

ORIGINAL RESEARCH

Antibiotic appropriateness at outpatient settings in Ethiopia: the need for an antibiotic stewardship programme

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Abstract

Background: Antibiotics are drugs of natural or synthetic origin used to treat various infections. The practice of excessive and inappropriate antibiotics use is the main global cause of bacterial resistance, which is one of the most serious global public health threats. It is estimated that about 50% of global antibiotic prescriptions are inappropriate. This study assesses the prevalence and pattern of inappropriate prescriptions of antibiotics amongst ambulatory care visits in Ethiopia.

Methods: A facility-based, cross-sectional study with a quantitative approach was conducted amongst randomly selected prescriptions issued for outpatients from May to June 2022 at Debre Markos Specialized Comprehensive Hospital, Northwest Ethiopia. Descriptive statistics, such as frequencies and percentages, were computed. For group comparisons, χ^2 and independent sample *t*-tests were computed. The statistical significance of the association was considered at $p < 0.05$.

Results: A total of 2640 antibiotics were prescribed for patients in the outpatient setting with various bacterial infections via 911 prescriptions, of which 49.5% were non-compliant with the national treatment guideline. Guideline non-compliant prescriptions increased

remarkably amongst patients in the outpatient setting diagnosed with community-acquired pneumonia (38.8% versus 30.1%; $p = 0.006$) and peptic ulcer disease (14.9% versus 9%; $p = 0.006$). Moreover, inappropriate prescription was significantly higher amongst patients taking amoxicillin/clavulanic acid (33.2% versus 48.2%; $p < 0.001$) and cephalexin (17.8% versus 24.3%; $p = 0.016$).

Conclusion: Large proportions of antibiotic prescriptions for outpatients were non-compliant with the national treatment guideline, suggesting that prescribers need to give special attention to outpatients whilst ordering antibiotics such as amoxicillin/clavulanic acid and cephalexin. Antibiotic stewardship efforts to optimize outpatient antibiotic prescriptions and reduce the use of potentially inappropriate antibiotics are needed in Ethiopia.

Keywords: ambulatory care, antibiotic prescriptions, antibiotics, Ethiopia.

Citation

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Introduction

Bacterial infections are one of the leading causes of morbidity and mortality worldwide.¹ Antibiotics represent the most widely prescribed therapeutic agents used to treat bacterial infections.^{2,3} In the last two decades, antibiotic consumption has been rising quickly, increasing

by 65%, mainly in low-income and middle-income countries.⁴⁻⁶ Although ~50% of hospitalized patients receive at least one antibiotic during their hospital stay, up to 90% of antimicrobial use takes place in outpatient settings.^{7,8}

Appropriate use of medications entails prescribing the appropriate medication to the right person at the right time and in the right dosage. The appropriate use of

antibiotics is critical to reducing the burden of antimicrobial resistance and establishing a cost-effective healthcare system.⁹ However, it is estimated that ~50% of antibiotic prescriptions globally are inappropriate, resulting in increased side-effects, high healthcare costs and the promotion of antibiotic resistance.^{10–13} Inappropriate antibiotic prescribing is detrimental at the societal level because it fosters the spread of antimicrobial resistance and harmful at an individual level because they are associated with adverse drug events, including allergic reactions (e.g. skin rashes or anaphylaxis) and microbiome disruption-related conditions (e.g. infections caused by *Clostridium difficile*).¹⁴ About 6.5% of morbidity, hospital admissions and mortality are related to improper antibiotic prescribing.^{15,16}

