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Original Research Article

Antibiotic prescription assessment in geriatrics using anatomical therapeutic chemical/defined daily dose classification and World Health Organization-essential medicines list AWaRe guidelines: a prospective and observational study

Francis Ezika*, Balakeshwa Ramaiah, Blessy K. George, Shibi M. Thomas, Jeeva George

Doctor of Pharmacy, Karnataka College of Pharmacy, Bangalore, Karnataka, India

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*Correspondence:

Dr. Francis Ezika,
Email: ezikafrancis@gmail.com

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ABSTRACT

Background: Geriatric patients are individuals with compromised overall functioning. The objective of this study was to assess the prescribing pattern and evaluate the therapeutic efficacy of the prescribed antibiotics.

Methods: The prescribed antibiotics were grouped using anatomical therapeutic chemical classification (ATC) and World Health Organization defined daily dose (WHO DDD)/100-bed days was calculated to analyse consumed antibiotics. The neutrophils and lymphocyte count before and after therapy was used to assess the therapeutic efficacy.

Results: Disease frequency was categorised using the International classification of disease (ICD-11) which reported 126 diseases, with 50 cases grouped under respiratory system. Selection of antibiotic was mainly definitive (37.14%) with dual therapy (55.71%) and with antibiotic sensitivity test (61.43%). Cephalosporins, was the most prescribed antibiotic class, specifically ceftriaxone. For every 100 bed days, 6.7 DDD of antibiotics were consumed in which 103 antibiotics were administered via intravenous route and 42 oral routes. The deviation of prescribed daily dose (PDD) from the DDD was performed for prescribed antibiotics of varying doses. Significant percentage deviation was observed for azithromycin (-70%) and piperacillin+tazobactam (-4.79%). The negative sign of the deviation indicates that the mean PDDs were higher than their respective WHO DDD. Furthermore, 81.38% of consumed antibiotic was from watch category of WHO essential medicine list (EML). Interestingly, the decrease in neutrophils and increase in lymphocytes prove the therapeutic efficacy of antibiotics.

Conclusions: Watch antibiotics was the most prescribed and therapeutic efficacy was frequent with dual antibiotics therapy and in monotherapy of piperacillin-tazobactam.

Keywords: Antibiotics, Defined daily dose, ATC classification, AWaRe classification, Prescribed daily dose

INTRODUCTION

Research studies raise concerns of inappropriate antibiotic use within geriatric populations, thus leading to the development of antibiotic resistance. Countries with large population, such as India, have a significant portion of their population, falling within the age group of 60 to 85 years and above. This is attributed to the Indian's increasing life expectancy and is projected to reach 70

years by 2025.¹ A geriatric patient is a person with impaired overall function and with chronic illness(es), physical impairment and/or cognitive impairment.² Declined performance capacity, physiological functions and loss of homeostatic reserve with advanced age occurs to a different degree in each organ and in each patient.³ There is a direct correlation between the consumption of antibiotics and the development of their resistance. To control the irrational consumption of medicine World Health Organization (WHO) in alliance with International

network of rational use of drugs (INRUD) developed a set of core drug use indicators namely, prescribing indicators, patient care indicators and healthcare facility indicators.⁴

The prescribing indicators measures the performance of the healthcare providers in five main key areas related to proper use of medicines.⁵ To conduct a drug utilization evaluation and promote quality of drug use, WHO recommends ATC classification and antibiotics for systemic use (ATC code J01) which serves as the classification system in which drugs are grouped based on the organ of the body they act on, and their chemical, pharmacological and therapeutic properties. The DDD system is used as the unit of measurement for international standard of drug utilization analysis.⁶ WHO defines DDD as the assumed average maintenance dose per day for a drug used for its main indication in adults, and is expressed in various units, such as grams, milligrams or million units, which differs by the route of administration and dosage formulation.⁷ DDD/100 bed days is preferably used DDD indicators among the other types for inpatients in which a bed day is defined as any day a patient is confined to the bed and spends a night in the hospital. The DDD and PDD provides beneficial information for medications that are administered over an extended period to treat chronic disease as observed in elderly population. The DDD (fixed unit of measurement) should not be confused or used interchangeably with PDD (actual prescribed dose) which is defined by the WHO as the average dose prescribed according to a representative sample of prescription.⁸ Colistin doses should always be expressed as in IU of colistimethate sodium (that is 12,500 IU is equivalent to 1mg of colistimethate sodium or CMS).⁹

The AWaRe classification is an analytical tool used to support antibiotic monitoring and stewardship activities. The AWaRe classification of antibiotics was developed by WHO in 2017 and was revised in 2019, 2021, and 2023 respectively in which antibiotics are categorised into three different groups namely: Access, Watch, and Reserve. The Access group includes antibiotics that have a narrow spectrum of activity, cost effective, good safety profile with low resistance and are often recommended as first or second choice for treatment of common infections. The Watch group are costlier antibiotics with broad spectrum of activity and are recommended only as first choice treatment option for severe infections or for resistant causative pathogens. The reserve group antibiotics are the last choice therapy option used mainly for multidrug resistant infections.^{10,11}

The neutrophilia (increased neutrophils) is an acknowledge infection marker whilst physicians are less acquainted with lymphocytopenia (decreased lymphocytes) as an indicative parameter of infectious disease management. These parameters (neutrophils and lymphocyte counts) are simple, easily derived and thereby can be employed into daily clinical practice.¹² Hence the differential blood count (neutrophils and lymphocytes) of the geriatric patients of before and after antibiotics

treatment was used for efficacy assessment of the prescribed antibiotics. The significance of this study to healthcare professionals and the public healthcare was to limit and/or eliminate inappropriate antibiotic use, which will reduce microbial resistance due to prolonged antibiotic usage associated with chronic illness and discourage or stop unnecessary antibiotic prescriptions.

