Original Research Article

Benefits of Accepting Infectious Diseases Pharmacist Recommendations: A 5-Year Outcome Study in a Multihospital System

Hospital Pharmacy
2024, Vol. 59(3) 300–309

DOI: 10.1177/00185787231213807
journals.sagepub.com/home/hpx
Sage

Taylor Babiarz[1], Justin Schmetterer[2], Kelley Merrick[2], Tanja Jelic[2], and Thomas Roberts[2]

Abstract

Background: Infectious diseases (ID) pharmacists are pivotal members of antimicrobial stewardship teams. Prospective audit and feedback is a strong recommendation by The Infectious Diseases Society of America Guidelines for Antimicrobial Stewardship Programs (ASP). Utilizing customized ASP intervention documentation tools known as "ivents" in Epic, we aimed to assess the impact of interventions by measuring outcomes that were accepted compared to those that were rejected in a multihospital health system over 5 years. **Methods:** A multicenter, retrospective cohort study was conducted to compare clinical outcomes among intensive care unit (ICU) and non-ICU patients with accepted and rejected ASP interventions over 5 years from October 2015 to December 2020. Outcomes measured included antibiotic days of therapy per 1000 patient days (DOT/1000 PD), antibiotic doses per 1000 patient days (doses/1000 PD), hospital length of stay (LOS), in-hospital mortality, hospital-acquired *Clostridioides difficile* infection (HA-CDI), community-onset *C. difficile* infection (CO-CDI) within 30 days, and hospital readmission within 30 days. Coarsened exact matching (CEM) was used as a non-parametric matching method to balance covariates between groups and to control for confounding. **Results:** ASP recommendations by ID pharmacists were well-received by providers in a multihospital system over 5 years as evidenced by an overall acceptance rate of 92%. Acceptance of ASP interventions was associated with substantial reductions in antibiotic utilization without adversely affecting mortality or hospital readmissions. While high-risk *C. difficile* antibiotic use increased significantly due to frequent de-escalation to ceftriaxone among non-ICU patients with accepted interventions, rates of HA-CDI and CO-CDI within 30 days did not worsen. Furthermore, hospital LOS was notably shorter by an average of 1 day for non-ICU patients with accepted interventions, which resulted in substantial cost avoidance of $7 631 400. **Conclusion:** Collaboration with ID pharmacists to optimize antimicrobial stewardship was associated with significant reductions in antibiotic utilization, costs, and hospital LOS without worsening patient outcomes.

Keywords
anti-infectives, infectious diseases, clinical services, outcomes research

Background

Introduction

With the continued rise of antimicrobial resistance and declining effectiveness of current antimicrobial agents, the importance of antimicrobial stewardship is nationally recognized for standard integration into health care. Antimicrobial stewardship programs (ASP) are associated with improved outcomes, including decreased antimicrobial utilization, fewer adverse consequences of antimicrobials, decreased length of hospital stay, and lower health care costs.[1] However, evidence for ASPs benefiting clinical outcomes is inconsistent. While some studies show ASPs are associated with better mortality and microbiological outcomes, others indicate no differences in mortality or rates of *Clostridioides difficile* infections.[2-5] Despite this, literature has extensively established the safety and effectiveness of ASPs without worsening clinical outcomes. One method ASPs often implement to improve antibiotic utilization and patient outcomes is prospective audit and feedback. This process consists of actively reviewing antimicrobials after they are prescribed and providing recommendations for optimization thereafter. The Infectious Diseases Society of America (IDSA) guidelines

[1]Memorial Hermann Northeast Hospital, Humble, TX, USA
[2]Presbyterian Healthcare Services, Albuquerque, NM, USA

Corresponding Author:
Taylor Babiarz, Memorial Hermann Northeast Hospital, 18951 North Memorial Drive, Humble, TX 77338, USA.
Email: taylor.babiarz@memorialhermann.org

on implementing an ASP strongly recommend prospective audit and feedback as an essential component of a stewardship program.[1] The CDC Core Elements that drive antimicrobial stewardship accreditation standards in hospitals also endorse prospective audit and feedback as a priority intervention for stewardship programs.[6]

ASPs that are co-directed by an infectious diseases (ID) physician and an ID-trained pharmacist are beneficial in improving patient care through expertise in infectious diseases and antimicrobial optimization. Presbyterian Healthcare Services (PHS) is a 9-hospital system that serves the state of New Mexico and has a co-directed ASP. Since its establishment almost 2 decades ago, the PHS ASP has illustrated through annual reports of metrics that ID pharmacists have a widespread influence on the health system, making thousands of prospective audit and feedback interventions each year that result in enhanced antimicrobial use, reduced antimicrobial costs, and overall improved patient care. Additionally, a recent single-center, observational pilot study conducted internally at the largest hospital within PHS demonstrated reductions in antibiotic utilization with ID pharmacist-driven antimicrobial stewardship. Given the previous evidence, this study aimed to further evaluate the impact of ID pharmacists on an inpatient ASP for a multihospital health system over 5 years.

