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Antibiotic prescriptions to the inpatients having non-bacterial diagnosis at medicine departments of two private sector hospitals in Madhya Pradesh, India: a cross sectional study

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Abstract

Objectives: To present and compare antibiotic prescribing among inpatients among most common non-bacterial diagnoses group at medicine departments of a teaching (TH) and a non-teaching hospital (NTH) in Central India.

Setting: An observational cross-sectional study was conducted at two tertiary care settings at Ujjain district, Madhya Pradesh, India.

Participants: The data was collected manually, using a customized form. All inpatients, who stayed at-least for one night in either of the hospitals during 2008-2011, with complete records were included.

Outcome measures: Inpatients were grouped based on the presence or absence of a bacterial infectious diagnosis along with viral or malaria fever or cardiovascular diseases. Classes of antibiotics prescribed to these groups, and adherence to the available prescribing guidelines were compared between the hospitals using WHO anatomical therapeutic chemical classification and International Classification of Diseases-10.

Results: Of total 20303 inpatients included in the study, 66% were prescribed antibiotics. Trade name prescribing and use of broad spectrum antibiotics were more frequent at the NTH compared to the TH ($p<0.001$). At the TH, significantly higher proportion of patients in 'fever without registered bacterial infection' group; were prescribed antibiotics (82%) compared with the NTH (71%, $p<0.001$). Patients admitted with 'cardiovascular diagnosis without bacterial infections' received antibiotics prescriptions at both hospitals; (NTH- 47% and TH- 37%) which was significantly higher at the NTH ($p<0.001$).

Conclusions: Antibiotic prescribing to the inpatients without bacterial infections i.e. viral fever, malaria and cardiovascular diseases and use of broad spectrum antibiotics for non-indicated episodes were common at both hospitals. Treatment of non-bacterial infections with

antibiotics might be a potential risk for the development of bacterial resistance, a global public health threat. Taking account of unnecessary prescribing in the hospitals, development and implementation of local prescribing guidelines, followed by prescription analysis with antibiotic stewardship programs are the main recommendations for the settings.

Strengths and limitations

- Prospective study over a long time period of three years and inclusion of all patients, irrespective to their age and sex strengthens the representativeness of the results.
- Data collecting tools were same at both study locations and the staff who collected the data was trained by the same person at both locations to minimize the variances.
- An observational non-interventional study design would have minimized the steering effect to the prescribers.
- Some data may have been lost in translation from analogue to digital records however large number of patients included in the study is likely to minimize the effect.
- The grouping of diagnoses might have produced false low antibiotic prescribing, specifically in suspected bacterial diagnosis groups however, in absence of confirmed etiology this was indispensable.

BACKGROUND

Increasing morbidity and mortality due to infectious diseases, despite of the availability of the lifesaving antibiotics is an alarming situation, globally,[1]. These incidences of mortalities due to infections are higher in low- and middle-income countries than in high-income countries,[2–4]. WHO has reported a high burden of communicable diseases in India, and infections are responsible for 28% of the total mortality in the country,[5, 6]. Additionally, antibiotic resistance in India is reported to be high. However, figures cannot be generalized to all Indian settings as the bacterial resistance patterns widely vary between its regions and settings,[7].

Irrational (both over- and under-) use of antibacterials, is of global concern. It results in unnecessary treatment costs, is a potential risk for the development of antibiotic resistance and side effects such as antibiotic associated diarrhoea caused by *C. Difficile* or gastroenteritis,[8]. According to a report, the global consumption of antibiotics increased by 36% between 2000 and 2010 of which five countries including India (Brazil, Russia, India, China and South Africa) accounted for 76% of this increase,[9]. Despite of the paucity of studies that describe antibiotic prescribing from India, Van Boeckel et al presented India on the top of the list of antibiotic consumption with 12.9×10^9 units in 2010 where one unit indicates a pill, capsule or ampoule,[1,9]. However, this increase might also have meant that segments of the population that previously had no access to antibiotics can now access antibiotics yet it cannot be disregarded that antibiotic resistance is a sequel of antibiotic use,[10].

It is thus imperative to map the prescribing patterns of antibiotics on a local level to address the potential need of improvement and to counter the consequences of inappropriate prescription of antibiotics. Indian private sector facilities are the major healthcare providers but are usually not included in these base line surveys,[11,12].

OBJECTIVES

The study was conducted to present, analyse and compare antibiotic prescribing to the inpatients enrolled for most common non-bacterial diagnoses at the medicine departments of a teaching (TH) and a non-teaching hospital (NTH) in Central India.

METHODS

Study design

A cross sectional observational design was selected to conduct the study.

Setting

The study was conducted at the medicine departments of two tertiary care hospitals from private sector in Ujjain district, India. The hospitals are addressed as teaching hospital (TH) and non-teaching hospital (NTH). Both hospitals are run by the same trust. The TH is located in a rural area of Ujjain district and had 570 beds at the time of the study. The NTH is located in the central part of Ujjain city and had 350 beds at the time of the study. The TH provides medical services including medical treatment and free of charge medicines to all patients while the NTH charges for the medical facilities on a 'no profit-no loss' basis. Patients from the NTH have to buy prescribed medicines from pharmacies inside or outside of the hospital. The physicians at the TH are salary paid and do not have any direct exposure with the sales representatives of pharmaceutical companies. Furthermore, the management at the TH is responsible for the purchase and supply of the drugs. Essential medicine list was available at the TH but was not implemented during the study period while prescribing guidelines were not present in any of the hospitals. Almost all physicians practicing at the NTH also had private practice and could be contacted by the representatives of pharmaceutical companies easily. The payments of the physicians at the NTH increase above par according to the number of patients they admit in the hospital and the number of visits made to the inpatients.

A well-equipped microbiology laboratory was present to process the samples free of cost for all from the TH and with nominal charges from the NTH.

Participants

Inclusion and exclusion criteria

Patients who stayed for at least one night at medicine departments of either of the two hospitals were considered as inpatients and included in the study. Patients who had incomplete records or admitted to the medical intensive care units within the medicine departments were not included in the analysis. Treatment recommendations including dose and frequency varies for the patients under 15 years of age and the DDD measurement is not applicable to them, thus were also excluded,[14].

Variables

The patient information was analysed for age, sex, diagnosis, duration of hospitals stay, if they received antibiotic treatment, and duration of antibiotic treatment. The prescriptions were analysed for the type of antibiotics prescribed, its dose, and frequency. The antibiotics were classified according to the Anatomical Therapeutic Chemical (ATC) classification given by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC),[13]. Defined Daily Doses (DDDs) were calculated for all prescribed antibiotics,[13]. DDD is a technical unit for comparative purposes and is the average daily dose of the specific drug for its main indication in adults,[14]. Fixed dose combinations of antibiotics (FDCs) that did not have an ATC code assigned by WHOCC were assigned the code 'J01RA*' according to Sharma et al,[15]. FDCs that did not have a DDD were assigned one by examining the constituents and the proportions in which they were found in one unit dose. DDD was then calculated on the basis of number of units and converted to dose in gram.

The NLEMI is based on the WHO list of essential medicines (WHOLEM) and adapted to the disease panorama of India,[16]. These lists serve as guidelines to promote the prescribing of safe, cheap and effective drugs to the population,[16, 17]. Adherence to these lists was evaluated for all prescriptions.

Data sources and considerations

The data collection process is described in detail earlier,[11, 12]. In brief, the data was collected prospectively between April 1st, 2008 and March 31st, 2011, for all patients admitted to the medicine departments at the TH and the NTH. This would have minimized the chances of any selection bias. The data was collected manually by the nurses on a specially designed form which was attached to the patient's file. The nurses and new recruits were trained regularly for the data collection by the last author.

Inpatients were categorized based on registered diagnoses in the patient file, using the 'International Classification of Diseases' (ICD-10). The patients could have multiple registered diagnoses. Following the aim of the study, best possible efforts were done to distinguish the patients who had any indications for secondary antibiotic prophylaxis from those who did not,[18, 19, 20]. To obtain a better overview of the diseases the patients were categorized into 3 main groups; (a) cardiovascular, (b) non-infectious fevers and (c) other diagnoses. The group (c) included patients having either indicated or confirmed bacterial infections; 75% of all patients in the NTH and 67% in the TH. The groups (a) and (b) with non-infectious diseases were purposefully selected for detail study (Figure 1).

Figure 1. The process of selection and grouping of inpatients admitted in medicine departments of the TH and the NTH based on their diagnosis.

In order to identify and analyse the patients without any suspected bacterial infection as per the aim, these groups were further divided into four sub-groups as presented in Figure 1. The cardiovascular group was divided in two sub-groups; sub-group 1: 'cardiovascular diseases

with no registered bacterial infection', sub-group 2: 'cardiovascular diseases with suspected bacterial infection'. Similarly, the non-infectious fever group was divided as sub-group 3: 'malaria or viral fever with no registered bacterial infection' and sub-group 4: 'malaria or viral fever with suspected bacterial infection' (Figure 1).

