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Evaluation of Antibiotic Use and Financial Costs in University Hospital Intensive Care Units

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ABSTRACT

Intensive care units (ICUs) are the primary target for antibiotic consumption monitoring due to their high antibiotic usage. Antimicrobial resistance (AMR) is a major global public health concern. We conducted a five-year, monocentric, retrospective, and observational study to assess the use and cost of antibiotics in the intensive care units at the Oradea County Emergency Clinical Hospital in Romania. The amount was expressed in DDD/100 patient days, and the prescription antibiotic's cost was in EUR. Half of the top ten antibiotics prescribed, or 84.81% of the total, were ceftriaxone and amoxicillin/clavulanic acid. Contrary to popular belief, fewer antibiotics are classified as access, and most are classified as WHO Watch. The most expensive antibiotic therapy prescriptions in the intensive care units were for ceftazidime/avibactam, cefoperazone/sulbactam, colistin, meropenem, tigecycline, ceftriaxone, amoxicillin/clavulanic acid, moxifloxacin, ertapenem, vancomycin, linezolid, ciprofloxacin, and piperacillin/tazobactam. Medication costs for ceftriaxone, amoxicillin/clavulanic acid, ertapenem, and piperacillin/tazobactam stayed mostly constant, whereas meropenem, tigecycline, vancomycin, moxifloxacin, and ciprofloxacin exhibited an upward trend. Our findings shed light on different aspects of antibiotic misuse, enabling cost-cutting solutions and a significant step towards the rationalisation of antibiotic use.

Keywords: Intensive care units, Financial Assessment, Antibiotic Use Pattern, Antimicrobial resistance

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Introduction

Antimicrobial resistance (AMR) has made the proper use of antibiotics in hospitals and ambulatory care facilities crucial, as it needs to regulate outcomes and medical costs. The use of antibiotics is particularly high in critical care units (ICUs), which may account for over 25% of hospital spending, even though they have the fewest beds [1].

AMR is also being exacerbated by the use of carbapenems, polymyxin, and oxazolidinone antibiotics, which are used to treat hospital-acquired infections brought on by bacteria that are resistant to drugs [2, 3]. Concerns have been raised over the rise in Enterobacterales that produce carbapenemase, particularly *Klebsiella pneumoniae* and *Acinetobacter baumannii*, as well as increased vancomycin resistance in *Enterococcus* species and trimethoprim-sulfamethoxazole resistance. To stop AMR from getting worse, the World Health Organisation (WHO) issued a warning signal in 2011 and urged quick and effective measures to reduce it [4-6]. Antimicrobial-resistant bacteria are known to arise as a result of improper antibiotic use, which also has an economic impact due to increased medical costs. Antimicrobial stewardship initiatives must be put into place in both communities and hospitals.

Assessing the extent of the problem—that is, the present antimicrobial pattern across departments and sectors, like hospital and ambulatory care—is the first step in the fight against antibiotic overuse [7]. Both the epidemiology of circulating strains and accurate monitoring of antibiotic usage are necessary. Understanding the degree of antibiotic resistance comes next, giving hospitals and other organisations valuable information to put the right policies and procedures in place for the appropriate use of antibiotics.

Although assessing antibiotic consumption presents difficulties, the ATC/DDD method, developed by the WHO International Working Group for Drug Statistics Procedure, is a popular and practical instrument for tracking and comparing antibiotic use. It creates Defined Daily Doses (DDDs) for medications been given an ATC code and classifies medications following the ATC system [8].

Despite the small incidence of bacterial or fungal co-illnesses, Many antimicrobials are prescribed and used for respiratory tract infections, including the current coronavirus, that are primarily viral in origin [9, 10]. A significant contributor to morbidity and death, urinary tract infections (UTIs) are prevalent infectious diseases in the community and clinical setting. Even when the right antibiotic therapy is used, these infections are often linked to consequences or recurrence, and they significantly increase treatment expenses [11, 12].

