8-1-2015

Evaluation of pharmacy generalists performing antimicrobial stewardship services

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Recommended Citation

Carreno JJ, Kenney RM, Bloome M, McDonnell J, Rodriguez J, Weinmann A, Kilgore PE, and Davis SL. Evaluation of pharmacy generalists performing antimicrobial stewardship services Am J Health Syst Pharm 2015; 72(15):1298-1303.

NOTES

Evaluation of pharmacy generalists performing antimicrobial stewardship services

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Purpose. Improvements in medication use achieved by pharmacy generalists using a care bundle approach to antimicrobial stewardship are reported.

Methods. A six-month prospective, repeated-treatment, quasi-experimental study involving three month-long intervention periods and three month-long control periods was conducted in the setting of an existing antimicrobial stewardship program at a large hospital. The intervention involved prospective audit and feedback conducted by pharmacy generalists who were trained in an antimicrobial stewardship care bundle approach. During control months, a pharmacy generalist who was not trained in antimicrobial stewardship rounded with the multidisciplinary team and provided standard-of-care pharmacy services. The primary endpoint was compliance with a care bundle of four antimicrobial stewardship metrics: documentation of indication for therapy in the medical record, selection of empirical therapy according to institutional guidelines, documented performance of indicated culture testing, and deescalation of therapy when indicated.

Results. Two-hundred eighty-six patients were enrolled in the study: 124 in the intervention group and 162 in the control group. The cumulative rate of full compliance with all care bundle components during the six-month study was significantly greater during intervention months than during control months (68.5% versus 45.7%, $p < 0.001$). After adjusting for infection type, antimicrobial stewardship provided by an intervention-group pharmacist was associated with improved care bundle compliance (adjusted odds ratio, 2.70; $p < 0.001$). No significant differences in patient outcomes during intervention and control months were detected.

Conclusion. Pharmacy generalists trained to comply with a systematic care bundle approach enhanced the quality of antimicrobial management.

Am J Health-Syst Pharm. 2015; 72:1298-303

Antimicrobial resistance and the growing scarcity of safe and effective antimicrobials have been recognized worldwide.[1] Antimicrobial stewardship programs (ASPs) have been advocated to promote judicious use of antimicrobials; to improve patient outcomes, safety, and resistance patterns; and to reduce healthcare costs.[2-6] Pharmacists with formal infectious diseases training are often leaders of ASPs.[2,7]

Unfortunately, there are not enough specialty-trained pharmacists to provide antimicrobial stewardship services in all healthcare settings that would benefit from these programs.[4,8] Additionally, proposed standards for pharmacists practicing infectious diseases pharmacotherapy may be impractical in resource-limited settings.[8,9] Moreover, there are numerous barriers to wider implementation of pharmacist-led ASPs.[9]

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Funded through a 2012 Pharmacy Practice Model Initiative Demonstration Grant from the ASHP Research and Education Foundation.

Dr. Carreno is a speaker for Cubist Pharmaceuticals, Inc. Dr. Kenney's spouse is an employee and stockholder in Medtronic, Inc. Dr. Davis received a research grant from Cubist and Forest/Actavis and consulting honoraria from Cubist, Durata, Forest, Melinta, Pfizer, and Premier. The other authors have declared no potential conflicts of interest.

DOI 10.2146/ajhp140619

In order to implement ASPs more broadly, novel approaches are needed. Use of a care bundle (a checklist of evidence-based activities) is one potential strategy whose use was previously reported in *AJHP* in the context of antimicrobial stewardship.[5] Another potential solution is to engage practitioners who are not infectious diseases specialists and provide them with efficient tools to implement interventions.[4,5,7] As described in the medical literature, hospitalists have partnered with infectious diseases physicians to enhance antimicrobial stewardship.[10,11] This philosophy can also be applied to pharmacy generalists.[4] There are limited data to demonstrate the effectiveness of using pharmacy generalists in ASPs. The aim of this study was to evaluate the ability of pharmacy generalists to enhance antimicrobial stewardship services provided to inpatients at a large, tertiary care hospital.

