The Need for Antimicrobial Stewardship: Prospective Study on Antimicrobial Utilization Pattern at Gondar Referral Hospital, North West Ethiopia

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: The aim of the present study was to assess antimicrobials utilization pattern among patients admitted in internal medicine wards.
Setting: The study was conducted at Gondar University Hospital, Northwest Ethiopia.
Methods: Prospective follow-up study design was used to assess antimicrobial utilization pattern of patients in internal medicine wards. Patients admitted in four internal medicine wards were followed prospectively over a month and a half.
Main Outcome Measures: WHO/INRUD hospital and patient care indicators for the use of antimicrobials were utilized to measure rational drug use. Descriptive and analytical statistics were done using SPSS version 19.
Results: A total of 142 patients were admitted in four wards during the study period. Of these, 85(59.8%) were initiated on one or more antimicrobials in their treatment regimen. Over the course

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of the study, a total of 238 patient antimicrobials were prescribed, of which 42% were intravenous. Average number of antimicrobials per hospitalization was found to be 2.8±1.4. Pneumonia was the most frequent diagnosis and Cephalosporin, notably Ceftriaxone was the most frequently prescribed medication. From total diagnoses undertaken, 45.8% were treated in-line with the national standard treatment guideline. Median duration of total antimicrobial course was 13 days, while the average hospital stays of patients were 17 days.

Conclusion: Higher consumption of antimicrobials and conspicuously broad-spectrum antibiotics was observed during the study period. Most of the antimicrobials were prescribed empirically rather than waiting laboratory diagnosis for definitive therapy. Utilization pattern of antimicrobials was, mostly not in concordance with the national standard treatment guideline. Hence, there is a need for further large scale study on the utilization pattern of antimicrobials nationwide and antimicrobial stewardship in Gondar University Hospital.

1. INTRODUCTION

Antimicrobial agents are among the most commonly used and misused of all drugs. The inevitable consequence of the widespread use of antimicrobial agents has been the emergence of antimicrobial-resistant pathogens, fueling an ever-increasing need for new drugs. The current worldwide increase in antimicrobial resistance and, simultaneously, the downward trend in the development of new antibiotics have serious public health and economic implications [1,2].

The pace of antimicrobial drug development has slowed dramatically, with only a handful of new agents, few of which are novel, being introduced into clinical practice each year. Reducing inappropriate antimicrobials use is thought to be the best way to control resistance. Although awareness of the consequences of antimicrobial misuse is increasing, overprescribing remains widespread especially in health settings of developing countries, driven largely by patient demand, time pressure on clinicians, and diagnostic uncertainty [3,4].

Optimal and judicious selection of antimicrobial agents for the therapy of infectious diseases requires clinical judgment and detailed knowledge of microbiological and pharmacological factors [3-5]. Antimicrobials have three general uses: empirical therapy, definitive therapy, and prophylactic or preventive therapy. When used as empirical or initial therapy, the antimicrobial should cover all the likely pathogens because the infecting organism has not yet been defined. Either combination therapy or, preferably, treatment with a single broad-spectrum agent may be employed. However, once the infecting microorganism is identified, definitive antimicrobial therapy should

be instituted with a narrow-spectrum, low-toxicity agent to complete the course of treatment [6,7]. Failure to document the bacterial etiology so that a narrow-spectrum agent can be used and failure to narrow the spectrum when an organism has been identified are two common ways in which antimicrobials are misused [8,9].

Since antimicrobial are the most commonly prescribed drugs in developing countries, prescribing and utilization pattern should be studied and control mechanisms must be in place to avoid drug resistance, treatment failure, adverse drug reactions, super infections and extra cost. However, such studies and antimicrobial use guidelines are not available in resource limited settings.

The purpose of the present study was to explore antimicrobial utilization pattern with respect to INRUD/WHO antimicrobial use indicators in Gondar University Hospital. In addition, it was undertaken to find treatment outcomes after antimicrobial use and inpatient stay in the wards. The results of this study could help to know how antimicrobials are utilized and indicate possible areas of additional research and interventions.

