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Evaluation of prescribing patterns of antibiotics using selected indicators for antimicrobial use in hospitals and Access, Watch, Reserve (AWaRe) classification by World Health Organization

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ABSTRACT
INTRODUCTION: Antibiotic Resistance poses greater threat to the world. Irrational use of antibiotics is one major contributing factor for it. Evaluation of antimicrobial use with help of indicators and World Health Organization (WHO) classification of antibiotics as Access, Watch, and Reserve category. We aimed to evaluate the prescribing pattern of antibiotics using Access, Watch, and Reserve classification by World Health Organization and selected indicators for antimicrobial use in the hospitals.
METHODS: 1000 prescriptions were analyzed during the study for antibiotic prescribing patterns. Antibiotic consumption was calculated using defined daily dose methodology. Prescribing pattern was evaluated using World Health Organization classification of antibiotics as Access, Watch, and Reserve category and using selected indicators (Hospital and Prescribing) for antimicrobial use in the hospitals.
RESULTS: 1128 antibiotics were prescribed during the study.19-44 age group were prescribed with high number of antibiotics (n=510). Females were prescribed with high number of antibiotics (n=602). Azithromycin was most commonly consumed antibiotic (14.97 DDD/1000/day). Four antibiotics from Access category and five antibiotics from Watch category were prescribed in the study. Watch category of antibiotics were consumed high in number. There were no standard treatment guidelines in the hospital. 98.0% of antibiotics are consistent with the hospital formulary and prescribed in generic names. The average number of antibiotics prescribed was 1.12. The average duration of antimicrobial treatment was 5.24 days. The percentage of patients prescribed with antimicrobials for pneumonia in accordance to treatment guidelines was 13.28%.
DISCUSSION AND CONCLUSION: There is irrational use of antibiotics. There is need for

maintaining standard treatment guidelines in the hospital because it prevents irrational use of antibiotics.

Keywords: Access, Watch, Reserve, indicator, prescribing, antibiotic, evaluation, hospital, WHO.

INTRODUCTION

Antibiotic resistance poses greater threat to global public health[1,2] and was specially mentioned as a serious threat to public health, economic growth, and global economic stability.[3] Increased antibiotic resistance rates may lead to prolonged hospitalization and duration of treatment, increased treatment costs and mortality.[4] The major contributing factor for this resistance is inappropriate or irrational use of antibiotics. Irrespective of the alarming increase in the resistance, there is an increased irrational prescribing practice of antibiotics across different regions.[5-13] In 2017, WHO commissioned comprehensive reviews on antibiotic use for specific infections in order to update Essential Medicines List.[14] The expert committee then formulated Access, Watch, Reserve (AWaRe) classification of antibiotics with the goals of better accessibility and clinical outcomes, decreased possibility for antimicrobial resistance, and to safeguard effectiveness of the last resource antibiotics.[15] Access group of antibiotics are first and second choices for empirical treatment of 21 common or severe clinical syndromes. The Access group of antibiotics are core set of antibiotics and should be made always available in every place at an appropriate quality, dose, duration, formulation, and price. The Watch group includes antibiotics with higher toxicity concerns or resistance potential compared with the Access group. The Watch group antibiotics assist the development of tools for stewardship at local, national and global levels. Reserve group antibiotics are last-resort options and used for specific patients and clinical settings in case of failure of other alternatives. Prioritising this group as key targets of high-intensity national and international stewardship programmes preserves their effectiveness.[15] Thus, AWaRe index help estimates the relative use of narrow-spectrum and broad-spectrum antibiotics. Strengthening Pharmaceutical Systems (SPS) Program also developed selected indicators for investigating antimicrobial use in hospitals, which complements the existing WHO indicators of outpatient antimicrobial use. These indicators provide a simple tool for fast and assuredly figuring out critical aspects of antimicrobial use and to recognize problems with antibiotic use in hospitals.[16] So, we aimed to evaluate the prescribing pattern of antibiotics using WHO AWaRe classification and selected indicators for investigating antimicrobial use in the hospitals by Strengthening Pharmaceutical Systems Program.