Another significant source of AMR is employing antibiotics for managing hospital-acquired infections, and during the coronavirus pandemic, the distribution of bacteria growing in culture and the rates of antibiotic resistance changed. According to a study by Hughes *et al.* [13], bacterial co-infection was rare during the early stages of COVID-19 hospitalisation. However, subsequent research showed that bacterial infection started to emerge in patients with severe COVID-19 who needed to be admitted to the intensive care unit (ICU) and receive mechanical ventilation therapy. These cases are characterised as co-infections with Haemophilus influenzae, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*. All patients are given antibiotics for infections caused by these organisms in hospitals and the community [13, 14]. During the coronavirus pandemic, the two most important antibiotic-resistant bacteria responsible for healthcare-associated infections (HAIs) were *Acinetobacter baumannii* and vancomycin-resistant enterococci [15].

To track changes in AMR and direct empirical antimicrobial therapy, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standard Institute (CLSI) have published suggested methodologies for cumulative susceptibility test data. Cumulative susceptibility test data from a microbiology lab can be used to further investigate data on circulating strains [16, 17]. According to CLSI rules, only organisms with a minimum of 30 isolates should be reported to provide sufficient statistical power, and data regarding cumulative susceptibility should be generated annually. It is preferable to include the patient's age, type of department, location (ambulatory or hospital), and particular clinical circumstances in the same report. Duplicates can be found and removed by adding more information about the patient and cultures from the report. Regardless of the type of material, the first pathogen isolate per patient was considered, as recommended by CLSI and EUCAST. By comparing the antibiotic sensitivity rates of isolated isolates from year to year, the trend of AMR may be observed, and solutions can be proposed.

To establish goals for reducing antibiotic use and expenses, this paper aims to investigate the prevalence, characteristics, and expenses of antibiotic prescriptions in intensive care units.

Materials and Methods

This retrospective study was carried out at the Oradea County Emergency Clinical Hospital for five years (2017-2021), using electronically recorded data at the level of the hospital concerning intensive care units (adults), intensive care for coronary and neurological patients, and newborns. This hospital is classified in the first category, meaning an extended competence level for the ICU departments and a higher level of maternity care.

Antibiotic administration and cost data were collected from the hospital's InfoWorld software program through reports containing antibiotics administered, dose, route of administration, and costs. These data were extracted from the information system of the pharmacy. From the point of view of costs, antibiotics consumption was extracted as RON and expressed in EUR considering the exchange rate every year. The prescribed quantities were expressed in DDD/100 patient-days (DDD/100 PD), according to the Statistical Methodology of Medicine of

WHO, using the Anatomical Therapeutic Chemical (ATC)/DDD Index 2022 [18]. We performed an analysis of antibiotic consumption using the AWARe classification developed by the World Health Organization (WHO) expert committee using the 2017 Essential Medicines List (EML) [19-22]. The updated 2021 AWARe classification includes a total of 258 antibiotics classified into access, watch, reserve, and not recommended groups, considering the impact of different antibiotics or classes on the development of antimicrobial resistance and the importance of their proper use. The access group consists of antibiotics with the best therapeutic value, while reducing the potential for resistance development, being the first or second choice for the 25 most common infections. The watch group includes antibiotics indicated for several critical infectious diseases, but these may be a target of antibiotic resistance, and their prescriptions should be monitored. The reserve Group is the last option when other antibiotics have failed for highly selected patients (such as infections caused by multidrug-resistant bacteria), monitored very closely, and prioritized as targets of administration schedules to ensure continued efficacy.

Although it was not required, each patient's written informed consent was acquired at the time of admission, and the execution of the research was authorised by the hospital's ethics board.

Every statistical analysis was conducted using Excel software, and the Mann-Kendall test was used to analyse trends in antibiotic prescribing; results were deemed statistically significant if $P < 0.05$, indicating a statistically significant increasing or decreasing trend. Results were expressed as means and percentages employing descriptive statistics.

Results and Discussion

Between 2017 and 2020, the number of patient days in intensive care units (ICUs) was essentially the same; however, in 2021, it increased significantly, by over seven times more than the year before (**Figure 1**).

