg Med **2012**; 3:102–7.
20. Goff DA, Bauer KA, Reed EE, et al. Is the "low-hanging fruit" worth picking for antimicrobial stewardship programs? Clin Infect Dis **2012**; 55:587–92.
21. Olans RN, Olans RD, DeMaria A Jr. The critical role of the staff nurse in antimicrobial stewardship–unrecognized, but already there. Clin Infect Dis **2016**; 62:84–9.
22. American Nurses Association. Redefining the Antibiotic Stewardship Team: Recommendations from the American Nurses Association/Centers for Disease Control and Prevention Workgroup on the Role of Registered Nurses in Hospital Antibiotic Stewardship Practices. Silver Spring, MD: American Nurses Association; **2017**.
23. Vasina L, Dehner M, Wong A, et al. The impact of a pharmacist driven 48-hour antibiotic time out during multi-disciplinary rounds on antibiotic utilization in a community non-teaching hospital. Open Forum Infect Dis **2017**; 4(Suppl 1): S272–S3.
24. Polisetty RS, Borkowski J, Jochum E, et al. Multicenter study to evaluate the impact of antibiotic time out in four community hospitals. Open Forum Infect Dis **2016**; 3(Suppl 1):988.
25. Chung GW, Wu JE, Yeo CL, et al. Antimicrobial stewardship: a review of prospective audit and feedback systems and an objective evaluation of outcomes. Virulence **2013**; 4:151–7.
26. Morrill HJ, Caffrey AR, Gaitanis MM, LaPlante KL. Impact of a prospective audit and feedback antimicrobial stewardship program at a Veterans Affairs medical center: a six-point assessment. PLoS One **2016**; 11:e0150795.
27. Yu K, Rho J, Morcos M, et al. Evaluation of dedicated infectious diseases pharmacists on antimicrobial stewardship teams. Am J Health Syst Pharm **2014**; 71:1019–28.
28. Smith T, Philmon CL, Johnson GD, et al. Antimicrobial stewardship in a community hospital: attacking the more difficult problems. Hosp Pharm **2014**; 49:839–46.
29. McCallum AD, Sutherland RK, Mackintosh CL. Improving antimicrobial prescribing: implementation of an antimicrobial i.v.-to-oral switch policy. J R Coll Physicians Edinb **2013**; 43:294–300.
30. Box MJ, Sullivan EL, Ortwine KN, et al. Outcomes of rapid identification for gram-positive bacteremia in combination with antibiotic stewardship at a community-based hospital system. Pharmacotherapy **2015**; 35:269–76.
31. Hersh AL, Newland JG, Gerber JS. Pediatric antimicrobial discharge stewardship: an unmet need. JAMA Pediatr **2016**; 170:191–2.
32. Scarpato SJ, Timko DR, Cluzet VC, et al; CDC Prevention Epicenters Program. An evaluation of antibiotic prescribing practices upon hospital discharge. Infect Control Hosp Epidemiol **2017**; 38:353–5.
33. Jones JM, Leedahl ND, Losing A, et al. A pilot study for antimicrobial stewardship post-discharge. J Pharm Pract **2017**; 31:140–4.
34. Madaline T, Nori P, Mowrey W, et al. Bundle in the Bronx: impact of a transition-of-care outpatient parenteral antibiotic therapy bundle on all-cause 30-day hospital readmissions. Open Forum Infect Dis **2017**; 4:ofx097.
35. Dyer A, Ashley ED, Anderson DJ, et al. Inpatient plus post-discharge durations of therapy to identify antimicrobial stewardship opportunities at transitions of care. Open Forum Infect Dis **2017**; 4(Suppl 1): S19–20.
36. Nobre V, Harbarth S, Graf JD, et al. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. Am J Respir Crit Care Med **2008**; 177:498–505.
37. Murray C, Shaw A, Lloyd M, et al. A multidisciplinary intervention to reduce antibiotic duration in lower respiratory tract infections. J Antimicrob Chemother **2014**; 69:515–8.