MATERIALS AND METHODS

A descriptive cross-sectional study was conducted on 1000 patients with varying diseases in a tertiary care hospital, for a duration of six months (01/08/2019 to 31/01/2020). The study was approved by the Institutional Human Ethics Committee (VIPT/IEC/61/2019). The prescriptions containing at least one antibiotic, prescriptions of all ages and various departments with at least one antibiotic was included in the study. Prescriptions without antibiotics were excluded in the study. Simple random sampling was used to select the prescriptions. The estimated sample size was 651 (margin of error 5%, confidence level 99%, population size of 324000, and a response distribution of 50%). However, we collected data for 1000 prescriptions. The aim of the study was explained clearly to the patients and obtained informed consent form from willing patients. Sociodemographic data including age, gender, and clinical details including name of the department, diagnosis, name of the antibiotic, dose, indication etc. were collected from the patient's prescription.

World Health Organization (WHO) Access, Watch, and Reserve (AWaRe) classification (2019) was used to evaluate the rational use of antibiotics. Selected indicators for antimicrobial use for hospitals (Hospital indicators and Prescribing indicators) developed by Strengthening Pharmaceutical Systems Program was used to investigate antimicrobial use. Defined Daily Dose (DDD) per 1000 inhabitants per day was calculated using the following formula. Descriptive statistics (mean and standard deviation) was calculated using Minitab (version 18.0)

$$\text{DDD/1000/ day} = \frac{\text{Total number of dosage units prescribed} * \text{Dosage strength} * 1000}{DDD * Duration\ of\ the\ study * Total\ sample\ size}$$

RESULTS

1,128 antibiotics were prescribed during the study. The mean age of patients in our study was 33.04 ±18.59 years. 19-44 age group patients were prescribed with a high number of antibiotics (n=510, 45.21%) (Table 1). Females were prescribed with a higher percentage of antibiotics than males (53.47% vs. 46.63%, respectively, Table 2). The general medicine department consumed a higher proportion of antibiotics (36.79%, Table 3).

[redacted]

S.No.	Name of the antibiotic	1-18 years	19-44 years	45-63 years	≥64 years	Total (%)
1	Amoxicillin +Clavulanic acid	131	122	51	18	322 (28.54)
2	Cefixime	43	110	64	19	236 (20.92)
3	Azithromycin	42	107	57	25	231 (20.47)
4	Metronidazole	21	67	34	13	135 (11.96)
5	Ciprofloxacin	8	39	17	2	66 (5.85)
6	Ofloxacin	11	29	13	3	56 (4.96)
7	Amoxicillin	21	21	8	2	52 (4.60)
8	Doxycycline	3	9	6	1	19 (1.68)
9	Norfloxacin	2	6	3	0	11 (0.97)
	n (%)	282(25.00)	510(45.21)	253(22.43)	83(7.35)	1128

n= number, %=percentage

[redacted]

S.No.	Name of the antibiotic	Males	Females	Total
1	Amoxicillin +Clavulanic acid	135	187	322
2	Cefixime	112	124	236
3	Azithromycin	108	123	231
4	Metronidazole	75	60	135
5	Ciprofloxacin	30	36	66
6	Ofloxacin	31	25	56
7	Amoxicillin	26	26	52
8	Doxycycline	6	13	19
9	Norfloxacin	3	8	11

n (%)	526(46.63)	602(53.37)	1128

n= number, %=percentage

S.No.	Name of the antibiotic	G.M	ENT	Ortho	Ped	Pul	Others
1	Amoxicillin +Clavulanic acid	94	124	14	35	22	33
2	Cefixime	82	40	68	7	8	31
3	Azithromycin	90	27	2	22	60	30
4	Metronidazole	83	19	2	11	0	20
5	Ciprofloxacin	28	25	3	0	1	9
6	Ofloxacin	15	11	0	7	1	22
7	Amoxicillin	14	21	2	5	3	7
8	Doxycycline	2	0	11	0	0	6
9	Norfloxacin	7	1	0	0	1	2
	n (%)	415(36.79)	268(23.75)	102(9.04)	87(7.71)	96(8.51)	160(14.18)

n=number, %=percentage, G.M= General Medicine, ENT= Ear, Nose, Throat; Ortho=Orthopaedics, Ped=Pediatrics, Pul=Pulmonology, others= dermatology; general surgery; endocrinology; gastroenterology; nephrology; neurology; urology; dental, gynaecology

Defined Daily Dose for Azithromycin was high among other antibiotics (14.97 DDD/1000/day, Table 4) Four antibiotics from the access category; five from the watch category of AWaRe classification are prescribed (Table 5).