METHODS

A prospective observational study was conducted in the department of general medicine, intensive care unit, nephrology, neurology, and urology in Bangalore Baptist hospital, Bangalore India from June 2023 to November 2023 to assess the prescription usage of antibiotics in geriatric patients who met the inclusion criteria. Patient information was obtained from the medication charts, and the relevant laboratory values were meticulously reviewed and recorded.

Inclusion and exclusion criteria

Geriatric patients of both sexes who were registered and admitted in a tertiary care hospital, aged above 60 years and prescribed with at least one antibiotic with or without comorbidity disease were included in the study. Patients with ailments other than that resulting from bacterial infections, unconscious and comatose patients, outpatients and surgical geriatric patients undergoing antibiotic treatment were excluded from the study.

A total number of 70 cases of geriatric patients receiving antibiotic treatment were analysed in this study. Data on the prescribed antibiotic drugs, lab reports of neutrophils and lymphocyte counts before and after antibiotic administration were recorded. The prescribed antibiotic consumption was evaluated using the WHO DDD with the PDD and WHO core prescribing indicator. Antibiotics were categorised using ATC and AWaRe system of classification and correlated with essential medicine list policy. The neutrophils and lymphocyte count before and after therapy were used to measure the efficacy of the antibiotics administered. The collected data were statistically analysed (using Shapiro–Wilk’s and Levene’s tests for the normality and variance homogeneity of data). The one-sample t-test was determined for the difference in absolute deviation of PDD from the respective WHO DDD, using a hypothesized mean difference (test value) equal to zero with a significance level of 5% and associated p value for the deviation was derived.

Informed consent

Participants were provided with detailed information about the study and were required to give written consent.

Confidentiality

Data were anonymized and stored securely to protect the privacy of the participants.

RESULTS

The study consists of 70 geriatric patients with 64% males and predominance of the patients was aged between 71 to 80 years which had male gender majority receiving antibiotics. Socio-demographic variables were assessed. Smoking and alcoholism habitual lifestyle history was recorded with 67.14% as non-smokers and 70% as non-alcoholics. The associated comorbidities of the geriatric patients included in this study were also documented with 12.86% having diabetes mellitus-hypertension-others, diabetes mellitus-hypertension (11.43%) and 11.43% others (includes anaemia, arthritis, hypothyroidism, parkinsonism, acute coronary syndrome non-ST elevated myocardial infarction, and peripheral vascular disease) whereas 5.71% patients had no known comorbidity (Table 1). ICD-11 classification of disease was used to group the observed disease patterns, and 126 diseases was reported. The disease of respiratory system recorded 39.8% and the disease of genitourinary system was 31% and the least disease cases of 29.3% was found under certain infectious or parasite disease (Table 2).

The various characteristics of antibiotics prescribed for geriatric patients showed that 22.86% of patients were monotherapy, and two antibiotic agents were given to 55.71 % of patients. The remaining 21.43% of patients received 3 or more antibiotics. Selection of antibiotics revealed 30% as empirical therapy, 37.14% as definitive therapy and 32.86% as prophylactic therapy. Antibiotic sensitivity test was done for 61.43% and was unperformed for 38.57%. The antibiotic prescribed was examined using WHO prescribing core indicator for usage pattern. A total unit of 1764 antibiotics were prescribed in 70 prescriptions. The average number of antibiotics per prescription was 2.09 and 94.48% were prescribed with generic name, out of which 6.69% injections were administered. Out of the 145 antibiotic prescribed, 130 (89.66%) were from the national list of essential medicines (NLEM) 2022, India and 132 (91.03%) were in compliance with WHO-EML, 2023 (Table 3).

The overall antibiotics consumption was determined using the PDD, DDD, the PDD/WHO DDD ratio, ATC/DDD classification system and the DDD of the prescribed antibiotics was used to calculate the DDD per 100 bed days. The deduced result indicated that 2.58 DDD of azithromycin, 1.29 DDD of piperacillin+tazobactam and 1.14 DDD of ceftriaxone were consumed per 100 bed days during the period of this study. The ratio of PDD/WHO DDD was used as a measure to determine the adequacy of drug dosing, where the calculated ratio was greater than 1 (overdosing) with teicoplanin, azithromycin, clarithromycin, amoxicillin+clavulanate (orally), and levofloxacin, whereas less than 1 indicates underdosing and found in meropenem, ciprofloxacin, cefoperazone+sulbactam, colistin, ertapenem and amoxicillin+clavulanate intravenously (Table 4).

