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Characterization of drug-related problems in gram-negative bloodstream infections with clinical pharmacist input - a prospective study

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ABSTRACT

Patients with Gram-negative bacilli bloodstream infections (GNB-BSIs) have a high mortality and morbidity rate. This can result in an increased length of hospitalizations and risk of polypharmacy. This study investigates drug-related problems (DRPs) and associated factors during antimicrobial treatment in GNB-BSI patients. The prospective observational study was conducted between April 2023 and April 2024 at a 970-bed tertiary care university hospital in Istanbul. The study included 150 adult patients with a mean age of 58 years, and 57.3% of patients were male. Multivariable logistic regression analysis highlighted significant associations between DRPs and the presence of comorbidities, the duration of the patient's hospitalization, time to adequate antimicrobial therapy and the number of prescribed medications per patient ($p<0.05$). In conclusion, this study underscores the significance of clinical pharmacists' collaboration with clinicians in the identification and assessment of drug-related problems (DRPs) within the clinical department.

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INTRODUCTION

Gram-negative bacilli bloodstream infections (GNB-BSIs) are a major public health problem due to their high rates of morbidity and mortality[1]. Timely initiation of appropriate antibiotic therapy is critical in the treatment of BSIs. to decrease mortality and poor outcomes[2,3]. However, the increasing prevalence of antimicrobial resistance (AMR) poses a significant challenge to the treatment and management of GNB-BSIs[4,5].

The resistance crisis highlights the need for multidisciplinary antimicrobial stewardship (AMS) programs that require collaboration between healthcare professionals, including infectious disease specialists, clinical pharmacists and microbiologists, to monitor antibiotic use and resistance patterns and implement evidence-based guidelines[6].

Clinical pharmacists play a critical role in AMS programs and drug-related problems (DRPs) in infectious disease[7,8]. These problems can take many various forms, including inappropriate drug selection, dosing errors, drug interactions, and patient non-compliance, among others[9]. The overall use of antibiotics, associated costs, duration of treatment and infections caused by multi-drug resistant organisms have been reduced by the participation of clinical pharmacists. Furthermore, the use of appropriate antibiotics[10,11].

DRPs in bloodstream infections (BSIs) is a major concern as it leads to treatment failures and increases healthcare costs[12]. The pharmacist-led review of DRPs has become a pivotal strategy in the prevention and mitigation of drug-related harm[13].

The primary objective of this study was to examine the prevalence and types of DRPs in critically ill patients, specifically those in hematology-oncology and intensive care units, who developed GNB-BSI in our hospital. The secondary objective was to identify factors associated with an increased risk of DRPs.

METHODOLOGY

Study design, setting and population

We conducted a prospective study between April 2023 and April 2024 in Istanbul, Turkey. Our facility was a tertiary care university hospital with a 90-bed of intensive care units (ICU) and a 970-bed capacity comprehensive

hematology and oncology wards. On the other hand, hematopoietic stem cell transplantation and solid organ transplantation were also performed

This study was conducted with the participation of a clinical pharmacist. The clinical pharmacist had a daily ward round with the responsible physician and other healthcare professionals. She observed the clinical follow-up of the patients, the treatments they received, the DRPs that developed and the progression of DRPs.

Patients who met the following inclusion criteria were included in the study.

Inclusion criteria

Inpatients≥18 years of age,

Patients with GNB-BSI,

Patients in the hematology ward, oncology ward, solid organ transplantation ward, hematopoietic stem cell transplantation ward or ICU.

Exclusion criteria

Patients who refused to participate the study,

Patients were re-admitted during the data collection period,

Patients were discharged within 48 hours after the initial positive blood culture signal,

Patients that refused treatment or did not receive treatment,

Patients who died within 48 hours after the initial positive blood culture signal,

During the study period, GNB-BSIs were identified in 172 patients, but 150 patients were included in the final,

During the study period, GNB-BSIs were identified in 172 patients, but 150 patients were included in the final analysis. The reason for exclusion (n=22) was due to patients who died or were discharged within 48 hours after the first blood culture. Figure 1 shows the flowchart of the study design.