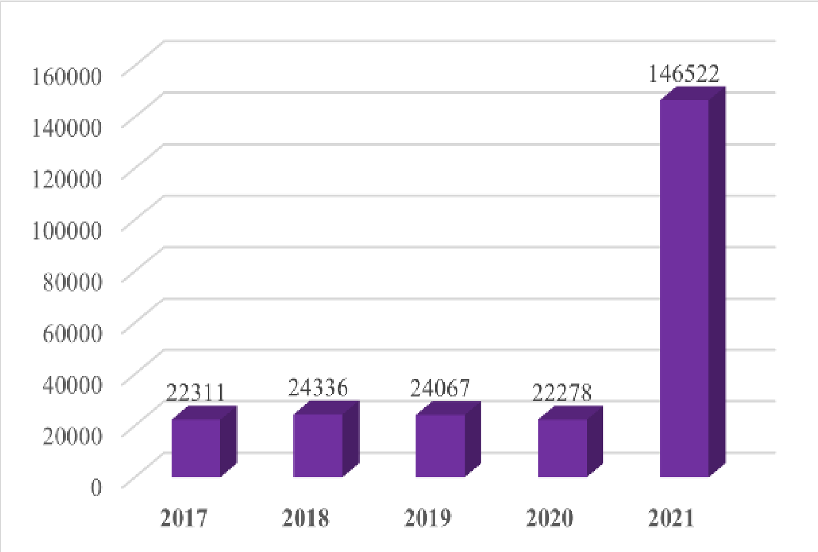

Figure 1. The quantity of patient days from 2017 to 2021

Despite this rise, the amount of antibiotics used in intensive care units (ICUs) remained largely unchanged over the five years under review. The antibiotics prescribed were based on the COVID-19 pandemic conditions, and the ICUs had the lowest antibiotic consumption, measured in DDD/100 PD, when compared to the entire hospital. Nonetheless, it is noteworthy that hospital-level antibiotic consumption increased significantly in 2021, whereas ICU-level antibiotic consumption did not rise (**Table 1**).

Table 1. Antibiotic consumption in the ICUs is expressed as DDD/100 PD.

	2017	2018	2019	2020	2021
ICUs	398.87	368.77	381.04	389.66	344.59
Total hospital	1978.26	1661.21	1664.38	2381.77	5981.80

80.98% of the total antibiotic doses stipulated over 5 decades were for ceftriaxone (47.78%), amoxicillin/clavulanic acid (6.83%), metronidazole (5.71%), cefoperazone/sulbactam (5.49%), ciprofloxacin (4.44%), cefuroxime (4.43%), meropenem (3.59%), and moxifloxacin (2.71%). Ceftriaxone and amoxicillin/clavulanic acid make up half of the entire number of medications given, while the first ten antibiotics recommended account for 84.81% of the total if we also look at the dosages of levofloxacin and vancomycin (**Table 2**). Rather, imipenem/cilastatin/relebactam, ofloxacin, cefazolin, rifampicin, and cefaclor were prescribed in tiny dosages and not in all of the years that were examined.

Table 2. The cumulative DDD/100 PD for the first ten antibiotics administered in intensive care units from 2017 to 2021

ATC code	Active substance	DDD/100 PD (%)
J01DD04	Ceftriaxone	899.56 (47.78)
J01CR02	Amoxicillin/clavulanic acid	128.64 (6.83)
J01XD01	Metronidazole	107.59 (5.71)
J01DD62	Cefoperazone/sulbactam	103.37 (5.49)
J01MA02	Ciprofloxacin	83.62 (4.44)
J01DC02	Cefuroxime	83.41 (4.43)
J01DH02	Meropenem	67.58 (3.59)
J01MA14	Moxifloxacin	50.93 (2.71)
J01MA12	Levofloxacin	37.83 (2.01)
J01XA01	Vancomycin	34.33 (1.82)

With an average of 98.89%, the most commonly prescribed antibiotics were given primarily parenterally, which is consistent with the evaluated departments' specificity or the fact that some of them are only available in injectable form.