S. No.	Name of the antibiotic	ATC Code	DDD	DDD/1000/day
1	Amoxicillin +Clavulanic acid	J01CR02	1.5g	8.64
2	Cefixime	J01DD08	0.4g	9.17
3	Azithromycin	J01FA10	0.3g	14.97
4	Metronidazole	P01AB01	2g	3.15
5	Ciprofloxacin	J01MA02	1g	2.56
6	Ofloxacin	J01MA01	0.4g	2.17
7	Amoxicillin	J01CA04	1.5g	1.34
8	Doxycycline	J01AA02	0.1g	1.47
9	Norfloxacin	J01MA06	0.8g	0.42
	Total	---	---	43.89

ATC= Anatomic, Therapeutic and Chemical; DDD= Defined Daily Dose

S.No.	Name of the antibiotic	Class of antibiotic	AWaRe Category	Listed in EML

1	Amoxicillin +Clavulanic acid	Beta lactam-beta lactamase inhibitor	Access	Yes
2	Metronidazole	Imidazole	Access	Yes
3	Amoxicillin	Penicillins	Access	Yes
4	Doxycycline	Tetracycline	Access	Yes
5	Cefixime	Third generation cephalosporin	Watch	Yes
6	Azithromycin	Macrolide	Watch	Yes
7	Ciprofloxacin	Fluoroquinolone	Watch	Yes
8	Ofloxacin	Fluoroquinolone	Watch	No
9	Norfloxacin	Fluoroquinolone	Watch	No

AWaRe= Access, Watch, Reserve, EML= Essential Medicines List, WHO= World Health Organization

There were standard treatment guidelines for infectious diseases and essential medicines list in the hospital. Average number of days that a set of key antimicrobials is out of stock was 3.2 days/month. 98.3% of key antimicrobials are available on the day of the study (Table 6). Average number of antibiotics prescribed per hospitalization was 1.12. 98% of antimicrobials are consistent with hospital formulary list and are prescribed by generic name. 13.28% of antimicrobials for pneumonia patients are prescribed in accordance with standard treatment guidelines (Table 7).

[redacted]

S.No.	**Name of the indicator**	**Result**
1	Existence of standard treatment guidelines for infectious diseases	No
2	Existence of approved hospital formulary list or essential medicines list	Yes
3	Availability of a set of key antimicrobials in the hospital stores on the day of the study	98.30%
4	Average number of days that a key antimicrobial is out of stock	3.2 days/month

[redacted]

S.No.	**Name of the indicator**	**Result**
1	Percentage of antimicrobials prescribed consistent with the hospital formulary list	98.00%
2	Average duration (in days) of prescribed antimicrobial treatment	5.24±1.35
3	Percentage of antimicrobials prescribed by generic name	98.00%
4	Average number of antibiotics prescribed per hospitalization	1.12
5	Percentage of patients prescribed with pneumonia who are prescribed antimicrobials in accordance with standard treatment guidelines	13.28%

DISCUSSION

We observed high prescribing of antibiotics in 19-44 age group patients. Interestingly, the number of antibiotics in the elderly was low (7.35%). In general, the elderly are more vulnerable to infections, and thus a higher number of antibiotics are expected to prescribe for them. Prescribing antibiotics overly for the elderly was a common practice, and the physicians here was the exception for that as it was evident from table 1. Females were prescribed with a high number of antibiotics than males (53.37% vs. 46.3%, respectively). Relatively, females are less exposed to external environments than males, and however, in our study, females were prone to more infections. The general medicine department covers a wide variety of diseases. So, the general medicine department consumed a higher percentage of antibiotics (36.79%). Commonly prescribed antibiotic in our study was amoxicillin + clavulanic acid (n=322). Cefixime (n=236) and azithromycin (n=231) were the next widely prescribed antibiotics. Atif et all. [11] reported ceftriaxone as the most commonly prescribed antibiotic (71.8%). The most frequently prescribed antibiotic class was cephalosporins (81.5%), while antibiotic combination was ciprofloxacin + metronidazole (52.1%). A repeated point prevalence survey on the appropriateness of antimicrobial prescribing reported penicillins with beta-lactamase inhibitors were the most frequently prescribed antibiotics (30%) which was very near to our study.[6] Azithromycin (14.97 DDD/1000/day) was the most common antibiotics, followed by cefixime (9.17 DDD/1000/day) and amoxicillin and clavulanic acid (8.64 DDD/1000/day). Similar to our study, Mule et al.[17] reported higher consumption of azithromycin (107.83 DDD/1000/day) in their research. In contrast, a population-based study on trends of antibiotic use in Korea, reported Penicillins (mean consumption 4.52 DDD/1000/day) as a commonly used antibiotic subgroup, followed by 2nd-generation cephalosporins (4.47 DDD/1000/day), macrolides (3.32 DDD/1000/day), and fluoroquinolones (2.75 DDD/1000/day).[18] Another study on antibiotic consumption in pediatrics patients reported high consumption of penicillins (271.22 DDD/1000/day) followed by cephalosporins (98.46 DDD/1000/day), and macrolides (72.70 DDD/1000/day) in pulmonology department.[19] Dipika Bansal[20] reported higher consumption of Ceftriaxone (143.22 DDD/1000 patient-days), followed by doxycycline (85.02 DDD/1000 patient-days), and azithromycin (66.37 DDD/1000 patient days, oral; 59.37 DDD/1000 patient days per oral).