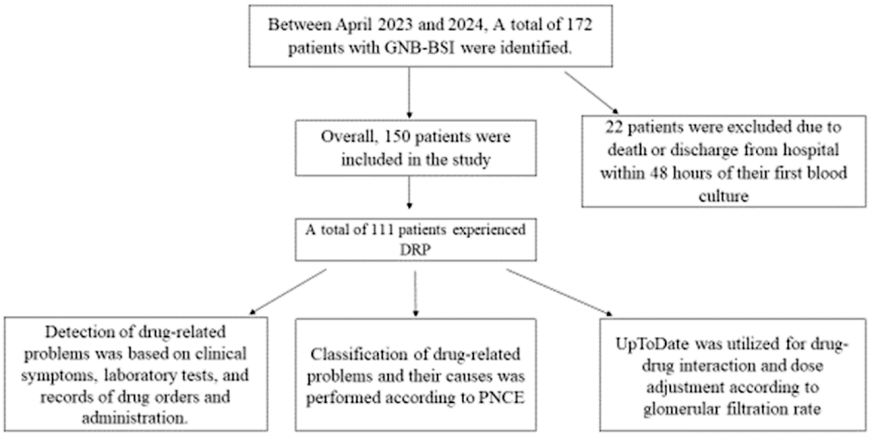

Figure 1. Flowchart of the study design

The study was approved by the Istanbul Medipol University Local Ethics Committee for non-interventional clinical research (E-10840098-772.02-803/31.01.2023).

Data collection

Gram stain was performed when there was a sign of microbial growth on the blood cultures. Monitoring of patients was begun with detection of a GNB. The follow-up of the patients continued throughout the treatment process of the bloodstream infection until discharge or death.

The patients' sociodemographic characteristics, comorbidities, Body Mass Index (BMI), medical history, the time interval between the onset of BSI and the initiation of appropriate antimicrobial therapy, antimicrobials used, length of hospital stay since the first positive blood culture (days), number of prescribed medications, profile bacteria that caused BSI, carbapenem resistant, and DRPs were recorded.

The Pharmaceutical Care Network Europe (PCNE) classification version 9.01 was used to determine of DRPs in the patients[14]. In the event of a life-threatening situation, the clinicians implemented the necessary interventions.

Researching of the PubMed database revealed a paucity of studies on the topic of DRP in adult patients with infectious diseases. The objective of the study was to ascertain the incidence of DRP and to identify associated risk factors.

Statistical analysis

Statistical analysis included both descriptive and inferential statistics. Frequency, proportion, mean and standard deviation (SD) were applied as descriptive statistics measures. Inferential statistics analysis was performed by using categorical data as input. To this end, the distribution of categorical variables was summarized by count and proportions with the purpose to perform comparison based on the DRP status (namely, the presence or absence of DRPs). In this regard, the chi-square test was performed, which was followed by univariate and multivariate logistic regression. The Chi-square test (χ^2) was applied to test difference in distribution of categorical variables between the two study groups (namely patients with DRPs and without DRPs). In order to assess the association between the variables in more detail and to gain complementary insights regarding the covariates of DRPs, crude odds ratios and adjusted odds rations were computed using univariate and multivariate logistic regression, respectively. The statistical significance of association between the studied independent variables and DRPs was tested using the multivariate logistic regression analysis method. To this end, significance of variables was summarized by single p value or multiple p values, depending on the number of categories. In case of more than one category, the overall p values were provided. For the evaluation of all inferential statistics results, the statistical significance level $p<0.05$ was considered as the cut-off threshold value for significance. The SPSS software (version 22) was utilized for statistical analysis.

RESULTS and DISCUSSION

A total of 150 patients with bloodstream infections were included in the study and in total 237 DRPs were identified in 74% of the patients. The median age of the patients was 58 years and 86% were male. The socio-demographic data of the patients are shown in Table 1.