Table 1: Socio-demographic and comorbidities distribution of the study participants.

Parameters	Number of patients	Percentage (%)
Age group (years)		
61-70	27	38.57
71-80	33	47.14
81-90	8	11.43
>90	2	2.86
Mean±SD	72.97±8.09	
Gender		
Male	45	64
Female	25	36
Comorbidities		
DM	2	2.86
HTN	5	7.14
COPD	2	2.86
IHD	1	1.43
Others	8	11.43
DM-HTN	8	11.43
HTN-IHD	1	1.43
DM-others	6	8.57
HTN-others	4	5.71
IHD-others	1	1.43
DM-HTN-COPD	1	1.43
DM-HTN-IHD	5	7.14
DM-HTN-others	9	12.86
DM-IHD-others	2	2.86
HTN-COPD-others	1	1.43
HTN-IHD-others	2	2.86
DM-HTN-COPD-others	3	4.29
DM-HTN-IHD-others	4	5.71
DM-HTN-COPD-IHD-others	1	1.43
None	4	5.71
Smoking history		
Smoker	23	32.86
Non-smoker	47	67.14
Alcohol history		
Alcoholic	21	30
Non-alcoholic	49	70

Descriptive statistics was used to analyse the PDD and deviation of the mean PDD from the WHO DDD of the antibiotics containing different doses. Substantial relative deviation of the average PDD from WHO DDD was observed for colistin or colistimethate sodium (51.39%), ciprofloxacin (33.75%), meropenem (20.33%), azithromycin (-70%), and piperacillin+tazobactam (-4.79%) with a significance level less than 5%. The resultant negative sign indicates that the mean PDDs were greater than their corresponding DDDs from WHO (Table 5). A comparative route (intravenous versus oral) of administration in geriatric patients was utilized to assess the prescription of antibiotics in geriatric patients. The intravenous (IV) route of administration was mostly

preferred with ceftriaxone (31.07%) and piperacillin+tazobactam (26.21%) whilst 88.10% was seen with azithromycin as per oral (PO) route of administration (Table 6).

Table 2: Distribution pattern of disease based on ICD-11 classification of diseases (n=126).

ICD-11 classification of disease and code	N (%)
Certain infectious or parasite diseases	
1A00 - 1A09	22 (17.5)
1D01.0	1 (0.8)
1G40 - 1G41	14 (11.1)
Disease of the respiratory system	
CA00 - CA07	4 (3.2)
CA20 - CA27	20 (15.9)
CA40 - CA43	21 (16.7)
CB41	5 (4.0)
Disease of genitourinary system	
GB60 - GB61	18 (14.3)
GB70 - GB71	7 (5.6)
GC08	14 (11.1)

The WHO-EML AWaRe 2023 category was employed for the classification of the antibiotics consumed. The percentage of the prescribed units of antibiotics consumed by the enrolled elderly population in this study was 11.16% for access antibiotics, 81.38% for watch antibiotics, 4.93% for not recommended antibiotics and 2.49% for reserve antibiotics (Table 7). Cephalosporins were observed to be the highest consumed antibiotic class (58.57%), specifically ceftriaxone, and then macrolides (54.29%), mainly azithromycin. Polymyxin-E (colistin) and lincosamides (clindamycin) class of antibiotics were the least prescribed (Figure 1). The differential blood cell counts (neutrophils and lymphocytes), before and after treatment with antibiotics for each patient was used for efficacy assessment. There were no reported adverse drug events or drug interactions in the prescriptions during the study period. The therapy regimen with greater percentage reduction in neutrophils after treatment in elderly population was observed in combination of colistin-meropenem (26.5%), cefoperazone+sulbactam-piperacillin+tazobactam (24.5%), and piperacillin+tazobactam (11.67%) monotherapy.

Table 3: Characteristics of antibiotics prescribed in geriatric patients.

Antibiotic characteristics	N (%)
Number of antibiotics prescribed	
One antibiotic	16 (22.86)
Two antibiotics	39 (55.71)
Three or more antibiotics	15 (21.43)
Selection of antibiotics	
Empiric	21 (30)
Definitive	26 (37.14)
Prophylactic	23 (32.86)
Lab investigation	
Antibiotic sensitivity test	
Done	43 (61.43)
Not done	27 (38.57)
WHO/INRUD prescribing core indicator	
WHO core indicator	Result (optimal value)
Average number of antibiotics per prescription	2.09
Percentage of antibiotics prescribed in generic name	94.48 (100)
Percentage of antibiotic injection prescribed	6.69 (13.4-24.1)
Percentage of antibiotics from NLEM - 2022	89.66 (100)
Percentage of antibiotics from WHO-EML - 2023	91.03 (100)

The antibiotics with minimal decrease of neutrophils was seen in meropenem (2%) and no change in cefoperazone+sulbactam, and ciprofloxacin+tinidazole. Nonconformity was detected in azithromycin (25% decrease) in 2 patients, cefuroxime (4% increase) and in combination therapy of ceftriaxone-metronidazole-azithromycin-piperacillin+tazobactam (1% increase) in 1 patient (Figure 2).