Methods

Study Design

A multicenter, retrospective cohort study was conducted to compare clinical outcomes between patients with accepted and rejected ASP interventions in both ICU and non-ICU patients over 5 years from October 2015 to December 2020. The ID pharmacy team, which consisted of 2 ID pharmacists and 1 annual ID pharmacist resident, provided prospective audit and feedback across the health system and documented ASP interventions using customized ASP "ivents" in the electronic health record through Epic Systems. Interventions were made in person, telephonically, and via Epic secure chat. Patients were considered to have accepted interventions if the primary provider adjusted antibiotic therapy by the following morning based on the recommendation and rejected interventions if not. Patient cases were discussed with ID physicians as needed for additional support.

Study Participants

Patients who were admitted to 1 of 8 hospitals within PHS and received antibiotics for infections with an ASP intervention documented as either accepted or rejected were included. Patients from 1 of our smaller hospitals, Kaseman Hospital, were excluded due to its primarily behavioral health patient population. Patients were also excluded if they had more than 1 documented ASP intervention during the same admission, an ASP intervention response outside of accepted or rejected, or an ASP intervention not associated with an antibiotic order.

Primary Outcomes

Primary outcomes included days of therapy per 1000 patient days (DOT/1000 PD) and doses/1000 PD of total antibiotics, anti-methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotics (vancomycin, linezolid, and daptomycin), anti-pseudomonal β-lactams (aztreonam, cefepime, piperacillin/tazobactam, and meropenem), and high-risk *C. difficile* antibiotics (ceftriaxone, clindamycin, ciprofloxacin, and moxifloxacin).

Secondary Outcomes

Secondary outcomes included hospital length of stay (LOS), in-hospital mortality, hospital-acquired *C. difficile* infection (HA-CDI), community-onset *C. difficile* infection (CO-CDI) within 30 days, and hospital readmission within 30 days.

Statistics

Baseline characteristics were compared between the accepted and rejected intervention groups. Continuous variables were expressed as medians with interquartile ranges. Categorical variables were expressed as units and percentages. Comparisons were performed using pooled *t*-test or Wilcoxon rank-sum test for continuous variables and Fisher's exact test or Pearson chi-square test for categorical variables. Significance was defined as $P < .05$, and all tests were 2-sided. Coarsened exact matching (CEM) was used as a non-parametric matching method to balance covariates between groups and to control for confounding. Factors used for CEM were based on top predictors for LOS such as severity of illness, age, major diagnostic category, ICU status, and case type (surgical versus not).

Results

A total of 5330 patients with ASP interventions were identified across the multihospital system over the 5 years (Figure 1). There were 4922 patients with accepted ASP interventions and 408 patients with rejected ASP interventions, resulting in an overall acceptance rate of 92%. The types of ASP interventions are illustrated in Figure 2 and described in Table 1. Most ASP interventions involved de-escalation of broad-spectrum antibiotics (58%), miscellaneous recommendations (11%), restricted antimicrobials (11%), and bug-drug mismatches (9%).

Baseline characteristics were largely well-balanced between groups for both ICU and non-ICU patients as shown in Tables 2 and 3, respectively. It is important to note that the much larger, unmatched groups of ICU and non-ICU patients