Table 1. Characteristics of the patients with GNB-BSIs

Characteristics	Frequency n (%)	Mean (SD)
Gender Male Female	 86 (57.33) 64 (42.67)	
Age, years 18-45 (n, %) 46-65 (n, %) >65 (n, %)	 39 (26) 69 (46) 42 (28)	58 (16.28)
Body Mass Index (BMI) Weight (kg) Height (m)		25.93 (6.34) 70 (20) 1.65 (12.25)
Comorbidities 1 2 3 4 5	 61 (40.67) 44 (29.33) 20 (13.33) 14 (9.33) 7 (4.67)	2.13 (1.28)
The 10 most common comorbidities Hypertension Cancer Type 2 Diabetes Mellitus Leukemia Kidney failure Lymphoma Coronary Artery Disease Multiple Myeloma Chronic Heart Failure Liver failure	 45 (30) 43 (28.67) 40 (26.67) 27 (18) 27 (18) 17 (4.67) 11 (7.33) 11 (7.33) 10 (6.67) 7 (4.67)	
Length of hospital stay since the first positive blood culture, (days)		15 (34.24)
Number of prescribed medications		20 (7.41)
Total number of patients readmitted to hospital within 30 days	42 (28)	

Note: SD: standard deviation.

Immunosuppressed and critically ill patients accounted for 77% of the total patient population. The Table 2 presents the characteristics of the pathogens in the initial blood culture.

Table 2. Characteristics of the pathogens in the initial blood culture

	Frequency (n)	Percentage (%)
Gram-negative bacteria Carbapenem resistant	150 58	100 38.67
Escherichia coli Carbapenem resistant	66 9	44 14
Klebsiella spp. Carbapenem resistant	50 26	33.33 52
Pseudomonas spp. Carbapenem resistant	19 19	12.66 100
Enterobacter spp. Carbapenem resistant	6 2	4 33.33
Acinetobacter spp. Carbapenem resistant	1 1	0.66 100
Other Gram-negative bacteria Carbapenem resistant	8 1	5.3 13

The most common pathogens were *E. coli* 44% (n=66) and *K. pneumoniae* 33.3% (n=50). The frequency and percentage of antibiotics used are shown in Figure 2.

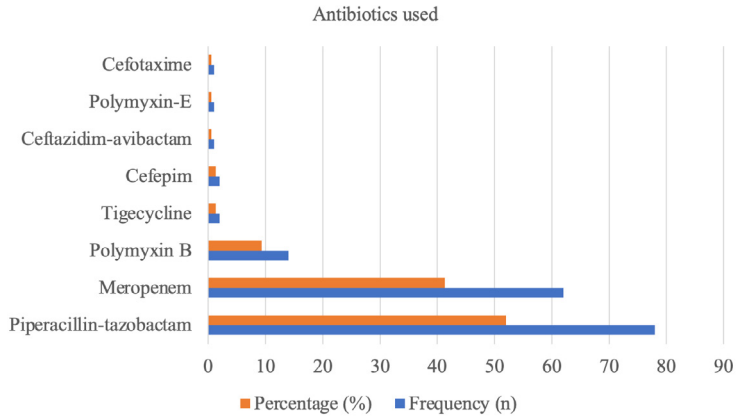

Figure 2. The frequency and percentages the antibiotics used.

The most commonly used antibiotics were piperacillin-tazobactam with 52%. Table 3 illustrates the time interval between initial appropriate antibacterial treatment and the onset of symptoms indicative of a bloodstream infection.

Table 3. The time interval between the onset of BSI and the initiation of appropriate antimicrobial therapy

Time to adequate antimicrobial therapy	Frequency (n)	Percentage (%)
<6 hour	80	53.33
7-24 hour	47	31.33
25-48 hour	17	11.33
>49 hour	6	4
TOTAL	150	100

It was observed that 85% of patients received appropriate antibacterial treatment within the first 24 hours after the onset of symptoms consistent with a bloodstream infection.

The primary types of DRPs were treatment effectiveness (P1) (33%), treatment safety (P2) (53%), and other issues (P3) (14%). The problems are shown in Figure 3, and the causes of DRPs are shown in Table 4.