2. METHODS

2.1 Study Design

This study was conducted using quantitative, prospective cross-sectional study among patients attending internal medicine wards of University of Gondar Referral Hospital.

2.2 Study Area and Period

The study was conducted in University of Gondar Hospital internal medicine wards from April 10 -

May 25, 2013. University of Gondar referral hospital is found in Gondar, historic and former capital of the empire located in North West Ethiopia, 738 Km away from the capital of Ethiopia, Addis Ababa. The hospital is one of the oldest and prestigious teaching referral hospitals in the country. It has about 460 beds rendering services like HIV, VCT, PMTCT service, family planning, surgery, fistula, ophthalmology, chronic disease management, TB, pediatrics follow up and others.

2.3 Study Population

The study populations were all patients attending internal medicine wards of Gondar University Hospital and initiated on treatment regimen which contains one or more antimicrobial drugs during the study period.

2.4 Inclusion and Exclusion Criteria

2.4.1 Inclusion criteria

Patients admitted for medical care in internal medicine wards of Gondar University Hospital with one or more antimicrobial prescribed on their medication charts or prescription.

2.4.2 Exclusion criteria

Patients admitted in the wards and with no antibiotics on their medication, pediatric patients and pregnant mothers.

2.5 Data Collection Methods

Data collection formats were developed with appropriate parameters of study. The data were collected by using observation from the recorded data on the chart, prescriptions, total antimicrobial administration and assessment of patients about their progress. In addition, cost related issues were analyzed by estimating the current Ethiopian market price of drugs.

2.6 Data Quality Control

To ensure quality of the data, the following activities were done; Pre-test to modify data collection formats, review of the collected data, cross check of activity among the data collectors and double data entry was carried out.

2.7 Data Analysis and Interpretations

Descriptive statistical analysis of frequencies was done by using SPSS version 19. Association between age, sex, types of therapy, route of administration, drug-drug interaction, use of AMDs in line with STG and number of drugs with outcome had been made by using cross tabulation and Chi square in confidence interval of 95% by considering presence of association with p value of < 0.05. The findings were presented by frequency tables.

2.8 Ethical Considerations

The proposal was submitted to the ethical review board of School of Pharmacy, University of Gondar and ethical clearance was obtained to conduct the research in the medical wards. Information on the purpose and procedures of the study was given verbally to all patients. Written informed consent was obtained from the study participants. The study was conducted in the adult wards, hence children under the age of 18 years were not included in the study. All patient information was kept confidential using coding system.

3. RESULTS

A total of 142 patients were admitted in four internal medicine wards during the study period. Of these patients, 69(48.6%) were males and 73(51.4%) were females. Among the admitted patients, 85(59.86%) were initiated on one or more antimicrobials on their medication charts. 71(83.53%) of those initiated on antimicrobials were adults and the rest 14(16.47%) were geriatrics. The mean age of patients was 51.5±33.5 years.

The average number of all drugs including antimicrobials and non-antimicrobials per patient was 3.4±1.22. A total of 238 (49.7%) antimicrobials were prescribed for 85 patients of which 42% were intravenous and 58% were orally administered. Average antimicrobial encounter per prescription was found to be 2.8±1.12 and median duration of total antimicrobial course was 13 days. The average hospital stay for all the admitted patients was fund to be about 17 days. Whilst pneumonia was the most frequent diagnosis, cephalosporins were among the most widely used antimicrobial classes with prescriptions frequency of about 20.60% followed by sulphonamides (14.28%) and nitroimidazoles (9.66%) Table 1. The average cost of antimicrobials per patient was about 272.47 Ethiopian birr (15.27 USD) per one and half a month.

