Inapropriate Use of Antibiotics Effective Against Gram Positive Microorganism in Under Restrictive Antibiotic Policies in ICU; A Prospective Observational Study

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Research article

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Abstract

Background Gram-positive spectrum antibiotics such as vancomycin, teicoplanin, daptomycin ,and linezolid are frequently used in empirical treatment combinations in critically ill patients Although they are included in the national antibiotic restriction program, thought to be inappropriate, unnecessary and suboptimal use is high due to their widespread use. In our study, in addition to their widespread use, gram-positive spectrum antibiotics were evaluated due to their use in more limited and clear clinical indications. This study aims to determine the frequency of inappropriate uses of gram-positive spectrum antibiotics and risk factors for inappropriate use according to different quality parameters.

Methods This clinical study was conducted prospectively between 01.10.2018 and 01.10.2019 in the medical and surgical ICUs of Gazi University Faculty of Medicine Hospital with a total bed capacity of 55. Patients older than 18 years of age onset of gram-positive spectrum antibiotics (vancomycin, teicoplanin, linezolid ,and daptomycin) were included. Patients under the age of eighteen or immunosuppressed (neutropenic, HIV-infected patients with hematologic or solid organ malignancies) were not included in the study. The demographic and clinical features of the patients were recorded. The treatment was also evaluated and recorded by 2 infectious diseases specialists and 2 clinical pharmacists except for the clinical staff at 24-hour intervals from the first day to the last day of treatment. SPSS software for Windows, version 17 (IBM, Armonk, NY) was used to analyze the data. Categorical variables are presented as number and percentage, and non-categorical variables are presented as mean ± standard deviation.

Results In the use of antibiotics, the incidence of non-compliance with at least one of the determined quality parameters was 83%. Multivariate analysis was performed to evaluate risk factors for inappropriate antibiotic use, and creatine values were found to increase the risk of inappropriate antibiotic use.

Conclusions In spite of the restricted antibiotic program, inappropriate antibiotic use in ICUs is quite common. In particular, it is necessary to establish local guidelines in collaboration with different disciplines for the determination and follow-up of de-escalation and optimal treatment doses

Background

Infection development is an important cause of morbidity and mortality in intensive care units (ICU), leading to the widespread use of antibiotic [1]. {, #1@@hidden}{Kallen, 2018 #382}{, 2018 #382}{Kallen, 2018 #404}It is reported that 41% to 85% of ICU patients use at least one antibiotic and antibiotic consumption is 10 times higher in ICUs compared to other units [2]. This widespread usage increases the unnecessary and inappropriate use of antibiotics and causes an increase in antimicrobial resistance [3]. Antimicrobial resistance has generally incerased risk of poor clinical outcomes and death in ICU patients [3]. It is stated that approximately 20% to 50% of hospitalized patients and 30% to 60% of patients in ICU use unnecessary, inappropriate or suboptimal antibiotic treatment [2-5]. Inappropriate use of empirical

antibiotic treatments increases the frequency of early and late period mortality, lenght of hospital stay and healthcare-associated costs in ICU patients [4]. Antibiotic stewardship programs are widely used to optimize antibiotic use in hospitals [6, 7]. Implementation of these programs can lead to significant benefit for clinical outcomes, adverse events and costs [3, 8].
To develop an effective program, it is necessary to determine the priority targets by evaluating inappropriate antibiotic use [6]. Antibiotic restriction lists should be implemented as part of ASPs and should be supported by other ASP strategies such as emprical teratment guidelines, de-escalation, preauthorization and / or prospective audit and feedback [8]. The effectiveness of antibiotic restriction programs may decerase over time and target oriented revisions may be required to prevent overuse or misuse of antibiotics [9].

Gram-positive spectrum antibiotics such as vancomycin, teicoplanin, daptomycin ,and linezolid are frequently used in empirical treatment combinations in critically ill patients [10]. In our country, these Gram-positive antibiotics after beta-lactams and fluoroquinolones are reported to be the most commonly used antibiotics in ICUs [2]. Due to its widespread use, it is thought to be inappropriate, unnecessary, and suboptimal utilisation. However they are covered by the antibiotic restriction program.