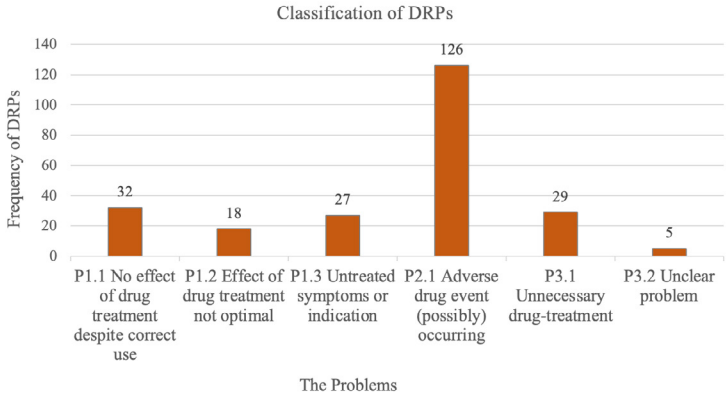

Figure 3. The problems, PCNE classification for drug-related problems V9.1

Table 4. The causes, PCNE classification for drug-related problems V9.1

Causes (including possible causes for potential problems)	**268**	
	Number	**%**
N1. Drug selection	115	42.91
N2. Drug form	0	-
N3. Dose selection	25	9.32
N4. Treatment duration	82	30.59
N5. Dispensing	-	-
N6. Drug use process	6	2.23
N7. Patient related	-	-
N8. Patient transfer related	19	7.01
N9. Other	21	7.83

The most common causes of DRPs were drug selection (42.91%), treatment duration (30.59%), and dose selection (9.3%). By the day-28, 13.3% (n=20) patients had died, 52.6% (n=79) patients had been discharged from the hospital, 2% (n=3) patients were still followed in the ICU, and 32% (n=48) patients were still followed in the wards.

Based on the estimates of the performed $\chi 2$ tests (in the form of $\chi 2$ statistics and p values), it is plausible to conclude that a significant difference ($p<0.05$) exists between patients with DRP and patients without DRP with respect to the following categorical variables: age ($p=0.043$), presence of comorbidity ($p=0.002$), length of stay at hospital ($p=0.024$), time to adequate antimicrobial therapy ($p=0.012$) and number of prescribed medications per patient ($p<0.001$) (Table 5).

Table 5. Chi-square test results for difference in distribution of variables between patients with DRPs and without DRPs

Variables	Category	DRPs Yes n (%)	DRPs No n (%)	χ^2 statistic	χ^2 p-value
Sex	Female	44 (68.75)	20 (31.25)	1.60	0.206
	Male	67 (77.90)	19 (22.10)		
Age (years)	18-45	23 (58,97)	16 (41)	6.28	0.043*
	46-65	54 (78,26)	15 (21,74)		
	>65	34 (80,95)	8 (19)		
Presence of comorbidity	No	42 (61.76)	26 (38.24)	9.68	0.002*
	Yes	69 (84.15)	13 (15.85)		
Length of stay at hospital (days)	<7	37 (63.79)	21 (36.21)	5.12	0.024*
	≥7	74 (80.43)	18 (19.57)		
Time to adequate antimicrobial therapy (hours)	<12	60 (66.67)	30 (33.33)	6.29	0.012*
	≥12	51 (0.85)	9 (0.15)		
Number of prescribed medications per patient	7-14	19 (55.88)	15 (44.12)	23.0	< .001*
	15-19	23 (57.50)	17 (42.50)		
	20-29	51 (92.73)	4 (7.27)		
	>30	18 (85.71)	3 (14.29)		
Carbapenem resistance	No	63 (68.48)	29 (31.52)	3.77	0.052
	Yes	48 (82.76)	10 (17.24)		

DRPs: drug related problems; * indicates significance at p<0.05.

Furthermore, the results of univariate and multivariate logistic regression analyses, which were performed as a further step to assess associations between the studied variables, are shown in the Table 6.