Table 1. Common classes of antimicrobials used in the internal medicine wards during the study period, University of Gondar Hospital, April-May 2013, /N = 238/

Class	Frequency	Percentage
Cephalosporins	48	20.2
Sulphonamides	32	13.4
Nitroimidazoles	27	11.3
Quinolones	25	10.5
Penicillins	23	9.7
Tetracyclines	22	9.2
Antifungals	20	8.4
Antiprotozoals	18	7.6
Aminoglycosieds	16	6.7
Others	7	2.9

A total of 107 diagnoses have been made during the study period, of which 72.9% were treated empirically while 27.1% treated definitively. Several antimicrobials were utilized, with ceftriaxone 35(14.7%), cotrimoxazole 28(11.8%), metronidazole 25(10.5%), doxycycline 21(8.8%) & cloxacillin 18(7.6%) accounting for majority of the individual drugs. Most commonly utilized antimicrobials are summarized in Table 2.

Antimicrobials were used for various indications of infectious diseases during the study period. The most common indications were: Pneumonia 16(11.8%), UTI 10(15.9%), and meningitis 9(13.1%). Among these diagnoses, 49(45.79%) of the diseases were treated inline with the national standard treatment guideline where as 58(54.21%) were not and only 5 sensitivity tests were performed. Major diagnoses of infectious diseases for which antimicrobials were prescribed are shown in Table 3.

Drug-drug interaction and possible occurrence of adverse drug reaction was evaluated on combination of antimicrobials or with other medications using micromedex software and the results are summarized on Table 4. 14(16.47%) patients were on monotherapy while 32(37.65%) were having two drugs and 39(45.88%) took three or more drugs. Accordingly, 70(82.35%) of them encountered DDI, majority of which (35.71%) had moderate drug-drug interaction. In addition, prognoses of patients was evaluated during the follow-up period and majority of them showed good improvement with 64(75.3%) discharged at different time intervals. On the other hand, 18(21.2%) cases were staying in the wards for longer period /more than 45 days/ because of poor prognosis while conditions of 3 patients were found to be worsened and died during the study period.

Table 2. Prescribing frequency of common antimicrobials used in the medical wards, University of Gondar Hospital, April 10- May 25, 2013, /N =238/

S. no	Drugs name	Frequency	Percentage
1	Ceftriaxone	35	14.7
2	Cotrimoxazole	28	11.8
3	Metronidazole	25	10.5
4	Doxycycline	21	8.9
5	Cloxacillin	18	7.6
6	Ciprofloxacin	15	6.3
7	Gentamicin	14	5.9
8	Acyclovir	12	5.0
9	Norfloxacin	11	4.6
10	Coartem	10	4.2
11	Fluconazole	9	3.8
12	Ceftazidime	7	2.9
13	Sulfadiazine	6	2.5
14	Pyrimethamine	5	2.1
15	Praziquantel	3	1.3
16	Miconazole	2	0.8
17	Others	17	7.1

Associations between ages, sex, types of therapy, route of administration, drug-drug interaction, and use of antimicrobials in line with national standard treatment guideline with outcome was done by using cross tabulation and Chi square Table 5. There was a significant correlation between utilization of antimicrobials in line with standard treatment guideline (p=0.001) and treatment outcome. In addition, there was significant association between type of therapy and sex with treatment outcome (p=0.033).

Number of drugs was also strongly associated with drug-drug interaction. However, there was no association between number of medications and treatment outcome (p=0.063). Moreover, there was no association between drug-drug interactions, age, and route of administration with treatment out come. Association values of different variables with treatment outcome and drug-drug interaction are shown in Table 5 below.

Table 3. Major diagnoses for which antimicrobials were prescribed in four internal medicine wards, University of Gondar Hospital, April 10-May 25, 2013, /N = 107/

Diagnosis	Number of patients	Percentage
Pneumonia	19	17.8
UTI	17	15.9
Meningitis	14	13.1
Infective endocarditis	11	10.3
Toxoplasmosis	9	8.4
Pneumocistis carini jerovici	9	8.4
Candidiasis	8	7.5
Intestinal parasitosis	7	6.5
Malaria	6	5.6
Amoebiasis	4	3.7
Typhoid fever	3	2.8