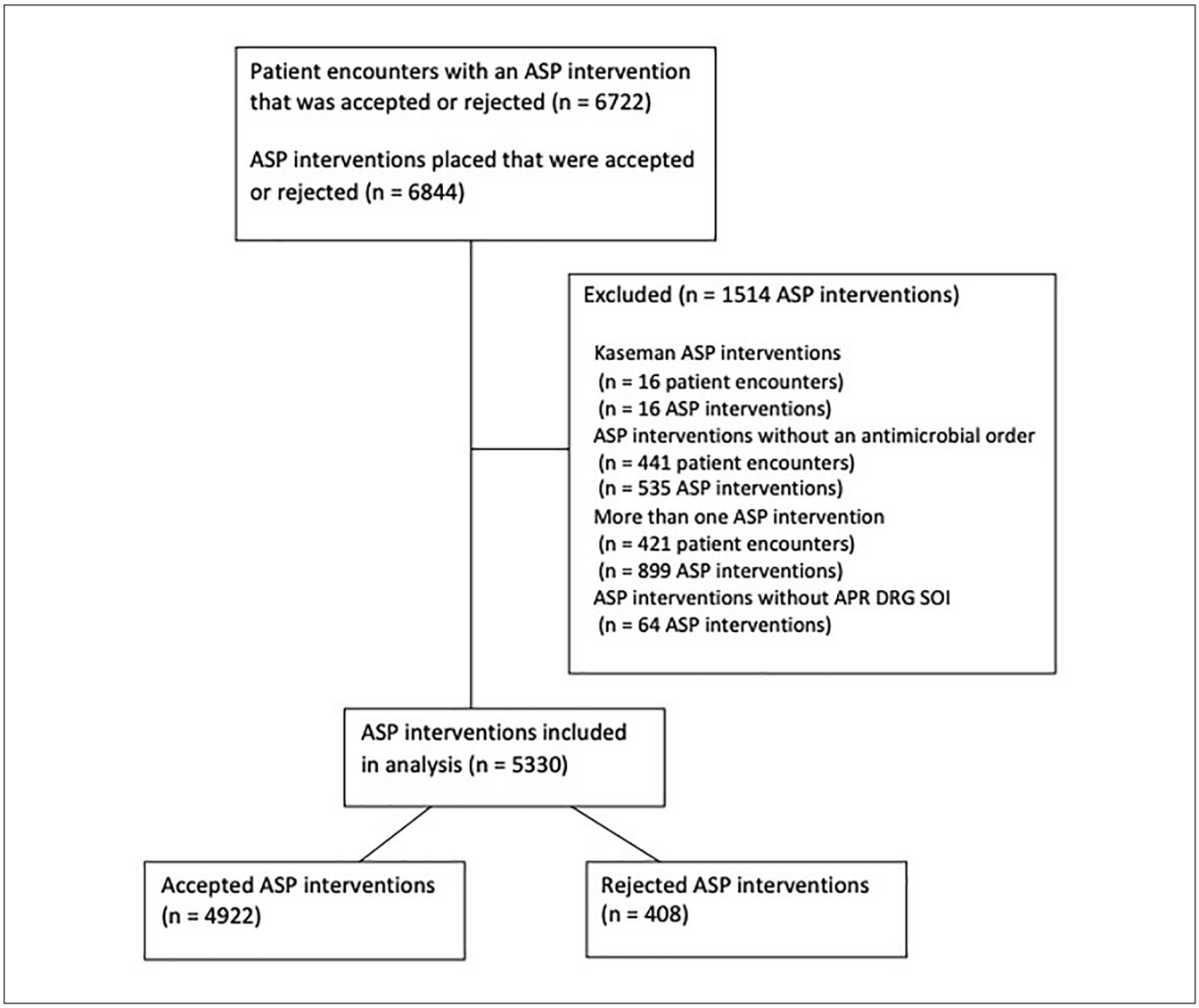

Figure 1. Sample selection.
Note. ASP = antimicrobial stewardship program; APR DRG = All Patients Refined Diagnosis Related Groups; SOI = severity of illness.

were well-balanced before matching. After CEM, ICU and non-ICU patient populations were significantly smaller in size, but baseline characteristics remained proportional between accepted and rejected intervention groups for both ICU and non-ICU patients. Furthermore, despite the varying levels of ICU care and potential for differences in patient acuity across the health system, the All Patients Refined Diagnosis Related Groups (APR DRG) severity of illness and risk of mortality scores were similar between both groups for ICU and non-ICU patients. However, there were notable differences between the accepted and rejected intervention groups. Before matching ICU patients, the rejected group had significantly more surgical cases and patients with pneumonia. After matching ICU patients with CEM, the accepted group had significantly more immunocompromised patients and fewer patients with pneumonia. Before matching non-ICU patients, the accepted group had significantly more patients with diabetes and urinary tract infections and fewer patients with intra-abdominal infections and pneumonia. After matching non-ICU patients with CEM, baseline characteristics were similar between groups.

Primary Outcomes

All outcomes for ICU and non-ICU patients are presented in Tables 4 and 5, respectively. Among unmatched ICU patients, the accepted group had a significant reduction in total antibiotic doses/1000 PD by 15% (2388 vs 2812, $P = .0369$) when compared to the rejected group. The accepted group also had significant decreases in anti-MRSA DOT/1000 PD by 25%

