A Retrospective Before-and-After Study Evaluating the Impact of Clinical Pharmacist Involvement on Patients Hospitalized with Bacteremia

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ABSTRACT **Background:** Bloodstream infections (BSI) are associated with high morbidity and mortality. Inappropriate empirical antimicrobial therapy leads to poor outcomes.

Objectives: To evaluate the impact of clinical pharmacist intervention on the appropriateness of antibiotic treatment in patients hospitalized with bacteremia.

Methods: A retrospective study was conducted at the Soroka Medical Center in Israel. The intervention was implemented starting in July 2018. We compared 170 patients who received pharmacist intervention (August 2018 to June 2019) to 173 control patients (January 2017 to July 2018). The primary outcome was a composite of appropriate antibiotic choice and dosage.

Results: Pharmacist intervention significantly improved appropriate antibiotic dosing (97.6% vs. 91.3%, $P = 0.011$) and selection based on pathogen sensitivity (100% vs. 95.4%, $P = 0.007$). The most significant effect was observed in patients with intermediate renal function (CrCl 30–60 ml/min). Multivariate analysis confirmed pharmacist intervention as a strong predictor of appropriate treatment (odds ratio 5.00, 95% confidence interval 1.64–15.25, $P = 0.005$). The intervention group had longer hospital stays (median 15 vs. 9 days, $P < 0.001$) and lower 7-day relapse rates (2.4% vs. 8.7%, $P = 0.010$).

Conclusions: Clinical pharmacist interventions significantly improved the appropriateness of antibiotic treatment in patients with bacteremia, particularly in those with intermediate renal function. Despite longer hospital stays, the intervention group had lower early relapse rates than the control group. These findings support the integration of clinical pharmacists into antimicrobial stewardship programs.

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KEY WORDS: antimicrobial stewardship, bacteremia, clinical pharmacist, drug resistance, renal insufficiency

Bloodstream infections (BSI) are associated with high morbidity, mortality, and increased healthcare costs [1,2]. Alarmingly, 11–30% of patients with BSI receive inappropriate empirical antimicrobial therapy [3], which is linked to significantly higher mortality rates [4-7]. Managing BSI is complex due to its heterogeneous nature, necessitating strategies such as source control, early complication detection, and appropriate antimicrobial stewardship [8].

Infectious disease specialists (IDS) have been shown to improve prognosis, reduce broad-spectrum drug use, and facilitate appropriate treatment [9,10]. However, international guidelines increasingly recognize the essential role of clinical pharmacists in antimicrobial stewardship (AMS) [11]. Pharmacists help optimize regimens, audit outcomes, and educate healthcare professionals. Studies have demonstrated that pharmacist involvement leads to improved antimicrobial therapy, reduced costs, and enhanced patient care [11,12].

While previous interventions often focused on specific pathogens like *Staphylococcus aureus* [13-15] or specific drugs like vancomycin [16], few studies have examined the broader impact of pharmacist intervention on antibiotic appropriateness across a wide range of pathogens. At Soroka Medical Center, a clinical pharmacist intervention program was implemented for all bacteremia patients. In this study, we aimed to evaluate antibiotic treatment appropriateness before and after this intervention, focusing on treatment accuracy, renal dose adjustment, and adherence to sensitivity results.

PATIENTS AND METHODS

STUDY DESIGN AND SETTING

This retrospective before-and-after study was conducted at Soroka Medical Center, a large tertiary care facility in southern Israel, between December 2016 and March 2019.

PARTICIPANTS

We included 343 adult patients with confirmed bacteremia. The intervention group comprised 170 patients hospitalized after 1 August 2018, when a pharmacist's review of antimicrobial therapy was implemented. The control group included 173 patients hospitalized prior to the intervention. The pharmacist-led intervention was initiated in July 2018. For the control group, we selected a convenience sample of patients diagnosed with BSI before this date. The sample was non-consecutive and did not include all eligible patients. The inclusion criteria were not being admitted to the intensive care unit at admission, aged ≥ 18 years, a positive blood culture confirmed to have true bacteremia. Cases considered likely to be contaminants were excluded, such as single positive cultures of coagulase-negative staphylococci or anaerobic organisms without clinical correlation.

Exclusion criteria for confirmed bacteremia cases included death before culture review, infectious disease specialist involvement before pharmacist intervention, missing data, or pre-intervention pharmacist consultations requested by physicians.