Table 4. Number of all medications taken per-patient in internal medicine wards, University of Gondar Hospital, April 10-May 25, 2013, /N = 478/

Number of drugs	Number of patients	Percentage %
1	24	16.3
2	29	22.4
3	27	21.2
4	24	16.5
5	17	10.6
6	13	7.1
7	8	5.9

Table 5. Associations between different variables, treatment outcome and drug-drug Interaction, with their correspondence p- value, University of Gondar Hospital, April 10 - May 25, 2013

S. no	Variables	DDI (P value)	Outcome (P-value)
1	Sex	0.340	0.033
2	Age	0.176	0.324
3	Type of therapy	0.016	0.033
4	Number of drugs	0.001	0.063
5	Route of administration	0.115	0.287
6	Drug-drug interaction	____	0.555
7	Use in line with STG	0.355	0.001

4. DISCUSSION

Since the introduction of antimicrobials into medical practice, there have been calls for a rational use. Apposite antimicrobial treatment greatly improves the prognosis of infectious diseases [10]. However, overuse of antimicrobials may increase the risks of drug resistant pathogens, drug-drug interaction, side effects and costs of medical care. The right agent at the right dose and dosing interval with right duration can achieve both a favorable clinical outcome and prevent the occurrence of resistance. Reports showed that about 20–50% of antimicrobial use in humans was questionable or inappropriate [10-12].

Accurate information about prescribing and use patterns in hospitals is valuable in improving the quality of antimicrobial prescribing and utilization. According to this study, percentage of hospitalizations with one or more antimicrobials prescribed was 59.86%, higher than WHO/INRUD recommendations [13]. This might be due to the fact that the study has been conducted in internal medicine wards and in a tropical country where infectious diseases are highly rampant. Antimicrobial prescription frequency was 30.6% in multicenter point-prevalence study of hospitalized patients in Turkey, quite less compared to this study. The antibiotic prescription frequency was reported as 77.8% from a University Hospital in China, higher than this study, and 65% from a pediatric teaching hospital in Costa Rica, comparable with this study [14-16].

Average antimicrobial encounter per prescription which measures the extent of antimicrobial use in hospitals was found to be 2.8±1.42, out of the acceptable range (1.6-1.8) recommended by WHO/INRUD [17]. Taking multiple medications at a time might lead to drug-drug interaction and adverse drug reaction. Studies have shown that as a new drug is prescribed and added to another drug, the risk of drug-drug interactions and adverse reactions increase exponentially [18]. Inline with this argument, drug-drug interaction was detected in 82.35% of the study subjects when analyzed using micromedex software with a potential adverse drug reaction, majority of which (35.71%) had moderate interaction. Moreover, the median duration of total antimicrobial course was 13 days while average hospital stay was about 17 days, both higher than recommendations of INRUD and WHO. The optimal duration of therapy for many

bacterial infections has not been determined, but the current recommendation is usually 7–10 days of treatment [13,18].

This prolonged course of treatment could be associated with continued use of antimicrobials for several days past standard recommendations and past the time that they were clinically cured. Moreover, discontinuing antimicrobials may have been overlooked. The length of treatment with antimicrobials should not exceed the recommended duration. If patients who receive antimicrobials do not improve within the recommended time, it is possible that the treatment is not appropriate or the diagnosis is incorrect. Prolonged hospital stay is costly, increases the risk to the patient of nosocomial infections, and promotes the emergence of organisms resistant to antimicrobials. If the hospital stay is too short, antimicrobial treatment may be ineffective because of sub-therapeutic treatments, relapses, promotion of AMR, and finally, increased costs. In this study, it was found that the average cost of antimicrobials per patient was about 272.47 Ethiopian birr (15.27 USD) which seems costly for most ordinary Ethiopians. Antimicrobials typically account for 20 to 40 percent of hospital expenditures on medicines. Inappropriate treatment, such as prescribing more antimicrobials than recommended as shown above, prescribing higher doses or longer treatments than required and prescribing brand-name instead of generic antimicrobials might be the causes for high costs.