The prescribed antibiotics with significant increase in lymphocytes percentage was found in combination therapies like ceftriaxone-azithromycin-piperacillin+tazobactam-meropenem (21%), azithromycin-meropenem (19%), and as a single therapy in piperacillin+tazobactam (10.66%). Outliers was found in azithromycin (22% increase) in 2 patients and azithromycin-piperacillin+tazobactam-clarithromycin-meropenem (31% increase) in only 1 patient (Figure 3).

Table 4: Antibiotics consumption based on ATC/DDD classification in geriatric patients.

Class (N)	Drug	ATC code	WHO DDD (mg)	PDDs (mg)	PDD/WHODD ratio	DDDs (mg)	DDDs/100 bed days
Penicillin (27)	Piperacillin and tazobactam (IV)	J01CR05	14000	14670	1	163.42	1.29
Glycopeptide (2)	Teicoplanin (IV)	J01XA02	400	600	>1	11	0.09
Macrolide (37)	Azithromycin (PO)	J01FA10	300	510	>1	327.12	2.58
Carbapenem (14)	Meropenem (IV)	J01DH02	3000	2390	<1	73.83	0.58
Cephalosporin (32)	Ceftriaxone (IV)	J01DD04	2000	2000	1	144	1.14

Continued.

Class (N)	Drug	ATC code	WHO DDD (mg)	PDDs (mg)	PDD/WHODD ratio	DDDs (mg)	DDDs/100 bed days
Fluoroquinolone (3)	Ciprofloxacin (IV)	J01MA02	800	530	<1	7	0.06
Imidazole (11)	Metronidazole (IV)	J01XD01	1500	1500	1	47	0.37
Fluoroquinolone (2)	Ciprofloxacin and tinidazole (PO)	J01RA11	2200	2200	1	6	0.05
Cephalosporin (8)	Cefoperazone and sulbactam (IV)	J01DD62	4000	3750	<1	19.75	0.16
Polymyxin (3)	Colistin (IV)	J01XB01	720	350	<1	8.44	0.07
Macrolide (1)	Clarithromycin (PO)	J01FA09	500	1000	>1	12	0.09
Penicillin (1)	Amoxicillin and clavulanate (PO)	J01CR02	1500	1875	>1	8	0.06
Lincosamide (1)	Clindamycin (IV)	J01FF01	1800	1800	1	5	0.04
Carbapenem (1)	Ertapenem (IV)	J01DH03	1000	500	<1	4	0.03
Penicillin (1)	Amoxicillin and clavulanate (IV)	J01CR02	3000	2400	<1	2.67	0.02
Cephalosporin (1)	Cefuroxime (PO)	J01DC02	500	500	1	6	0.05
Fluoroquinolone (1)	Levofloxacin (IV)	J01MA12	500	1000	>1	8	0.06

Table 5: Descriptive statistics of the PDD and deviation of average PDD from WHO DDD the prescribed antibiotics with varying doses.

Antibiotics	Number of prescriptions	WHO DDD (g)	Mean PDD (g)	Absolute deviation of mean PDD from WHO DDD	Relative deviation of mean PDD from WHO DDD (%)	SD of relative deviation	P value deviation (α : 0.05)
Piperacillin+tazobactam (4.5 g and 2.25 g)	27	14	14.67	-0.67	-4.79	32.56	0.001
Azithromycin (0.25 g and 0.5 g)	37	0.3	0.51	-0.21	-70	30.97	<0.001
Meropenem (0.5 g and 1 g)	14	3	2.39	0.61	20.33	18.70	<0.001
Cefoperazone+sulbactam (1.5 g and 3 g)	8	4	3.75	0.25	6.25	34.72	<0.001
Ciprofloxacin (0.2 g and 0.4 g)	3	0.8	0.53	0.27	33.75	28.87	<0.001
Colistin (0.08 g and 0.16 g) CMS	3	0.72	0.35	0.37	51.39	16.98	<0.001

Table 6: Intravenous versus oral route of administration of the prescribed antibacterial agents.

Intravenous (IV) antibacterial agents		Oral (PO) antibacterial agents	
Drug	Number of patients (%)	Drug	Number of patients (%)
Piperacillin+tazobactam	27 (26.21)	Azithromycin	37 (88.10)
Teicoplanin	2 (1.94)	Ciprofloxacin+tinidazole	2 (4.76)
Meropenem	14 (13.59)	Amoxicillin+clavulanate	1 (2.38)
Ceftriaxone	32 (31.07)	Cefuroxime	1 (2.38)
Ciprofloxacin	3 (2.91)	Clarithromycin	1 (2.38)
Metronidazole	11 (10.68)		
Cefoperazone+sulbactam	7 (6.80)		
Colistin	3 (2.91)		
Clindamycin	1 (0.97)		
Ertapenem	1 (0.97)		
Amoxicillin+clavulanate	1 (0.97)		
Levofloxacin	1 (0.97)		
Total	103 (100)		42 (100)