We observed azithromycin as a drug of choice for upper respiratory tract infection. However, according to the WHO model list of essential medicines list, azithromycin belongs to the Watch category and is preferred the first-choice antibiotic for sexually transmitted infections, cholera, gonorrhea.[21] Amoxicillin and clavulanic acid were prescribed for pneumonia, urinary tract infections, and otitis media in our study. According to the WHO model list of essential medicines list, amoxicillin and clavulanic acid belongs to the Access category. It is the preferred first-choice antibiotic for community-acquired pneumonia, skin and soft tissue infections, lower urinary tract infections, hospital acquired pneumonia, and COPD. It is the second-choice antibiotic for bone and joint infections, otitis media, surgical prophylaxis.[21] Cefixime was prescribed for bone and joint infections, chronic suppurative otitis media, urinary tract infection. However, according to the WHO model list, cefixime belongs to Watch group antibiotics and is preferred as the second choice for acute diarrhea/dysentery and gonorrhea.[21]

We observed the absence of standard treatment guidelines for infectious diseases in the hospital. However, there is an approved hospital formulary list or essential medicines list in the hospital. A study by Atif et al.[10] reported a similar result, whereas Shahbazi et al.[7] reported contrast results. Irrational prescribing or inappropriate prescribing of antibiotics is a crucial contributing factor for antimicrobial resistance. Standard Treatment Guidelines allow the prescribers to follow the standard, avoids irrational prescribing, and provides quality patient care without any compromise. It also prevents unnecessary drug reactions, out of pocket expenditures to the patient, and promotes recovery in time for the patient. Treatment Guidelines for Antimicrobial Use in common syndromes, 2019 by Indian Council of Medical Research [22] offers guidelines for antimicrobial use in common infectious diseases with dose, frequency of administration, duration, and monitoring antimicrobial use. They are available for free of cost. Framed according to the Indian scenario, if followed, they help in preventing irrational or inappropriate antimicrobial use.

The main drawback was the absence of standard treatment guidelines in the hospital. Although remaining indicators are satisfactory, prescribing without standards is worrying. According to the Indian Council for Medical Research [22], the preferred antimicrobial agent for pelvic inflammatory disease, and alternative antibiotic for typhoid fever, bacterial sinusitis was cefixime. However, in our study, cefixime was also prescribed for throat infection, upper respiratory tract infection, fever, chronic otitis media etc. Ofloxacin was indicated for epididymo-orchitis [22], whereas it was prescribed for topical ulcer, alcoholic gastritis, perianal infection. Likewise, standard treatment guidelines can prevent inappropriate prescribing practices.

98.3% of key antimicrobials are available in the hospital stores on the day of our study. Atif et al.[10], Shahbazi et al.[7], and Woldu et al.[23] reported a lesser percentage of key antimicrobial availability in the hospital stores on the day of their study (93.8%, 90.1%, and 78.5% respectively). The availability of key antimicrobials all the time is essential because the practitioners will start prescribing antimicrobials that are not indicated for the disease, or they may prescribe branded forms of the critical antimicrobials for purchase from outside the hospital. Branded types of drugs are more economical and increase the out of pocket expenditures for the patient.

The average number of days that a set of essential antimicrobials is out of stock in our study was 3.2 days/month. Atif et al.[10] reported a similar result (3.3 days/month). However, Shahbazi et al.[7] and Woldu et al.[23] reported the high average number of days of out of stock for essential antimicrobials (6.78days/month and 15-45days over 12month period). This indicator provides information about healthcare capacity and practices to maintain inventory control, procurement and correct distribution. [10]

The average number of antibiotics prescribed per hospitalization in our study was 1.12. Atif et al.[10], Shahbazi et al.[7], and Osama and Ibrahim[2] reported the high average number of antibiotics than our study (2.35, 2.85, and 2.7, respectively). Prescribe the antibiotics whenever needed and appropriate. However, in real situations, patients are unaware of antimicrobial resistance, influenced by false beliefs, and behavioral factors often ask the physician to prescribe an antibiotic or think that the physician was not competitive enough because he/she didn't prescribe an antibiotic. Awareness of patients about antimicrobial resistance due to the irrational use of antibiotics can prevent these circumstances.