Table 6. Bivariate and Multivariate logistic regression analysis result of DRPs covariates among patients

Variables	Category	DRPs Yes n (%)	DRPs No n (%)	COR (95% CI)	AOR (95% CI)	p-value	Overall p-value
Sex	Female	44 (68.75)	20 (31.25)	1	1		
	Male	67 (77.90)	19 (22.10)	1.603 (0.769-3.340)	1.421 (0.563-3.586)	0.457	
Age (years)	18-45	23 (58.97)	16 (41)	1	1		0.466
	46-65	54 (78.26)	15 (21.74)	2.504 (1.063-5.900)	1.953 (0.670-5.688)	0.220	
	>65	34 (80.95)	8 (19)	2.957 (1.087-8.038)	1.631 (0.462-5.758)	0.448	
Presence of comorbidity	No	42 (61.76)	26 (38.24)	1	1		
	Yes	69 (84.15)	13 (15.85)	3.286 (1.524-7.085)	2.877 (1.122-7.375)	0.028*	
Length of stay at hospital (days)	<7	37 (63.79)	21 (36.21)	1	1		
	≥7	74 (80.43)	18 (19.57)	2.333 (1.110-4.905)	2.770 (1.041-7.372)	0.041*	
Time to adequate antimicrobial therapy (hours)	<12	60 (66.67)	30 (33.33)	1	1		
	≥12	51 (0.85)	9 (0.15)	2.833 (1.232-6.519)	4.993 (1.586-15.716)	0.006*	

Number of prescribed medications per patient	7-14	19 (55.88)	15 (44.12)	1	1		0.000*
	15-19	23 (57.50)	17 (42.50)	1.068 (0.425-2.687)	1.260 (0.394-4.036)	0.697	
	20-29	51 (92.73)	4 (7.27)	10.066 (2.965-34.173)	14.379 (3.427-60.343)	0.000*	
	>30	18 (85.71)	3 (14.29)	4.737 (1.171-19.155)	6.974 (1.330-36.567)	0.022*	
Carbapenem resistance	No	63 (68.48)	29 (31.52)	1	1	1	0.951
	Yes	48 (82.76)	10 (17.24)	2.210 (0.982-4.971)	0.969 (0.351-2.673)	0.951	

DRPs: drug related problems; AOR: adjusted odds ratio; CI: confidence interval; COR: crude odds ratio.; * indicates significance at $p<0.05$.

Here, univariate logistic regression provided crude (unadjusted) odd rations, while multivariate logistic regression analyses computed adjusted odd ratios and p values. To this end, multivariate regression analysis delineated statistically significant association between DRPs (the dependent variable) and the following covariates (independent variables): presence of comorbidity ($p=0.028$), length of stay at hospital ($p=0.041$), time to adequate antimicrobial therapy ($p=0.006$) and number of prescribed medications per patient ($p<0.001$). Overall, the significant associations between these four variables and the mentioned DRP status were detected by both the $\chi 2$ tests and the multivariate logistic regression. Consequently, the $\chi 2$ test estimates and the observed odds ratios altogether suggest that presence of comorbidity, increase in length of stay at hospital, increase in time to adequate antimicrobial therapy and increase in number of prescribed medications per patient are potential risk factors of DRPs.

The prevalence and types of DRPs

The DRPs was detected in nearly three-quarters of our patients, and the most common antimicrobial treatment was piperacillin-tazobactam. The incidence of DRPs ranges from 8.54% to 99.16% (12). A single-center study has reported antibiotic-associated DRPs 87.3% in patients with community-acquired pneumonia[15]. On the other hand, in a prospective study on patients with various systemic bacterial infections, the rate of DRPs was found 71.51%[16]. In addition, two studies among patients with COVID-19 in showed that 65.3% and 33.2% of patients had at least one drug related problem, respectively[17,18]. DRPs have been reported within a wide range in the literature, and the rate of DRPs in our

study was considered high compared to previous reports. The wide range of DRPs is thought to be due to differences in the way the trials were conducted, the characteristics of the patients included, and the follow-up practices of the centers. With all that, our study is thought to reflect more reliable data because of its prospective design.

The most commonly observed DRPs in previous studies were treatment safety and treatment efficacy, ranging from 29.9% to 77.18% and 18.44% to 47.9%, respectively, similar to our study[16,19,20]. The leading causes of these DRP types were often related to drug selection and dose selection[21,22]. Our results were partially in contrast with these findings since we identified drug selection and treatment duration as the most common causes for DRPs. The duration of antibiotic use was extended in our study. The effect of appropriate dose and duration of antibiotic use on clinical outcomes, adverse reaction of antibiotics and AMR is well known[2,4]. However, our study contributed to the literature by presenting striking data emphasizing the association of inappropriate doses and durations of antibiotic use with DRPs. This results also highlight the critical role of a clinical pharmacist, even for a single parameter such as treatment duration.