All cases of chronic obstructive pulmonary disease (COPD) were included in the bacterial infection groups since the aetiology of disease was seldom specified but these patients should receive less restricted antibiotic treatment. All patients with rheumatic heart disease (RHD) were categorized among patients with suspected bacterial infection, since the WHO guidelines for secondary prevention after rheumatic fever sets the duration of preventive antibiotic treatment from five years up to life-long, depending on a number of factors e.g. Time since last episode of rheumatic fever and severity of valve engagement,[19]. It also supports an individual assessment in every patient case. An antibiotic prescribed for a day was considered as one prescribing occasion and prescribed DDDs were calculated per 1000 patients for the four sub-groups. According to WHOCC, oral metronidazole (P01AB01) is coded as an antiprotozoal drug, but in the National List of Essential Medicines of India (NLEMI) oral metronidazole is coded as an antibacterial drug and was therefore considered as an antibacterial in this study,[16].

Ethics statement

Being an observational study, the data collection did not interfere with the treatment or caused any extra risks for the patients. Moreover, the names of the prescribers were not recorded to rule out the effect of being observed. All patients were assigned a unique code during the data entry to maintain anonymity of the inpatients. This unique code was used to compare details of patient information and antibiotic prescriptions for the analysis. The ethics committee of Ruxmaniben Deepchand Gardi Medical College, Ujjain, approved the study with approval number: 41/2007.

Statistical Methods

All frequency and percentage of categorical values were calculated. Sum, median, mean, range and standard deviation were calculated for continuous numerical values. Values were rounded off to the closest whole number for percentage, prescription tables and in the text. The independent t-test was used for comparison of normal distributed and continuous variables. The chi-square test was used for comparison of categorical values. Fischer´s exact test was used for expected <0.05 and Pearson chi-square test was used for expected values >0.05. Bonferroni´s correction for multiple comparisons was used and p- values <0.001 were chosen for significance level to minimize the risks of type one errors. The data were analysed with Excel, SPSS version 22 (SPSS Inc., Chicago, IL, USA) and STATA version 13.1 (Stata Corp, College station, TX, USA).

RESULTS

During the study period, totally 21558 patients were admitted in the two medicine departments, 7177 patients were admitted in the TH and 14381in the NTH (Figure 1). As per the inclusion criteria, 20303 (94%) patients qualified as inpatients (6961 in the TH and 13342 in the NTH) and were included for further analysis.

In the TH 4540/6961 inpatients (65%) and in the NTH, 8900/13342 inpatients (67%) were prescribed antibiotics. An average of eight prescribing occasions were found per patient at the TH whereas in the NTH five antibiotic prescriptions were found per patient. Overall significantly higher proportion of the antibiotics prescribed in the TH adhered to the NLEMI; 77% prescriptions (27649/35732) than in the NTH; 60% (24683/ 41068, p<0.001).

Seven percent of all antibiotic prescriptions were made by using generic names in the TH which was significantly higher compared with the NTH (2%, p<0.001). At the TH, trade names; 'Cipro', 'Doxy', Genta' and 'Metrogyl' were used as local abbreviations for ciprofloxacin, doxycycline, gentamycin and metronidazole respectively. Longer duration of

stay and longer duration of antibiotic treatment was observed at the TH (mean days; 6 and 6 respectively) compared to the NTH (mean days; 3 and 4 respectively, p<0.001).

Distribution of inpatients in diagnosis groups and antibiotic prescription patterns

The most common diagnoses differed at the two hospitals. At department level in the TH, chronic obstructive pulmonary disease (COPD) (10%), viral fever (7%) and hypertension (5%) were more common and at the NTH; viral fever (10%), malaria (6%) and COPD (5%, Table 1). Among the non-infectious diagnoses group; cardiovascular (ICD-10 codes beginning with 'I') accounted for 48% of the group at the TH and 30% at the NTH. In the fever group, malaria was significantly more common at the NTH (74% patients) and viral infection was significantly more common at the TH (66% patients, p<0.001). Totally at the NTH broad-spectrum antibiotics such as third-generation cephalosporins (J01DD) and FDCs (J01RA*) comprised 52% of prescribing occasions of which FDCs accounted for 23% of occasions. At the TH these classes accounted for 13% of the total prescribing occasions with FDCs<1%. Demographic details and class wise distribution of prescribed antibiotic among all selected diagnoses groups of patients is presented in Table 2 and 3 respectively.

At the NTH, cephalosporin (J01D) was the most commonly prescribed class in the cardiovascular group (>35%), where third-generation cephalosporins (J01DD) constituted a major part of it (>30%) followed by FDCs (>20%). Fluoroquinolones (J01M) was the most commonly prescribed antibiotic class in the TH in both cardiovascular and fever groups (>30%, and >40% respectively).

Table 1: Diagnoses of the four groups of inpatients at medicine departments at one teaching and one non-teaching hospitals in Ujjain, India

Cardiovascular with no registered bacterial infection			Cardiovascular with suspected bacterial infection			Malaria or Viral Fever with no registered bacterial infection			Malaria or Viral Fever with suspected bacterial infection		
Diagnosis group	**TH**	**NTH**	**Diagnosis group**	**TH**	**NTH**	**Diagnosis group**	**TH**	**NTH**	**Diagnosis group**	**TH**	**NTH**
	n(%)	**n(%)**		**n(%)**	**n(%)**		**n(%)**	**n(%)**		**n(%)**	**n(%)**
Total	**1068**	**1738**	**Total**	**438**	**254**	**Total**	**693**	**1177**	**Total**	**55**	**28**
Hypertension	328(31)	470(27)	COPD	209(48)	77(30)	**Malaria**	237(34)	872(74)	COPD	10(18)	5(18)
Cerebro vascular accident	126(12)	383(22)	Rheumatic Heart Disease	130(30)	102(40)	Cerebral smalaria caused by P. Falciparum	4(1)	11(1)	Urinarytrac tinfection	5(9)	7(25)
Acute Myocardial Infarction	28(3)	202(12)	Pulmonary Tuberculosis	19(4)	18(7)	Malaria caused by P. Falciparum UNS	9(1)	9(1)	Tyfoid fever	8(15)	2(7)
Chronic Ischemic Heart Disease	17(2)	189(11)	Urinarytract infection	17(4)	15(6)	Malaria caused by P. Vivax UNS	16(2)	61(5)	Acute gastroenteritis	4(7)	6(21)
Coronary Artery Disease	98(9)	101(6)	Acute Gastroenteritis	14(3)	12(5)	Malaria UNS	208(30)	791(67)	Disease of airways UNS	8(15)	0(0)
Left Ventricle Failure	44(4)	69(4)	Lower airway infection UNS	13(3)	0(0)	**Viral fever**	456(66)	305(26)	Disease of upper airways UNS	7(13)	0(0)
Congestive Heart Failure	56(5)	39(2)	Sepsis	0(0)	5(2)				Pulmonary Tuberculosis	4(7)	2(7)
Dilated Cardiomyopathy	79(7)	6(<1)	HIV with infection	8(2)	1(<1)				HIV with infection	2(4)	0(0)
Unspecified Cardiomyopathy	21(2)	54(3)	Rheumatic Fever	1(<1)	4(2)				Rheumatic Heart Disease	2(4)	1(4)
Multiple Valve Disease	61(6)	7(<1)	Endocarditis	0(0)	4(2)				Pelvic Inflammatory Disease	2(4)	0(0)
Angina Pectoris	10(1)	35(2)	Pneumonia	1(<1)	4(2)				Pneumonia	0(0)	1(4)
Acute Ischemic Heart Disease	31(3)	11(1)	Others	26(6)	12(5)				Other diagnoses	3(5)	4(14)
Deep Vein Thrombosis UNS	13(1)	19(1)									
Mitral Stenosis	21(2)	2(<1)									
Hypertensive Heart Disease	20(2)	1(<1)									
Cardiac arrest	2(<1)	16(1)									
Other	113(11)	134(8)									

Abbreviations: n(%)- Number of patients (percentage in that diagnosis group), NTH-non-teaching hospital, TH-teaching hospital, COPD-chronic obstructive pulmonary disease, UNS-unspecified, P.-plasmodium, HIV-human immunodeficiency virus.