In this prospective observational study, it is aimed to evaluate gram-positive anti-bacterial utilizations in intensive care units with different evaluation criteria, to determine the frequency of inappropriate usage and to determine the intervention targets to ensure optimum use.

Methods

This clinical study was conducted prospectively between 01.10.2018 and 01.10.2019 in the medical and surgical ICUs of Gazi University Faculty of Medicine Hospital with a total bed capacity of 55. Patients older than 18 years of age onset of gram-positive spectrum antibiotics (vancomycin, teicoplanin, linezolid ,and daptomycin) were included. Patients under the age of eighteen or immunosuppressed (neutropenic, HIV-infected patients with hematologic or solid organ malignancies) were not included in the study.

The demographic and clinical features of the patients were recorded. The treatment was also evaluated and recorded by 2 infectious diseases specialists and 2 clinical pharmacists except for the clinical staff at 24-hour intervals from the first day to the last day of treatment. Demographic data of patients (age, sex, body mass index, etc.), comorbid diseases, charslon comorbidity indices, indications for antibiotic treatment, presence of sepsis or septic shock, clinical and laboratory findings (microbiological samples and results, creatinine clearance calculated using the cockcroft-gault equation, eGFR (estimated glomerular filtration rate)) were recorded. This study was approved by the Institutional Review Board of Gazi University School of Medicine and was conducted according to the Helsinki Declaration and good clinical practice. (No:02)

2.a. Definitions

The quality parameters evaluated for inappropriate use in the study are given in Table 1.

Inappropriate antibiotic use; It is defined as non-compliance with at least one of the quality parameters (Documented antibiotic indication, appropriate microbiological sampling, appropriate dose, de-escalation and duration of treatment).

3. **Statistical method**

SPSS software for Windows, version 17 (IBM, Armonk, NY) was used to analyze the data. Categorical variables were presented as number and percentage, and non-categorical variables were presented as mean ± standard deviation. A Chi-square test was used to compare categorical variables. The suitability of the non-categorical variables to the normal distribution were evaluated by Shapiro - Wilk test. Mann - Whitney U test was used for comparison of non - normally distributed variables and Student -T test was used for comparison of normally distributed variables. In the univariate analysis, variables with a p-value <0.20 and not correlated with each other were included in the logistic regression model. Charlson comorbidity index, central catheter, treatment approach, CRP, sepsis, procalcitonin and creatinine levels were included in the logistic regression model. The cases where the type-1 error level is below 5% are statistically significant.

Results

During the study, 200 treatments were evaluated in 169 patients. The Clinical features of the patients were evaluated and presented in Table 2.

In the use of antibiotics, the incidence of non-compliance with at least one of the determined quality parameters was 83%. Non-compliance with the criteria determined as antibiotic indication, appropriate microbiological sampling, appropriate dosing, de-escalation and duration of treatment; 47%, 28%, 26.5-35 %, 61.8-71.5% and 36 %, respectively (Table 3).

The determined quality criteria have been evaluated for reasons of non-compliance in themselves. The most common inappropriateness of microbiological sampling was found to be associated with insufficient sampling (85.7%). Dosing errors were often associated with a lack of dose adjustment according to renal clearance (54.3%). The longer duration of antibiotic use was the main reason for treatment duration inappropriatness (77.5%).(Figure 1.)

Factors associated with inappropriate use of antibiotics were analyzed and presented in Table 4.

Multivariate analysis was performed to evaluate risk factors for inappropriate antibiotic use, and creatinine values were found to increase the risk of inappropriate antibiotic use. Elevating creatinine levels increased the risk of inappropriate antibiotic use by approximately 2 times (OR; 1.985, 95% CI 1.196-3.292, p=.008) (Table 5).

(Table 5).

