Research Article

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Evaluating Antibiotic Utilization in Intensive Care Units Using WHO Defined Daily Dose and Drug Utilization 90% Methods

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ABSTRACT

It is essential to assess the drug utilization evaluation patterns of antimicrobials in the Intensive Care Unit (ICU) to safeguard rational use of antibiotics. We aimed to evaluate the drug utilization patterns of antibiotics using World Health Organization (WHO) methodologies, namely Defined Daily Dose (DDD)/100 patient days and Drug Utilization 90% (DU 90%) in the ICU. We conducted a drug utilization evaluation study in three medicine intensive care units on a sample of 397 patients. We used World Health Organization- Anatomic Therapeutic Classification (ATC)/Defined Daily Dose (DDD) and Drug Utilization 90% methods to measure drug utilization. We classified the commonly used antibiotics into Access, Watch, and Reserve (AWaRe) category proposed by WHO. The average number of antibiotics per prescription was 2.14±1.28 and average duration of treatment with an antibiotic was 6.25 ± 3.37. The DDD/100 patient days for cefoperazone + sulbactam was 2.64. The drugs included in the DU90% segment, indicating the most often used antibiotics, were cefoperazone + sulbactam, ceftriaxone, cefpodoxime, azithromycin, piperacillin + tazobactam, amikacin, metronidazole, levofloxacin, meropenem, and cefixime. Seventy-two percent of antibiotics in DU90% segment fell into the 'Watch' category. Culture sensitivity tests were often not performed, and there was a heavy reliance on the use of antibiotics from the Watch group.

Keywords: Defined daily dose, Drug utilization 90%, Antibiotics, Antibiotic stewardship, Cephalosporins.

1. Introduction

Infectious diseases contribute to significant mortality rates, especially in developing countries. However, the irrational use of antimicrobial drugs to treat these infectious diseases has given rise to drug resistant strains. Therefore, addressing this irrational use of antibiotics is essential to control the emerging antimicrobial drug resistance [1-3]. Indiscriminate prescribing of antimicrobial medications, for example, prescribing antibiotics for viral infections without considering the etiological microorganism, poses a severe threat to future antibiotic development. Thus, it is crucial to promote the rational use of these drugs by periodic monitoring and regulating their use [4-6].

In the intensive care unit (ICU), the severity and complexity of cases are high and empirical antibiotic therapy, especially broad-spectrum antibiotics is commonly used, with approximately 70% of ICU patients receiving at least one antibiotic daily [7]. Hence, assessing the drug utilization evaluation pattern of these antimicrobials in the ICU is essential to safeguard the rational use of antibiotics [8]. Evaluating antibiotic use reflects the effectiveness of antimicrobial resistance control programmes in hospitals. It also offers insights into antibiotic usage patterns in hospitals, in terms of quality and quantity [9]. In accordance with the World Health Organization (WHO), the standard method for quantitatively evaluating the use of antibiotics is Anatomical Therapeutic Classification (ATC) / Defined Daily Dosage (DDD) [10]. DDD is the assumed average maintenance dose per day for a drug when used for its main indication in adults. A DDD value higher than the WHO standard indicates the likelihood of irrational use of antibiotics, whereas smaller DDD value indicates a more judicious use of antibiotics [9]. The drug utilization 90% (DU90%) determines the number of drugs accounting for 90% of use in DDDs [11]. Our study aimed to evaluate the drug utilization patterns of antibiotics using World Health Organization (WHO) methodologies, namely Defined Daily Dose (DDD)/100 patient days and DU 90% in the ICU.

2. Material and Methods

2.1. Study design, setting, duration, sampling technique, and sample size

We conducted a cross-sectional hospital-based drug utilization evaluation study on 397 patients for a duration of one year (November 2022 to November 2023) in three intensive care units. We used simple random sampling to select the patients. The estimated sample size is 377 patients with a margin of error of 5%, 95% confidence interval, a response distribution of 50% and size of population is 20000. We collected data from 397 patients. The institutional ethical committee approved the study (Vignan Institute of Pharmaceutical Technology, The Institutional Human Ethical Committee, Ref. No. VIPT/IEC/220/2022, dated 24/10/2022). We explained the aim and objectives unequivocally to the patients and assured the confidentiality and privacy of their data. We obtained written informed consent upon their willingness to participate in the study.