Longer treatment courses are recommended for some diseases, for example, not less than 14 days for meningitis, up to six weeks for osteomyelitis. Too short a course of treatment may prolong patient morbidity and promote emergence of drug-resistant organisms. Too long course of therapy increases patient exposure to antimicrobials, increasing the risk of adverse drug reactions and unnecessary expenditure on antimicrobials. Frequent and yet, unnecessary changes in antimicrobial therapy would also contribute to AMR resistance, high costs, and increased patient morbidity.

From this study, it was found out that 58% antimicrobial agents were prescribed for oral administration, while 42% for parenteral use, less than a study carried out in Kathmandu valley, Nepal, with 55% of antimicrobials given in the form of injections. But, it was comparable to a study done at Gujarat Tertiary teaching Hospital, reported that 41.81% antimicrobial agents were prescribed as parenteral formulation [19,20].

Pneumonia was the most frequent diagnosis and the most frequently utilized antimicrobial classes were cephalosporins, (20.60%), notably the third generation cephalosporin, ceftriaxone, prescribing frequency was 14.7%. Similar to this, a prospective study done using WHO core drug use indicators among inpatients in Sri Ramachandra Hospital, Pakistan revealed that, third generation cephalosporins were the most commonly prescribed broad spectrum antibiotics even before the culture sensitivity results [21]. The use of these newer and broad spectrum antimicrobials is in contrast to recommendations of the national treatment guideline and WHO where narrow spectrum and older antibiotics should have been used first. The second most frequent antimicrobial classes prescribed in this study were sulphonamides (14.28%) followed by nitroimidazoles (9.66%). Wider use of ceftriaxone observed in this study may be attributed to ability to penetrate CSF, coverage of most gram negative microorganisms and easier local availability of injection form of the drug. In addition, ceftriaxone is recommended by the Ethiopian national standard treatment guideline as an alternative drug for most cases of hospital acquired pneumonias (nosocomial pneumonias), pneumonia due to common organisms and community acquired hospitalized patients (severe pneumonia) amid its high level usage in Gondar Hospital as a first line. In contrast to this, a study in Bangladesh reported that 39.4% Doxycycline, 35.64% Gentamicin and 26.87% Cotrimoxazole were among the frequently utilized antimicrobials while in a study done in Libya, the major antimicrobial to be prescribed was amoxicillin+clavulanic acid [22,23].

Health professionals are expected to adhere and prescribe antimicrobials recommended by standard treatment guideline for treating a given infectious diseases. On top of that, this study has revealed that there was significant association between use of the standard treatment guideline and positive treatment outcome. But, only 45.8% of all the diagnoses were treated in accordance with the standard treatment guideline. Out of the 107 diagnoses made, 72.9 % were treated empirically and only 5 sensitivity tests were performed which might contribute to the high level of using antimicrobials without adequate laboratory information. In a study conducted in Tertiary Care Hospital in Charoenkrung, Pracharak Hospital, Bangkok, it has been reported that 88.6% were prescribed empirically which is relatively higher than the figure from this study [24].

5. CONCLUSION

Wide spectrums of clinical diagnoses were made and various antimicrobials were utilized from various drug classes. Percentage of hospitalizations with one or more antimicrobials prescribed was higher than the recommended values. Moreover, average number of antimicrobials per hospitalization in which antimicrobials were prescribed was also higher compared to recommendations of WHO/INRUD. Average duration of prescribed antimicrobial treatment and average duration of hospital stay of patients who receive antimicrobials was longer than recommended values. Most of the antimicrobials were prescribed on clinical judgment instead of adequate laboratory information in majority of the patients. Educational interventions emphasizing rational prescribing along with a multidirectional effort to create an updated local formulary, and a strict antimicrobial prescribing policy can help averting these problems. Hence, there is a need to implement antimicrobial stewardship programs in Gondar University hospital. Large scale national studies on the antimicrobial utilization pattern should also be conducted to investigate the magnitude of the problem and subsequent interventions.

6. FUNDING

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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