A common way to measure the appropriateness of antibiotic use is by evaluating whether they are prescribed in accordance with local guidelines and, if these are unavailable, to national or international guidelines.¹⁷ The implementation of appropriate prescription practices is crucial towards mitigating inappropriate and excessive utilization of antibiotics, thus mitigating the rapid growth of bacterial resistance to antibiotics.¹⁵ Understanding the extent and pattern of antibiotic use is essential for defining regional intervention programmes to promote rational use of antibiotics and subsequently curb the spread of antibiotic resistance. There is little evidence about the patterns and appropriateness of antibiotic use in outpatient departments in developing nations like Ethiopia, in which there are indications of inappropriate use of antibiotics in the country. Therefore, this study was conducted to explore how antibiotics are prescribed to adult patients attending the outpatient department at Debre Markos Specialized Comprehensive Hospital (DMSCH) – a state-owned tertiary care level hospital located in northwest Ethiopia. The hospital serves approximately five million people in the surrounding area through seven pharmacy units, which include inpatient, chronic care, outpatient, antiretroviral, emergency, gynaecology and ophthalmology pharmacies. Amongst these units, the outpatient pharmacy department (OPD) provides services for ambulatory patients attending the hospital as well as to outpatients with referral papers from all over the region.

Methods

Study design, period and area

A facility-based, cross-sectional study with a quantitative approach was employed amongst randomly selected prescriptions issued for outpatients from 1 May to 1 June 2022 at DMSCH, Northwest Ethiopia. The hospital is located 300 km northwest of Addis Ababa, the capital city of Ethiopia. DMSCH is expected to provide healthcare

services to more than 3.5 million people in its catchment area.

Study population and inclusion criteria

All prescriptions issued for outpatients at DMSCH were the data source, whilst the study object was prescriptions issued for adult outpatients (18 years and older) for the management of bacterial infections during the time of data collection at DMSCH. Prescriptions that contained multiple or unspecified diagnoses, prescriptions with incomplete information and illegible prescriptions were excluded from the study.

Study variables

The dependent variable was inappropriate antibiotic prescriptions. Whereas sociodemographic variables, including age and sex, type of bacterial infection, and antibiotic-related characteristics, such as type, frequency and dose of the antibiotics prescribed, were the independent variables.

Operational definition

Inappropriate antibiotic prescription is defined as a prescription that is non-compliant by considering dose, duration, route, frequency and indication with pharmacotherapy recommendations of clinical guidelines and existing literature.¹⁸

Data collection tools and procedure

After examining the current literature, the authors developed a structured questionnaire that was utilized for collecting data. The questionnaire was divided into three major sections, including (1) the baseline characteristics of outpatients with antibiotic prescriptions and the types of bacterial diagnosis for which antibiotics were prescribed; (2) the list of antibiotics and their dosage and duration of therapy; and (3) the types of inappropriate antibiotic prescriptions. After assessing the eligibility criteria, prescriptions containing antibiotics for outpatients aged 18 or older who attended the hospital from 1 May to 1 June 2022 were included in the study. The patient's age, sex, diagnosis, type and dosage of antibiotics, duration of therapy and route of administration were recorded from the prescriptions. Finally, the evaluation of antibiotic prescription appropriateness was determined using the recommendations of the 2021 Ethiopian national standard treatment guideline as there is no local treatment guideline in the study setting.¹⁹ Each antibiotic in the prescriptions selected for a specific diagnosis was checked for both the appropriateness of drug selection and the appropriateness of dosage and duration of therapy; the first group contains those antibiotics that were selected inappropriately for the diagnosis mentioned on the prescriptions, whilst the second group contains

those antibiotics that were selected appropriately, but the duration/dose of the antibiotics was inappropriate for the respective diagnosis the antibiotics prescribed for. A multidisciplinary team consisting of one senior Internist, one General practitioner and one Pharmacist performed the evaluation by comparing it to the 2021 Ethiopian standard treatment guideline.²⁰ Each prescription of medication was evaluated for appropriateness in dose, frequency, duration and indication for each specific patient based on the underlying diagnosis. Antibiotic regimen appropriateness was independently reviewed by each team member, and disagreement was always solved in short discussions between the specialists.