2.2. Study participants: inclusion and exclusion criteria

We included patients who are 18 years or older, admitted to the ICU, had received at least one antibiotic during their stay, and the patients should provide a written informed consent. We excluded patients who are on antibiotic therapy prior to ICU admission to avoid confounding by continuation of pre-existing treatments, patients with terminal illnesses, patients transferred from other ICUs where antibiotic therapy may have started elsewhere, and patients with multiple antibiotic allergies.

2.3. WHO- Access, Watch, and Reserve (AWaRe) framework for use of antibiotics

AWaRe [12] classification of antibiotics was created to assist antibiotic stewardship at global, national, and local levels and to decrease antimicrobial resistance. This classification emphasizes the significance of antimicrobial rational use. However, it is not a model for including antibiotics on national essential medicine lists (NEML). Access group antibiotics have broad spectrum activity and shows lower resistance potential. Watch group antibiotics have a high potential for resistance and include many of the top-priority drugs that are critically important for human medicine. Watch groups of antibiotics are more likely to lead to bacterial resistance. These antibiotics should be the focus of stewardship programs and monitoring efforts. The reserve group of antibiotics should be saved for treating suspected or confirmed infections caused by multi-drug-resistant organisms. These medications should be reserved for specific

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patients and situations where no other options are suitable or have failed.

2.4. Antibiotic utilization- DDD/100 patient days and DU 90%

We calculated the drug utilization of antibiotics using Anatomic Therapeutic Chemical (ATC)/ Defined Daily Dose (DDD) methodology. We calculated DDD/100 patient days and DU90% for commonly prescribed antibiotics [9, 10]. The total length of stay (LOS) for the entire study period of one year was 5263 days.

$$\frac{\text{DDD}}{100}\text{ patient days} = \frac{\text{Quantity of dosage antibiotic used by the patient (gram)}}{\text{DDD (in gram)}} \text{X} \frac{100}{\text{LOS}}$$

$$\text{DU 90\%} = \frac{\frac{\text{DDD}}{100}\text{patient days of the antibiotic}}{\text{Total}\frac{\text{DDD}}{100}\text{ patient days}} \text{X 100\%}$$

2.5. Data Collection and data analysis

Data such as age, gender, diagnosis, past medical history, number of antibiotics prescribed and duration of treatment were noted down from the patient's case sheet. We used descriptive statistics to represent the data. For each antibiotic class we calculated the frequency of commonly prescribed antibiotics, the mean treatment duration in days, the maximum treatment duration in days, and the quartile duration in days to indicate the most common treatment intervals. The frequency and percentages of antibiotics use were calculated. The AWaRe classification for commonly prescribed antibiotics was also noted to evaluate prescribing practices. The mean number of antibiotics per prescription was also calculated. We used Jeffrey's Amazing Statistical Programme (JASP version 0.18.3.0) to calculate descriptive statistics.

3. Results and Discussion

3.1. Clinical and sociodemographics of patients

The average number of antibiotics per prescription was 2.14±1.28 and the average duration of treatment with an antibiotic was 6.25 ± 3.37 days. Only 12.10% of patients experienced polypharmacy, expressed as the use of ≥ 5 drugs. Furthermore, 73.58% of the drugs prescribed were from the Essential Drugs List (EDL) (Table 1). The most frequently prescribed category of antibiotics was third-generation cephalosporins and beta-lactamase inhibitors. Within this category, cefoperazone + sulbactam was the most commonly used drug, accounting for 22.4% of prescriptions, followed by other third-generation cephalosporins at 20.4%. Ceftriaxone (14.6%), cefixime (3.3%), and cefpodoxime (2.5%) were the top drugs in this group. The combination of penicillins and beta-lactamase inhibitors made up 13% of prescriptions, with piperacillin + tazobactam (9.3%) and amoxicillin + clavulanate (3.7%) being the most prevalent (Table 2).

3.2. Drug utilization evaluation of antibiotics in ICU

Additionally, out of the 14 commonly prescribed antibiotics, 64.3% (9 out of 14) belonged to the Watch category of the WHO classification. The average duration of treatment was notably longer for linezolid (7.92 ± 4.02 days). Piperacillin and tazobactam had the longest maximum treatment duration, extending up to 19 days (Table 2). The drugs included in the DU90% segment, indicating the most often used antibiotics, were cefoperazone + sulbactam, ceftriaxone, cefpodoxime, azithromycin, piperacillin + tazobactam, amikacin, metronidazole, levofloxacin, meropenem, and cefixime. Among these, the highest defined daily doses were recorded for cefoperazone + sulbactam (2.64), ceftriaxone (2.56), and cefpodoxime (2.11) (Table 3).

