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RESEARCH ARTICLE

ANTIBIOTICS CONSUMPTION AMONG HOSPITALIZED PATIENTS IN INTENSIVE CARE UNITS AT SANA'A CITY, YEMEN

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Abstract

Background: Monitoring antibiotic consumption is crucial to addressing antimicrobial resistance. The aim of current study was to investigate the use and consumption of antibiotics in an intensive care unit in Sana'a, Yemen using DDD and DOT methods, and to our knowledge it is the first of its kind to study this topic.
Methods: A retrospective study on data from the ICU register. The study was carried out from September 2021 to February 2022 on hospitalized patients of five ICUs of main hospitals at 2020. Antimicrobial consumption data were mostly collected manually. Data were analyzed and presented as defined daily dose (DDD) and days of therapy (DOT) per 1000 patient-days.
Results: A total of 1970 patients were included in this study and the overall consumption of antibiotics in ICUs was as high as 18,017.91 DDD per 1000 patient-days and as high as 17448.73 DOT per 1000 patient-days. The study results found that ceftriaxone, vancomycin, and meropenem were most frequently consumed using DDD and DOT methods among ICU patients, with results by DDDs per 1000 patient-days being 2479.23, 2124.55, and 1830.54, respectively, and results by DOTs per 1,000 patient days being 2,112.69. 2055.33 and 1890.86. The highest amount of antibiotics consumption among WHO AWaRe classification was for "watch" group of 26267.4 and 14674.5 DDDs per 1000 patient per day.
Conclusions: A high consumption of antimicrobial agents such as ceftriaxone, vancomycin and meropenem was found in ICUs of five selected hospitals. There was a significant increasing in "Watch" group antibiotics use and about three-fourths of the prescribed antibiotics were from this group. The study results can be used as a basis before designing any intervention aimed at improving antibiotic use in hospital intensive care units.
Keywords: Antibiotic consumption, AWaRe classification, DDD, DOT, ICUs.

INTRODUCTION

Antibiotics are currently encountering significant global public health challenges, such as antimicrobial resistance and inappropriate use[1]. According to the World Health Organization (WHO), more than two-thirds of antibiotics are administered in hospitals, and approximately 30% of these are used inappropriately on a global scale[2]. A strong correlation exists between high antibiotic consumption and resistance, which is exacerbated by irrational antibiotic use at both individual and community levels[3].

The misuse and resistance of antibiotics have emerged as critical public health issues, with alarming evidence accumulating over recent years regarding their inappropriate utilization[4,5]. In low- and middle-income countries (LMICs), about one-third of antibiotic use is inappropriate, with nearly 90% of prescribed antibiotics being broad-spectrum agents, such as third or fourth-generation cephalosporins, highlighting the need for Antimicrobial Stewardship Programs in hospitals[6].

To monitor the consumption of antimicrobials and promote the prudent use of antibiotics, the WHO developed a methodology for antimicrobial consumption surveillance using a metric, the defined daily dose (DDD), as per the anatomical, therapeutic and chemical classification (ATC) system. The WHO has classified antibiotics into three categories as AWaRe: Access for antibiotics needed for common infections that should be available and accessible, Watch for broad-spectrum antibiotics that should be used with caution because of their high potential to develop resistance and reserve for antibiotics that

should be reserved for the treatment of multidrug-resistant infections and used only when other alternatives fail[7].

The intensive care unit (ICU) is often called the epicenter of infections, due to its extremely vulnerable patients, the wide use of invasive devices and broad-spectrum antimicrobials, which favors the emergence of multidrug resistance (MDR). The prognosis of patients who develop hospital-acquired infections (HAI) in the ICU is poor and the mortality rates are higher if it involves an MDR organisms. Inappropriate use of broad- spectrum antimicrobials is frequent, partly because of unwarranted prescriptions of antimicrobials, which may be caused by uncertainty regarding the type of infection, among other possible explanation[8-11].