In our study, 98.00% of the antibiotic prescribing was consistent with the formulary list. Two studies reported similar results.[10, 11] In contrast, Shahbazi et al.[7] reported 100% consistent prescribing with the hospital formulary list. The hospital formulary list optimizes medication use. Lack of awareness of formulary list to physicians, deficiency of listed antibiotics, or prescribing with brand names instead of generic names may cause non-adherence to such hospital policy.[22]

Physicians will not prescribe the medication if they are unaware of the formulary list. It results in a waste of health resources because the stocked-up drugs reach expiry date and become useless. In our study, the antibiotics prescribed using the generic name was 98.00%. This prescribing practice was far better than Atif et al.[10], Green et al.[25], and Shahbazi et al. [22] (52.5%, 88%, and 13.18%, respectively). Prescribing drugs by generic names was essential in developing countries because it prevents the economic burden on poor people. Patients' misconceptions about generic drugs versus brand drugs allow easy exploitation and make them prefer branded drugs over generic drugs. Besides, prescribing generic names often prevents confusion about multiple names for the same product. [16] Patients also habituated to buy the drug with the same brand name only, although the same drug was available in generic form or in another brand. There is a need to strengthen the awareness of generic drugs, their availability in patients. In India, the central government set up a "Jan Aushadhi" scheme wherein pharmacies will sell generic drugs and all medicines in that pharmacies are affordable to the people.
The mean duration of antimicrobial treatment prescribing was 5.24 days, and similar results are reported by Atif et al.[10] and Shahbazi et al.[7](5.4 days and 5.65 days, respectively). The duration of antibiotic treatment varies according to the severity of the disease and the nature of the drug. Since there is no consensus on the optimal duration of therapy for the majority of the infectious diseases, it is better to treat for at least 7-10 days. A short course of treatment may lead to antimicrobial resistant microbes. At the same time, prolonged exposure increases the risk of adverse drug reactions, antimicrobial resistance, and also unwanted expenditure on antibiotics. [16]
The percentage of pneumonia patients prescribed with antimicrobials according to standard treatment guidelines was 13.28%. Shahbazi et al.[7] reported 19.23% of the same. However, in our study, there was no use of standard treatment guidelines. Green et al.[25] also reported that pneumonia patients in their study were also prescribed with antibiotics without any standard treatment guidelines.
Four antibiotics from the Access category and five antibiotics from the Watch category are prescribed in our study. World Health Organization's AWaRe classification specified that the antibiotics consumed from the Access group should be at least 60%.[26] In our study, 46.80% of antibiotics from the Access category was prescribed. Watch group antibiotics accounted for 53.19 % of the total antibiotics prescribed. It indicates the overuse of the Watch group antibiotics. A study on pediatric antibiotic prescribing in China also reported a similar overuse. [27] A pediatric survey reported varied consumption of AWaRe antibiotics among countries. Access group antibiotics consumption for children in Slovenia accounted for 61.2%, whereas in China, it is 7.8%. Watch group antibiotics consumption for children is highest in Iran (77.3%) whereas it is lowest in Finland (23.0%). In neonates, Singapore accounted for 100% Access group antibiotics, whereas China registered the lowest consumption of Access group (24.2%). [28]
The study has a few limitations. One of the hospital indicators, Expenditure on antimicrobials as a percentage of total hospital medicine costs, was not calculated due to administrative policies in the hospital. One of the prescribing indicators, the average cost of antimicrobials prescribed per hospitalization, was not calculated due to organizational policies. We collected data from outpatient departments only, so we are unable to calculate two prescribing indicators i.e., antimicrobials used in surgical prophylaxis and the average number of antibiotic doses in the cesarean section.

CONCLUSION

Our study observed irrational prescribing practices. Strict implementation of the use of standard treatment guidelines prevents inappropriate prescribing. Prescribing drugs by generic name and percentage of antibiotic prescribing consistent with hospital formulary should reach 100% for better results.

Conflicts of interest: The authors declare no conflicts of interest.

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