Table 2: Demographic details and antibiotic prescribing information of the inpatients at medicine departments at one teaching and one non-teaching hospitals in Ujjain, India

	Medicine Department			Cardiovascular with no registered bacterial diagnosis			Cardiovascular with suspected bacterial infection			Malaria or Viral Fever with no registered bacterial diagnosis			Malaria or Viral Fever with suspected bacterial infection		
	TH	**NTH**	**p-value**	**TH**	**NTH**	**p-value**	**TH**	**NTH**	**p-value**	**TH**	**NTH**	**p-value**	**TH**	**NTH**	**p-value**
Inpatients; n	6961	13342		1068	1738		438	254		693	1177		55	28	
Age; mean years (SD)	45(17)	43 (18)	**<0.001**	53 (14)	55 (15)	**<0.001**	49 (17)	51 (17)	0.222	36 (15)	35 (16)	0.387	37 (14)	40 (20)	0.440
Inpatients prescribed AB; n (%)	4540 (65)	8900 (67)	0.034	392 (37)	808 (47)	**<0.001**	299 (68)	179 (71)	0.545	569 (82)	831 (71)	**<0.001**	53 (96)	21 (75)	0.006[a]
Duration of hospital stay; mean days (SD)	6 (5)	3 (3)	**<0.001**	6 (5)	3 (3)	**<0.001**	7 (5)	4 (3)	**<0.001**	4 (4)	3 (2)	**<0.001**	5 (3)	4(2)	0.796
Duration of AB treatment; mean days (SD)	6 (4)	4 (2)	**<0.001**	6 (4)	4 (2)	**<0.001**	7 (4)	4 (2)	**<0.001**	5 (3)	4 (2)	**<0.001**	5 (2)	5(2)	0.419
Total AB prescription; n	35732	41068		2741	3366		2388	855		3210	3451		316	128	
Prescriptions per patient	7.8	4.6		7	4		8	4.8		5.6	4.2		6	6.1	
AB prescriptions by generic name; n (%)	2341 (7)	685 (2)	**<0.001**	175 (6)	47 (1)	**<0.001**	282 (12)	46 (5)	**<0.001**	61 (2)	52 (2)	0.214	19 (6)	5 (4)	0.374[a]
Prescriptions of AB found in NLEMI; n (%)	27640 (77)	24683 (60)	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-

Abbreviations: AB-antibiotics, NTH: non-teaching hospital, SD-standard deviation, TH: teaching hospital. Significant p-values are shown in bold. Independent sample t-test was used to compare age, duration of hospital stay and duration of antibiotic treatment. Pearson chi-square was used to compare prescription details with expected value >5. [a]Fischer´s exact test was used to compare expected values <5.

Table 3: Class wise distribution of prescribed antibiotics in four selected diagnoses groups at one teaching and one non-teaching hospitals in Ujjain, India

	Cardiovascular with no registered bacterial infection			Cardiovascular with suspected bacterial infection			Malaria or Viral with no registered bacterial infection			Malaria or Viral Fever with suspected bacterial infection		
Name of AB; ATC-code	**TH**	**NTH**	**p-value**	**TH**	**NTH**	**p-value**	**TH**	**NTH**	**p-value**	**TH**	**NTH**	**p-value**
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Total prescriptions	2741	3366		2388	855		3210	3451		316	128	
Tetracyclines; J01A: J01AA	284 (10)	5 (0)	**<0.001**	243 (10)	0 (0)		553 (17)	75 (2)	**<0.001**	83 (26)	0 (0)	
Beta-lactam ABs, penicillin; J01C	458 (17)	498 (15)	0.041	622 (26)	184 (22)	0.009	111 (3)	245 (7)	**<0.001**	12 (4)	7 (5)	0.431
Extended-spectrum penicillins; J01CA	83 (3)	99 (3)	0.843	122 (5)	99 (12)	**<0.001**	19 (1)	51 (1)	**<0.001**	0 (0)	2 (2)	
Combination of penicillin incl. Beta-lactamase AB; J01CR	373 (14)	399 (12)	0.040	500 (21)	85 (10)	**<0.001**	92 (3)	194 (6)	**<0.001**	12 (4)	5 (4)	1.0[a]
Other Beta-lactam; J01D	488 (18)	1391 (41)	**<0.001**	353 (15)	304 (36)	**<0.001**	665 (21)	1792 (52)	**<0.001**	40 (13)	39 (30)	**<0.001**
1st gen. cephalosporins; J01DB	7 (0)	16 (1)	0.163	0 (0)	5 (1)		0 (0)	9 (0)		0 (0)	0 (0)	
2nd gen. cephalosporins; J01DC	0 (0)	98 (3)		0 (0)	27 (3)		0 (0)	168 (5)		0 (0)	0 (0)	
3rd gen. cephalosporins; J01DD	481 (18)	1254 (37)	**<0.001**	353 (15)	272 (32)	**<0.001**	665 (21)	1606 (47)	**<0.001**	40 (13)	39 (30)	**<0.001**
4th gen. cephalosporins; J01DH	8 (0)	23 (1)	0.032	0 (0)	0 (0)		0 (0)	9 (0)		0 (0)	0 (0)	
Sulfonamide with timethoprime; J01E: J01EE	8 (0)	0 (0)		18 (1)	0 (0)		8 (0)	0 (0)		0 (0)	0 (0)	
Macrolides, lincosamides J01F	16 (1)	2 (0)	**<0.001**	4 (0)	6 (1)	0.025*	15 (0)	7 (0)	0.060	3 (1)	4 (3)	0.110[a]
Macrolides; J01FA	12 (0)	2	0.002	4 (0)	6 (1)		15 (0)	7 (0)		3 (1)	4 (3)	
Lincosamides; J01FF	4 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Aminoglycoside; J01G: J01GB	78 (3)	73 (2)	0.090	149 (6)	46 (5)	0.364	17 (1)	60 (2)	**<0.001**	11 (3)	9 (7)	0.102
Quinolones; J01M: J01MA	1031 (38)	301 (9)	**<0.001**	731 (31)	112 (13)	**<0.001**	1526 (48)	464 (13)	**<0.001**	126 (40)	37 (29)	0.030
Fixed dose combination of ABs; J01R: J01RA*	12 (0)	929 (28)	**<0.001**	31 (1)	170 (20)	**<0.001**	34 (1)	669 (19)	**<0.001**	6 (2)	17 (13)	**<0.01**
Other ABs; J01X	167 (6)	176 (5)	0.145	132 (6)	30 (4)	0.020	149 (5)	138 (4)	0.197	20 (6)	15 (12)	0.056
Glycopetide ABs; J01XA	15 (1)	176 (5)	**<0.001**	0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Imidazole dervatives; J01XD	152 (6)	0 (0)		132 (6)	30 (4)	0.020	149 (5)	137 (4)	0.176	20 (6)	15 (12)	0.056
Other ABs; J01XX	0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	1 (0)		0 (0)	0 (0)	
Drugs for treatment of tuberculosis; J04A	0 (0)	0 (0)		24 (1)	0 (0)		0	0 (0)		0 (0)	0 (0)	
Antibiotics; J04AB (Treatment for Tuberculosis)	0 (0)	0 (0)		6 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Hydrazides; J04AC	0 (0)	0 (0)		6 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Other drugs for treatment of tuberculosis; J04AK	0 (0)	0 (0)		12 (1)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Nitromidazole derivatives; P01AB (Oral Metronidazole)	201 (7)	0 (0)		81 (3)	3 (0)	**<0.001**	132 (4)	1 (0)	**<0.001**	15 (5)	0 (0)	

Abbreviations: : n(%)- Number of patients (percentage in antibiotic class),AB-antibiotics, ATC-WHO anatomic therapeutic chemical classification, NTH: non-teaching hospital, TH: teaching hospital. Significant p-values shown in bold. Pearson chi-square and [a]Fischer´s exact test were used to compare antibiotic prescribing details, gen- generation.

Third-generation cephalosporins (J01DD) constituted 47% and 30% prescriptions among sub-group 3 and 4at the NTH, followed by FDCs in 19% and 29% prescriptions respectively. Overall, antibiotic prescriptions were significantly more common among the patients in 'malaria or viral fever with no registered bacterial infections group' than in the 'cardiovascular diseases with no registered bacterial infections' ($p<0.001$). None of the records from the four sub-groups had requisition for sending samples for bacterial culture.

The most frequently prescribed antibiotic substance measured in DDD/1000 patients at department level of the TH was ciprofloxacin (J01MA02) and at the NTH was ceftriaxone (J01DD04). DDDs calculated as DDD per 1000 patients in four sub-groups are described in Table 4. Ciprofloxacin had highest prescribed DDDs/1000 patient followed by doxycycline and ceftriaxone in both hospitals (Figure 2).