Yemen is among the developing nations where antimicrobial resistance (AMR) promote inappropriate and overuse of antimicrobial consumption are posing a danger to public health[12-24]. The magnitude of antimicrobial consumption in Yemen unknown, because no previous published studies and reports that addressed this subject using WHO metrics, so this study aimed to estimate antibiotic consumption in ICUs of hospitals by using DDD and DOT methods in Sana'a, Yemen. The study results can be used as base before designing any intervention aiming to optimize antibiotics utilization in hospitals ICUs.

MATERIALS AND METHODS

Study design

Aretrospectivestudy of medical records for all admissions to the ICUs. The study was carried out from September 2021 to February 2022on hospitalized patients in ICUs of main hospitals at 2020.

Study area:

This study was conducted in five main hospitals at Sana'a city–Yemen, three of them were public hospitals and two were private. Public hospitals included Al-Thawra Modern General Hospital (ATH) AL- Jomhori Teaching Hospital (AJH) and 48 Hospital (48H), while private hospitals included Dr. Abdulkader Almutawakel Hospital (AMH) and University Science and Technology Hospital (USTH).

Study population

All patients admitted in ICUs of these hospitals at 2020. All the data was collected manually from patient records except data of USTH was electronic.

Sample size

All adult patients admitted to ICUs with prescribed and received antibiotics of five hospitals during 2020 were included (1970 patients) in this study.

Excluded data

All children admitted to ICUs was excluded because the WHO developed the DDD as a unit of drug use, which is defined as the average daily dose of a drug for its main indication in adults.. Patients who lacked data on prescribed and received medications also were excluded.

Data collection

Data of patients in ICUs were extracted from the ICU patient register by fourth-year Laboratory Medicine students that well trained according to an organized questionnaire containing several variables included the age of a patient, sex, entry day, discharge day, inpatient days or admission, inpatient days or admission name of antimicrobial with strength, strength antibiotic type (tab, vial, amp, syr, sus), antibiotic description (dose No/day/period), route of administration (oral, IM,IV) antibiotic scientific name, antibiotic class, antibiotic subclass.

Defined Daily Dose Method (DDD)

To estimated antimicrobial use using the DDD method, the total number of grams of each antimicrobial used during the period of study were summed and divided by the WHO-assigned DDD. Dividing total grams of use by the DDD (grams/day) yields an estimate of the number of days of antimicrobial therapy. All DDDs were based on the 2020 version of the ATC classification system. To express aggregate use, total DDDs were normalized per 1000 patient-days.

Days of Therapy Method (DOT)

To estimate antibiotic use using the DOT method, one DOT represented the administration of a single agent on a given day, regardless of the number of doses administered or dosage strength. A single patient receiving two antimicrobial drugs would be recorded as receiving 2 DOTs (1 for each antimicrobial administered) and so on according to the number of antimicrobials received daily. To express aggregate use, total DOTs were normalized to 1000 patient-days.

World Health Organization Essential Medicine List (WHO 2019) "Access, Watch, and Reserve (AWaRe)" antibiotics classification were used to assess antibiotic use pattern among participants.

Statistical analysis

All data were coded and entered into a Microsoft Excel file. The spreadsheet was used for the calculation of DDDs based on the strength of each antibiotic, the number of dose units and the DDD values allocated by the World Health Organization. The statistical analyses were done using SPSS version 22.0 software package for windows. Measures of relative consumption, expressed as a percentage of total consumption of groups of antibiotics, were derived for each antibiotic and DDD for "Watch" and "Access" category of antibiotics was calculated.

Ethical Approval

Ethical clearance was obtained from the qualified authorities. The study protocol was approved by the ethics committee of hospitals and 21 September University.

RESULTS

A total of 1970 patients were included in this study. The data of admitted patients of ICUs hospitals at 2020 was collected from patient recorders of five selected hospitals at Sana'a city. This study was conducted from September 2021 to February 2022 and the following results were found:

Demographic characteristics of study participants

A total of 1970 patients their data were collected,1197 from University Science and Technology Hospital (USTH), while only 167, 345, 156 and 105 were

collected from 48 Hospital (48H), AL-Thawra Modern General Hospital (ATH), Al-Jomhori Teaching Hospital (AJH), and Dr. Abdulkader Almutawakel Hospital (AMH), respectively.