Regardless of the assessed year, 72.12% of the antibiotics prescribed in the intensive care units (ICUs) came from the watch group, whereas only 19.52% came from the access group, according to the AWARe classification. During the five years under evaluation, there was no trend towards a decrease in the prescription of antibiotics from these classes, and the non-recommended group was used more frequently than the reserved ones. Please take into account that the sole medications our hospital prescribed were cefoperazone and sulbactam, which are in the not recommended group. Prescriptions for access class antibiotics were somewhat higher than the five-year average in 2019 and 2020, although they began to fall in 2021. In three years—2017, 2020, and 2021—watch class antibiotic prescriptions were higher than the five-year average, with a minor decline in 2021. The prescribed dosage of antibiotics from the reserve antibiotic category increased but changed in cycles (**Table 3**).

Table 3. In intensive care units, antibiotics are provided based on the AWARe classification, which is stated as DDD/100 PD.

AWARe grup (%)	DDD/100 PD				
	2017	**2018**	**2019**	**2020**	**2021**
Access (19.52)	78.02	70.80	80.14	80.83	57.75
Watch (72.12)	299.37	262.77	269.28	279.34	247.27
Reserve (2.87)	5.97	12.42	14.27	7.44	13.88
Not recommended (5.49)	15.53	22.79	17.29	22.06	25.69

Antibiotics in intensive care units (ICUs) cost an average of 178,288.89 EUR per year, with a rising trend, particularly in recent years (**Table 4**). The cost of antibiotic therapy in intensive care units is rising along with the overall hospital expenses.

Table 4. Antibiotic therapy costs at ICUs expressed in EUR

	2017	**2018**	**2019**	**2020**	**2021**	**Total**
ICUs	91,516.85	120,680.6	154,193.6	177,709.7	347,325.7	891,426.5
Total hospital	334,439.5	312,514.8	333,500.8	314,689.3	594,452.2	1,889,597

Prescriptions for ceftazidime/avibactam, cefoperazone/sulbactam, colistin, meropenem, tigecycline, ceftriaxone, amoxicillin/clavulanic acid, moxifloxacin, ertapenem, vancomycin, linezolid, ciprofloxacin, and piperacillin/tazobactam accounted for the highest costs associated with antibiotic therapy in the intensive care units (ICUs). These prescriptions totalled 780,983.9 EUR, or 87.69% of the total expenses.

Table 5. Consumption of antibiotics and associated expenses, represented in euros, from 2017 to 2021