Our study highlighted that only 12.10% of patients experienced polypharmacy, characterized as the use of five or more drugs. In contrast, two other studies investigating the drug utilization pattern in the intensive care unit [13, 14] reported higher rates of polypharmacy at 10.78% and 8.1%, respectively. Anand et al. [15], reported the lowest rate of polypharmacy among these studies at 4.9%. Our study observed ceftriaxone's usage at 14.6%, while it was the most commonly used antibiotic in some studies [13, 15-18]. This antibiotic appears to be consistently prevalent across different studies, however with varying degrees of utilization.

The combination of piperacillin + tazobactam was another frequently mentioned antibiotic. Our study recorded its prescription at 9.3%, whereas Patra et al. 17 and Satapathy et al. 18, reported higher usage rates of 31.57 and 17.53 DDD/100 patient days, respectively. Panda et al. [13], and Anand et al. [15] also noted significant usage at 12.07 and 19.22 DDD/100 bed days, respectively, highlighting a consistent pattern of high utilization across vari-

Table 1. Clinical and sociodemographic characteristics of study patients (n=397)

Characteristic	Descriptive Statistic
Age, mean±SD[a]	51.47 ± 18.17
Duration of treatment, mean±SD	6.25 ± 3.37
Antibiotics per prescription, mean±SD	2.14 ± 1.28
Male, n (%)	259 (65.23)
Diagnosis based on organ system, n (%)	
Respiratory system	106 (26.70)
Cardiovascular system	40 (10.07)
Infectious disease	34 (8.56)
Others and combination of systems	217 (54.65)
Comorbidities, n (%)	
Two or more comorbidities	126 (25.71)
Hypertension	121 (24.69)
No comorbidity	93 (18.97)
Diabetes Mellitus Type 2	92 (18.77)
Asthma	44 (8.97)
COPD[b]	14 (2.85)
Number of antibiotics prescribed, n (%)	
<5 antibiotics	349 (87.90)
≥5 antibiotics	48 (12.10)
Frequency of drugs from EDL[c], n (%)	
EDL	629 (73.58)
Non-EDL	219 (26.42)

[a] SD= Standard Deviation, [b] COPD= Chronic Obstructive Pulmonary Disease [c] EDL= Essential Drugs List

ous studies. Our study reported included antibiotics such as cefoperazone + sulbactam, ceftriaxone, cefpodoxime, azithromycin, piperacillin + tazobactam, amikacin, metronidazole, levofloxacin, meropenem, and cefixime in their DU90% segment whereas Nasution et al. [9] reported levofloxacin, ceftriaxone, and meropenem were the antibiotics included in their DU90% segment.

The mean number of antibiotics prescribed in the study was 2.14 ± 1.28 and average duration of treatment with an antibiotic was 6.25 ± 3.37. The decision-making process for antibiotic management in the ICU is multifaceted, with various factors influencing the duration of treatment. For example, short-course antibiotic treatments (3 to 5 days) were as safe and effective as long treatment (7 to 10 days)

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Table 2. Distribution, treatment duration and AWaRe category of most frequently used antibiotic classes and drugs in the ICU patients

Class of the drug	Name of the drug	Frequency (%)	Treatment duration (in days)	Maximum Duration (in days)	Q1, Q2, Q3[e] (duration in days)	AWaRe category[f]
TGC[b] + BLI[c]	Cefoperazone + Sulbactam	190 (22.4%)	6.46 ± 3.07	16	4, 6.5, 9	Watch+Access
TGC	Ceftriaxone	124 (14.6%)	5.97 ± 3.11	17	4, 6, 7	Watch
	Cefixime	28 (3.3%)	3.64 ± 3.26	16	2, 3, 4	Watch
	Cefpodoxime	21 (2.5%)	4.80 ± 2.62	10	2.5, 4, 7	Watch
PN[d] + BLI	Piperacillin + Tazobactam	79 (9.3%)	6.27 ± 3.47	19	3, 6, 9	Watch
	Amoxicillin + Clavulanate	31 (3.7%)	4.51 ± 2.80	13	2, 4, 5	Access
Aminoglycoside	Amikacin	90 (10.6%)	6.46 ± 3.07	14	4, 6, 9	Access
Macrolide	Azithromycin	84 (9.9%)	6.91 ± 3.25	18	5, 7, 9	Watch
Nitroimidazole	Metronidazole	50 (5.9%)	5.64 ± 2.63	14	4, 5, 7	Access
Fluoroquinolones	Levofloxacin	20 (2.3%)	7.60 ± 4.88	16	3, 6.5, 13	Watch
	Moxifloxacin	19 (2.2%)	7.73 ± 2.67	14	3, 6.5, 13	Watch
Carbapenems	Meropenem	37 (4.4%)	7.08 ± 3.21	15	5, 7, 9	Watch
Oxazolidinones	Linezolid	14 (1.7%)	7.92 ± 4.02	16	5, 7, 11	Reserve
Nitrofurans	Nitrofurantoin	14 (1.7%)	6.42 ± 2.02	10	5, 7, 8	Access