Table 1: Socio-demographic characteristics of ICUs adult patients in hospitals.

Item	No. (%)
Gender	
Male	1328 (67.4)
Female	642 (33.6)
Age categories (years)	
15-29	339 (17.2)
30-44	414 (21)
45-59	459 (23.3)
≥60	758 (38.5)

The most participated patients showed that 60.7% in this study were from USTH while lowest participation from AMH was 5.3%. Among ICUs patients the males were the majority (67.4 %), more than females (33%) in this study. The age categories were distributed from 15 years to more than 60 years, and the highest number of participants belong to the oldest age category was (38.5%) while the lowest number belong to the youngest category was (17.2%), as showed in Table 1.

Antimicrobial prescription

As shown in Table 2, on average the number of consumed antimicrobial/patient, amount (in gram) of consumed antimicrobial/patient, number of admission days/patient and days of treatment/patient were 2.67, 8.67, 7.04, 17.45 among ICUs hospitals, respectively. Regarding route of antimicrobial administration, the parenteral route was the most common route in ICUs.

Table 2: Overall ICU-specific consumption.

Particular	%
Average No. of consumed Antimicrobial /patient	2.67
Average amount (in gram) of consumed Antimicrobial/ patient	8.67
Average of admission days/patient	7.04
Average days of treatment/patient	17.45
Route of administration	
Intravenous	88.90
Oral	11.1

Table 3: Distribution of antimicrobial consumption with DDD and DOT.

Antimicrobials	Grams (mean)	DDD (Sum)	DDD (%)	Rate DDD per 1000 patient	DOT (Sum)	DOT (%)	Rate of DOT per 1000 patient-days
Amikacin	3.39	762.3	2.1	386.93	1001	2.9	508.12
Amoxicillin	1.00	0.7	0.0	0.34	1	0.0	0.51
Amoxicillin /clavulanic acid	7.21	239.7	0.7	121.69	280	0.8	142.13
Ampicillin	9.01	31.6	0.1	16.02	73	0.2	37.06
Ampicillin/cloxacillin	1.32		0.0	0.00	106	0.3	53.81
Azithromycin	2.29	933.0	2.6	473.62	547	1.6	277.66
Aztreonam	4.00	2.0	0.0	1.02	8	0.0	4.06
Cefaclor	0.13		0.0	0.00	1	0.0	0.51
Cefadroxil	0.50	0.8	0.0	0.38	3	0.0	1.52
Cefazolin	12.00	4.0	0.0	2.03	3	0.0	1.52
Cefepime	12.87	1016.8	2.9	516.12	1617	4.7	820.81
Cefixime	5.26	2.0	0.0	1.02	17	0.0	8.63
Cefoperazone	11.13	384.0	1.1	194.92	619	1.8	314.21
Cefoperazone/sulbactam	12.22	311.5	0.9	158.12	505	1.5	256.35
Cefotaxim	10.13	177.3	0.5	89.97	272	0.8	138.07
Cefpirome	12.59	340.0	1.0	172.59	537	1.6	272.59
Cefpodoxime	0.68	8.5	0.0	4.31	11	0.0	5.58
Ceftazidime	10.74	134.3	0.4	68.15	233	0.7	118.27
Ceftriaxon/sulbactam	13.39	308.0	0.9	156.35	218	0.6	110.66
Ceftriaxone	8.38	4884.1	13.8	2479.23	4162	12.1	2112.69
Ceftriaxone/tazobactam	4.00		0.0	0.00	2	0.0	1.02
Cefuroxime	5.88	78.3	0.2	39.76	128	0.4	64.97
Ciprofloxacin	2.07	153.3	0.4	77.79	252	0.7	127.92
Clarithromycin	8.38	130.0	0.4	65.99	60	0.2	30.46
Clindamycin	7.67	1310.0	3.7	664.95	1216	3.5	617.26
Colistin	1.75	17.1	0.0	8.68	414	1.2	210.15
Doxycycline	1.16	2104.0	5.9	1068.02	966	2.8	490.36
Gentamicin	0.68	390.7	1.1	198.31	468	1.4	237.56
Imipenem	3.68	9.2	0.0	4.67	19	0.1	9.64
Imipenem/cilastatin	11.02	2270.1	6.4	1152.33	1947	5.7	988.32
Levofloxacin	2.35	2129.6	6.0	1081.02	1898	5.5	963.45
Lincomycin	1.60	1.8	0.0	0.90	2	0.0	1.02
Linezolid	5.96	1098.5	3.1	557.62	1025	3.0	520.30
Meropenem	12.71	3606.2	10.2	1830.54	3725	10.8	1890.86
Metronidazole	5.81	1209.4	3.4	613.91	1487	4.3	754.82
Moxifloxacin	1.83	3429.0	9.7	1740.61	3086	9.0	1566.50
Nitrofurantoin	1.60		0.0	0.00	8	0.0	4.06
Norfloxacin	0.05		0.0	0.00	3	0.0	1.52
Ofloxacin	0.80	2.0	0.0	1.02	2	0.0	1.02