Table 4: Most commonly prescribed antibiotics among the selected diagnoses groups presenting the prescribing occasions in DDDs/1000 patients at sixth level of the ATC classification

	Cardiovascular with no registered bacterial infection n (%)		Cardiovascular with suspected bacterial infection n (%)		Malaria or Viral Fever with no registered bacterial infection n (%)		Malaria or Viral Fever with suspected bacterial infection n (%)	
Name; ATC-code	**TH**	**NTH**	**TH**	**NTH**	**TH**	**NTH**	**TH**	**NTH**
Total DDDs/1000 patients	2062 (99)	1456 (100)	4514 (99)	3421 (100[#])	4480 (100[#])	3048 (100[#])	5432 (100[#])	5827 (100)
Doxycycline, J01AA02	491 (24)		1030 (23)		1463 (33)	296 (10)	2745 (51)	
Ampicillin, J01CA01	68 (3)		170 (4)					
Amoxicillin, J01CA04		81 (6)		435 (13)				
Amoxicillin + Clavulanic acid, J01CR02				566 (17)		88 (3)		
Piperacillin + Tazobactam, J01CR05						34 (1)		
Ampicillin + Cloxacillin, J01CR50	217 (11)		774 (17)				191 (4)	
Cefuroxime, J01DC02				95 (3)		136 (4)		
Cefprozil, J01DC10		75 (5)						
Cefotaxime, J01DD01	172 (8)	46 (3)	298 (7)	59 (2)	199 (4)	96 (3)	295 (5)	
Ceftriaxone, J01DD04	133 (6)	558 (38)	244 (5)	907 (27)	560 (13)	1052 (35)	164 (3)	1402 (24)
Azithromycin, J01FA10								476 (8)
Gentamicin, J01GB03	44 (2)		167 (4)	81 (2)				
Amikacin, J01GB06								321 (6)
Ofloxacin, J01MA01						202 (7)		
Ciprofloxacin, J01MA02	687 (33)	141 (10)	1057 (23)	527 (15)	1940 (43)	602 (20)	1185 (22)	2886 (50)
Norfloxacin, J01MA06			201 (4)				273 (5)	
Levofloxacin, J01MA12		73 (5)	202 (4)	129 (4)			145 (3)	
Cefoperazone + Sulbactam, J01RA*83		92 (6)		94 (3)		90 (3)		125 (2)
Ceftriaxone + Sulbactam, J01RA*84		228 (16)		277 (8)		199 (7)		
Ceftriaxone + Tazobactam, J01RA*85		162 (11)		156 (5)		162 (5)		250 (4)
Metronidazole, J01XD01	139 (7)		262 (6)	95 (3)	204 (5)	91 (3)	262 (5)	367 (6)
Metronidazole, P01AB01 (Oral)	111 (5)		109 (2)		114 (3)		172 (3)	

Abbreviations: : n(%)- Number of patients (percentage), AB: antibiotics, DDD: Defined Daily Dose, NTH: non-teaching hospital, TH: teaching hospital, [#] rounding off the percentages to nearest integer made the total more than 100%

Figure 2. Top 90% of prescription in the four selected groups measured in DDD/1000 patients, presented at fourth level of the ATC classification at one teaching and one non-teaching hospitals in Ujjain, India

DISCUSSION

To our knowledge this is the first study that presented antibiotic prescription practices at medicine departments in Indian private sector hospitals focusing the non-bacterial infection diseases. This also leads to a limitation as the results of present study could not be compared with any other study thus the results were compared with most equivalent studies available. Antibiotics were commonly prescribed to the inpatients at both study hospitals. Irrespective of the indications, broad-spectrum antibiotics and third-generation cephalosporins that are to be conserved for high risks co-morbidities and life-threatening bacterial infections were prescribed frequently. The study also highlights high rates of antibiotic prescriptions for the selected groups of non-bacterial infectious diseases such as cardiovascular disease, malaria and viral fever.

Antibiotic prescription in the cardiovascular and fever groups

The average prescription rate at the medicine departments were higher (TH: 65% and NTH: 67%, $p<0.001$) when compared with the rates at the medicine department of a Government hospital at Bathalapalli, (Andhra Pradesh) India (63%),[21]. Cardiovascular diseases are primarily non-infectious with a few exceptions such as rheumatic fever, endocarditis, pericarditis and myocarditis (bacterial or viral). COPD and RHD are the common associated diseases among the cardiovascular patients. Rheumatic fever is an immune response sequel to an infection and may cause endocarditis,[19, 22]. Pericarditis and myocarditis are however most commonly developed from viral pathogens where antibiotic treatment is not recommended routinely,[23, 24].

Interestingly, more than 35% of inpatients among 'cardiovascular group with no registered bacterial infection' were prescribed antibiotics in both hospitals. As per the treatment

guidelines and recommendations, only the patients who have confirmed infectious diagnosis are expected to receive an antibiotic prescription,[15, 16]. Therefore, the practice of prescribing antibiotics in absence of indications among the cardiovascular patients could be termed as unnecessary. Among the COPD and RHD patients the aetiology of current episode of hospitalization could be potentially expected to be non-bacterial e.g. viral infection. Although could not be confirmed due to unclear patients' records, but prescribing antibiotics to 35% cases in the group could not be justified.

FDCs were prescribed at higher extent to the cardiovascular patients at the NTH than at the TH. Rationality of the newer FDCs coded with ATC-code: J01RA* is not established yet and these combinations are neither listed in the NLEMI nor in the WHOLEM,[16, 17]. It is also evident that the constituents of these combinations are often present in smaller quantities than recommended which might lead to incept the development of antibiotic resistance,[25].

The sub-group 'malaria or viral fever with suspected bacterial infection' presented highest rate of antibiotic prescriptions among all four sub-groups (TH: 96%, NTH 75%). Our result also highlights that fever was perceived higher risk for the inpatients to receive antibiotic prescriptions, than having cardiovascular diseases. Fever is a common symptom among malaria, viral fever and bacterial infection. Therefore, the doctors might have prescribed antibiotics as a 'prophylactic' treatment to treat bacterial infection, if any. The result was higher yet comparable with a study at primary and secondary health care settings in Uttar Pradesh, India. That study showed that 85% of the fever patients were prescribed antibiotics,[26]. Additionally, in our study high percentage of patients with fever (malaria and viral fever) with 'no registered bacterial infection' were prescribed antibiotics (TH: 82%, NTH: 71%). An out-patient study from Uganda, a malaria endemic country, showed that 42% malaria patients were prescribed antibiotics without any registered indication,[27]. Although majority of the prescriptions in the study were empirical thus the rationality of the

prescriptions cannot be evaluated. However, prescribing antibiotics to non-bacterial infections is termed as irrational practice and need an imperative attention.

Adherence to the essential medicine lists and prescriptions by generic name

According to WHO, prescribing by generic name is part of rational prescribing and the drug policy applicable for both public and private Indian healthcare settings. Prescribing and purchasing by generic name is cost effective and provide flexibility to buy the available medicine of any company. However, the presumed adherence is higher at public hospitals, followed at 'private non-profit' hospitals and lastly at the 'private for-profit' hospitals,[11, 12, 28]. In present study, antibiotic prescriptions made by generic names among the patients of cardiovascular diseases with no registered bacterial infection (TH: 6%, NTH: 1% $p<0.001$) and with suspected bacterial infection (TH: 12% NTH: 5% $p<0.001$) were significantly lower at the NTH than at the TH. Third-generation cephalosporins (J01D, 29%) and FDCs (J01RA*, 23%) were most commonly prescribed classes at the NTH while quinolones were most commonly prescribed at the TH during the study period (J01M, 37%, NTH: 13%). Previous studies from Uttar Pradesh and Madhya Pradesh, India have also shown similar results for academic and non-academic hospitals,[11, 12, 15]. High prescribing of these classes are further supported by Van Boeckel et al, they observed a huge increase in the consumption of fluoroquinolones and cephalosporins all over the globe over past decade. This increase was mainly contributed by the rates of India and China,[9]. At the NTH prescriptions of FDCs varied between 19 and 28% among the selected sub-groups (TH: <2%) and the prescriptions of third-generation cephalosporins varied between 30 and 47% (TH: <22%). According to the WHO, prescription of multiple drugs when not indicated, prescribed in inadequate doses (often constituted in smaller quantity than recommended) and prescription of drugs that are not in accordance to the local or national clinical guidelines are all examples of actions deemed inappropriate,[29]. All these traits may be true for the prescriptions of the newer

FDCs (J01RA*) in present study, both study hospitals are from private sector and are regulated by the same trust on 'not for-profit' basis. The differences in the prescribing practices might be an influence of the fact that academic hospitals are a part of the educational process and regular educational activities conducted at these hospitals reflects in better adherence to the guidelines, as presented at the TH. Another reason for frequent prescribing of broad-spectrum antibiotics, new FDCs and use of trade names at the NTH could be explained by the results of a review by Blumenthal et al,[30]. The review concluded that physicians who had received gifts or money from the pharmaceutical companies were more likely to prescribe drugs produced by the company and less prone to use generic names. The pressure from pharmaceutical companies could be anticipated on the doctors at the NTH, due to unrestricted visits of pharmaceutical company representatives. Moreover, these new FDCs of antibiotics are more expensive than regular and generic formulations and generate extra earnings to the doctors. The restriction of these visits and the management control over the purchase and supply of medicines could be seen as main reasons for low FDCs prescribing and high use of generic names at the TH. Interestingly trade names were used as local abbreviations for the four antibiotics namely ciprofloxacin, doxycycline, gentamycin and metronidazole at the TH as discussed in method section. Only generic drugs were purchased and dispensed at the TH due to administrative control over purchase and supply of the drugs. Thus even if these antibiotics were prescribed by an abbreviation similar to the trade names these were included in adherence to generic name prescribing.

Duration of stay and duration of antibiotic treatment

In present study both duration of stay and duration of antibiotic treatment were longer at the TH compared to the NTH among all inpatients groups. This could be explained by the fact that the charges of healthcare and drugs were supplied free at the TH, making the stay economically feasible at the TH than at the NTH where they had to pay for all services and

medicines. This association of longer duration of stay and antibiotic treatment at TH has also been observed in previous studies from India,[11, 15, 31]. However, it is evident that the treatment given for both shorter or longer time period than recommended, is irrational and substantially contributes to the development of antibiotic resistance,[1, 29].