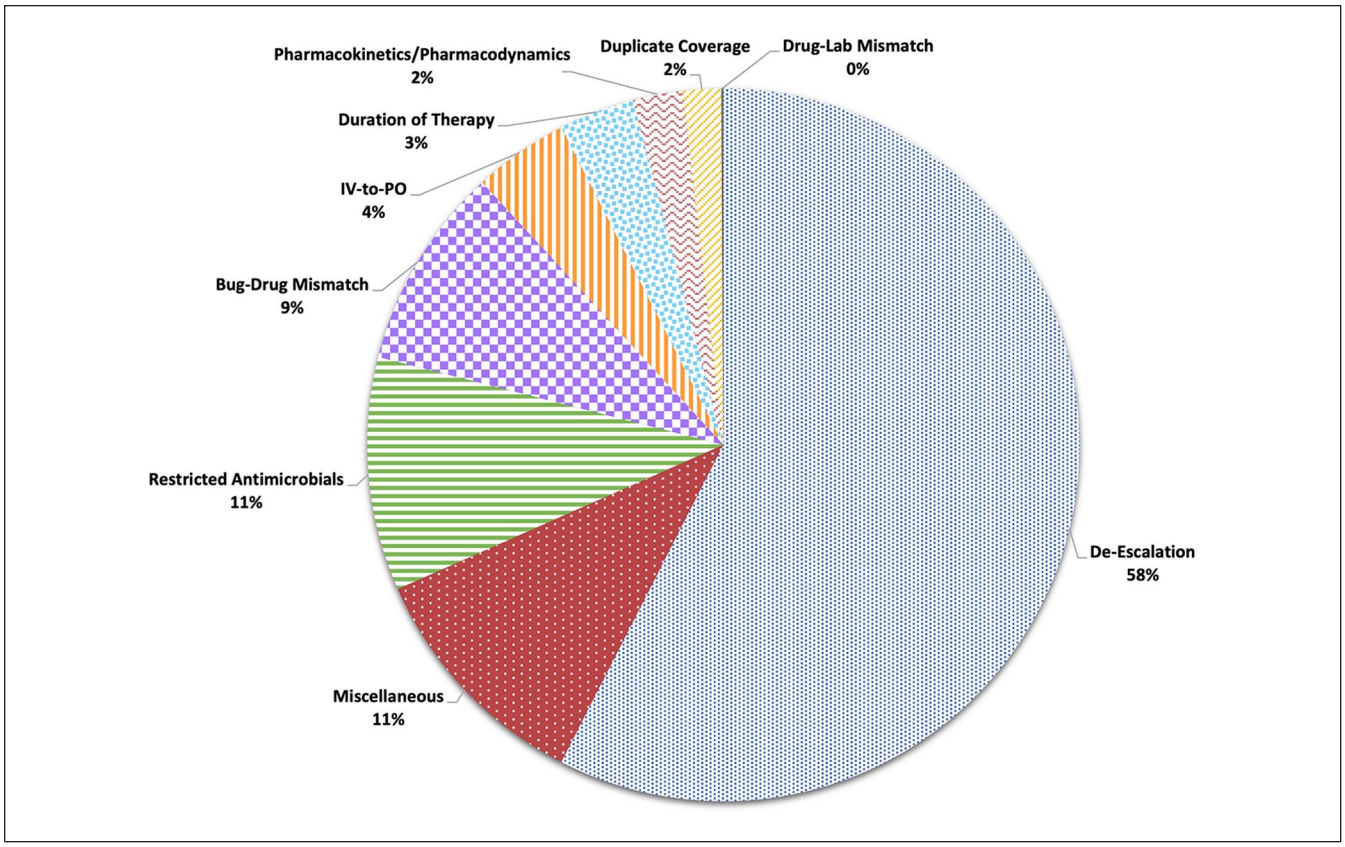

Figure 2. Antimicrobial stewardship intervention subtypes.

Table 1. ASP Intervention Definitions.

ASP intervention	Definition
Bug-drug mismatch	Identifying and modifying ineffective antimicrobial(s) to effective antimicrobial(s) based on cultures
De-escalation	Changing from broad-spectrum antimicrobial(s) to more narrow-spectrum antimicrobial(s)
Drug-lab mismatch	Identifying and modifying antimicrobial(s) based on laboratory results
Duplicate coverage	Discontinuing an antimicrobial with unnecessarily similar activity provided by another antimicrobial
Duration of therapy	Optimizing duration of therapy based on guideline recommendations and patient clinical status
IV-to-PO	Changing intravenous antimicrobials to oral antimicrobials
Miscellaneous	An intervention that does not fit into the other categories
Pharmacokinetic/pharmacodynamic	Optimizing antimicrobial dosing based on indication and applicable labs
Restricted antimicrobials	Monitoring restricted antimicrobials for appropriate use

(323 vs 429, $P=.0085$) and anti-MRSA doses/1000 PD by 34% (481 vs 725, $P=.0216$), as well as anti-pseudomonal DOT/1000 PD by 22% (500 vs 643, $P=.0026$) and anti-pseudomonal doses/1000 PD by 34% (1067 vs 1625, $P=.0004$). There was no statistical difference in high-risk *C. difficile* antibiotic use between groups. Similar results were seen for the smaller population of matched ICU patients, except there were no longer significant reductions in the use of anti-MRSA antibiotics. The matched ICU accepted group had significant reductions in total antibiotic doses/1000 PD by 22% (2159 vs 2781, $P=.0276$), anti-pseudomonal DOT/1000 PD by 28% (419 vs 581, $P=.0027$), and anti-pseudomonal doses/1000 PD by 40% (894 vs 1500, $P=.0008$).

Among the larger population of unmatched non-ICU patients, the accepted group had significant reductions in total antibiotic doses/1000 PD by 10% (2400 vs 2667, $P<.0001$) when compared to the rejected group. The accepted group also had significant decreases in anti-MRSA DOT/1000 PD by 25% (500 vs 667, $P<.0001$), anti-MRSA doses/1000 PD by 25% (750 vs 1000, $P<.0001$), anti-pseudomonal DOT/1000 PD by 26% (571 vs 775, $P<.0001$), and anti-pseudomonal doses/1000 PD by 35% (1167 vs 1789, $P<.0001$). Additionally, the accepted group had a

Table 2. Baseline Characteristics in ICU Patients.