Risk factors for DRPs

Our study underscores comorbidities, length of hospital stay, time to adequate antimicrobial therapy and increased number of drugs prescribed per patient as potential risk factors for DRPs.

We revealed that the DRPs was higher in patients with comorbidities, similar to previous studies[23-25]. Another factor that associated with development of DRPs was delays in initiating appropriate antimicrobial therapy in our study. This delay is strongly associated with worse clinical outcomes, including an increased risk of progression to organ failure[2] that causes more intervention and using a larger number of medications. Existing literature has shown that early and targeted antimicrobial therapy significantly reduces both complications and mortality in patients with BSIs[26,27]. And the third one was length of hospital stay that increases the risk of DRPs in our study which consistent with literature data[16,25]. The findings of the present study suggest an association between DRPs and a number of factors, including the presence of comorbidities, delays in the initiation of appropriate treatment and prolonged hospitalization. DRPs were thought to be associated with many factors, when all findings of our study were taken into consideration; the presence of comorbidities, delays in appropriate treatment and prolonged hospitalization. All of these factors are thought to be associated with polypharmacy. In conclusion, the factors that di-

rectly or indirectly influence polypharmacy should be considered significant in the context of DRP and the management of polypharmacy should be improved.

The increasing risk of drug interactions and adverse events by the polypharmacy is well-known[16,24]. We have also shown statistically significant association between development of DRPs and high number of the prescribed medications per patient. Our findings are compatible with the previous study that reported higher rates of DRPs in patients undergoing polypharmacy[28]. These results from our study have highlighted the importance of collaboration between the clinical pharmacologist and clinicians. The EUROBACT-2 study found that infrequent consultations with clinical pharmacists were associated with higher mortality rates, underscoring their critical role in optimizing antimicrobial therapy for hospital-acquired BSIs[29]. Clinical pharmacists improve patient outcomes through medication counseling, adherence support, and follow-up care, reducing adverse drug reactions and medication errors. Despite higher initial costs associated with their interventions, the overall economic impact is positive when considering the savings from avoided adverse drug events[30,31].

In our study, the relationship between DRPs and carbapenem resistance was not statistically significant in the Chi-square test and multivariate analysis. This hints that the actual effect could be context-dependent and much complex, making it more difficult to detect. The elaborate and comprehensive investigation with larger sample size is needed to clarify the impact of carbapenem resistance.

In this regard, this study emphasis for the importance of clinical pharmacists in the detection and evaluation of DRPs and in the management of antimicrobial therapy for GNB-BSIs in collaboration with infectious disease specialists in GNB-BSIs.

The large number of our cases and the prospective design of our study increase the reliability of our study. On the other hand, our single-center data, which reflects the clinical practice of our center, is a limitation of our study.

STATEMENT OF ETHICS

The study was approved by the Istanbul Medipol University Local Ethics Committee for non-interventional clinical research (E-10840098-772.02-803/31.01.2023).

CONFLICT OF INTEREST STATEMENT

The authors affirm that the research was carried out without any affiliations or financial associations that could be perceived as a possible conflict of interest.

AUTHOR CONTRIBUTIONS

Concept – Selda Aydin, Rumeysa Cakmak, Meyha Sahin, Mesut Yilmaz (authors contributed equally); Design – Selda Aydin, Rumeysa Cakmak, Mesut Yilmaz (authors contributed equally); Data Collection and Processing – Rumeysa Cakmak, Meyha Sahin, Elif Güner Yeniaydin; Statistical Analysis and Interpretation – Kıvanç Kök; Literature Search – Selda Aydin, Rumeysa Cakmak; Drafting of the Manuscript – Rumeysa Cakmak, Meyha Sahin; Critical Revision of the Manuscript – Selda Aydin, Rumeysa Cakmak, Kıvanç Kök, Mesut Yilmaz.

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