GENERALISABILITY

The data collection method is robust and reliable. The data collection method and tool could easily be adapted at other tertiary care hospitals that lack computerized patient records to suit the needs of the hospitals. Recruitment of the nursing staff routinely working in the department, for manual data collection would have helped to minimize the influence of study on the prescribers. High prescribing rates of antibiotics and use of FDCs among inpatients in these settings could broadly be considered as representative for similar health care settings in low-middle income countries.

CONCLUSION

At the TH, higher percentage of prescribing occasions adhered to the guidelines than at the NTH, however, the overall adherence was low. Fever was a risk factor to receive antibiotic prescription at both hospitals. Patients with non-bacterial infections such as malaria or viral fever or cardiovascular diseases were prescribed antibiotics at both medicine departments which could not be justified. Broad spectrum antibiotics with irrational combinations of antibiotics were commonly prescribed in the study hospitals in non-indicated conditions.

FUTURE IMPLICATIONS

Development and implementation of local diagnosis specific prescribing guidelines along with continuous follow-up of prescriptions under antibiotic stewardship programs is needed for the settings. The results from the TH indicate a promising effect of management control to minimise antibiotic prescribing, for better adherence to the NLEMI and use of generic names

compared to the NTH and could be tested in other settings. Improving hygiene is another recommendation for prevention of infections and to decrease the 'prophylactic' use of antibiotics. Lack of 'culture of sending cultures' is another concern at the settings. Motivating the physicians of both settings to send cultures before prescribing antibiotics is also suggested.

CONTRIBUTERSHIP STATEMENT

MS and CSL designed, visualized the research question and developed the data collection tool. MS conducted repeated training sessions for nursing personal for recording the data. MS was also responsible for coordination with the nursing staff, monitoring and supervision of the data collection and entry. CSL participated in planning the study design and the coordination of the study. KL, CSL and MS participated in the conception and design of the present study and revising the paper critically for substantial intellectual content. KL grouped and analyzed the data, performed the statistical analysis and contributed in drafting the manuscript along with MS, CSL, FJ and AS. KL, AS and MS were responsible for categorization of the patients. All authors read and approved the final version of the manuscript.

COMPETING INTERESTS

The authors have no competing interests to declare.

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DATA SHARING STATEMENT

As per the institutional policy, the data is available with the Institutional ethics committee. This is to protect the patient's confidentiality and to ensure the electronic security of the data. The data could be made available to all interested researchers upon request made to; The Chairman, Ethics Committee, R.D. Gardi Medical College, Agar Road, Ujjain, Madhya Pradesh, India 456006 (Email: iecrdgmc@yahoo.in, uctharc@sancharnet.in), giving all details of the article. The ethical approval number: 41/2007 needs to be quoted along with the request.

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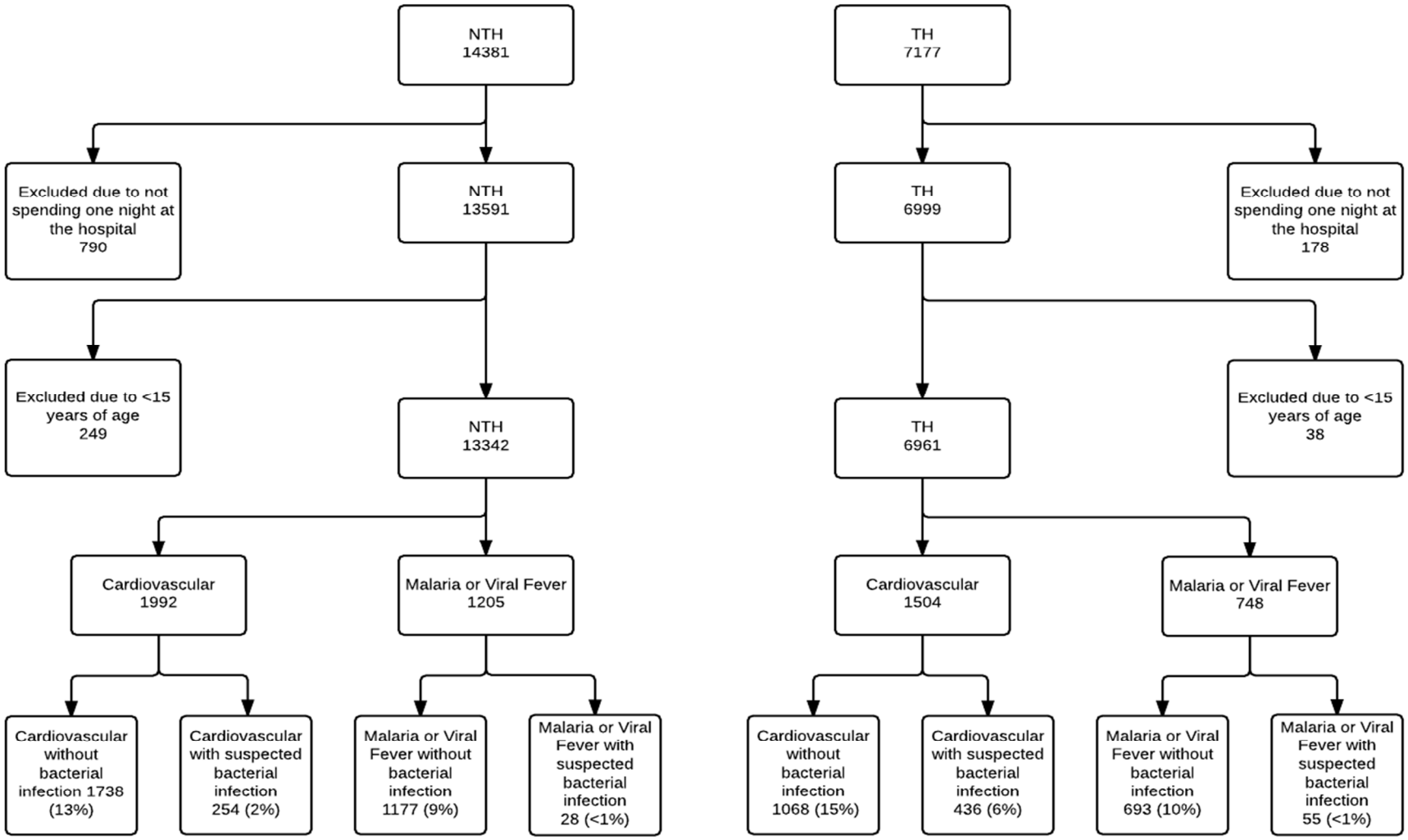
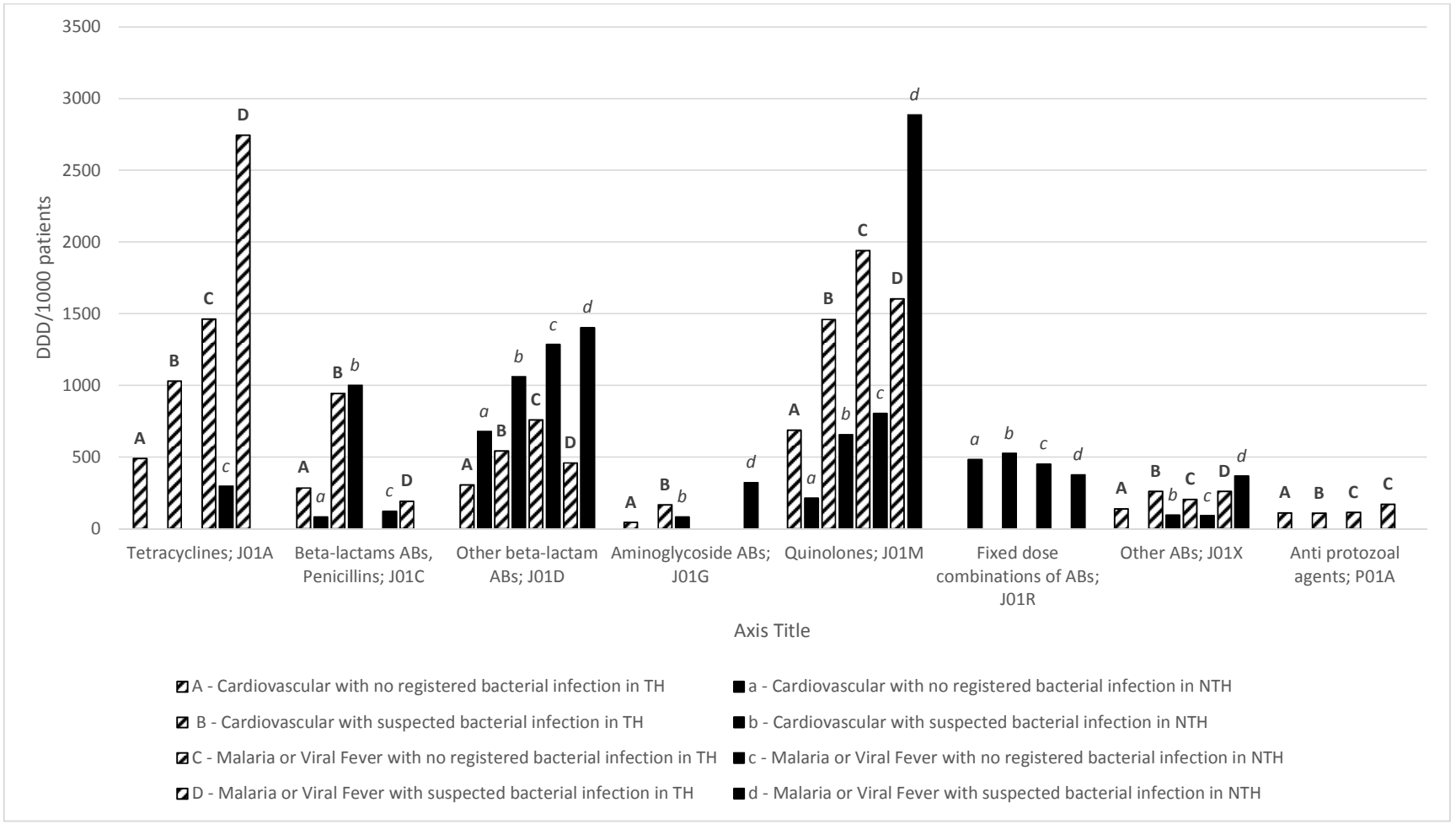
Figure 1. The process of selection and grouping of inpatients admitted in medicine departments of the TH and the NTH based on their diagnosis