	ICU patients					
	Unmatched			Matched with CEM		
Baseline characteristics	Accepted	Rejected	*P*-value	Accepted	Rejected	*P*-value
Ivents, N	722	85		70	70	
Age, mean (SD)	57.4 (18.2)	58.3 (17.5)	.6497	58.2 (16.1)	58.6 (16.1)	.8925
Female sex, N (%)	346 (47.9)	44 (51.8)	.5664	29 (41.4)	36 (48.6)	.3093
APR DRG severity of illness, N (%)			.7606			1.0000
Minor	7 (0.97)	0 (0.00)		0 (0.00)	0 (0.00)	
Moderate	35 (4.85)	3 (3.53)		0 (0.00)	0 (0.00)	
Major	120 (16.6)	15 (17.7)		10 (14.3)	10 (14.3)	
Extreme	560 (77.6)	67 (78.8)		60 (85.7)	60 (85.7)	
APR DRG risk of mortality, N (%)			.7144			.7791
Minor	19 (2.63)	3 (3.53)		0 (0.00)	0 (0.00)	
Moderate	36 (4.99)	4 (4.71)		3 (4.29)	2 (2.86)	
Major	127 (17.6)	11 (12.9)		10 (14.3)	8 (11.4)	
Extreme	540 (74.8)	67 (78.8)		57 (81.4)	60 (85.7)	
MS DRG case type, N surgical (%)	261 (36.2)	43 (51.2)	.0073	36 (51.4)	36 (51.4)	1.0000
MS DRG MDC (26 levels)			.4075			1.0000
Comorbidities						
Cancer, N (%)	79 (10.9)	13 (15.3)	.2766	9 (12.9)	10 (14.3)	1.0000
CHF, N (%)	165 (22.8)	21 (24.7)	.6845	20 (28.6)	17 (24.3)	.7020
CKD/AKI, N (%)	472 (65.4)	53 (62.4)	.6307	46 (65.7)	49 (70.0)	.7176
COPD, N (%)	121 (16.8)	19 (22.4)	.2246	10 (14.3)	16 (22.9)	.2771
Diabetes, N (%)	303 (42.0)	31 (36.5)	.3535	29 (41.4)	27 (38.6)	.8631
Immunosuppressed, N (%)	73 (10.1)	4 (4.71)	.1208	13 (18.6)	3 (4.29)	.0146
Obesity, N (%)	209 (29.0)	20 (23.5)	.3124	21 (30.0)	18 (25.7)	.7064
Infection type						
Intra-abdominal, N (%)	89 (12.3)	14 (16.5)	.3013	10 (14.3)	12 (17.1)	.8169
Pneumonia, N (%)	291 (40.3)	44 (51.8)	.0479	26 (37.1)	39 (55.7)	.0416
SSTI, N (%)	111 (15.4)	13 (15.3)	1.0000	9 (12.9)	12 (17.1)	.6368
UTI, N (%)	225 (31.2)	22 (25.9)	.3838	26 (37.1)	17 (24.3)	.1423
ASP ivent subtype, N (%)			.1008			.0111
Bug-drug mismatch	57 (7.89)	3 (3.53)		7 (10.0)	3 (4.29)	
De-escalation	429 (59.4)	66 (77.6)		33 (47.1)	55 (78.6)	
Drug-lab mismatch	1 (0.14)	0 (0.00)		0 (0.00)	0 (0.00)	
Duplicate coverage	15 (2.08)	1 (1.18)		1 (1.43)	0 (0.00)	
Duration of therapy	21 (2.91)	2 (2.35)		2 (2.86)	2 (2.86)	
IV-to-PO	5 (0.69)	0 (0.00)		0 (0.00)	0 (0.00)	
Miscellaneous	61 (8.45)	7 (8.24)		12 (17.1)	5 (7.14)	
Pharmacokinetic/pharmacodynamic	20 (2.77)	0 (0.00)		2 (2.86)	0 (0.00)	
Restricted antimicrobials	113 (15.7)	6 (7.06)		13 (18.6)	5 (7.14)	

Note. APR DRG = All Patients Refined Diagnosis Related Groups; MS DRG = Medicare Severity Diagnosis Related Groups; MDC = Major Diagnostic Category; CHF = congestive heart failure; CKD = chronic kidney disease; AKI = acute kidney injury; COPD = chronic obstructive pulmonary disease; SSTI = skin and soft tissue infection; UTI = urinary tract infection.

significant increase in high-risk *C. difficile* DOT/1000 PD by 33% (444 vs 333, $P = .0021$), but no major difference in high-risk *C. difficile* doses/1000 PD compared to the rejected group. Similar results were found for the smaller population of matched non-ICU patients, although the reduction in total antibiotic DOT/1000 PD was no longer significant. The matched non-ICU accepted group had significant decreases in total antibiotic doses/1000 PD by 11% (2385 vs 2667, $P = .0007$), anti-MRSA DOT/1000 PD by 25% (500 vs 667, $P = .0021$), anti-MRSA doses/1000 PD by 22% (785 vs 1000, $P = .0032$), anti-pseudomonal DOT/1000 PD by 22% (600 vs 768, $P < .0001$), and anti-pseudomonal doses/1000 PD by 30% (1250 vs 1789, $P < .0001$). The matched non-ICU accepted group also had a significant increase in high-risk *C. difficile* DOT/1000 PD by 50% (500 vs 333, $P = .0042$) but no large difference in high-risk *C. difficile* doses/1000 PD compared to the rejected group.

Table 3. Baseline Characteristics in Non-ICU Patients.