Data processing and analysis

The collected data were checked for completeness, accuracy and clarity before analysis. The data were coded, entered into Epi-data 4.6, and transferred to SPSS version 26 for statistical analysis. Descriptive statistics, including mean and standard deviation for continuous variables and frequency and percentage for categorical variables, were used to summarize the sociodemographic and relevant clinical characteristics of the study participants and the prescribing pattern of antibiotics. For group comparisons, χ^2 and independent sample *t*-tests were computed to assess the correlation between inappropriate antibiotic prescriptions with sociodemographic or relevant clinical characteristics of the study participants. The statistical significance of the association was considered at a *p* value of <0.05.

Informed consent statement

Patient consent was waived due to the use of anonymized routine data.

Ethical approval

This study was approved by Ethical Review Committee of Debre Markos University, College of Health Sciences. The information obtained from the study was not disclosed to any third party, and code numbers were used to identify prescriptions.

Results

Baseline characteristics and type of diagnosis amongst outpatient department visitors

There were a total of 2217 prescriptions provided for 1879 OPD patients during the 1-month study period, of which 1226 (55.3%) contained at least one oral antibiotic. Of these, only 911 prescriptions for 804 patients met the inclusion criteria and were therefore subject to review.

The reasons the remaining prescriptions (approximately 25%) were omitted following the exclusion criteria are described in Figure 1. The mean age of participants was 38±13.85 years whilst 48% of the study participants were women. Respiratory tract infections (30.6%), gastrointestinal tract infections (28.8%) and urinary tract infections (27.6%) were the top three diagnoses amongst outpatients that were treated with antibiotic prescriptions (Table 1).

Patterns of antibiotic prescriptions amongst outpatients with bacterial infection

A total of 2640 antibiotics were prescribed for outpatients with various bacterial infections via 911 prescriptions. Penicillins were the most commonly prescribed class of antibiotics, accounting for 41.46% of all prescriptions, followed by fluoroquinolones (15.83%) and tetracyclines (10.45%). From the individual drugs, amoxicillin was the most frequently prescribed antibiotic (19.73%), followed by ciprofloxacin (15.83%) and amoxicillin/clavulanic acid (13.86%) (Table 2).

Appropriateness of antibiotic prescriptions amongst outpatients with bacterial infection

From the total of 2640 antibiotics prescribed, 1308 (49.54%) were non-compliant with the national treatment guideline in 46% of patients. Amoxicillin (19.2%) and ciprofloxacin (15.9%) made up the largest proportion of guideline non-compliant prescriptions (Table 3).

Regarding the types of inappropriate antibiotic prescriptions there were two sub-divisions: the first containing those antibiotics that were selected inappropriately for the diagnosis mentioned on the prescriptions and the second containing those antibiotics that were selected appropriately but the duration/dose of

Figure 1. CONSORT diagram showing prescription eligibility assessment steps amongst outpatients attending Debre Markos Specialized Comprehensive Hospital.

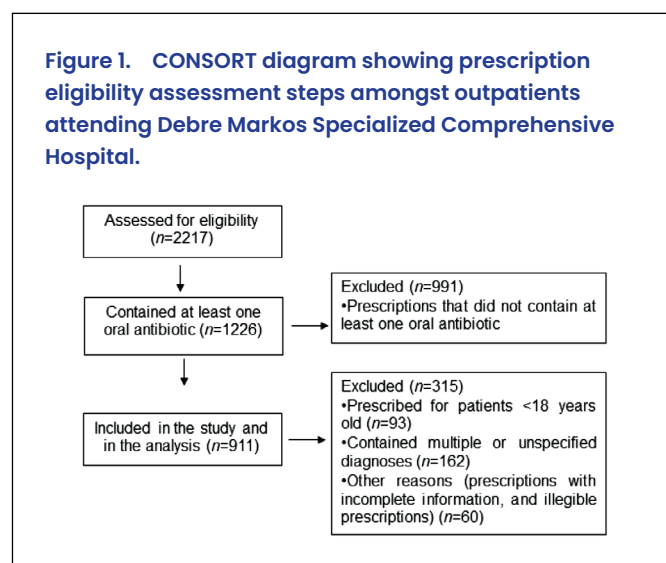


Table 1. Patient demographics and type of diagnosis amongst patients with bacterial infections attending outpatient department of Debre Markos Specialized Comprehensive Hospital.