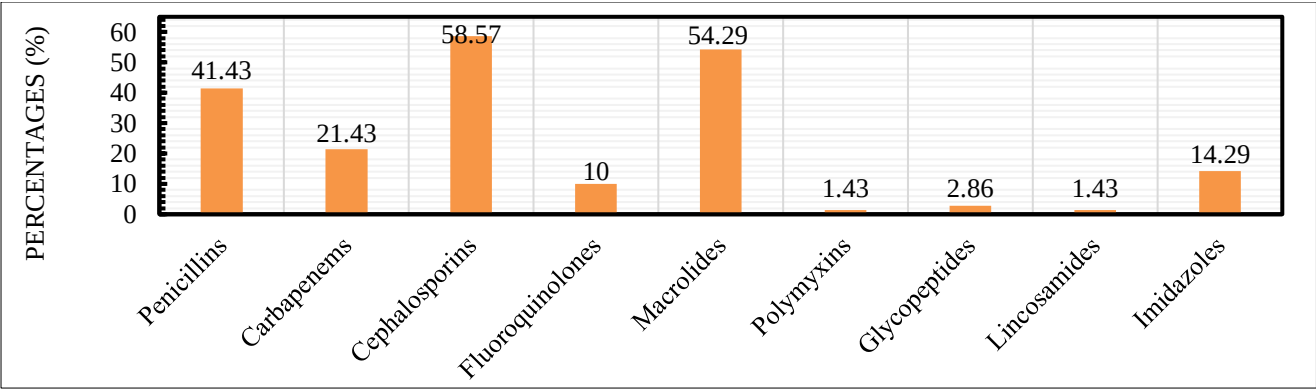


Figure 1: Prescribed antibiotic class distribution.

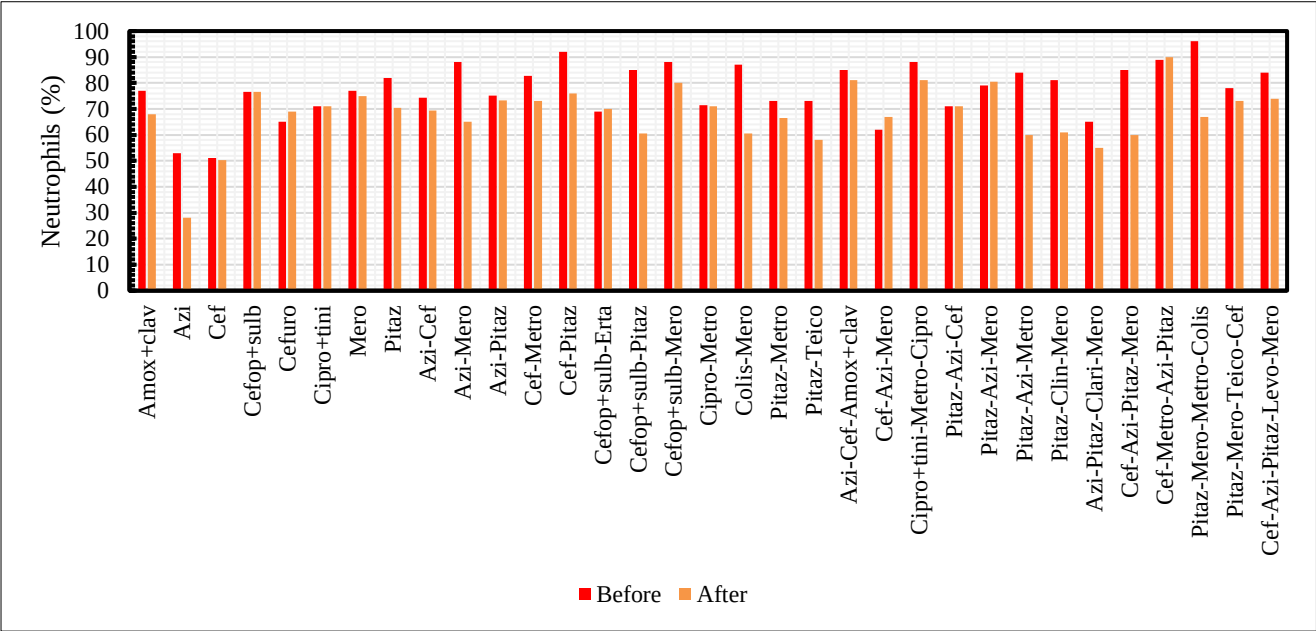


Figure 2: Neutrophils comparison of antibiotic therapy in the geriatric patients.