	Non-ICU patients					
	Unmatched			Matched with CEM		
Baseline characteristics	Accepted	Rejected	*P*-value	Accepted	Rejected	*P*-value
Ivents, N	4200	323		305	305	
Age, mean (SD)	61.4 (18.4)	62.7 (18.2)	.2071	63.1 (17.2)	62.3 (17.7)	.8423
Female sex, N (%)	2076 (49.4)	159 (49.2)	.9540	161 (52.8)	144 (44.2)	.4180
APR DRG severity of illness, N (%)			.0692			1.0000
Minor	269 (6.40)	22 (6.81)		17 (5.57)	17 (5.57)	
Moderate	953 (22.7)	78 (24.2)		75 (24.6)	75 (24.6)	
Major	1773 (42.2)	113 (35.0)		109 (35.7)	109 (35.7)	
Extreme	1205 (28.7)	110 (34.1)		104 (34.1)	104 (34.1)	
APR DRG risk of mortality, N (%)			.5830			.9996
Minor	773 (18.4)	65 (20.1)		56 (18.3)	56 (18.3)	
Moderate	1005 (23.9)	70 (21.7)		68 (22.3)	68 (22.3)	
Major	1421 (33.8)	104 (32.2)		98 (32.1)	97 (31.8)	
Extreme	1001 (23.8)	84 (26.0)		83 (27.2)	83 (27.2)	
MS DRG case type, N surgical (%)	1356 (32.4)	102 (31.6)	.8051	95 (31.2)	95 (31.2)	1.000
MS DRG MDC (26 levels)			.1898			1.000
Comorbidities						
Cancer, N (%)	530 (12.6)	42 (13.0)	.8620	36 (11.8)	41 (13.4)	.6260
CHF, N (%)	749 (17.8)	65 (20.1)	.2935	61 (20.0)	63 (20.7)	.9200
CKD/AKI, N (%)	1702 (40.5)	125 (38.7)	.5564	128 (42.0)	123 (40.3)	.7421
COPD, N (%)	702 (16.7)	64 (19.8)	.1655	52 (17.0)	62 (20.3)	.3499
Diabetes, N (%)	1720 (41.0)	106 (32.8)	.0039	112 (36.7)	104 (34.1)	.5535
Immunosuppressed, N (%)	309 (7.36)	20 (6.19)	.5049	20 (6.56)	19 (6.23)	1.0000
Obesity, N (%)	824 (19.6)	70 (21.7)	.3842	50 (16.4)	68 (22.3)	.0811
Infection type						
Intra-abdominal, N (%)	531 (12.6)	54 (16.7)	.0389	49 (16.1)	54 (17.7)	.6657
Pneumonia, N (%)	862 (20.5)	88 (27.2)	.0056	65 (21.3)	85 (27.9)	.0738
SSTI, N (%)	1239 (29.5)	92(28.5)	.7515	85 (27.9)	86 (28.2)	1.0000
UTI, N (%)	1215 (28.9)	75 (23.2)	.0296	88 (28.8)	71 (23.3)	.1399
ASP ivent subtype, N (%)			<.0001			.0218
Bug-drug mismatch	414 (9.86)	16 (4.95)		26 (8.52)	14 (4.59)	
De-escalation	2351 (56.0)	220 (68.1)		171 (56.1)	208 (68.2)	
Drug-lab mismatch	2 (0.05)	2 (0.62)		1 (0.33)	2 (0.66)	
Duplicate coverage	67 (1.60)	9 (2.79)		3 (0.98)	8 (2.62)	
Duration of therapy	143 (3.40)	17 (5.26)		15 (4.92)	16 (5.25)	
IV-to-PO	213 (5.07)	12 (3.72)		25 (8.20)	12 (3.93)	
Miscellaneous	486 (11.6)	24 (7.43)		29 (9.51)	22 (7.21)	
Pharmacokinetic/pharmacodynamic	97 (2.31)	4 (1.24)		7 (2.30)	4 (1.31)	
Restricted antimicrobials	427 (10.2)	19 (5.88)		28 (9.18)	19 (6.23)	

Note. APR DRG = All Patients Refined Diagnosis Related Groups; MS DRG = Medicare Severity Diagnosis Related Groups; MDC = Major Diagnostic Category; CHF = congestive heart failure; CKD = chronic kidney disease; AKI = acute kidney injury; COPD = chronic obstructive pulmonary disease; SSTI = skin and soft tissue infection; UTI = urinary tract infection.

Secondary Outcomes

Among unmatched ICU patients, the accepted group had a significantly shorter hospital LOS by 2 days (11 days vs 13 days, $P = .049$) and a reduction in-hospital mortality by 11% ($P = .0162$) compared to the rejected group. Other secondary outcomes including HA-CDI, CO-CDI within 30 days, and hospital readmission within 30 days were similar across groups. After matching ICU patients, no secondary outcomes were significantly different between groups.

Among unmatched non-ICU patients, the accepted group had a significantly shorter hospital LOS by 1 day (6 days vs 7 days, $P = .0075$) compared to the rejected group. Other secondary outcomes including in-hospital mortality, HA-CDI, CO-CDI within 30 days, and hospital readmission within

Table 4. Outcomes in ICU Patients.

	ICU patients					
	Unmatched			Matched with CEM		
Outcomes	Accepted (n = 722)	Rejected (n = 85)	*P*-value	Accepted (n = 70)	Rejected (n = 70)	*P*-value
Total antibiotic DOT/1000 PD, Median (IQR)	889 (714-1000)	909 (692-1000)	.6939	812 (664-980)	930 (679-1000)	.1480
Total antibiotic doses/1000 PD, Median (IQR)	2388 (1719-3333)	2812 (1926-3622)	.0369	2159 (1488-3083)	2781 (1838-3733)	.0276
Anti-MRSA DOT/1000 PD, N, Median (IQR)	583 323 (194-500)	74 429 (241-672)	.0085	63 333 (250-500)	63 438 (240-667)	.2279
Anti-MRSA doses/1000 PD, N, Median (IQR)	583 481 (250-846)	74 725 (284-1175)	.0216	63 500 (308-792)	63 700 (257-1143)	.3758
Anti-pseudomonal DOT/1000 PD, N, Median (IQR)	620 500 (314-714)	79 643 (350-846)	.0026	62 419 (250-584)	67 581 (345-833)	.0027
Anti-pseudomonal doses/1000 PD, N, Median (IQR)	620 1067 (643-1694)	79 1625 (800-2125)	.0004	62 894 (580-1279)	67 1500 (750-2083)	.0008
High-risk *C. difficile* DOT/1000 PD, N, Median (IQR)	514 375 (176-630)	49 333 (173-606)	.7093	46 354 (140-617)	40 333 (181-593)	.8353
High-risk *C. difficile* doses/1000 PD, N, Median (IQR)	514 438 (200-794)	49 429 (205-903)	.8834	46 394 (185-707)	40 375 (213-760)	.7618
Hospital LOS (days), median (IQR)	11 (7-18)	13 (9-22)	.0490	18 (9-26)	15 (9-23)	.3555
In-hospital mortality, %	16.9	28.2	.0162	22.9	31.4	.3421
HA-CDI, %	1.52	1.18	1.0000	2.86	1.43	1.0000
CO-CDI within 30 days, %	1.00	0.00	1.0000	0.00	0.00	
Hospital readmission within 30 days, %	21.2	11.5	.0931	25.9	12.5	.1330