Variable		Frequency (n)	Percentage (%)
Sex	Male	474	52.0
	Female	437	48.0
Age (mean ± standard deviation)		38±13.85	
Diagnosis	Respiratory tract infection	Community-acquired pneumonia	311 30.6
	Urogenital tract infections	Uncomplicated urinary tract infection	238 23.4
Recurrent urinary tract infection		23 2.3	
Complicated urinary tract infection		18 1.9	
Gastrointestinal tract infections	Typhoid fever	102 10.1	
	Amoebiasis	51 5.0	
	Giardiasis	33 3.2	
	Peptic ulcer disease ^a	107 10.5	
Skin and soft tissue infections	Osteomyelitis	61 6.0	
	Cellulitis	17 1.6	
Sexually transmitted diseases	Vaginal discharge	15 1.3	
Others ^b		41 4.1	

^aPeptic ulcer disease caused by *Helicobacter pylori*.

^bBronchitis, lung abscess, oral abscess, otitis media, rheumatic fever.

Table 2. Patterns of antibiotic prescriptions amongst patients with bacterial infections attending outpatient department of Debre Markos Specialized Comprehensive Hospital.

Class of antibiotics	Specific antibiotics	Frequency (n)	Percentage (%)
Cephalosporin	Cephalexin	190	7.19
Fluoroquinolone	Ciprofloxacin	418	15.83
Imidazole derivative	Metronidazole	234	8.86
	Tinidazole	26	1.04
Macrolide	Azithromycin	179	6.78
	Clarithromycin	92	3.48
Penicillin	Amoxicillin	521	19.73
	Amoxicillin/clavulanic acid	366	13.86
	Cloxacillin	208	7.87
Sulfonamide	Sulfamethoxazole/trimethoprim	87	3.29
Tetracycline	Doxycycline	276	10.45
Others ^a		43	1.62

^aBenzyl penicillin, ceftriaxone, nitrofurantoin, norfloxacin, tetracycline.

Table 3. Frequency of inappropriate antibiotic prescriptions amongst patients with bacterial infections attending outpatient department of Debre Markos Specialized Comprehensive Hospital.

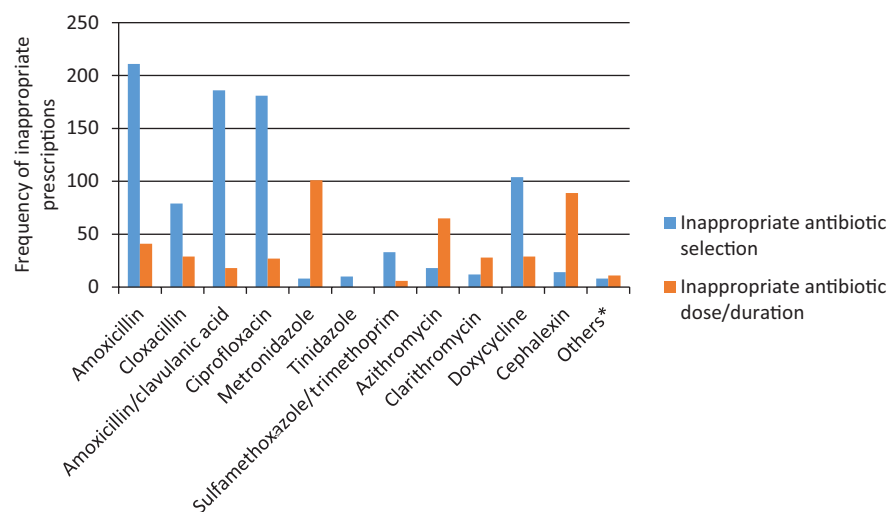
Class of prescribed antibiotics	Name of prescribed antibiotics	Frequency of non-compliance	Percentage (%)
Penicillin	Amoxicillin	252	19.2
	Amoxicillin/clavulanic acid	204	15.6
	Cloxacillin	108	8.3
Fluoroquinolones	Ciprofloxacin	208	15.9
Imidazole derivative	Metronidazole	109	8.4
	Tinidazole	10	0.8
Sulfonamide	Sulfamethoxazole/trimethoprim	39	2.9
Macrolides	Azithromycin	83	6.3
	Clarithromycin	40	3.0
Tetracycline	Doxycycline	133	10.2
Cephalosporin	Cephalexin	103	7.9
Others ^a		19	1.5