DATA COLLECTION

The blood culture database was screened, and baseline data was collected for eligible patients. The data collected included demographics, medical history (Charlson Comorbidity Index), laboratory values (glomerular filtration rate, white blood cells, and C-reactive protein), acute kidney injury level as defined by the Acute Kidney Injury Network (AKIN) stage, and bacteriological information (species, resistance, and antibiotic treatment).

INTERVENTION

The intervention involved a clinical pharmacist consultation for all eligible patients with positive blood cultures between August 2018 and June 2019. Pharmacist interventions were categorized as follows: dose adjustment according to renal function, appropriate dose adjustment, narrowing of antibiotic selection according to pathogen and resistance pattern, addressing drug-drug interactions, and recommending infectious disease consultation.

OUTCOMES

The primary outcome was a composite index of appropriate antibiotic choice (based on bacterial sensitivity) and dosage (according to kidney function). Blood cultures and antibiotic sensitivity testing were performed using standardized methods (Kirby-Bauer disk diffusion or VITEK® 2 system [bioMérieux, USA]) according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. Appropriate antibiotic choice was assessed post-susceptibility by clinical pharmacists, based on concordance with in vitro bacterial sensitivities according to CLSI standards. Dosing appropriateness was determined concurrently based on bacterial species and kidney function (AKIN classification and MDRD-calculated creatinine clearance), guided primarily by the *Sanford Guide to Antimicrobial Therapy*.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). A P-value < 0.05 was considered statistically significant. Descriptive statistics were reported as means and standard deviations (normal distribution), medians and interquartile ranges (non-normal distribution), or numbers and percentages (categorical variables). Univariate analysis was used to examine the relationships between individual variables and the primary outcome. Chi-square tests were used to compare categorical variables, whereas t-tests or Mann-Whitney tests were used for continuous variables. Multivariate logistic regression was used to analyze variables showing strong relationships or high clinical significance to determine their direct effects on the primary outcome.

RESULTS

Of the 508 patients with positive blood cultures, 343 met the inclusion criteria and were included in the study (170 in the intervention group and 173 in the control group). Exclusions (n=165) were due to missing medical information (n=63), complex infections requiring intensive care unit care (n=48), nonpathogenic bacteria in the blood (i.e., contaminants) (n=43), and other reasons (n=11).

Analysis of the baseline characteristics showed that both groups were similar in terms of sex distribution (approximately 60% men in both groups) and other key characteristics. However, there were some differences between

the intervention and control groups. Patients in the control group were older (mean age 69.8 vs. 65.7 years, $P = 0.018$) and had higher rates of diabetes with complications (15.6% vs. 8.8%, $P = 0.040$), dementia (22% vs. 10%, $P = 0.003$), and ischemic heart disease (8.1% vs. 2.9%, $P = 0.037$). The groups had the same median Charlson Comorbidity Index score (5.0, $P = 0.481$) but the patients in the intervention group had a higher prevalence of hematological malignancies (11.8% vs. 5.2%, $P = 0.029$). The baseline characteristics are presented in Table 1.

Analysis of the microbiological characteristics revealed some differences between the intervention and control groups of the study. Gram-positive bacteria were more prevalent in the control group (52.6% vs 45.3%, $P = 0.037$), while Gram-negative bacteria were more common in the intervention group (54.7% vs 47.4%, $P =$