Abbreviations: NTH: non-teaching hospital TH: teaching hospital

Figure 2: Top 90% of prescription in the four selected groups measured in DDD/1000 patients, presented at fourth level of the ATC classification at one teaching and one non-teaching hospitals in Ujjain, India



Abbreviations: AB-antibiotics NTH-non-teaching hospital, TH-teaching hospital, DDD- Defined Daily Doses

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2-3**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**5**
Objectives	3	State specific objectives, including any pre specified hypotheses	**6**
Methods			
Study design	4	Present key elements of study design early in the paper	**6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**6**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls ***Cross-sectional study***—Give the eligibility criteria, and the sources and methods of selection of participants	**7**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	***8***
Bias	9	Describe any efforts to address potential sources of bias	**9**
Study size	10	Explain how the study size was arrived at	**8**

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**8-10**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	**10**
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			Page Number
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**10,12**
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	**Figure 1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**10-12**
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	**11, 14-15**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**11,15,16 Figure 2**
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
		Discussion	
Key results	18	Summarise key results with reference to study objectives	**17**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**17**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**18-20**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**21**
		Other information	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**23**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Antibiotic prescriptions to the inpatients having non-bacterial diagnosis at medicine departments of two private sector hospitals in Madhya Pradesh, India: a cross sectional study

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Antibiotic prescriptions to the inpatients having non-bacterial diagnosis at medicine departments of two private sector hospitals in Madhya Pradesh, India: a cross sectional study

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Abstract

Objectives: To present and compare antibiotic prescribing among inpatients among most common non-bacterial diagnoses groups at medicine departments of a teaching (TH) and a non-teaching hospital (NTH) in Central India.

Setting: An observational cross-sectional study was conducted at two tertiary care settings at Ujjain district, Madhya Pradesh, India.

Participants: The data was collected manually, using a customized form. Complete records of all inpatients, who were >15 years of age and stayed at-least for one night in either of the hospitals during 2008-2011, were analysed.

Outcome measures: Inpatients were grouped based on the presence or absence of; a bacterial infectious diagnosis, viral/ malaria fever or cardiovascular diseases. Classes of antibiotics prescribed to these groups, and adherence to the available prescribing guidelines were compared between the hospitals using the notes from the patient files, and the diagnoses.

Results: Of 20303 inpatients included in the study, 66% were prescribed antibiotics. Trade name prescribing and use of broad spectrum antibiotics were more frequent at the NTH compared to the TH ($p<0.001$). At the TH significantly higher proportion of patients having fever without registered bacterial infection; were prescribed antibiotics (82%) compared with the NTH (71%, $p<0.001$). Patients admitted for cardiovascular diagnosis without registered bacterial infections received antibiotic prescriptions at both hospitals; (NTH- 47%and TH-37%); it was significantly higher at the NTH ($p<0.001$). None of the diagnoses were confirmed by microbiology reports.

Conclusions: Prescribing antibiotic including broad spectrum antibiotics to the inpatients without bacterial infections i.e. viral fever, malaria and cardiovascular diseases were common

at both hospitals which increase the risk for development of bacterial resistance, a global public health threat. Taking account of over prescribing of antibiotics, development and implementation of local prescribing guidelines, encouragement to use laboratory facilities, and prescription analysis, with antibiotic stewardship programs are the main recommendations for the settings.

Strengths and limitations

- Prospective study over a long time period of three years and inclusion of all patients, irrespective of their age and sex strengthens the representativeness of the results and overcome the seasonal variations.
- Data collecting tools were same at both study hospitals and the staff who collected the data was trained by the same person at both locations to minimize the variances.
- An observational non-interventional study design might have minimized the effect on the prescribers of being observed and audited.
- All possible efforts were made to minimize the risk of missing data by continuous monitoring and cross checking of the data. However, some data, for example few diagnoses might have been lost during translation from analogue to digital records.
- A big proportion of patients were categorised in the suspected bacterial diagnosis groups. Some of these diagnoses could have been categorised in non-bacterial diagnoses group if confirmed aetiology, i.e. microbiology reports, was present. This could have contributed to even higher antibiotic prescribing rates in the non-bacterial diagnoses group. However, due to absence of confirmed aetiology and observational study design this was indispensable.

BACKGROUND

Increasing morbidity and mortality due to infectious diseases, despite of the availability of the lifesaving antibiotics is an alarming situation, globally,[1]. These incidences of mortalities due to infections are higher in low- and middle-income countries than in high-income countries,[2–4]. The WHO has reported a high burden of communicable diseases in India, and infections are responsible for 28% of the total mortality in the country,[5,6]. Additionally, antibiotic resistance in India is reported to be high. However, figures cannot be generalized to all Indian settings as the bacterial resistance patterns widely vary between its regions and settings and most studies so far have been relatively limited in scope ,[7].

Irrational (both over- and under-) use of antibacterials, is of global concern. It results in unnecessary treatment costs, is a potential risk for the development of antibiotic resistance and side effects such as antibiotic associated diarrhoea caused by *Clostridium difficile* or gastroenteritis,[8]. According to a report, the global consumption of antibiotics increased by 36% between 2000 and 2010 of which five countries including India (Brazil, Russia, India, China and South Africa) accounted for 76% of this increase,[9]. Despite of the paucity of studies that describe antibiotic prescribing from India, Van Boeckel et al presented India on the top of the list of antibiotic consumption with $12.9x10^9$ units in 2010 where one unit indicates a pill, capsule or ampoule,[1,9]. However, this increase might also have meant that segments of the population that previously had no access to antibiotics can now access antibiotics yet it cannot be disregarded that antibiotic resistance is a sequel of antibiotic use,[10].

It is thus imperative to map the prescribing patterns of antibiotics on a local level to address the potential need of improvement and to counter the consequences of inappropriate prescription of antibiotics. Indian private sector are the major healthcare providers but little is known about prescribing patterns in this sector,[11–14].

OBJECTIVES

The study was conducted to present, analyse and compare antibiotic prescribing to the inpatients enrolled for most common non-bacterial diagnoses at the medicine departments of a teaching (TH) and a non-teaching hospital (NTH) in Central India.

METHODS

Study design

A cross sectional observational design was selected to conduct the study.

Setting

The study was conducted at the medicine departments of two tertiary care hospitals from private sector in Ujjain district, India. The hospitals are addressed as teaching hospital (TH) and non-teaching hospital (NTH). Both hospitals are run by the same trust. The TH is located in a rural area of Ujjain district and had 570 beds at the time of the study. The NTH is located in the central part of Ujjain city and had 350 beds at the time of the study. The TH provides medical services including medical treatment and free of charge medicines to all patients while the NTH charges for the medical facilities on a 'no profit-no loss' basis. Patients from the NTH have to buy prescribed medicines out-of-pocket from the pharmacies inside or outside the hospital. The physicians at the TH are salary paid and do not have any direct exposure to the sales representatives of pharmaceutical companies. Furthermore, the management at the TH is responsible for the purchase and supply of the drugs.

Hospital level Essential medicine list was available in written form at the TH but no specific implementation activities were conducted during the study period. Local prescribing guidelines were not present in any of the hospitals. Almost all physicians practicing at the NTH also had private practice and could be contacted by the representatives of pharmaceutical companies easily. The payments of the physicians at the NTH increase above

par according to the number of patients they admit in the hospital and the number of visits made to the inpatients. Both hospitals are tertiary care hospitals with a number of specialty departments such as; Pediatrics, Obstetrics and Gynecology, Surgery, Orthopedics, Pulmonary Medicine, and so on to treat specific patients. For example; patients presenting with complaints related to lungs and chest (other than heart) visit the Pulmonary Medicine department. A well-equipped microbiology laboratory was present to process the samples free of cost for all from the TH and with nominal charges from the NTH.