Cont...

Penicillin G	2.65	2.9	0.0	1.49	11	0.0	5.58
Piperacillin	8.70	13.7	0.0	6.94	106	0.3	53.81
Piperacillin/Tazobactam	61.86	981.0	2.8	497.94	1002	2.9	508.63
Polymyxin B	0.89	1320.0	3.7	670.05	1011	2.9	513.20
Rifaximin	4.23	586.0	1.7	297.46	356	1.0	180.71
Sodium fusidate	0.75		0.0	0.00	15	0.0	7.61
Sulfamethoxazole/trimethoprim	8.54		0.0	0.00	267	0.8	135.53
Tazobactam	135.00		0.0	0.00	10	0.0	5.08
Teicoplanin	3.41	307.0	0.9	155.84	171	0.5	86.80
Tetracycline	4.00	40.0	0.1	20.30	2	0.0	1.02
Tigecycline	0.59	580.0	1.6	294.42	452	1.3	229.44
Vancomycin	9.26	4185.4	11.8	2124.55	4049	11.8	2055.33
Total		35495.3	100.0	18017.91	34374	100.0	17448.73

Antimicrobial use patterns by using antibiotics metrics

Table 3 shows the most average of antimicrobial consumption regarding antimicrobial consumption using DDDs and DOT in ICUs patients were ceftriaxone, vancomycin, and meropenem reported 2479.23, 2124.55 and 1830.54 DDDs per 1000 patient-days, respectively. While the average amount of polymyxin B, tigecycline, and colistin were 670.05, 294.42, and 8.68 DDDs per 1000 patient-days, respectively. On the other side, the most average of antimicrobial consumption using DOTs, reported ceftriaxone, vancomycin, and meropenem with 2112.69, 2055.33, and, 1890.86 DOTs per 1000 patient-days, respectively. The same antibiotics were reported by both methods. The Table 4 shows a total consumption of antibiotic for systemic use was 18017 DDD per 1000 patient-days.

Table 4: Distribution of therapeutic/Pharmacological subgroup of antimicrobial with DDD and DOT.

Therapeutic/Pharmacological Subgroup (ATC)	Number of DDDs	Rates DDD per 1000 patient	Number of DOTs	Rates DOT per 1000 patient days
Aminoglycosides	1152.9	585.24	1469	745.69
Carbapenems	5885.5	2987.54	5691	2888.83
Cephalosporins	7649.4	3882.95	8328	4227.41
Glycopeptides	4492.4	2280.38	4220	2142.13
Glycylcycllines	580.0	294.42	452	229.44
Lincosamides	1311.7	665.86	1218	618.27
Macrolides	1063.0	539.61	607	308.12
Monobactam	2.0	1.02	8	4.06
Oxazolidnones	1098.5	557.62	1025	520.30
Penicillins	1269.5	644.43	1589	806.60
Polypeptaied	1337.1	678.73	1425	723.35
Quinolones	5713.9	2900.43	5241	2660.41
Sulfonamides		0.00	267	135.53
Tetracycline	2144.0	1088.32	968	491.37
Other	1795.4	911.37	1866	947.2
Total	35495.3	18017.91	34374	17448.73