ATC code	Active substance	2017	2018	2019	2020	2021
J01DD52	Ceftazidime/avibactam	-	-	24,992.75	44,843.38	126,007.5
J01DD62	Cefoperazone/sulbactam	19,464.39	25,271.76	20,771.46	28,446.33	54,283.91
J01XB01	Colistin	15,610.68	19,545.01	23,290.92	12,130.05	39,247.94
J01DH02	Meropenem	4,685.06	6,206.10	7,447.05	11,792.5	18,738.54
J01AA12	Tigecycline	815.92	7,493.44	13,608.35	8,874.25	14,289.16
J01DD04	Ceftriaxone	8,230.66	7,437.03	6,548.36	7,943.53	9,594.26
J01CR02	Amoxicillin/acid clavulanic	8,265.16	6,504.48	6,166.97	6,800.17	7,486.09
J01MA14	Moxifloxacin	4,743.28	5,092.32	5,163.54	7,980.41	10,996.77
J01DH03	Ertapenem	7,139.18	6,448.1	6,757.96	4,565.88	8,278.49
J01XA01	Vancomycin	785.41	4,647.28	4,871.44	7,716.68	13,035.2
J01XX08	Linezolid	1,420.41	5,919.91	4,168.86	2,986.54	10,756.89
J01MA02	Ciprofloxacin	2,614.02	2,687.68	3,438.44	4,573.88	5,305.93
J01CR05	Piperacillin/tazobactam	4,658.12	4,711.59	2,241.62	761.69	3,683.17
J01XA02	Teicoplanin	22.93	1,244.26	5,811.05	5,133.55	1,866.15
J01XD01	Metronidazol	2,737.57	2,183.39	2,275.28	1,868.39	2,671.02
J01DD02	Ceftazidime	1,259.25	1,527.31	1,908.65	2,642.25	3,808.69
J01DC02	Cefuroxime	2,422.46	2,018.01	2,740.09	1,657.65	1,133.42
J01MA12	Levofloxacin	1,876.5	2,391.06	611.03	1,721.50	2,740.82
J01FF01	Clindamycin	444.38	2,597.47	2,260.45	2,012.74	1,818.55
J01GB06	Amikacin	767.08	1,569.78	1,990.13	2,397.52	940.74
J01CR01	Ampicillin/sulbactam	900.01	2,114.29	1,423.15	1,636.40	1,400.50
J01DE01	Cefepime	-	322.39	1,713.09	1,911.16	1,819.67
J01FA09	Clarithromycin	1.55	339.86	567.44	4,427.47	183.42
J01DH51	Imipenem/Cilastin	482.97	615.97	1,638.27	1,277.91	1,089.28
J01DH56	Imipenem/cilastatin/relebactam	-	-	-	-	4,572.48
J01DD12	Cefoperazone	1,097.73	560.79	129.41	56.14	79.37
A07AA11	Rifaximin	420.98	299.15	353.33	285.65	489.65
J01GB03	Gentamicin	152.89	149.90	190.13	274.79	423.27
J01CE01	Benzylpenicillin	186.05	529.08	77.19	242.93	3.86
J01CA01	Ampicillin	163.95	192.66	267.64	198.08	216.52
J01CF04	Oxacillin	112.24	20.33	325.43	163.43	80.72
J01XX01	Fosfomycin	-	-	343.07	133.87	135.99
J01FA01	Erythromycin	-	-	56.36	16.35	120.85
J01DB04	Cefazolin	-	-	-	183.86	-
J01AA02	Doxycycline	4.16	9.38	17.51	23.47	12.12
J01FA10	Azithromycin	4.95	7.71	6.23	22.51	21.59
J01DD08	Cefixime	18.90	13.67	3.45	-	4.26
J04AB02	Rifampicin	-	-	9.38	3.51	3.82
J01CA04	Amoxicillin	0.14	4.62	3.14	2.89	2.57
J01DC04	Cefaclor	5.46	2.51	1.37	0.95	-
J01MA06	Norfloxacin	1.88	1.26	2.05	-	0.90
J01MA01	Ofloxacin	0.47	1.05	-	-	-

The antibiotics' cost trend is also shown in **Table 5**. Prescription expenditures for ceftazidime/avibactam, cefoperazone/sulbactam, and colistin are on the rise, accounting for up to 51.52% of total expenses over five years. While the expenses associated with prescriptions for ceftriaxone, amoxicillin/clavulanic acid, ertapenem, and piperacillin/tazobactam remained relatively stable, the costs associated with meropenem, tigecycline, vancomycin, moxifloxacin, and ciprofloxacin showed an increasing trend.

Table 6. Antibiotic prescription costs, expressed in euros, based on the AWARe categorisation

AWARe grup	2017	2018	2019	2020	2021
Access	13,733.69	15,875.44	14,997.08	15,804.73	15,056.02
Watch	40,471.83	46,575.09	52,362.77	64,625.17	83,130.32
Reserve	17,847.01	32,958.37	66,060.88	68,834.22	194,874
Not recommended	19,464.39	25,271.76	20,771.46	28,446.33	54,283.91

Using the AWARe categorisation, we assessed the expenses associated with antibiotic treatment. In the last three assessed years, the reserve class had the greatest expenses, while watch antibiotics had the highest prices in 2017 and 2018 (**Table 6**). Furthermore, the access class's expenses are comparatively stable, but the costs of the other classes show a slight rising trend through 2020 and a notable one at the 2021 level.

To identify the most commonly used antibiotics and those prescriptions that had a major impact on both the frequency of use and the budget, the study tracked the active ingredients, classes, and modes of administration of antibiotics. Aspects of clinicians' practices were thus brought to light, highlighting important points for potential actions taken by those in charge: the drug committee as well as the quality control system [23, 24].