Discussion

In this study, 83 % of the gram-positive spectrum antibiotics used in ICUs were found to be inappropriate. Compliance with the evaluation of de-escalation was very low in our ICUs. Renal failure was caused inappropriate use and increased the frequency of inappropriate use of antibiotics by about 2-fold.

In Turkey, 71.3% of patients in the ICU are treated with antibiotics [2]. This widespread using leads to unnecessary and inappropriate use. It is recommended to use different quality parameters to evaluate inappropriate antibiotics used. Dresser et al. recommend that presence of uncertainty of indication, the continuation of empirical treatment without evidence of infection, the unnecessary prophylaxis and drug contraindications as quality criteria for the evaluation of inappropriate antibiotic use. [11]. For the same evaluation, Kallen et al. recommended that appropriate microbiological sampling, therapeutic drug monitoring for vancomycin and aminoglycoside, taking surveillance cultures and periodically sharing local resistance data. [1]. The incidence of inappropriate empirical antibiotic use in ICUs varies between 14.1-78.9 % due to differences in evaluation criteria [4, 12]. In Turkey, this incidence ranges from 30 % to % 50 %. [13-15]. Our frequency of inappropriate antibiotic use was found higher than the literature, since the incompatibility with any of the criteria was considered sufficient to determine inappropriateness definition[6].

Since 2003, a national antibiotic restriction program has been implemented in Turkey. Previous studies have been shown that these programs reduce nosocomial infection, length of hospital stay, mortality and microbial resistance rates. They have a positive effect on health expenditures [3, 16, 17]. However, several studies were shown that increased prescriptions of non-restricted antibiotics may be eliminated these positive effects [2, 3]. In our study, it was shown that antibiotics, all of which are under a restricted antibiotic program, are used inappropriately with high frequency. This indicates that inappropriate antibiotic use in ICUs can not be prevented by restriction programs alone and that the system should be supported by prospective audit and feedback mechanisms [8]. The results of an intervention study conducted by Güçlü et al. was shown that antibiotic restriction programs can be activated by supporting prospective control and feedback mechanisms [3].

In our study, the most common reason for inappropriateness was the continuation of antibiotics without microbiological evidence, In ICU, the de-escalation algorithm reduces the duration of treatment and the frequency of microbial resistance without increasing mortality [3, 18-20]. In studies conducted in Turkey, it is stated that the necessity of de-escalation was 10 % [15]. On the other hand, the necessity of de-escalation in ICUs was shown to be higher. Mutters et al study was shown that compliance with the evaluation of therapy discontinuation or de–escalation was 2.4-8% [21]. In our study, the compliance of the early period (3 days) de-escalation was found to be quite low. The frequency of de-escalation was found to be slightly higher in the late period (5 days). Considering that the frequency of appropriate microbiological sampling is high, it is thought that this may have been due to late results (blood culture) or late recognition. Despite the increase compared to the early period, the frequency of late de-escalation was found to be low. The most important reason for this is thought to be the unwillingness of clinicians to discontinue treatment despite the culture results. It appears that the restricted antibacterial program alone does not seem to be sufficient for proper de-escalation in ICUs. There is a need to develop an effective de-escalation strategy supported by local treatment guidelines.