Table 1. Baseline demographic and clinical characteristics of study population

Variable			Intervention group (n=170)	Control group (n=173)	*P*-value
Age, years (mean ± SD)			65.7 ± 16.1	69.8 ± 15.9	0.018
BMI kg/m² (mean ± SD) (n=255)			26.8 ± 5.6 (n=125)	26.1 ± 7.2 (n=130)	0.360
Sex, n (%)	Male		92 (54.1)	86 (49.7)	0.414
	Female		78 (45.9)	87 (50.3)	
Diabetes, n (%)	Without complications		54 (31.8)	38 (22.2)	0.040
	With complications		15 (8.8)	27 (15.6)	
Liver disease, n (%)	Mild		10 (5.9)	7 (4.0)	0.244
	Moderate–severe		6 (3.5)	2 (1.2)	
Chronic pulmonary disease, n (%)			11 (6.5)	14 (8.1)	0.563
Renal disease, n (%)		Severe	30 (17.6)	40 (23.1)	0.208
Congestive heart failure, n (%)			35 (20.6)	36 (20.8)	0.960
Ischemic heart disease, n (%)			5 (2.9)	14 (8.1)	0.037
Cerebrovascular disease, n (%)			8 (4.7)	8 (4.6)	0.971
Solid malignancy, n (%)		Local	11 (6.5)	23 (13.3)	0.052
		Metastatic	18 (10.6)	11 (6.4)	
Hematologic malignancy, n (%)			20 (11.8)	9 (5.2)	0.029
Dementia, n (%)			17 (10.0)	38 (22.0)	0.003
Charlson Comorbidity Index (1–10), median [IQR]			5 [3–6]	5 [3–7]	0.481
Charlson Comorbidity Index > 4, n (%)			119 (70.0)	129 (74.6)	0.345
Laboratory values					
Estimated GFR (MDRD, L/min/1.73m²), n (%)	> 90		58 (34.1)	39 (22.9)	0.149
	60–90		32 (18.8)	38 (22.4)	
	30–60		40 (23.5)	44 (25.9)	
	< 30		40 (23.5)	49 (28.8)	
Leukocytosis (> 10.8 K/μL), n (%)			94 (55.3)	100 (58.1)	0.595
Elevated CRP (> 5 mg/L), n (%) (n=253)			98 (84.5) (n=116)	125 (91.2) (n=137)	0.098
AKIN stage, n (%) (n=311)	0		108 (71.1)	97 (61.0)	0.079
	1		36 (23.7)	44 (27.7)	
	2–3		8 (5.3) (n=152)	18 (11.3) (n=159)	

AKIN = acute kidney injury network, BMI = body mass index, CRP = C-reactive protein, GFR = glomerular filtration rate, MDRD = modification of diet in renal disease

Table 2. Bacteriological characteristics

Variable		Intervention group (n=170)	Control group (n=173)	*P*-value
Blood culture, microbiology, n (%)	MSSA	38 (22.4)	22 (12.7)	0.019
	MRSA	4 (2.4)	7 (4.0)	0.373
	CONS	11 (6.5)	8 (4.6)	0.455
	Streptococci	10 (5.9)	10 (5.8)	0.968
	Enterococci	18 (10.6)	14 (8.1)	0.427
	Enterobacteriaceae sensitive	43 (25.3)	69 (39.9)	0.004
	Enterobacteriaceae MDR/ ESBL/CPE	28 (16.5)	46 (26.6)	0.023
	Pseudomonas aeruginosa	12 (7.1)	8 (4.6)	0.336
	Acinetobacter baumanii	2 (1.2)	3 (1.7)	0.667
	Anaerobes	6 (3.5)	4 (2.3)	0.503
	Fungi	3 (1.8)	1 (0.6)	0.368
	Other	4 (2.4)	1 (0.6)	0.170
Resistant bacteria* (%)		74 (43.5)	82 (47.4)	0.472
Polymicrobial infection, n (%)		9 (5.3)	22 (12.7)	0.017
Any empiric antibiotic treatment, n (%)		160 (94.1)	130 (75.1)	<0.001
Empiric antibiotic treatment, n (%) (N=290)	Penicillin	45 (28.1)	26 (20.0)	0.110
	Cephalosporin	87 (54.4)	77 (59.2)	0.407
	Carbapenem	9 (5.6)	7 (5.4)	0.929
	Vancomycin	32 (20.0)	21 (16.2)	0.399
	Clindamycin	7 (4.4)	5 (3.8)	0.822
	Quinolone	17 (10.6)	7 (5.4)	0.107
	Metronidazole	18 (11.3)	15 (11.5)	0.939
	Aminoglycosides	28 (17.5)	30 (23.1)	0.238
	Other**	14 (8.8)	11 (8.5)	0.931
Directed antibiotic treatment, n (%)	Penicillin	60 (35.5)	42 (24.3)	0.023
	Cephalosporin	83 (49.1)	75 (43.4)	0.285
	Carbapenem	32 (18.9)	28 (16.2)	0.504
	Vancomycin	17 (10.1)	34 (19.7)	0.031
	Clindamycin	5 (3.0)	3 (1.7)	0.498
	Quinolone	37 (21.9)	41 (23.7)	0.691
	Metronidazole	10 (5.9)	16 (9.2)	0.245
	Aminoglycosides	20 (11.8)	31 (17.9)	0.114
	Other***	15 (8.9)	22 (12.7)	0.253

*Resistant bacteria were defined as MSRA, CONS, Enterococci, Enterobacteriaceae MDR/ESBL/CPE, *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, fungi

**Other empiric antibiotic treatment regimen included chloramphenicol, macrolides, TMX–SMX, tetracyclines, fosfomycin, and azoles