Methods

Study design and setting. An institutional review board–approved study was conducted at an 802-bed academic, tertiary care facility. The hospital has an established multidisciplinary ASP that uses antimicrobial restriction and prospective audit and feedback methods focused on targeted patients by an infectious diseases–trained pharmacist. The research entailed a prospective repeated-treatment quasi-experimental study with three observational control periods and three intervention periods.[12] Three patient care services were observed, with rotating pharmacist assignments. Intervention months with an ASP-trained pharmacist were followed by two months of control with non-ASP-trained pharmacists; this cycle was repeated. For each period, the study population was drawn from two inpatient medicine floors and one medical intensive care unit. The study units were selected on the basis of the institution's pharmacy practice model, which provides pharmacy services through patient care teams. Each patient care team is composed of clinical pharmacy specialists, pharmacy generalists, and pharmacy trainees. Pharmacy generalists rotate between assignments to clinical patient care services and drug distribution areas on a monthly basis. The nonrandomized quasi-experimental design was selected to coordinate with the preexisting patient care team assignments.

Inclusion and exclusion criteria. Patients were included in the study if they were 18 years of age or older and were initiated on i.v. antibiotic therapy during the pharmacy generalists' shift for an expected duration of at least 72 hours. Patients receiving i.v. antibiotics for prophylaxis, who had an absolute neutrophil count (ANC) of $<1000/mm^3$, or were pregnant were excluded.

Description of the intervention. Three pharmacy generalists were recruited to participate in a self-directed learning module followed by a standardized four-hour training program designed by infectious diseases pharmacists and an infectious diseases physician who practices in the area of antimicrobial stewardship. The training program consisted of national guideline and primary literature reading assignments, with a one-hour review session; review of the hospital antibiogram (one hour); and an overview of institutional guidelines for empirical and definitive antimicrobial selection (one hour). In addition, the pharmacists were educated on appropriate diagnostic cultures for common infections (one hour). A reference document listing appropriate diagnostic cultures was created through a systematic review of institutional and national guidelines and was approved by all coinvestigators. Finally, the pharmacists were trained to provide prospective audit and feedback according to an antimicrobial stewardship care bundle.[5] During both intervention and control phases of the research, the ASP pharmacists conducted routine audit and feedback according to ASP priorities, which included follow-up on sterile site cultures, restricted antimicrobials, and opportunities to switch therapy to a narrower-spectrum antimicrobial. Infectious diseases consultation was available at the discretion of the primary team during both study phases.

During the intervention periods, the trained study pharmacists provided clinical services on the study units. Clinical care involved the evaluation of all i.v. antimicrobial therapy using the care bundle checklist, prospective audit, and feedback to the primary team (delivered in person or via written communication or by both methods) with the aim of achieving care bundle compliance. The care bundle consisted of four quality indicators: (1) documentation of the indication for antibiotics in the medical record at the time of prescribing, (2) collection of indicated cultures, (3) empirical therapy selection according to institutional guidelines, and (4) a switch to a narrower-spectrum antimicrobial when microbiologically indicated. The study pharmacists documented compliance with care bundle metrics in the electronic clinical decision support system (Theradoc, Hospira, Salt Lake City, UT). Care bundle compliance was validated by the primary investigator. During control months, the primary investigator documented compliance with the care bundle, while pharmacy generalists without stewardship training were responsible for providing the standard of care on the study units. The control-group pharmacy generalists did not have specific knowledge of the study protocol. Each month a new physician team (including different senior staff) rotated through each individual unit, effectively resulting in a "washout" between intervention periods.

Endpoints. The primary outcome was compliance with the care bundle of four antimicrobial stewardship process metrics described earlier.[5,13] Secondary outcomes included compliance with the individual components of the care bundle; and resource utilization markers, including length of therapy per 1000 patient-days, days of therapy per 1000 patient-days, inhospital mortality, 30-day mortality, and infection-related readmission within 30 days.

Sample size calculation. Based on previous literature estimates,[5] a sample size of at least 85 patients per group was needed to detect a 20% difference between study groups with 5% alpha and 80% power.