^aNorfloxacin, nitrofurantoin, ceftriaxone.

the antibiotics was inappropriate for their respective diagnosis. Inappropriate selection of antibiotics was observed in 397 (43.6%) of the prescriptions with 776 of the antibiotics prescribed, in which amoxicillin was the most inappropriately selected medication whilst metronidazole was the most commonly prescribed medication with inappropriate duration/dose followed by cephalexin (Figure 2).

Distribution of inappropriate antibiotic prescriptions for various bacterial infections

There was no significant difference between patients in the group with compliance to the guidelines and that without compliance regarding age (39.10 ± 14.004 versus 38.36 ± 13.702 years, respectively; $p=0.605$) or sex

Figure 2. Types of inappropriate antibiotic prescriptions amongst patients with bacterial infections attending outpatient department of Debre Markos Specialized Comprehensive Hospital.

*Norfloxacin, nitrofurantoin, ceftriaxone.

(52.9% versus 51.1% men, respectively; $p=0.587$). Furthermore, the proportion of patients with urogenital tract infections, skin and soft tissue infections, and sexually transmitted diseases did not differ significantly between the two groups. On the other hand, the presence of community-acquired pneumonia as a diagnosis increased remarkably in the guideline non-compliance group (38.8% versus 30.1%; $p=0.006$). Moreover, cases of peptic ulcer disease were significantly more in the guideline non-compliance group (14.9% versus 9%; $p=0.006$) (Table 4).

Distribution of inappropriate antibiotic prescriptions amongst various prescribed antibiotics

Even though there was no statistically significant difference between prescriptions in the compliance and the non-compliance groups regarding the antibiotic prescription appropriateness of amoxicillin (55.1% versus

59.6%; $p=0.176$), cloxacillin (20.5% versus 25.5%; $p=0.071$), ciprofloxacin (43% versus 49.2%; $p=0.064$), metronidazole (25.6% versus 25.8%; $p=0.958$), tinidazole (3.3% versus 2.4%; $p=0.408$), sulfamethoxazole/trimethoprim (9.8% versus 9.2%; $p=0.758$), azithromycin (19.7% versus 19.6%; $p=0.985$), clarithromycin (10.7% versus 9.5%; $p=0.549$) and doxycycline (29.3% versus 31.7%; $p=0.432$), based on the 2021 Ethiopian standard treatment guideline, the guideline non-compliant inappropriate prescriptions were significantly more for outpatients prescribed with amoxicillin/clavulanic acid (33.2% versus 48.2%; $p<0.001$) and cephalexin (17.8% versus 24.3%; $p=0.016$) when compared with other antibiotics (Table 5).

Discussion

The overall antibiotic prescribing rate was found to be 55.3%, which was high and comparable with studies conducted in Ghana, Nigeria and China.^{21,22} Compared

Table 4. Distribution of inappropriate antibiotic prescriptions for various bacterial infection diagnosis amongst patients attending outpatient department of Debre Markos Specialized Comprehensive Hospital.