Table 5. Outcomes in Non-ICU Patients.

	Non-ICU patients					
	Unmatched			Matched with CEM		
Outcomes	Accepted (n = 4200)	Rejected (n = 323)	*P*-value	Accepted (n = 305)	Rejected (n = 305)	*P*-value
Total antibiotic DOT/1000 PD, Median (IQR)	1000 (800-1000)	1000 (833-1000)	.0132	1000 (800-1000)	1000 (833-1000)	.0926
Total antibiotic doses/1000 PD, Median (IQR)	2400 (1625-3333)	2667 (2000-3636)	<.0001	2385 (1564-3401)	2667 (2000-3651)	.0007
Anti-MRSA DOT/1000 PD, N, Median (IQR)	2675 500 (286-750)	186 667 (366-875)	<.0001	186 500 (329-750)	179 667 (375-875)	.0021
Anti-MRSA doses/1000 PD, N, Median (IQR)	2675 750 (375-1333)	186 1000 (500-1560)	<.0001	186 785 (429-1250)	179 1000 (500-1571)	.0032
Anti-pseudomonal DOT/1000 PD, N, Median (IQR)	2891 571 (364-778)	246 775 (569-1000)	<.0001	219 600 (417-833)	232 768 (565-1000)	<.0001
Anti-pseudomonal doses/1000 PD, N, Median (IQR)	2891 1167 (667-1750)	246 1789 (1200-2276)	<.0001	219 1250 (850-1875)	232 1789 (1219-2267)	<.0001
High-risk *C. difficile* DOT/1000 PD, N, Median (IQR)	2734 444 (250-667)	175 333 (192-600)	.0021	189 500 (250-707)	167 333 (192-600)	.0042
High-risk *C. difficile* doses/1000 PD, N, Median (IQR)	2734 500 (250-833)	175 429 (200-857)	.0528	189 571 (250-826)	167 429 (200-857)	.0746
Hospital LOS (days), median (IQR)	6 (4-10)	7 (5-11)	.0075	6 (4-10)	7 (5-12)	.0074
In-hospital mortality, %	2.33	3.41	.2539	2.62	3.61	.6423
HA-CDI, %	0.52	0.93	.4190	0.66	0.98	1.0000
CO-CDI within 30 days, %	1.05	0.00	.0714	1.01	0.00	.2487
Hospital readmission within 30 days, %	19.7	19.2	.8827	19.9	19.7	1.0000

30 days were similar across groups. After matching non-ICU patients, the reduction in hospital LOS by 1 day (6 days vs 7 days, $P = .0074$) remained significant for the accepted group.

Discussion

In this 5-year, multicenter, observational study of 5330 hospitalized patients who received antibiotics for infections and had ASP interventions documented as accepted or rejected, ASP recommendations by ID pharmacists were generally well-received by providers as indicated by the high overall acceptance rate of 92%. Interventions were rejected for a variety of reasons including pending imaging results, awaiting formal ID physician consultation, and provider perception of patient acuity. Acceptance of ASP interventions was associated with significant reductions in antibiotic usage without adversely affecting mortality or hospital readmissions for both ICU and non-ICU patients. These findings are consistent with previous studies demonstrating the effectiveness of ASPs with pharmacist involvement in decreasing unnecessary antimicrobial use without increasing mortality.[2-5]

It is important to note that ICU patients with accepted ASP interventions had significant decreases in antibiotic utilization despite having more immunocompromising conditions at baseline. While this could lessen the difference between groups as immunocompromised patients may require broader-spectrum antimicrobials for longer durations, the outcome was still significantly different. Additionally, the accepted and rejected groups of ICU patients had considerable numeric differences in in-hospital mortality and hospital readmissions within 30 days, although this finding was not statistically significant. The difference in in-hospital mortality may be due to confounding factors not accounted for by CEM. Because hospital readmissions were not limited specifically to infections, patients may have been readmitted for unrelated reasons and contributed to this difference.