Data analysis. All data were collected using a standardized form. Categorical data were analyzed using two-sided chi-square tests. Continuous parametric data were analyzed using a two-sided Student's *t* test, and nonparametric data were analyzed via a two-sided Mann–Whitney *U* test where appropriate. Multivariable regression was performed to identify independent predictors of care bundle compliance. Any variable with a clinical rationale that was found to be associated with care bundle compliance (i.e., $p < 0.2$ for comparison of intervention versus control) was analyzed using multiple backward stepwise logistic regression to create a model for predicting care bundle compliance. Statistical analysis was performed using SPSS, version 22.0 (IBM Corporation, Armonk, NY).

Results

A total of 721 patients were screened for study eligibility. Reasons for patient exclusion from enrollment were as follows: initiation of antibiotics during nonstudy periods ($n = 228$) or on nonstudy units ($n = 103$), patient not expected to receive antibiotics for at least 72 hours ($n = 82$), ANC value of <1000/mm^3 ($n = 18$), patient age of <18 years ($n = 2$), and pregnancy ($n = 2$). A total of 286 patients were enrolled, 124 in the intervention group and 162 in the control group.

Patient characteristics. Treatment and infection characteristics were similar in the intervention and control groups (Table 1). The most common sites of infection were the lower respiratory tract ($n = 79$, 27.6%) and the genitourinary tract ($n = 60$, 20.9%); 52 patients (18.2%) had two or more suspected sites of infection. The most commonly utilized antimicrobials were vancomycin ($n = 177$, 61.9%), cefepime ($n = 160$, 55.9%), third-generation cephalosporins ($n = 129$, 45.1%), metronidazole ($n = 106$, 37.1%), and macrolides ($n = 49$, 17.1%).

Care bundle compliance. Data on compliance with the care bundle over the six study months are graphically depicted in Figure 1. Compliance with all care bundle metrics was significantly higher during intervention months than during control months (85 of 124 patients [68.5%] versus 74 of 162 patients [45.7%], $p < 0.001$). Separate analyses of the four metrics showed that documentation of indication for therapy occurred significantly more often in the intervention group than in the control group (122 of 124 patients [98.4%] versus 151 of 162 patients [93.2%], $p = 0.04$), as did selection of empirical therapy in accordance with institutional guidelines (112 of 124 patients [90.3%] versus 115 of 162 patients [71.0%], $p < 0.001$); there was no significant difference between the intervention and control groups with regard to collection of indicated cultures (106 of 124 patients [85.5%] and 128 of 162 patients [79.0%], respectively; $p = 0.16$) or the proportion of patients who were switched to a narrower-spectrum antimicrobial (40 of 49 patients [81.6%] versus 49 of 61 patients [80.3%], $p = 0.86$).

Antimicrobial utilization. The median antimicrobial length of therapy was similar in the intervention group (6 days; interquartile range [IQR], 4–9 days) and the control group (6 days; IQR, 4–8 days; $p = 0.29$). The total length of therapy was 758 days per 1000 patient-days in the control group, compared with 689 days per 1000 patient-days in the intervention group. Values for total days of therapy per 1000 patient-days were 1463 per 1000 in the control group and 1367 per 1000 in the intervention group, respectively (statistical

Table 1.
Baseline Data on Patients in Study Population[a]

Variable	Intervention Group ($n = 124$)	Control Group ($n = 162$)	*p*
Median (IQR) age, yr	65 (53–73)	62 (51–75)	0.60
Male sex, no. (%)	64 (52)	75 (46)	0.37
Median (IQR) creatinine clearance, mL/min[b]	38 (15–72)	46 (21–74)	0.26
Mean (IQR) Charlson Comorbidity Index score	3 (2–4)	2 (2–4)	0.29
Hospital unit, no. (%)			
General practice unit 1	36 (29)	42 (26)	0.01[c]
General practice unit 2	35 (28)	73 (45)	
Medical intensive care unit	53 (43)	47 (29)	
Insured, no. (%)	118 (95)	148 (91)	0.21

[a]IQR = interquartile range.
[b]Estimated via Cockcroft–Gault equation.
[c]Calculated using chi-square test for 3 × 2 table comparison of general practice units 1 and 2 and the medical intensive care unit in the intervention and control groups.

analyses were not performed due to the small number of observation periods [i.e., three per group]).