Another important reason for inappropriateness in our study was the lack of proper antibiotic dose adjustment according to the eGFR. Renal failure and renal replacement therapies cause plasma concentration changes and affect drug concentrations [5]. Renal replacement therapies (RRT), especially continuous RRT, have also been shown to cause significant pharmacokinetic changes on the antibiotic groups we which evaluated [22-24]. Therefore, antibiotic doses may remain suboptimal in ICU patients when compared to the normal population. [5, 25, 26]. In our study, the frequency of RRT was 21.7%. And also, 6.7% of all patients received continuous RRT during the study. Also, elevation in creatinine serum level was found to be the determining major risk factor for the inappropriate use of antibiotics. Therefore, creatinine clearance changes need to be periodically evaluated to determine appropriate doses of antibiotics in collaboration with clinical pharmacists, infectious diseases specialists and clinical staff in ICUs [5]. There are several limitations to this study. First, our data was collected from a single center and appropriateness of antibiotics was evaluated for only antibiotics effective against Gram positive microorganism. This prevents general assessments on the effectiveness of the national antibiotic restriction programe. Second, there is no global consensus on the criteria for evaluation of inappropriate use of antibiotics in ICUs. Using different criteria may limit the applicability of the our study results. Third, observing outcome measures related with inappropriate use of antibiotics such as mortality, duration of hospital or ICU stay, changing antimicrobial resistance pattern and secondary infection such as *C.difficille* infections could not be evaluated. Despite all these limitations, the goal of the study to was to provide data about appropriateness use of antibiotics in order to improve an effective antimicrobial stewardship program. Therefore, these results should be supported by an interventional(before-after) study.

Conclusion

In spite of the restricted antibiotic program, inappropriate antibiotic use in ICUs is quite common. Appropriate use of antibiotics should be audited with predetermined quality parameters. In particular, it is necessary to establish local guidelines in collaboration with different disciplines for the determination and follow-up of de-escalation and optimal treatment doses. In patients undergoing renal replacement therapy with increased risk of suboptimal concentration, antibacterial treatment doses should be individualized and closely monitored.

Abbreviations

ICU:Intensive Care Unit, HIV: Human Immunodeficiency Virus, eGFR: estimated Glomerular Filtration Rate, RRT: Renal Replacement Therapy

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Gazi University School of Medicine, Ankara/Turkey and was conducted according to the Helsinki Declaration and good clinical practice. (No:02/14.01.2019). Written informed consent was obtained from adults (> 18 years old).

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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The funding body had no role in the study design, analysis and interpretation of results nor

in writing the manuscript.

Authors' contributions

HSO and KH designed the study, DMF KE and AA collected datas, HSO interpreted the results, and wrote the manuscript. All of writers read and approved the final manuscript.

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Tables

Table 1. The Quality Parameters for Inappropriate use of antibiotics

Abbreviations	Criteria	Assessment Day	Non-Compliance Definition	References
IUC-1	**Antibiotic Treatment Indication** Doumented rationale for starting antibiotics in patients charts	1st day	No provide rationale of antibiotics	[9]
IUC-2	**Appropriate microbiological sampling** - At least 2 sets of blood culture -Culture from suspected infection site -Time for taking culture samples	1st day	Inadequate blood or suspected-infection site culture Collection of culture after antibiotic administration	[3, 10, 11]
IUC-3	**Antibiotic Dosage** -Antibiotic dose according to body weight -Loading dosage use [a] -Adjustment of dosage according to the glomerular filtration rate (GFR) [b]	1st, 3st and 7st day	-Less than the recommended dose according to body weight or body mass index -No loading dose [a] -No antibiotic dose adjustment according to GFR	[12]
IUC-4	**De-escalation** [c, d, e] Discontinuation of antibiotic therapy based on microbiological results	3st and 7st day	Continuation of antibiotic therapy based on lack of antimicrobiological evidence	[3, 10, 11]
IUC-5	**Duration of treatment** [f] Discontinuation of antibiotic therapy according to local or international guidelines	14st and 21 st day	-Longer treatment than recommended -Shorter treatment than recommended	[13-16]

Abbreviations: IUC, Inappropriate use criteria
[a] Evaluated for vancomycin and teicoplanin.
[b] Calculated with GFR cockroft formula.
[c] The incubation time for samples other than blood cultures is 2 days and for blood samples a minimum of 5 days..For this reason, deescalation evaluation was performed on the 3rd and 7th days of treatment.
[d] De-escalation assessment was only performed for empirical antibiotic treatment
e De-escalation evaluation was not performed in patients whose treatment duration was less than 7 days.
[f] De-escalation or withdrawal of the patient (discharge, transfer, death, etc.) has not been evaluated for treatment duration.