It is also important to note that the COVID-19 epidemic and the period under study (2020 and 2021, specifically) partially overlapped. This made the practice of providing medications and antibiotics more challenging and unprecedented. As a work that focuses on particular management issues, we also took into account cost analysis, which aims to draw attention to certain aspects while also offering suggestions for enhancement, specifically the efficiency of the management of the resources that are now available.

ICUs indicate a higher rate of resistance among isolated pathogens than non-ICU settings, even though patient populations vary greatly, even in the same organisation, leading to significant variances in clinical conditions and medication needs. Even within the same hospital, there are variations among the intensive care units. As an example of country-level variances, aminoglycosides are not as commonly used in Italy and the UK as they are in Korea [25, 26]. Furthermore, different bacterial infections have different usage characteristics significantly between EU nations [27–29]. Ceftriaxone and amoxicillin/clavulanic acid make up half of the top 10 antibiotics given, which account for 84.81% of the total.

According to the WHO's 2019–2023 proposal, antibiotics from the access category must account for at least 60% of the nation's overall antibiotic use. Regardless of the assessed year, the majority of antibiotic prescriptions in our study, which only included intensive care units, came from the watch group, whereas just 19.52 percent came from the access group.

Research by Cupurdija *et al.* [30] showed that the overprescription of antibiotics is mostly responsible for the hospital treatment expenses of community-acquired pneumonia. Additional published research has demonstrated that the coronavirus pandemic resulted in to rise in the use of antibiotics, with our hospital's use peaking in 2021 [31]. According to the financial analysis of antibiotic use in intensive care units, costs increased significantly between 2017 and 2020, and by 4 times in 2021 in comparison to 2017. The average is 178,288.9 EUR over 5 years. The only expenses that exceeded this sum were those associated with antibiotic treatment in 2020 and 2021. Furthermore, ICUs incurred the highest costs associated with antibiotic therapy (47%), which equates to nearly half of the hospital's overall costs. While the lowest percentage of antibiotic doses (13.84%) was given to patients in critical care, the expenses were substantial. In terms of the quantity of dosages, this indicates a comparatively modest use of costly antibiotics. Ceftazidime/avibactam, cefoperazone/sulbactam, colistin, meropenem, tigecycline, ceftriaxone, amoxi illin/clavulanic acid, moxifloxacin, ertapenem, vancomycin, linezolid, ciprofloxacin, and piperacillin/tazobactam were the most commonly prescribed and costly antibiotics utilised in intensive care units. Despite being provided only since 2019, ceftazidime/avibactam prescription expenses were higher than the five-year norm. Colistin and cefoperazone/sulbactam also account for a significant portion of the overall budget spent on antibiotic therapy, over half of it (46.09%). Similar to ceftazidime/avibactam, the trend of those prescriptions is not declining. If the overall cost of antibiotics in the intensive care units was 91,516.92 EUR in 2017, the budget spent in 2021 was 347,344.2 EUR, representing an almost fourfold increase. Statistically, 9–12 of the 37–42 antibiotics used in each year under analysis were used more frequently than the yearly average, resulting in the delineation of antibiotics that doctors like or employ following the therapeutic protocol. Next are the study's limitations. First, it is a five-year monocentric study that has been made more complex by the COVID-19 pandemic. To lower usage and hospital expenses, measures that will control the use of antibiotics and other medical requirements must be put in place [32, 33]. The application of natural chemicals, preventing illnesses linked to medical care, and other strategies could be future directions for lowering antibiotic consumption and expenses [30-33].

Conclusion

According to our research, the majority of the first 10 antibiotics are in the Watch group, and over 80% of them are prescribed. Although the number of antibiotic doses is relatively modest, the cost of antibiotics is higher. Particularly in recent years, the average yearly expenditure of antibiotics in intensive care units has been on the rise. Measuring the prescription of antibiotics gives policymakers useful information, is a crucial first step in comprehending the overall financial effects on the hospital budget, and offers methods to enhance clinical results and expenses.

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