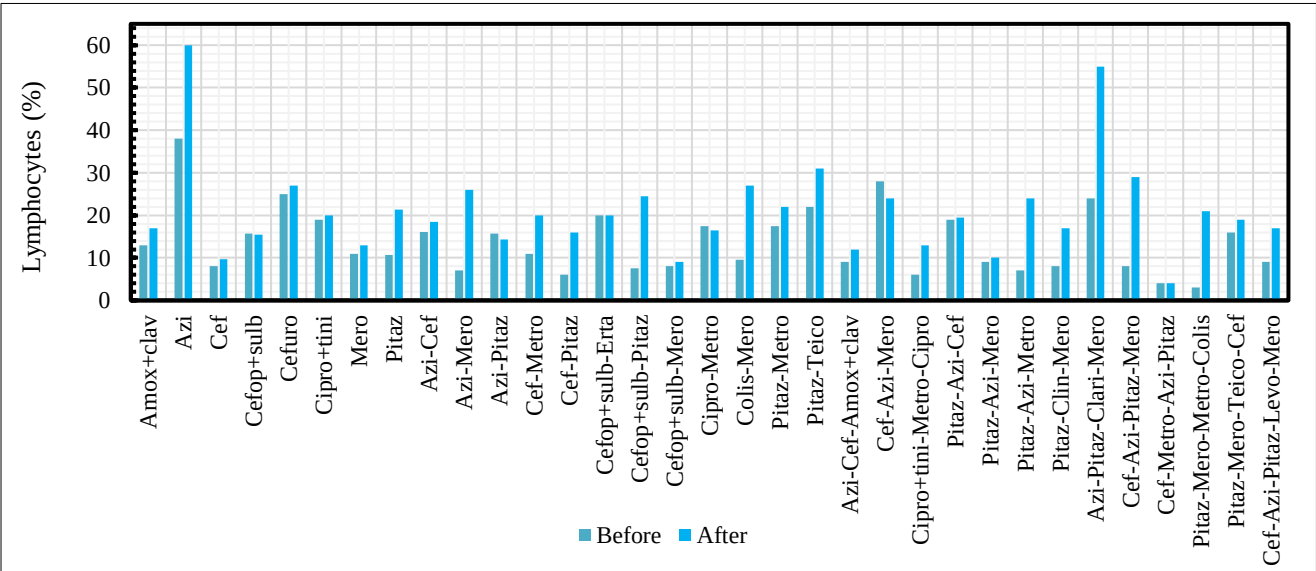


Figure 3: Lymphocytes comparison of antibiotic therapy in the geriatric patients.

Table 7: Classification of antibiotics according to WHO-EML AWaRe 2023 category.

WHO-EML AWaRe category	Antibiotic drug (listed on EML)	Prescribed units (%)	Cumulative frequency (%)
Access antibiotics	Metronidazole (yes)	150 (8.50)	8.50
	Amoxicillin and clavulanate (yes) oral	24 (1.36)	9.86
	Amoxicillin and clavulanate (yes) parenteral	8 (0.45)	10.31
	Clindamycin (yes)	15 (0.85)	11.16
	Total	197 (11.16)	
Watch antibiotics	Piperacillin and tazobactam (yes)	654 (37.07)	48.23
	Teicoplanin (no)	11 (0.62)	48.85
	Azithromycin (yes)	201 (11.39)	60.24
	Meropenem (yes)	232 (13.15)	73.39
	Ceftriaxone (yes)	286 (16.21)	89.60
	Ciprofloxacin (yes)	18 (1.02)	90.62
	Clarithromycin (yes)	12 (0.68)	91.30
	Ertapenem (no)	8 (0.45)	91.75
	Cefuroxime (yes)	6 (0.34)	92.09
	Levofloxacin (no)	8 (0.45)	92.54
	Total	1436 (81.38)	
Reserve antibiotics	Colistin (yes)	44 (2.49)	95.03
	Total	44 (2.49)	
Not recommended antibiotics	Ciprofloxacin and tinidazole (no)	12 (0.68)	95.71
	Cefoperazone and sulbactam (no)	75 (4.25)	99.96
	Total	87 (4.93)	
	Grand total	1764 (100)	

DISCUSSION

Healthcare professionals need to carefully assess the prescribing pattern for antibiotics based on disease and patient characteristics. Antibiotics are mostly prescribed to patients in various departments of ICU, urology, nephrology, neurology, and general medicine. These antibiotics are used for the treatment (either empirical, definitive or prophylactically) of various infections. Older adults tend to consume more medications compared to younger individuals due to the higher prevalence of chronic health conditions and comorbidities.

A total of 70 patients were included in the study, with 45 male patients having the predominance number and 25 female patients which is comparable to the study conducted by Bist et al as opposed to the research study by Jhaveri et al, which had more female participants.^{13,14} Research literature suggests that there is no correlation between the occurrence of infection and the gender of the patients.¹⁵ The majority of the participants were seen in the age group of 71-80 years having 33 patients with a percentage of 47.14% compared to other age groups which are 61-70, 81-90, and above 90 years giving a percentage of 38.57%, 11.43%, and 2.86% (least) respectively. Similar findings are found in the reference in a study conducted by Bartosch et al, in which faecal bacteria were studied in healthy elderly volunteers receiving antibiotic treatment for food poisoning (gastroenteritis).¹⁶