b= Third Generation Cephalosporin, c= Beta-Lactamase Inhibitor, d= Penicillin, e= Quartiles 1 (25%), Quartiles 2 (50%), Quartiles 3 (75%), f= Access, Watch, and Reserve (AWaRe).

in children aged ≥ six months with community acquired pneumonia [19]. Shorter courses can be effective in reducing antibiotic overuse [20] but there is a high prevalence (75%) of longer antibiotic courses than recommended [21]. Additionally, a single extra antibiotic treatment day is related to a 7% absolute raise in risk of antibiotic resistance, especially in settings with high transmission rates [22].

The percentage of antibiotics from EDL in our study was 78.05%. However, a high percentage of antibiotics from EDL can lead to inappropriate use and contribute to the emergence of antimicrobial resistance [23]. In our study, we observed 72% antibiotics in DU90% segment fall into 'Watch' category. In contrast, a few studies reported a lower proportion of DU90% antibiotics in Watch category [13-15, 17]. Nasution et al. [9] reported that 100% of Watch category antibiotics in DU90% segment. The five most common antibiotics in the DU90% segment among several studies is ceftriaxone [9, 13-18], metronidazole [13-16], piperacillin + tazobactam [13, 15, 16, 18], meropenem [9, 13, 15, 16], and amikacin [13-15,18].

The increased use of Watch category antibiotics in the ICU can lead to several concerning outcomes. Firstly, it can contribute to the increase and spread of multidrug-resistant bacteria, as seen during the COVID-19 pandemic [24]. Increased reliance on Watch category antibiotics, such as ceftriaxone, can lead to significant shifts in resistance patterns, as observed in various clinical settings [24, 25]. Furthermore, this is particularly problematic when the peak of antibiotic consumption does not align with the rise of the pathogenic agents, they are intended to treat [24]. Additionally, the increased use of the antibiotics, particularly in the Watch and Reserve

Table 3. Antibiotics utilization in ICU represented as DU90% and DDD/100 patient days

Name of the drug	ATC code	DDD (in grams)	Total amount (grams)	DDD/100 Patient days	DU90%	Cumulative percentage
Cefoperazone + Sulbactam	J01DD62	4	556.8	2.64	16.90	16.90
Ceftriaxone	J01DD04	2	269.6	2.56	16.39	33.29
Cefpodoxime	J01DD13	0.4	44.5	2.11	13.51	46.80
Azithromycin	J01FA10	0.5	43	1.63	10.44	57.24
Piperacillin + Tazobactam	J01CR05	14	1048.5	1.42	9.09	66.33
Amikacin	J01GB06	1	64.5	1.23	7.87	74.20
Metronidazole	J01XD01	1.5	73.05	0.93	5.95	80.15
Levofloxacin	J01MA12	0.5	16.5	0.63	4.03	84.18
Meropenem	J01DH02	3	85	0.54	3.46	87.64
Cefixime[g]	J01DD08	0.4	11.2	0.53	3.40	91.04
Amoxicillin + Clavulanate	J01CR02	3	72.225	0.46	2.94	93.98
Moxifloxacin	J01MA14	0.4	8.4	0.40	2.56	96.54
Linezolid	J01XX08	1.2	16.8	0.27	1.73	98.27
Nitrofurantoin	J01XE01	0.2	2.8	0.27	1.73	100

g= DU90% segment

categories, has been linked to the evolution of resistance [26].

DU90% approach is useful in antibiotic stewardship, aiming to optimize antibiotic use and combat antibiotic resistance. The DU90% segment helps identify the most frequently prescribed drugs, which cover 90% of an antibiotic's use, providing a clear picture of prescribing trends and aiding in the evaluation of adherence to clinical guidelines [27]. In the context of antibiotic utilization, DU90% is instrumental in identifying potential overuse or misuse of antibiotics, which is crucial given the global challenge of antibiotic resistance. For instance, a study demonstrated that a significant amount of antibiotics, specifically cephalosporins, were consistently utilized, highlighting the need for monitoring and potential adjustment in prescribing practices to ensure rational use [28].