Participants

Inclusion and exclusion criteria

Patients who stayed for at least one night at medicine departments of either of the two hospitals were considered as inpatients and included in the study. Patients who had incomplete records or admitted to the medical intensive care units within the medicine departments were not included in the analysis. Treatment recommendations including dose and frequency is different for patients under 15 years of age and the DDD measurement is not applicable to them, thus they were also excluded,[15].

Variables

The patient information was analysed for age, sex, diagnosis, duration of hospitals stay, if they received antibiotic treatment, and duration of antibiotic treatment. The prescriptions were analysed for the type of antibiotics prescribed, its dose, and frequency. The antibiotics were classified according to the Anatomical Therapeutic Chemical (ATC) classification given by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC),[16].Defined Daily Doses (DDDs) were calculated for all prescribed antibiotics,[16]. DDD is a technical unit for comparative purposes and is the average daily dose of the specific drug for its main indication in adults,[15]. Fixed dose combinations of antibiotics (FDCs) that did not have an ATC code assigned by WHOCC were assigned the code 'J01RA*' according to Sharma et

al,[17]. FDCs that did not have a DDD were assigned one by examining the constituents and the proportions in which they were found in one unit dose. DDD was then calculated on the basis of number of units and converted to dose in gram. Total number of antibiotics prescribed during hospital stay was counted per patient and was termed as prescribing occasions.

The List of Essential Medicines of India (NLEMI) is based on the WHO list of essential medicines (WHOLEM) and adapted to the disease panorama of India,[18]. These lists serve as guidelines to promote the prescribing of safe, cheap and effective drugs to the population,[18,19]. Adherence to these lists was evaluated for all prescriptions.

Data sources and considerations

The data collection process is described in detail elsewhere,[13,14]. In brief, the study was conducted prospectively between April 1st, 2008 and March 31st, 2011. Patient throughput in the TH and the NTH amounted to 29026 and 41561 patients respectively. The data were manually collected by the nurses using a specially designed form attached to the patient's file at the medicine department of the TH and the NTH. All patients were included to minimize the possibility of selection bias. Every admission in the department was considered as a new patient. The nurses and new recruits were trained regularly for the data collection by the last author (MS). The data collection form was updated daily based on patient's day to day progress. All notes written in the patient files by the treating consultant were recorded and included for the analysis. It was possible that a patient could have more than one diagnosis. Therefore all indications, diagnoses and/or symptoms recorded in the patient files, were transferred to the data collection form. The data was translated to digital data files using EPI Info 3.1 and Microsoft Excel. Two specifically trained data entry operators translated the diagnoses as per 'International Classification of Diseases' (ICD-10 codes),[20,21] and the

generic names of the prescribed antibiotics were translated to WHO assigned ATC-codes and Defined Daily Doses (DDDs) per day,[15].

In order to exclude all clinically suspected cases of bacterial infection and following the aim of the study, best possible efforts were made to distinguish the patients who had any indications even for secondary antibiotic prophylaxis from those who did not,[22–24]. The patients were categorized into three main groups using the diagnoses registered in the patient files and the ICD-10 codes; Group (a) cardiovascular diseases, (b) non-bacterial fevers and (c) all diagnoses other than Group (a) and (b) including all types of bacterial infections. Sixty seven percent of patients in the TH and 75% in the NTH were included in Group (c). All cases of chronic obstructive pulmonary disease (COPD) were also included in Group c. Although aetiology of the disease was seldom specified in the records but these patients should receive less restricted antibiotic treatment.

Groups (a) and (b) were selected for detail study of the antibiotic prescribing for non-bacterial diagnoses as per the study aim. In 'Group (a)', hypertension, acute myocardial infarction and valvular heart disease were the most common diagnoses. In 'Group (b)' different types of malaria and cases of viral fever were included. These non-bacterial fevers were common in both study settings. It has previously been reported that antibiotics are prescribed to a high extent to patients having malaria or viral fever in malaria endemic countries like Uganda (Figure 1),[25]. Moreover, Groups (a) and (b) comprised the largest homogenous patient groups in our study settings.

Figure 1. The process of selection and grouping of inpatients admitted in medicine departments of the TH and the NTH based on their diagnosis.

These groups were further divided into four sub-groups to identify and analyse the patients exclusively having non-bacterial diagnoses corresponding to our study aim. The cardiovascular group (Group a) was divided in two sub-groups; 'cardiovascular diseases with

no registered bacterial infection' (sub-group 1), 'cardiovascular diseases with suspected bacterial infection' (sub-group 2). Similarly, the non-infectious fever group (Group b) was divided 'malaria or viral fever with no registered bacterial infection' (sub-group 3) and 'malaria or viral fever with suspected bacterial infection' (sub-group 4, Figure 1).

All patients with rheumatic heart disease (RHD) were categorized in sub-group 2, since the WHO guidelines for secondary prevention after rheumatic fever sets the duration of preventive antibiotic treatment from five years up to life-long, depending on a number of factors e.g. time since the last episode of rheumatic fever and severity of valve engagement and supports an individual assessment of every case,[22,23].

An antibiotic prescribed for a day was considered as one prescribing occasion. Prescribed DDDs were calculated per 1000 patients. According to WHOCC, oral metronidazole (P01AB01) is coded as an antiprotozoal drug, but is coded as an antibacterial in the NLEMI. Therefore it was considered as an antibacterial in this study,[18].

Ethics statement

Being an observational study, the data collection did not interfere with the treatment or caused any extra risks for the patients. Moreover, the names of the prescribers were not recorded to minimize the effect of being observed. All patients were assigned a unique code during the data entry to maintain anonymity of the inpatients. This unique code was used to compare details of patient information and antibiotic prescriptions for the analysis. The ethics committee of Ruxmaniben Deepchand Gardi Medical College, Ujjain, approved the study with approval number: 41/2007.

Statistical Methods

All frequency and percentage of categorical values were calculated. Sum, median, mean, range and standard deviation were calculated for continuous numerical values. Values were

rounded off to the closest whole number for percentage, prescription tables and in the text. The independent t-test was used for comparison of normally distributed and continuous variables. The chi-square test was used for comparison of categorical values. Fischer's exact test was used for expected values below 5 and Pearson chi-square test was used for expected values above 5. Bonferroni's correction for multiple comparisons was used and p- values <0.001 were chosen for significance level to minimize the risks of type one errors. The data were analysed with Excel, SPSS version 22 (SPSS Inc., Chicago, IL, USA) and STATA version 13.1 (Stata Corp, College station, TX, USA).

RESULTS

During the study period, totally 21557 patients were admitted to the two medicine departments, 7176 patients in the TH and 14381 in the NTH (Figure 1). Of the admitted patients, records of 20 patients were incomplete, 949 (5%) stayed less than one night and 285 patients (1%) were aged <15 years. Therefore, as per the inclusion criteria 1254 patient records were excluded and 20303 (94%) records were included for further analysis (6961 at the TH and 13342 at the NTH, Figure 1).

Most common diagnoses in the TH were chronic obstructive pulmonary disease (COPD, 10%), viral fever (7%) and hypertension (5%) while in the NTH were viral fever (10%), malaria (6%) and COPD (5%, Table 1). Antibiotics were prescribed to 4540/6961 inpatients (65%) in the TH and 8900/13342 (67%) in the NTH (Table 2). An average of eight and five prescribing occasions was found per patient at the TH and the NTH respectively. Overall a significantly higher proportion of the antibiotics prescribed in the TH adhered to the NLEMI; 77% prescriptions (27649/35732) than in the NTH; 60% (24683/41068, p<0.001).

Seven percent of antibiotics in the TH were prescribed using generic names it was significantly higher compared to the NTH (2%, p<0.001). Some antibiotics were prescribed

using trade names at the TH e.g., "Cipro", "Doxy", "Genta"' and "Metrogyl". However, these were local abbreviations devised by the staff for ciprofloxacin, doxycycline, gentamycin and metronidazole respectively. Even though these four antibiotics were prescribed using trade names, generic antibiotics were dispensed from the hospital pharmacy. A longer duration of stay and longer duration of antibiotic treatment was observed at the TH (mean days; 6 and 6 respectively) compared to the NTH (mean days; 3 and 4 respectively, $p<0.001$).

Distribution of inpatients in Groups a and b, and antibiotic prescription patterns

Cardiovascular diseases accounted for 48% of patients in Group (a) and (b) at the TH and 30% at the NTH. In the non-bacterial fever group, malaria was significantly more common at the NTH (74%) and viral fever was significantly more common at the TH (66%, $p<0.001$, Table 1).