Variable				Compliance to guideline (n=488)		Non-compliance to guideline (n=423)		χ^2 test	p value		
				Frequency	%	Frequency	%				
Sex of outpatients with antibiotic prescription				Male	258	52.9	216	51.1	0.296	0.587	
				Female	230	47.1	207	48.9			
Age of outpatients (mean \pm SD) ^a				39.10 \pm 14.004		38.36 \pm 13.702		0.517	0.605		
Diagnosis	Respiratory tract infections	CAP	Yes	147	30.1	164	38.8	7.537	0.006 ^b		
	Urogenital tract infections	Uncomplicated UTI	Yes	121	24.8	117	27.7	0.963	0.326		
			Recurrent UTI	Yes	12	2.5	11	2.6	0.018	0.892	
			Complicated UTI	Yes	11	2.3	7	1.7	0.420	0.517	
	Gastrointestinal tract infections	Typhoid fever	Yes	50	10.2	52	12.3	0.955	0.328		
			Amoebiasis	Yes	33	6.8	18	4.3	2.695	0.101	
				Giardiasis	Yes	20	4.1	13	3.1	0.682	0.409
					Peptic ulcer disease	Yes	44	9.0	63	14.9	7.551
	Skin and soft tissue infections	Osteomyelitis	Yes	31	6.4	30	7.1	0.198	0.656		
			Cellulites	Yes	9	1.8	8	1.9	0.003	0.958	
	Sexual transmitted diseases	Vaginal discharge	Yes	7	1.4	8	1.9	0.292	0.589		
	Others ^c		Yes	23	4.7	18	4.3	0.110	0.740		

^aAge is a continuous variable expressed as mean \pm SD and p value was computed with an independent t -test.

^bStatistically significant.

^cOther diagnosis includes oral abscess, otitis media and rheumatic fever.

CAP, community-acquired pneumonia; UTI, urinary tract infection.

Table 5. Distribution of inappropriate antibiotic prescriptions by considering indication, dose, route, frequency and duration for patients attending outpatient department of Debre Markos Specialized Comprehensive Hospital.

Variables				Compliance to guideline (n=488)		Non-compliance to guideline (n=423)		χ^2 test	p value
				Frequency	%	Frequency	%		
Utilized antibiotics	Penicillins	Amoxicillin	Yes	269	55.1	252	59.6	1.834	0.176
		Amoxicillin/ clavulanic acid	Yes	162	33.2	204	48.2	21.298	<0.001 ^a
		Cloxacillin	Yes	100	20.5	108	25.5	3.267	0.071
	Fluoroquinolone	Ciprofloxacin	Yes	210	43.0	208	49.2	3.440	0.064
	Imidazole derivative	Metronidazole	Yes	125	25.6	109	25.8	0.003	0.958
		Tinidazole	Yes	16	3.3	10	2.4	0.684	0.408
	Sulfonamide	Sulfamethoxazole/ trimethoprim	Yes	48	9.8	39	9.2	0.100	0.752
	Macrolide	Azithromycin	Yes	96	19.7	83	19.6	0.001	0.985
		Clarithromycin	Yes	52	10.7	40	9.5	0.359	0.549
	Tetracycline	Doxycycline	Yes	143	29.3	133	31.7	1.679	0.432
	Cephalosporin	Cephalexin	Yes	87	17.8	103	24.3	5.839	0.016 ^a
	Others ^b		Yes	24	4.9	19	4.5	0.092	0.762

^aStatistically significant.

^bOther antibiotics include benzyl penicillin, norfloxacin, nitrofurantoin, tetracycline, ceftriaxone.

with results from Congo, India and Pakistan,^{23–25} a lower use of antibiotics was reported by the current study; this discrepancy might be due to the fact that these studies involved the assessment of antibiotic use in hospitalized patients, taking both oral and parenteral antibiotics. Moreover, our finding was much lower than that of the Netherlands in outpatient clinics.²⁶ The possible reason for this variation might be that their study included all antimicrobials, thus broadening the medication category, whilst our study focused solely on antibiotics.