Table 2. Clinical Features of Patients		
Variables	N	%
Age, mean ± SD	63.9±18.7	
Gender, Female	79	46,7
BMI (kg/m^2),mean ± SD	26.5±5.81	
Intensive Care Units (ICUs)		
Medical ICUs	95	56.2
Surgical ICUs	74	43.8
Duration of hospital stay (day), mean ± SD	16.4±17.8	
Duration of ICU stay (day), mean ±SD	10.2±14.4	
CCI, mean ± SD	4.40±2.43	
Central venous catheters	100	59.2
Invasive mechanical ventilation	120	71
Renal failure		
CrCI, (mL/min) ≥ 50	89	52.7
CrCI, (mL/min) 30-49	25	14.8
CrCI, (mL/min) 10-29	45	26.6
CrCI, (mL/min) <10	10	5.9
Intermittant renal replacement therapy	37	21.9
Continous renal relacement therapy	7	4.1
Abbreviations: SD, standart deviation; BMI, Body mass index; ICU; Intensive care unit, CCI, Charlson comorbidity index; CrCI, Creatinine clearance		

Table 3. Frequency of Inapropriate Use of Antibiotics (%)					
	1. Day	3. Day	7. Day	14. Day	Total
IUC-1	47.0				
IUC-2	28.0				
IUC-3	26.5	35.0	35.0		
IUC-4		78.5	61.8		
IUC-5				36.0	
Total					83.0
Abbreviations: IUC, Inappropriate use criteria					

Table 4. Factor Associated with Inappropriate Use of Antibiotics

		Inapropriate Use N(%)	Appropriate Use N(%)	P value
Age, mean ± SD *		64.3±18.7	61.6±20.8	.522
Gender**	Female	78(47)	16(47.1)	.994
	Male	88(53)	18(52.9)	
BMI (kg/m^2), mean ± SD*		26.3±6.24	27.0±5.68	.228
CCI, mean ± SD*		4.51±2.48	3.82±2.35	.200
ICU**	Medical	95(57.2)	20(58.8)	.864
	Surgical	71(42.8)	14(41.2)	
Duration of Hospital Stay ± SD * (Day)		23.2±27.0	20.9±26.6	.439
Duration of ICU stay ± SD * (Day)		16.8±25.8	16.5±27.6	.591
Source of Infection **				
Sepsis		70(49.3)	9(29)	.040
Septic Schock		59(30.5)	7(20.6)	.091
Pneumoniae		111(66.9)	20(58.8)	.369
Blood Stream Infection (BSI)		46 (27.9)	5(14.7)	.109
Others		20 (12.0)	11 (32.4)	.003
Unknown		32 (19.3)	3(8.8)	.118
Antibiotic treatment approach**				
Emprical therapy		114(68.7)	18(52.9)	.078
Agent spesific therapy		52(31.3)	16(47.1)	
Central Venous Catheter		109(65.7)	16(47.1)	.041
Laboratory Paremeters*				
WBC (x10.e^3/µL), mean ± SD		14.672± 19.179	14.802±10.087	.460

PLT (x10.e^3/µL), mean ± SD	221.879±139.955	244.323±156.829	.482
Lactate (mMol/L), mean ± SD	2.06±1.70	2.22±1.91	.644
GFR (mL/min), mean ± SD	50.6±32.5	69.4±26.8	.001
Cr (mg/ dL), mean ± SD	1.93±1.74	0.90±0.79	<.001
CRP (mg/L), mean ± SD	133±92.8	156±112	.041
Procalcitonin (ng/ mL), mean ± SD	18.7±85.5	14.9±68.5	.013

*Mann-Whitney U test was used.