The vast majority of consumption among therapeutic/Pharmacological subgroups consisted of cephalosporins (3882 DDD per 1000 patient-days), while carbapenems (2987 DDD per 1000 patient-days) and quinolones (2900 DDD per 1000 patient per days). The rate of DOTs per 1000 patient-days were cephalosporins was 4227.41DOTs per 1000 patient-days, while carbapenems was 2888.83DOTs per 1000 patient-days, and quinolones was 2660.41DOTs per 1000 patient-days.

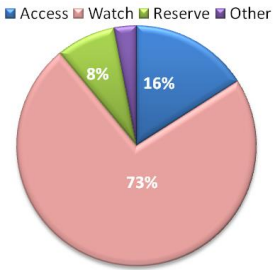

Figure 1: Distribution of antimicrobial utilization in ICUs by AWaRe.

Antibiotics use patterns based on WHO AWaRe classification

Figure 1 showed the most commonly used antibiotics by AWaRe category were those from the Watch category 73%, followed by the Access category 16%.

In Table 5, the highest amount of antibiotics consumption among WHOAWaRe classification was for "watch" group of 26267.4 DDDs and 14674.5 DDDs per 1000 patient per days.

Table 5: Distribution of antibiotics consumption by DDD per 1000 Patient per day by WHO AWaRe system.

WHO AWaRe Category	Number of DDDs	Rates DDD per 1000 patient
Access	6121.2	3419.7
Watch	26267.4	14674.5
Reserve	1804.6	1008.2
Other	5347.0	2987.2
Total	34836.7	19461.9

DISCUSSION

Excessive exposure to antibiotics fosters a complicated relationship between antibiotic resistance and the irrational use of these medications[25]. Understanding the extent of antibiotic exposure and patterns of antibiotic use is crucial for preventing inappropriate usage and its consequences[26]. The findings of this study highlight a significant concern regarding ICU-specific antimicrobial consumption in five hospitals in Sana'a, Yemen.

The high consumption rates, as indicated by both DDD and DOT methods, mirror patterns observed in other regions grappling with antimicrobial resistance challenges. In the present study the total consumption by DDD/1000 patient- days of antimicrobials was 18017 that higher than reported from studies in Brazil, Saudi Arabia, Romania and from 130 European hospitals that reported 14368.85 and 812.5, 1172.40, 792±147, respectively[7,8,27,28].

In current study, ceftriaxone, vancomycin, and meropenem were the most frequently consumed antibiotics in ICUs irrespective of the metrics used. this finding align with study conducted in Saudi Arabia which also reported the highest usage of ceftriaxone and vancomycin[29]. Similarly, studies carried out in Brazil and America Latin observed that meropenem and vancomycin were the most highly consumed antibiotics[27,30]. The frequent prescription of broad spectrum antibiotic like ceftriaxone in intensive care units has been consistently reported in various studies[27,31-34]. These observations are in the line with our findings, indicating a common trend in the high utilization of these antibiotics in critical care setting. On the other hand, the majority of international studies have showed that penicillins[35-37] are the most frequently consumed antimicrobials in adult ICUs.

The high usage of cephalosporins, carbapenemsand quinolones aligns with global consumption patterns, particularly in low and middle-income countries where empirical therapy is common due to limited diagnostic facilities[38]. The elevated consumption of these broad-spectrum antibiotics raises concerns about the potential acceleration of antimicrobial resistance. In line with our findings, the majority of international studies have showed that cephalosporins[39-41] are the most frequently consumed antimicrobials in adult ICUs.

Cephalosporins consumption was 3882.95 by DDD / 1000 patient-days higher than 2135.08 and 264.19 that reported from other studies[8, 27]. The consumption of carbapenems in this study was considerably higher than the rates reported by several reports around the world. For example, it was 2987 DDDs per 1000 patient-days in current ICUs compared with 255.9 in Saudia[7],36.9 in French ICUs[35], 37.8 in the US National Nosocomial Infections Surveillance (NNIS) medical-surgical ICUs[36], 81.4 in German ICUs[37], 90.0 in the International Nosocomial Infection Control Consortium (INICC) ICUs[39], 58–143 in Swedish ICUs[40], 196.5 in Italian ICUs[41], and 257.1 in Australian and New Zealand ICUs[42].