Factors associated with care bundle compliance. Data on associations of evaluated variables and care bundle compliance are presented in Table 2. Patients with bloodstream infections were significantly more likely to receive treatment involving complete care bundle compliance than those without bloodstream infections (unadjusted odds ratio [OR], 2.61; $p = 0.03$). With adjustment for the presence of abdominal or lower respiratory tract infections, patients in the intervention group were significantly more likely than those in the control group to receive care bundle–compliant antimicrobial therapy (adjusted OR, 2.70; $p < 0.001$). No other variables tested were significantly associated with care bundle compliance. No significant differences were identified in patient outcomes between the intervention and control groups with regard to inhospital mortality (4.8% versus 7.4%, $p = 0.375$), 30-day mortality (9.7% versus 9.9%, $p = 0.955$), or rates of infection-related readmission within 30 days (12.1% versus 8%, $p = 0.251$).

Discussion

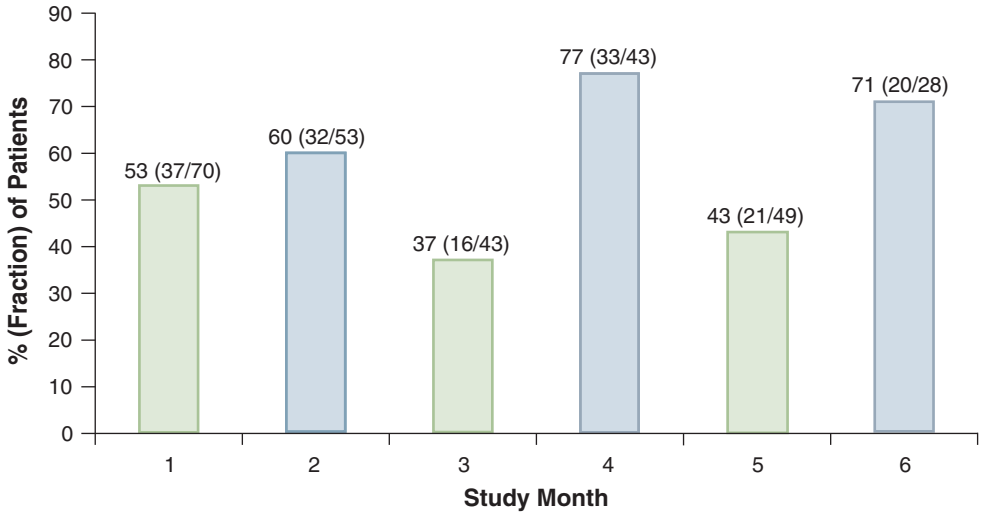
In our study, pharmacy generalists who received standardized training significantly improved the quality of antibiotic management (as measured by care bundle compliance) relative to routine pharmacy services. In a previous study at the same study site, Toth and colleagues[5] demonstrated an increase in compliance with care bundle metrics (from 16% to 54%) through the use of the same care bundle approach. DiazGranados and Abd[4] also recently explored expanded use of ASPs with pharmacy generalists. In their study, they suggested that antimicrobial stewardship responsibilities can be performed by pharmacy generalists under the supervision of an infectious diseases physician. The results of our study add support for that suggestion.

The study data presented here further justify the role of pharmacy generalists in performing antimicrobial stewardship, as well as the utility of a stewardship care bundle, by providing reproducibility (i.e., data were collected on three separate but parallel inpatient units through multiple observations).

The study had several notable limitations, including potential volunteer bias. Also, the study measurements excluded antimicrobial therapy initiated outside of the pharmacist's clinical daytime shift so that only the direct impact of the intervention pharmacist was evaluated. Expanding this intervention to other pharmacy shifts could improve effectiveness but may be impractical, as there may not be enough qualified pharmacists to oversee all shifts. Two out of the three pharmacy generalists involved in the study were graduates of ASHP-accredited residencies, and the third had practiced for approximately 20 years before participation in the study; however, none of these pharmacists met proposed standards for pharmacists practicing in the area of infectious diseases pharmacotherapy.[8]

A quasi-experimental study design was used, and such methodology is subject to several limitations, including the potential for unaccounted

Figure 1. Compliance with the antimicrobial stewardship care bundle at the study site during designated intervention months (blue) and control months (green), as determined by the percentage of study patients whose antimicrobial therapy was in compliance with all care bundle components.



confounders. To minimize this source of bias, we attempted to identify the most important confounders a priori and used regression techniques to identify independent predictors of care bundle compliance. Regression to the mean (and maturation) are also potential threats to the validity of the study findings.[12] In our study, control group compliance with the care bundle was 46%; in the aforementioned prior study at the same study site, a 16% compliance rate was observed.[5] This improvement in the baseline level of compliance over time suggests that prescribers at the institution may be maturing in their antimicrobial management practices. However, maturation and regression to the mean do not appear to account for the differences observed through monthly observations during our six-month repeated treatment study (Figure 1).