***Other directed AB treatment regimen included chloramphenicol, macrolides, TMX–SMX, tetracyclines, fosfomycin, tigecycline, rifampin, daptomycin, linezolid, colistin, caspofungin, azoles

CPE = carbapenem resistant enterococcus, CONS = coagulase negative staphylococcus, ESBL = extended spectrum beta lactamase, MDR = multidrug resistant, MRSA = methicillin resistant *Staphylococcus aureus*, MSSA = methicillin susceptible *staphylococcus aureus*

0.037). The most frequent pathogens in both groups were *Escherichia coli* (28.8% in the intervention group vs. 24.9% in the control group) and *Klebsiella pneumoniae* (11.2% in the intervention group vs. 9.2% in the control group). Notably, *Staphylococcus aureus* infections were significantly more frequent in the control group (15% vs. 10.6%, $P = 0.047$). The bacteriological characteristics are shown in Table 2.

Although there were some differences between the intervention and control groups of the study, overall, the intervention group received more tailored treatment than the control group (97.6% vs. 87.3%, $P < 0.001$). When interventions were performed, dose correction (12.2%) and antibiotic changes based on culture results were the most common, followed by renal considerations (6.7%). All patients in the intervention group received sensitivity-adapted treatment, compared to 95.4% in the control group ($P = 0.007$). Treatment appropriate to kidney function was higher in the intervention group (97.6% vs. 91.3%, $P = 0.011$). However, in the intervention group, 66.5% of cases did not require any change in treatment.

Median hospitalization length was longer in the intervention group (15 days [IQR 9–26] vs. 9 days [IQR 5–16], $P < 0.001$). Seven-day relapse rates were lower in the intervention group (2.4% vs. 8.7%, $P = 0.010$). No significant differences were found in mortality during hospitalization (14.1% vs. 17.4%, $P = 0.399$), at 30 days (13.5% vs. 19.1%, $P = 0.165$), or at 6 months (34.1% vs. 34.7%, $P = 0.912$). The 30-day readmission rate was similar between the groups (32.4% vs. 30.2%, $P = 0.672$). The outcomes are summarized in Table 3.

Univariate analysis of appropriate treatment found that the relative contribution of clinical pharmacist intervention was the strongest positive contributor (odds ratio [OR] 6.05, 95% confidence interval [95%CI] 2.04–17.95, $P = 0.001$). Dividing kidney function into three levels, a distinct positive trend was found in both the intermediate group with CrCl 30-60 (OR 0.14, 95%CI 0.03–0.65, $P = 0.012$) and the CrCl < 30 group (OR 0.19, 95%CI 0.04–0.89, $P = 0.035$). However, multivariate analysis found significance only for the intermediate group (OR 0.22, 95%CI 0.05–0.97, $P = 0.045$) and for the pharmacist intervention (OR 5.00, 95%CI 1.64–15.25, $P = 0.005$). The analysis results are presented in Table 4.

DISCUSSION

In this study, we evaluated the impact of clinical pharmacist intervention on the appropriateness of antibiotic treatment in patients hospitalized with bacteremia. Our findings demonstrate significant improvements in antibiotic selection and dosing. Unlike previous studies that addressed specific bacteria or regimens [11,16], our study examined a broad range of pathogens.

Clinical pharmacist involvement significantly increased the rate of appropriate antibiotic dosing according to renal function and the selection of antibiotics matching pathogen sensitivity. This finding aligns with previous research demonstrating that pharmacist involvement enhances patient care [12-15]. The most significant effect was observed in patients with intermediate renal function (CrCl 30–60 ml/min). This group is often at risk of being missed

Table 3. Admission outcomes

		Intervention group (n=170)	Control group (n=173)	*P*-value
Length of stay in days, median [IQR]		15 [9–26]	9 [5–16]	< 0.001
Intensive care unit transfer, n (%)		5 (2.9)	3 (1.7)	0.501
In-hospital mortality, n (%)		24 (14.1)	30 (17.4)	0.399
30-day mortality (since admission), n (%)		23 (13.5)	33 (19.1)	0.165
6-month mortality (since admission), n (%)		58 (34.1)	60 (34.7)	0.912
7-day relapse, n (%)		4 (2.4)	15 (8.7)	0.010
30-day readmission, n (%)		55 (32.4)	52 (30.2)	0.672
Appropriate treatment, n (%)	Total	166 (97.6)	151 (87.3)	< 0.000
	Culture-based treatment	170 (100)	165 (95.4)	0.007
	Adjusted to renal function	166 (97.6)	158 (91.3)	0.011