Utilization of high-risk *C. difficile* antibiotics (ie, fluoroquinolones, ceftriaxone, or clindamycin) increased significantly among non-ICU patients with accepted ASP interventions and was likely driven by frequent de-escalation of broader-spectrum antibiotics to ceftriaxone. However, this is unlikely to be clinically relevant as rates of HA-CDI and CO-CDI within 30 days were not negatively impacted. Although antibiotic exposure is an important modifiable risk factor for developing CDI, other factors like infection control measures may have played a larger role in preventing CDI in this patient population as healthcare-associated CDIs decreased during this time at our largest hospitals.[7]

Additionally, hospital LOS was significantly shorter by 1 day for non-ICU patients with accepted ASP interventions, which is comparable to a 2017 Cochrane review suggesting ASP interventions can reduce LOS by 1.12 days.[2] We attributed LOS reduction to transitioning to more narrow spectrum antimicrobials, duration of therapy optimization, and IV to PO conversion. Utilization of more targeted antimicrobials enhances provider ability to transition to PO options and may lead to more favorable responses to therapy.[8,9] Of note, de-escalation interventions often included IV-to-PO and duration recommendations which likely contributed to the low volume of IV-to-PO interventions as these may overlap. A recent systematic review of hospital ASPs also demonstrated that reducing LOS is a major determinant of cost savings.[10] Based on internal data using average cost per day, LOS reduction cost avoidance was $7 631 400. Thus, the substantial reduction in hospital LOS for non-ICU patients translates to considerable cost savings and reinforces the clinical and economic value of ASPs with ID pharmacists.

Strengths and Limitations

Strengths of this study include its large patient population from a multihospital system spanning urban and rural areas. Baseline characteristics of patients were also generally well-balanced between the accepted and rejected intervention groups before matching. Additionally, CEM was used to adjust for confounding and ensure fair comparisons between groups. The primary outcomes for ICU and non-ICU patients were similar before and after matching, highlighting the study's internal validity. However, this study has several important limitations. First, it was a retrospective observational study, and there is potential for selection bias due to inherent differences between patients with accepted and rejected ASP interventions. Patients with multiple ivents during the same admission were excluded from the study population, which may have also introduced selection bias toward less complicated cases. Furthermore, ICU patients from different hospitals within the health system may vary in illness severity. Nonetheless, APR DRG severity of illness and risk of mortality scores were well-balanced among all ICU patients before and after matching, so outcomes were unlikely impacted by this. In addition, most inpatients at PHS hospitals were adults, and results may not be generalizable to pediatric patients. There may also be other confounding variables, such as chronic steroid use, unaccounted for in this study. Lastly, the 5-year data was not further divided into yearly or quarterly timeframes to assess for trends or variability as there would be small sample sizes that limit the chances of finding significant differences.

Our stewardship program has been established for nearly 2 decades at our institution. Experienced providers within the system are generally familiar with the program and have an appreciation for antimicrobial stewardship. This likely influenced our high acceptance rate of 92%. Although we didn't identify patterns between specific providers for rejected interventions, numerous factors may play into the acceptance of interventions made by our ASP team. These may encompass patient volume of providers, provider perceptions of the patient's clinical status, and other non-measurable behavioral attitudes at the time of the intervention.

Conclusion

ASP recommendations by ID pharmacists were well-received by providers in a multihospital system over 5 years as evidenced by an overall acceptance rate of 92%. Acceptance of ASP interventions was associated with substantial reductions in antibiotic utilization without adversely affecting mortality or hospital readmissions. While high-risk *C. difficile* antibiotic use increased significantly due to frequent de-escalation to ceftriaxone among non-ICU patients with accepted interventions, rates of HA-CDI and CO-CDI within 30 days did not worsen. Furthermore, hospital LOS was notably shorter by an average of 1 day for non-ICU patients with accepted interventions, which translated to considerable cost savings.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Justin Schmetterer receives financial compensation for serving in AbbVie® and Paratek® Speakers Bureau. All other authors declare that there is no conflict of interest.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Taylor Babiarz https://orcid.org/0009-0003-6157-0189

References

1. 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(10):e51-e77.
2. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev*. 2017;2(2):CD003543.
3. Li Z, Cheng B, Zhang K, et al. Pharmacist-driven antimicrobial stewardship in intensive care units in East China: a multicenter prospective cohort study. *Am J Infect Control*. 2017;45(9):983-989.
4. Wang H, Wang H, Yu X, et al. Impact of antimicrobial stewardship managed by clinical pharmacists on antibiotic use and drug resistance in a Chinese hospital, 2010–2016: a retrospective observational study. *BMJ Open*. 2019;9:e026072.
5. Mas-Morey P, Valle M. A systematic review of inpatient antimicrobial stewardship programmes involving clinical pharmacists in small-to-medium-sized hospitals. *Eur J Hosp Pharm*. 2018;25(e1):e69-e73.
6. CDC. *Core Elements of Hospital Antibiotic Stewardship Programs*. US Department of Health and Human Services, CDC; 2019. https://www.cdc.gov/antibiotic-use/core-elements/hospital.html. Accessed June 7, 2023.
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(7):e1-e48.
8. Mertz D, Koller M, Haller P, et al. Outcomes of early switching from intravenous to oral antibiotics on medical wards. *J Antimicrob Chemother*. 2009;64:188–199.
9. Xu S, Wang X, Song Z, et al. Impact and barriers of a pharmacist-led practice with computerized reminders on intravenous to oral antibiotic conversion for community-acquired pneumonia inpatients. *J Clin Pharm Ther*. 2021;46(4):1055-1061.
10. Nathwani D, Varghese D, Stephens J, Ansari W, Martin S, Charbonneau C. Value of hospital antimicrobial stewardship programs [ASPs]: a systematic review. *Antimicrob Resist Infect Control*. 2019;8:35.