Amongst all antibiotic prescriptions, penicillins were the most commonly prescribed antibiotics, followed by fluoroquinolones, as observed in studies conducted in Europe and Nepal,^{27,28} whereas macrolides were the most prescribed antibiotics in studies from China, Malaysia and the USA.^{22,29,30} This finding illustrated that there is a difference in antibiotic utilization patterns and selection between communities/countries due to factors such as patient pressure, time constraints, medication availability and diagnosis uncertainty.³¹ Regarding specific medication prescriptions, amoxicillin was the most frequently prescribed antibiotic, similarly to a study conducted in India.³²

Regarding the common infectious diseases encountered, respiratory tract infections were the most common indication for visiting the OPD followed by diseases

of the gastrointestinal tract and urogenital system. The common individual diseases were community-acquired pneumonia, uncomplicated urinary tract infection and typhoid fever, commonly referred to as diseases of poverty and may be indicative of low socioeconomic development; worm infestation and respiratory diseases are common in poor developing countries.^{33,34} A similar study conducted in Malaysia reported upper respiratory tract infections followed by skin and soft tissue infections as the most common indications.²⁹

Findings from various studies about inappropriate antibiotic prescription vary widely. A study conducted in the USA amongst ambulatory care visitors reported that approximately 30% of antibiotic prescriptions for outpatients were not appropriate.¹⁸ Another study conducted between 2017 and 2019 in primary healthcare facilities in China showed that 70.5% of antibiotic prescriptions were inappropriate.³⁵ A systematic review including studies from six countries in the Gulf region revealed that inappropriate antibiotic prescriptions reach up to 80%.³⁶ The possible reason for the observed difference might be a variation in the guidelines used to evaluate the appropriateness of antibiotic prescribing. In the current study, 49.54% of prescriptions did not adhere to the guideline, in line with a study conducted in Malaysia.²⁹

Penicillins and fluoroquinolones made up the largest proportion of guideline non-compliant prescriptions mainly due to inappropriate selection of antibiotic agent and/or inappropriate dose/duration, and prescriptions for respiratory tract infection were the most frequently inappropriate. In line with other findings,^{18,37,38} 19.2% of amoxicillin and 15.9% of ciprofloxacin use for unjustified indications were noted. Thus, ciprofloxacin and amoxicillin prescriptions have mainly deviated from standard treatment guidelines, facilitating the development of resistance strains to these medications. Besides inappropriate indications, wrong dosage and duration were also the causes for inappropriateness of prescriptions, which is concerning because dose and duration are critical not to exceed the minimum inhibitory concentration of a drug in the organism.^{39–41} Inappropriate dose/duration was common particularly in the treatment of gastrointestinal infections and urinary tract infections, where by metronidazole and cephalexin were given at a lower and higher daily dose, respectively, than the recommended doses.

Strengths and limitations

To our knowledge, this is the first study to review antibiotic prescription appropriateness focusing primarily on the OPD in Ethiopia with a broad range of antibiotics

used. However, some limitations need to be addressed. First, the diagnoses of patients were determined based solely on what was written on the prescriptions. Second, factors needed for dose adjustments and selection of medications, such as monitoring parameters, clinical condition of patients or clinical and laboratory response of patients to the treatment, were not available because medical records were not accessed. Therefore, we recommend future studies with prospective follow-up designs to address the gaps of the current study.

Conclusions

The present study demonstrated that large proportions of antibiotic prescriptions for outpatients were non-compliant with the standard treatment guidelines. The study suggests that prescribers need to give special attention to outpatients whilst ordering antibiotics such as amoxicillin and ciprofloxacin. Antibiotic stewardship efforts to optimize outpatient antibiotic prescriptions and reduce the use of potentially inappropriate antibiotics are needed in Ethiopia. Additional studies are needed to explore antibiotic prescriptions in outpatient care settings and determine potential influencing factors associated with guideline non-compliant antibiotic prescriptions.

Contributions: Conceptualization, RBA; Data curation, TKZ and BMA; Formal analysis, MAA and RBA; Methodology, RBA, TKZ, MAA and BMA; Project administration, BMA and RBA; Supervision, TKZ, RBA, MAA and BMA; Writing original draft, RBA; Writing review and editing, RBA, TKZ, MAA and BMA. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Availability of data and materials: All relevant data are in the manuscript. Additional data used to support the findings of this study are available from the corresponding author upon request.

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