The consumption of vancomycin in this study was 1830.54 DDDs per 1000 patient-days which was higher than Saudi ICUs 98.2[7], NNIS, INICC, and German ICUs (36.7–91.9)[36,37,39], also in Italian and Australian and New Zealand ICUs (146.9–191.8)[42,43]. In contrary, study carried out by T.L. de Castro *et al*., in 2023 reported higher rate of carbapenems and vancomycin consumption than our results; 3110,02 and 2322.6 DDDs per 1000 patient-days[27].

Comparing the current ICU-specific DOT rates, this study had DOTs per 1000 patient-days of 2888.83 for carbapenems consumption that significant higher than 235.7 and 196.3 reported by studies done in an adult ICU in Saudi Arabia[7] and Canada[41]. Vancomycin reported 2055.33 by DOTs per 1000 patient-days, that higher than reported in the previous studies; 129.5 and 187.2[7,41].

The most frequently consumed antibiotics according to therapeutic/pharmacological subgroup were cephalosporin's, carbapenem and quinolones consisting mainly of parenteral. The current study showed that 73% of antibiotics used were from the "Watch" group antibiotics. This finding is slightly higher than the survey that reported in Ethiopia; 66%[27], 66.1% in West and Central Asia[44], and 64.4% in four low and middle-income countries[45]. This "watch" includes antibiotics that are at a higher risk of resistance and should be prioritized for stewardship efforts[46]. The high consumption rates of these antibiotics in our study reiterate the necessity for stringent guidelines to monitor and control their use.

The high consumption of broad spectrum antimicrobials was due to the prevalence of infections caused by gram-negative bacteria that produce extended-spectrum β-lactamase (ESBL) and methicillin-resistant *Staphylococcus aureus* (MRSA), respectively[30]. One of the reasons for the significant differences in antibiotic consumption in our study compared to similar studies in other countries can be attributed to the ongoing military conflict in Yemen. This conflict has led to a significant influx of injured soldiers and civilians into the capital's hospitals. In addition, the COVID-19 outbreak that occurred during the study period had a major impact on the healthcare system in Yemen. Many COVID-19 patients, including those with severe and critical illness, were admitted to the study hospitals. Furthermore, there is a lack of a clear, standardized treatment policy for critical cases. So, all these factors may contribute to the substantial difference in antibiotic consumption in the study hospitals. Additionally, the high prevalence of antibiotic-resistant bacteria in these hospitals has led to the excessive use of broad-spectrum antibiotics[47-49].

Limitations of the study

A major limitation of this study was the inability to access all data of patients admitted to most hospitals due to administrative constraints and the unavailability of an electronic patient data system which facilitates data acquisition rather than manually collecting them from the ICU registry. Finally, the study was not designed to take into account working differences between ICUs in patient mix or predominant bacterial pathogens and their susceptibility patterns.

CONCLUSIONS

Current results show a high consumption of broad-spectrum antimicrobial agents such as cephalosporin and carbapenem in addition to vancomycin by patients of intensive care units of 48H, ATH, AJH, AMH and USTH. The consumption of ceftriaxone, vancomycin, and meropenem were the highest using both DDD and DOT methods among ICU patients. The findings highlight the urgent need for an effective antimicrobial stewardship program in these hospitals with focusing on ICUs specific antimicrobial consumption. The study results can be used as base before designing any intervention aiming to optimize antibiotics utilization in hospitals ICUs.

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AUTHOR'S CONTRIBUTION

Al-Tahish GA: writing original draft, methodology, investigation. **Alyahawi AA:** formal analysis, data curation, conceptualization. Final manuscript was read and approved by all authors.

DATA AVILIABILITY

The data will be available to anyone upon request from the corresponding author.

CONFLICT OF INTEREST

None to declare.

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