**Chi-squared test was used.

Abbreviations; SD, standart deviation; BMI, Body mass index; CCI, Charslon comorbidity index; ICU, Intensive care unit; WBC, White blood cell; PLT; Platelet; GFR, Glomerular filtration rate; Cr, Creatinine, CRP, C-reactive protein

Table 5. Risk Factors for Inappropriate Antibiotic Use in Multivariate Analysis

	B	S.E	Sig.	O.R	% 95 C.I
CCI	-.042	.093	.650	.959	.799-1.150
Sepsis	-.552	.776	.477	.576	.126-2.635
Antibiotic tretament approach	-.504	.442	.255	.604	.254-1.438
Central venous catheter	.322	.415	.438	1.380	.612-3.112
CRP	-.003	.002	.136	.997	.993-1.001
Procalcitonin	.000	.002	.889	1.00	.995-1.005
Creatinine	.685	.258	.008	1.985	1.196-3.292

Abbreviations: B, unstandardized regression weight; CI, confidence interval; OR, odds ratio; SE, standard error; CCI, Charslon comorbidity index; CRP,C-reactive protein

Figures

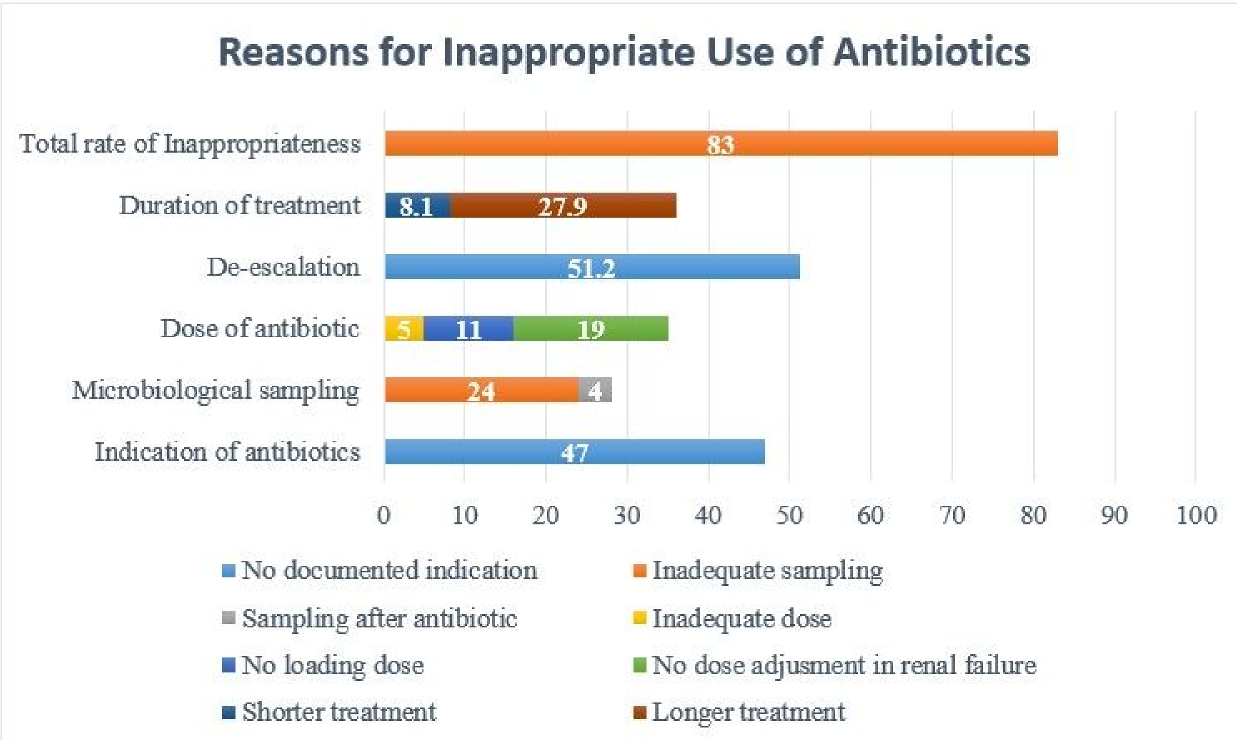

Figure 1

Reasons For Inappropriate use of Antibiotics

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