Finally with regard to limitations, our study was conducted in the setting of an established ASP that uses multiple strategies advocated in national guidelines. While data collected in this setting may not be generalizable to all hospitals, we hypothesize that care bundle compliance benefits even greater than those reported here might be observed in settings that have clinical pharmacy services but lack a formal ASP.

Of interest, we observed an overall enhancement of the existing ASP with pharmacy generalist intervention, particularly with regard to improving the quality of empirical therapy selection and documentation of indications for antibiotics in the medical record. We speculate that these improvements related to the presence of a pharmacy generalist on the primary team (i.e., the pharmacist was well positioned to intervene at the time of prescribing and medical record documentation). The ASP currently operates with one antimicrobial stewardship pharmacist full-time equivalent providing audit and feedback throughout the 802-bed hospital. The ASP pharmacist prioritizes sterile-site infection management and antibiotic deescalation. Accordingly, we observed in the bivariable analysis that patients with a bloodstream infection were more likely to be managed in compliance with the care bundle and that deescalation was performed in approximately 80% of both intervention and control patients.

The study results add to the literature demonstrating that a care bundle approach may facilitate more effective utilization of limited resources.[3,14-16] Care bundles have been used effectively in the prevention of ventilator-associated pneumonia,[14] in the resuscitation and management of patients with sepsis,[15] and in the management of *Staphylococcus aureus* bacteremia[16] and candidemia.[3] These promising findings lend support for future research on the implementation of antimicrobial stewardship care bundles and their impact on outcomes of infection.

Table 2.
Association of Evaluated Patient Variables With Care Bundle Compliance, by Analytical Method[a]

Variable	Bivariable Regression		Multivariable Regression	
	OR (95% CI)	*p*	Adjusted OR[b] (95% CI)	*p*
Enrollment in intervention group	2.59 (1.59–4.23)	<0.001	2.70 (1.64–4.46)	<0.001
Age	0.99 (0.98–1.01)	0.23	Not tested	
Female	0.77 (0.70–1.96)	0.55	Not tested	
Insured	0.82 (0.33–2.08)	0.26	Not tested	
Admitted to ICU at baseline	1.10 (0.68–1.82)	0.68	Not tested	
Charlson Comorbidity Index score	0.95 (0.85–1.05)	0.30	Not tested	
Infection site[c]				
Abdominal	0.66 (0.37–1.18)	0.16	0.59 (0.31–1.11)	0.10
Bloodstream[d]	2.61 (1.07–6.35)	0.03	2.24 (0.89–5.59)	0.09
Bone	0.47 (0.11–2.00)	0.47	Not tested	
Central nervous system	1.20 (0.20–7.31)	1.00	Not tested	
Genitourinary tract	1.36 (0.82–2.55)	0.23	Not tested	
I.V. catheter	2.19 (0.57–8.43)	0.36	Not tested	
Lower respiratory tract	0.72 (0.45–1.18)	0.19	0.62 (0.37–1.05)	0.08
Skin and soft tissue	1.29 (0.66–2.55)	0.45	Not tested	
Upper respiratory tract	1.20 (0.20–7.31)	1.00	Not tested	
Wound	0.80 (0.11–5.73)	0.82	Not tested	

[a]OR = odds ratio, CI = confidence interval, ICU = intensive care unit.
[b]Goodness of fit Nagelkerke $R^2 = 0.11$.
[c]Infection sites were not mutually exclusive and were analyzed separately.
[d]Includes both secondary and primary bacteremia or fungemia.

Conclusion

Pharmacy generalists trained to comply with a systematic care bundle approach enhanced the quality of antimicrobial management.

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