Of the 70 patients enrolled in the study, 32.86% were smokers and 30% were alcoholics which makes them prone to infection and delayed positive therapeutic outcomes while undergoing antibiotic treatment due to antibiotic drug interactions. Several factors are responsible for the increased susceptibility to infection, including excessive alcohol consumption, tobacco use, and cigarette smoking.¹⁷ These factors diminish an individual's local immunity to fight infections or adequately respond to the given therapy. Smoking history has historically been a significant risk factor for chronic obstructive pulmonary disease (COPD). The findings of this study further support this association, as smoking was prevalent among males in study population.¹⁸ Most patients (50) were diagnosed with respiratory tract infection including lower respiratory tract infection (LRTI), COPD and were grouped under the disease of the respiratory system according to the ICD-11 disease classification succeeded by 39 patients in disease of genitourinary system including urinary tract infection (UTI), kidney infections (KI) such as acute kidney injury (AKI) and chronic kidney disease (CKD). A similar result was found, in a study conducted by Prasad et al on prescribing analysis and utilization of antibiotics in geriatric in-patients, admitted to Shimoga Institute of Medical Science Tertiary Care Hospital, Shimoga, Karnataka, India shows respiratory disease was the main cause of admission to the hospital followed by cardiovascular diseases.¹⁹ Relatively, 12.86% had diabetes mellitus-hypertension-others, diabetes mellitus-hypertension (11.43%) and 11.43% others (includes anaemia, arthritis, hypothyroidism, parkinsonism, acute

coronary syndrome non-ST elevated myocardial infarct, and peripheral vascular disease) comorbidities whereas 5.71% of the patients had no known comorbidity. Similar findings are found in a study conducted by Bist et al in a research study with various comorbid conditions such as, hypertension, and diabetes mellitus and the disease patterns observed in the patients with respiratory tract infections.¹³ Bacterial infection can worsen pre-existing clinical conditions like diabetes as infections can trigger the release of stress hormones like cortisol which can raise blood sugar, worsen insulin resistance and impair functioning of white blood cells (weakened immune system) and high blood pressure can damage blood vessels, making the patients more susceptible to infections.

As a result of the calculated average value, most of the geriatric population was treated with two antibiotics (55.71%), followed by single antibiotic agent (22.86%) and three or more antibiotics (21.43%). Similar results were obtained in the study by Chandrasekhar et al where single monotherapy, dual therapy and three or more antibacterial agents were used (with ascending percentage increase respectively).²⁰ This study showed that 37.14% patients received antibiotics as definitive therapy, 32.86% as prophylactic therapy and 30% empirically, as the antibiotic sensitivity test was done in 61.43% patients and not performed (38.57%) for the bacterial infection which was contrary to the study directed by Senthilkumar et al where the relevant investigations were not done in the majority of the patients, on the study of antibiotic use among geriatric patients in tertiary care hospital of South India.²¹ Culture and antibiotic sensitivity test play an essential role in selection of the appropriate antibiotic which promotes definitive therapy for bacterial infection and dual therapy was mostly seen to cover broad spectrum of activity as well as aerobic and anaerobic bacterial which can often require two antibiotics. This study revealed that the average number of antibiotics per prescription was 2.09 from which the antibiotic prescribed in generic name was 94.48% (ideal 100%) and administered through the intravenous route was 6.69% (optimal range: 13.4% - 24.1%). The mean number of antibiotics per prescription should be as low as possible and yet sufficient to ensure therapeutic efficacy which will reduce the possibilities of drug related complications such as drug-drug interactions and polypharmacy. Regarding the essential medicine prescription, the percentage of antibiotics prescribed from NLEM, 2022 was 89.66% and 91.03% from the WHO-EML, 2023 which was below the optimal value (100%) of WHO/INRUD prescribing core indicator but more than that of Tushar et al study carried out in Maharashtra, India.^{22,23} The disparity between the percentage of antibiotic prescribed from the NLEM and EML is ascribed to the fact that positive therapy response is mainly evidence-based practice to the individuals in a particular locality or region.

The prescription usage of antibiotics was evaluated using the PDD, DDD, PDD/WHO DDD ratio and DDD/100 bed days. The DDD per 100 bed days showed that 2.58 DDD

of azithromycin, 1.29 DDD of piperacillin+tazobactam and 1.14 DDD of ceftriaxone were consumed predominantly. The pharmacokinetics and tolerability profiles of azithromycin makes it particularly beneficial for treating infections while piperacillin+tazobactam and ceftriaxone has a very good wide spectrum of activity coverage. The ratio of PDD/WHO DDD affirms overdosing (>1) was present in teicoplanin, azithromycin, clarithromycin, levofloxacin, and amoxicillin+clavulanate (orally), and underdosing (<1) in meropenem, ciprofloxacin, cefoperazone+sulbactam, colistin, ertapenem and amoxicillin+clavulanate intravenously. Statistically relative deviations (varied doses) of the average PDD from WHO DDD was observed for colistin or colistimethate sodium (51.39%), ciprofloxacin (33.75%), meropenem (20.33%), azithromycin (-70%), and piperacillin+tazobactam (-4.79%) with a significance level of 0.05. The negative sign indicates that the mean PDDs were greater than their associated WHO DDDs. The PDD/WHO DDD ratio was >1 or <1 and resultant negative sign values for some prescribed antibiotics was because of the doses and frequencies as well as comorbid conditions and dosage adjustments needed for the individual patient's conditions to ensure positive treatment outcome.