IQR = interquartile range

Table 4. Univariable and multivariable analysis (logistic regression) for appropriate treatment

Variable		Odds ratio	95% confidence interval	*P*-value for univariable analysis	*P*-value for multivariable analysis
Intervention		6.05	2.04–17.95	0.001	0.005
Age		0.97	0.94–0.99	0.025	
Sex, female		0.38	0.16–0.91	0.030	0.035
Severe chronic renal disease		1.45	0.48–4.34	0.511	
Diabetes		1.03	0.45–2.34	0.948	
Liver disease		2.05	0.27–15.78	0.491	
Congestive heart failure		1.47	0.49–4.42	0.489	
Ischemic heart disease		0.68	0.15–3.12	0.620	
Cerebrovascular event		0.33	0.09–1.23	0.099	
Malignancy		2.86	0.66–12.43	0.161	
Dementia		0.27	0.11–0.62	0.002	0.054
Charlson Comorbidity Index score ≥ 4		0.60	0.22–1.64	0.320	
Estimated GFR (MDRD, ml/min/1.73m²) (with > 90 as reference)	60–90	0.35	0.06–1.95	0.230	0.427
	30–60	0.14	0.03–0.65	0.012	0.045
	< 30	0.19	0.04–0.89	0.035	0.087
AKIN (with stage 0 as reference)	Stage 1	0.53	0.22–1.30	0.168	
	Stage 2–3	0.81	0.17–3.82	0.793	
Antibiotic-resistant bacteria*		0.70	0.31–1.55	0.375	

AKIN = Acute Kidney Injury Network, GFR = glomerular filtration rate, MDRD = modification of diet in renal disease

*Antibiotic-resistant bacteria defined as MRSA, CONS, Enterococci, Enterobacteriaceae MDR/ESBL/CPE, *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, fungi

for dose adjustments, highlighting the value of pharmacist expertise in addressing this critical gap.

While physicians generally made sound decisions based on sensitivity data, the additional improvement with pharmacist involvement demonstrated the value of dedicated antimicrobial stewardship. Pharmacists contribute beyond mere access to information, likely due to their proactive evaluation of patient-specific factors and drug interactions. This condition underscores the importance of multidisciplinary collaboration where pharmacists complement physicians' clinical knowledge.

We observed a longer length of stay in the intervention group, contrasting with some previous studies [17]. However, the intervention group also had a significantly lower 7-day relapse rate, suggesting that longer stays may have facilitated more thorough treatment. Future research should investigate the relationship between length of stay, treatment adequacy, and long-term outcomes.

Several limitations exist. First, this was a single-center study, limiting generalizability. Second, the control group was a non-consecutive convenience sample necessitated by time and staffing constraints during manual chart review, which introduces selection bias. Third, as a retrospective before-and-after study, our findings may have been influenced by unmeasured temporal changes or concurrent interventions. Fourth, baseline differences were observed: the control group was older with more co-morbidities. However, multivariate regression analysis confirmed the intervention as an independent predictor of appropriate treatment.

CONCLUSIONS

A clinical pharmacist intervention program can significantly improve the appropriateness of antibiotic treatment in patients with bacteremia, particularly in terms of dosing adjustments for renal function and antibiotic selection based on pathogen sensitivity. The most pronounced effect was observed in patients with intermediate renal function, addressing a critical gap in care. Although the intervention was associated with longer hospital stays, it also resulted in lower early relapse rates, suggesting more comprehensive treatment. These findings underscore the

value of integrating clinical pharmacists into antimicrobial stewardship programs and bacteremia management.

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Capsule

Metabolite glues as a means of purine sensing and chemotherapeutic response

Small endogenous metabolites are traditionally viewed as substrates or signaling molecules. **Witus** et al. discovered an unexpected mechanism whereby purine metabolites function as endogenous molecular glues, stabilizing protein-protein interactions that regulate purine biosynthesis. The study demonstrated that purines directly promote binding between a rate-limiting enzyme in the purine synthesis pathway and its endogenous inhibitor, thereby providing a feedback mechanism that tightly controls nucleotide production. Structural and biochemical analyses revealed how metabolite-dependent protein interactions regulate metabolic homeostasis. The authors further showed that this mechanism influences cellular responses to thiopurine chemotherapy. Manipulating metabolite glue formation enhanced sensitivity to thiopurine drugs, suggesting a novel strategy to improve treatment efficacy while potentially reducing toxicity.

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