The maximum number of days an antibiotic prescribed in the ICU in our study ranged from 16-19 days. The maximum duration for antibiotic use in a medical ICU can vary significantly depending on the type of infection, the patient's response to treatment, and the presence of any complications. For instance, a meta-analysis highlighted the non-inferiority of short courses (less than four weeks) of intravenous antibiotics compared to longer courses for treating prosthetic joint infections [29]. This suggests that shorter antibiotic courses can be effective and might reduce the side effects and costs associated with prolonged antibiotic use. Moreover, a study across 41 hospitals aimed at improving antibiotic duration for community-acquired pneumonia found that a 5-day course was often adequate and associated with fewer antibiotic-related adverse events [30]. Consequently, this indicates that shorter antibiotic courses, guided by clinical benchmarks and best practices, can be effective for uncomplicated cases. However, Ceftriaxone's long-term use could be necessary for sustained infections, yet it carries a risk of pseudomembranous colitis and, in prolonged use, could lead to C. difficile infection [31]. Additionally, Piperacillin + Tazo-

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bactam is often used for complex hospital-acquired infections; extended use might be justified in ICU settings but monitoring for liver function and electrolyte imbalance is crucial [32]. Finally, Linezolid is effective against resistant gram-positive infections, but its use for more than two weeks is associated with myelosuppression, peripheral neuropathy, and optic nerve damage, requiring careful monitoring and potentially dose adjustments [33].

The DDD per 100 patient days in our study showed significant variation compared to some other studies, primarily due to variations in study population size and duration of hospital stay. For instance, the study conducted by Nasution et al. [9], had a smaller population of 57 patients and a shorter total duration of 308 days, which is considerably lower than those in our study. Calculating DDDs per bed day helps benchmark in-hospital drug use. For instance, 70 DDDs per 100 bed days of sedatives means that 70% of inpatients receive one DDD of a sedative daily, or each inpatient receives 0.7 DDDs [34]. The DDD/100 patient days for cefoperazone + sulbactam was 2.64 which indicates that 2.64% of inpatients receive one DDD of cefoperazone + sulbactam each day. It may imply a relatively low level of use of this antibiotic in this setting or the time we analysed. Additionally, the DDD value is below the WHO standard value suggesting a more selective use. However, with a DDD value greater than WHO standard value, cefpodoxime use suggests an irrational use. These discrepancies between the observed DDDs and the WHO standards highlight areas where antibiotic use may not be fully rational, thus pointing to potential areas for improvement in antibiotic stewardship within the hospital.

Our study has a few limitations. During the study period, only seven culture sensitivity tests were ordered, and we are unable to represent the information due to sufficient data on culture sensitivity reports. The use of convenience sampling can limit the generalizability of the study results. The Defined Daily Dose (DDD) methodology may not accurately reflect actual patient doses, especially in cases of dose adjustments based on patient-specific factors such as renal function or severity of illness.

4. Conclusion

Our study found that standard treatment guidelines were not consistently followed in the ICU. Additionally, culture sensitivity tests were often not performed, and there was a heavy reliance on the use of antibiotics from the Watch group. Therefore, we recommended and proposed a continuing education module on antibiotic stewardship, the creation of an antibiotic stewardship committee, and ongoing drug utilization evaluation by establishing benchmarks. Future research should focus on implementing and evaluating stewardship interventions that monitor outcomes related to resistance patterns. The institutional ethical committee approved the study (Vignan Institute of Pharmaceutical Technology, The Institutional Human Ethical Committee, Ref. No. VIPT/IEC/220/2022, dated 24/10/2022). We explained the aim and objectives unequivocally to the patients and assured the confidentiality and privacy of their data. We obtained written informed consent upon their willingness to participate in the study.

Conflict of Interest

The authors have no conflicts of interest, financial or otherwise, to declare.

Statement of Contribution of Researchers

Concept – V.K.M.; Design – V.K.M., G.V.; Supervision – V.K.M., G.V.; Resources S.M.P., V.T.D.Y., S.K.C., A.R.; Data Collection and/or Processing – S.M.P., V.T.D.Y., S.K.C., A.R.; Analysis and/or Interpretation – V.K.M., G.V., S.M.P., V.T.D.Y., S.K.C., A.R.; Literature Search – S.M.P., V.T.D.Y., S.K.C., A.R..; Writing – V.K.M., G.V., S.M.P., V.T.D.Y., S.K.C., A.R.; Critical Reviews – V.K.M., G.V., S.M.P., V.T.D.Y., S.K.C., A.R

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