Different route (intravenous versus oral) of administration was utilised, the most frequent route was the intravenous route with ceftriaxone (31.07%), and piperacillin+tazobactam (26.21%), and per oral route with azithromycin (88.10%). Comparatively, the same result was deduced from the research study by Ramanath Katta et al where many of the patients received antibiotics parenterally, followed by both parenteral and oral routes, and as oral route alone.²⁴ The intravenous route of administration was mostly preferred due to faster onset of action and it bypasses the first pass hepatic metabolism as the active drugs or metabolites are directly injected into the bloodstream and thus ensures bioavailability and bioequivalence. Antimicrobial resistance is a menace to the global public health and development which led to the development of the new classification system of antibiotics by the WHO as part of the 2017 model list of essential medicines.¹⁰ The WHO-EML AWaRe classification established that 11.16% of antibiotics was prescribed from the access group, and 81.38% in the watch group. The most prescribed antibiotics were piperacillin+tazobactam (37.07%) and ceftriaxone (16.21%) which belongs in the watch group of antibiotics. However, colistin (2.49%) was in the reserve group and ciprofloxacin+tinidazole (0.68%) and 4.25% of cefoperazone+sulbactam from the not recommended antibiotics group and was not listed in the WHO-EML. Watch antibiotics were mostly prescribed even though that the WHO recommends against it perhaps due to limited availability of alternative antibiotics, lack of awareness, or lack of accurate and timely diagnostic tools of infection which can lead to the use of broad-spectrum antibiotics including those from watch group, to cover a wide range of potential pathogens.

Among the various antibiotic classes ordered, cephalosporins (58.57%) emerged as the most frequently prescribed with ceftriaxone in 32 (31.07%) patients representing the predominant of this class, in commensuration with the study performed by Senthilkumar et al which had cephalosporin as the most consumed antibiotic, specifically cefotaxime and ceftriaxone in the admitted geriatric patients and also in the study conducted by Ramanath et al.^{21,25} Ceftriaxone, a third-generation cephalosporin antibiotic, demonstrates broad-spectrum activity.²⁶ Ceftriaxone therapy dosage adjustments are probably not necessary for elderly subjects. However, in elderly patients who are enfeebled, malnourished, and have significant renal impairment, a reduction in the dosage of ceftriaxone may be required.²⁷ Azithromycin belonging to macrolides class of antibiotics, was the second most used antibiotic in 37 patients of the study population. The bio-disposition and pharmacodynamics of azithromycin make it advantageous in treating respiratory tract infections, sepsis, and enterocolitis.²⁸

In bacterial infections, neutrophils of the white blood cells are increased above the normal range (55-70%), and the lymphocytes are decreased below the normal range (20-40%).^{29,30} Neutrophilia and lymphocytopenia are well recognized as infection markers and have shown their potential in predicting bacteraemia or the severity of several infectious diseases.³¹ A remarkable decrease in neutrophilic percentage was found in colistin-meropenem (26.5%), cefoperazone+sulbactam-piperacillin+tazobactam (24.5%) and azithromycin-meropenem (23%) and there was prominent increase in the lymphocytopenia percentage with antibiotic combination of ceftriaxone-azithromycin-piperacillin + tazobactam-meropenem (21%), azithromycin-meropenem (19%), and piperacillin+tazobactam-meropenem-metronidazole-colistin (18%). Non-homogeneity in results was obtained in the neutrophils (like azithromycin with 25% decrease) and lymphocytes (such as azithromycin-piperacillin+tazobactam-clarithromycin-meropenem with 31% increase and 22% increase in single therapy with azithromycin) counts after antibiotic therapy which was attributed to confounding variables such as smoking, alcoholics, and patients who were discharged against medical advice (DAMA) and comparatively very less number of patients were in these category and thus considered statistically insignificant.

Limitations

This study encountered various limitations such being conducted in single centre rather than multiple centres with only prescribed antibiotic agents on geriatric patients constraining the applicability of the obtained result across different clinical settings. The study's limited duration and absence of funding confined the volume of data gathered and the research scope. These aforementioned factors collectively influenced the extent and relevance of the study's findings.

CONCLUSION

In this study 70 antibiotic prescriptions were analysed, which had vast majority of males and preponderance of the patients was aged between 71 to 80 years. Socioeconomic data revealed that greater participants were non-smokers and non-alcoholics with comorbidities of diabetes mellitus-hypertension-others being more frequent. Pattern of diseases distribution using ICD-11 classification established that the disease of respiratory system and the disease of genitourinary system was more prominent. Dual antibiotic therapy was mostly prescribed mainly after the antibiotic sensitivity tests was performed to ensure definitive selection of antibiotics. Out of the 145 antibiotics prescribed, the average number of antibiotics per prescription was 2.09, which had 6.7 DDD of antibiotics consumed, of which azithromycin was salient during the study period. Descriptive statistical analysis of relative deviation of the mean PDD from the WHO DDD of the varied doses prescribed elicits that prescribed daily dose of azithromycin and piperacillin+tazobactam was greater than the WHO defined daily dose whereas colistin and ciprofloxacin had a notable relative deviation. The most prevalent route of administration was intravenous, mainly ceftriaxone belonging to cephalosporins the most consumed class of antibiotics, followed by macrolides, and penicillins which all belongs to the watch antibiotics group. The WHO recommends that more than 60% of overall antibiotics should be from the access group as the watch and reserve antibiotic group has a higher potential for development of antimicrobial resistance.

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