Broad-spectrum antibiotics such as third-generation cephalosporins (J01DD) and FDCs (J01RA*) comprised 52% of the prescribing occasions at the NTH of which FDCs accounted for approximately half (Table 3). These classes accounted for 13% of total prescribing occasions and <1% FDCs. At the NTH, cephalosporins (third-generation cephalosporins J01DD, >30%) were most commonly prescribed for the cardiovascular diseases (>35%), followed by FDCs (>20%). Fluoroquinolones (J01M) was the most commonly prescribed antibiotic class in the TH in both (a) and (b) groups (>30% and >40% respectively).

Table 1: Diagnoses of the four groups of inpatients at medicine departments at one teaching and one non-teaching hospitals in Ujjain, India

Group (a): Cardiovascular diseases						Group (b): Malaria or Viral fever					
Cardiovascular with no registered bacterial infection Sub-group 1			Cardiovascular with suspected bacterial infection Sub-group 2			Malaria or Viral Fever with no registered bacterial infection Sub-group 3			Malaria or Viral Fever with suspected bacterial infection Sub-group 4		
Diagnosis group	**TH**	**NTH**	**Diagnosis group**	**TH**	**NTH**	**Diagnosis group**	**TH**	**NTH**	**Diagnosis group**	**TH**	**NTH**
	n(%)	**n(%)**		**n(%)**	**n(%)**		**n(%)**	**n(%)**		**n(%)**	**n(%)**
Total	**1068**	**1738**	**Total**	**438**	**254**	**Total**	**693**	**1177**	**Total**	**55**	**28**
Hypertension	328(31)	470(27)	COPD	209(48)	77(30)	**Malaria**	237(34)	872(74)	COPD	10(18)	5(18)
Cerebro vascular accident	126(12)	383(22)	Rheumatic Heart Disease	130(30)	102(40)	Cerebral malaria caused by *P. falciparum*	4(1)	11(1)	Urinarytrac tinfection	5(9)	7(25)
Acute Myocardial Infarction	28(3)	202(12)	Pulmonary Tuberculosis	19(4)	18(7)	Malaria caused by *P. falciparum* UNS	9(1)	9(1)	Tyfoid fever	8(15)	2(7)
Chronic Ischemic Heart Disease	17(2)	189(11)	Urinarytract infection	17(4)	15(6)	Malaria caused by *P. vivax* UNS	16(2)	61(5)	Acute gastroenteritis	4(7)	6(21)
Coronary Artery Disease	98(9)	101(6)	Acute Gastroenteritis	14(3)	12(5)	Malaria UNS	208(30)	791(67)	Disease of airways UNS	8(15)	0(0)
Left Ventricle Failure	44(4)	69(4)	Lower airway infection UNS	13(3)	0(0)	**Viral fever**	456(66)	305(26)	Disease of upper airways UNS	7(13)	0(0)
Congestive Heart Failure	56(5)	39(2)	Sepsis	0(0)	5(2)				Pulmonary Tuberculosis	4(7)	2(7)
Dilated Cardiomyopathy	79(7)	6(<1)	HIV with infection	8(2)	1(<1)				HIV with infection	2(4)	0(0)
Unspecified Cardiomyopathy	21(2)	54(3)	Rheumatic Fever	1(<1)	4(2)				Rheumatic Heart Disease	2(4)	1(4)
Multiple Valve Disease	61(6)	7(<1)	Endocarditis	0(0)	4(2)				Pelvic Inflammatory Disease	2(4)	0(0)
Angina Pectoris	10(1)	35(2)	Pneumonia	1(<1)	4(2)				Pneumonia	0(0)	1(4)
Acute Ischemic Heart Disease	31(3)	11(1)	Others	26(6)	12(5)				Other diagnoses	3(5)	4(14)
Deep Vein Thrombosis UNS	13(1)	19(1)									
Mitral Stenosis	21(2)	2(<1)									
Hypertensive Heart Disease	20(2)	1(<1)									
Cardiac arrest	2(<1)	16(1)									
Other	113(11)	134(8)									

Abbreviations: n (%): Number of patients (percentage in that diagnosis group), NTH: non-teaching hospital, TH: teaching hospital, COPD: chronic obstructive pulmonary disease, UNS: unspecified, *P.-plasmodium*, HIV: human immunodeficiency virus.

Table 2: Demographic details and antibiotic prescribing information of the inpatients at medicine departments at one teaching and one non-teaching hospitals in Ujjain, India

	Group (a): Cardiovascular diseases									Group (b): Malaria or Viral Fever					
	Medicine Department			Cardiovascular with no registered bacterial diagnosis (Sub-group 1)			Cardiovascular with suspected bacterial infection (Sub-group 2)			Malaria or Viral Fever with no registered bacterial diagnosis (Sub-group 3)			Malaria or Viral Fever with suspected bacterial infection (Sub-group 4)		
	TH	NTH	p-value	TH	NTH	p-value	TH	NTH	p-value	TH	NTH	p-value	TH	NTH	p-value
Inpatients; n	6961	13342		1068	1738		438	254		693	1177		55	28	
Age; mean years (SD)	45(17)	43 (18)	**<0.001**	53 (14)	55 (15)	**<0.001**	49 (17)	51 (17)	0.222	36 (15)	35 (16)	0.387	37 (14)	40 (20)	0.440
Inpatients prescribed AB; n (%)	4540 (65)	8900 (67)	0.034	392 (37)	808 (47)	**<0.001**	299 (68)	179 (71)	0.545	569 (82)	831 (71)	**<0.001**	53 (96)	21 (75)	0.006[a]
Duration of hospital stay; mean days (SD)	6 (5)	3 (3)	**<0.001**	6 (5)	3 (3)	**<0.001**	7 (5)	4 (3)	**<0.001**	4 (4)	3 (2)	**<0.001**	5 (3)	4(2)	0.796
Duration of AB treatment; mean days (SD)	6 (4)	4 (2)	**<0.001**	6 (4)	4 (2)	**<0.001**	7 (4)	4 (2)	**<0.001**	5 (3)	4 (2)	**<0.001**	5 (2)	5(2)	0.419
Total AB prescription; n	35732	41068		2741	3366		2388	855		3210	3451		316	128	
Prescriptions per patient	7.8	4.6		7	4		8	4.8		5.6	4.2		6	6.1	
AB prescriptions by generic name; n (%)	2341 (7)	685 (2)	**<0.001**	175 (6)	47 (1)	**<0.001**	282 (12)	46 (5)	**<0.001**	61 (2)	52 (2)	0.214	19 (6)	5 (4)	0.374[a]
Prescriptions of AB found in NLEMI; n (%)	27640 (77)	24683 (60)	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-

Abbreviations: AB: antibiotics, NTH: non-teaching hospital, SD: standard deviation, TH: teaching hospital. Significant p-values are shown in bold. Independent sample t-test was used to compare age, duration of hospital stay and duration of antibiotic treatment. Pearson chi-square was used to compare prescription details with expected value >5. [a]Fischer´s exact test was used to compare expected values <5.

Table 3: Class wise distribution of prescribed antibiotics in four selected diagnoses groups at one teaching and one non-teaching hospitals in Ujjain, India

	Group (a): Cardiovascular diseases						Group (b): Malaria or Viral fever					
	Cardiovascular with no registered bacterial infection (Sub-group 1)			Cardiovascular with suspected bacterial infection (Sub-group 2)			Malaria or Viral Fever with no registered bacterial infection (Sub-group 3)			Malaria or Viral Fever with suspected bacterial infection (Sub-group 4)		
Name of AB; ATC-code	**TH**	**NTH**	**p-value**	**TH**	**NTH**	**p-value**	**TH**	**NTH**	**p-value**	**TH**	**NTH**	**p-value**
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Total prescriptions	2741	3366		2388	855		3210	3451		316	128	
Tetracyclines; J01A: J01AA	284 (10)	5 (0)	**<0.001**	243 (10)	0 (0)		553 (17)	75 (2)	**<0.001**	83 (26)	0 (0)	
Beta-lactam ABs, penicillin; J01C	458 (17)	498 (15)	0.041	622 (26)	184 (22)	0.009	111 (3)	245 (7)	**<0.001**	12 (4)	7 (5)	0.431
Extended-spectrum penicillins; J01CA	83 (3)	99 (3)	0.843	122 (5)	99 (12)	**<0.001**	19 (1)	51 (1)	**<0.001**	0 (0)	2 (2)	
Combination of penicillin incl. Beta-lactamase AB; J01CR	373 (14)	399 (12)	0.040	500 (21)	85 (10)	**<0.001**	92 (3)	194 (6)	**<0.001**	12 (4)	5 (4)	1.0[a]
Other Beta-lactam; J01D	488 (18)	1391 (41)	**<0.001**	353 (15)	304 (36)	**<0.001**	665 (21)	1792 (52)	**<0.001**	40 (13)	39 (30)	**<0.001**
1st gen. cephalosporins; J01DB	7 (0)	16 (1)	0.163	0 (0)	5 (1)		0 (0)	9 (0)		0 (0)	0 (0)	
2nd gen. cephalosporins; J01DC	0 (0)	98 (3)		0 (0)	27 (3)		0 (0)	168 (5)		0 (0)	0 (0)	
3rd gen. cephalosporins; J01DD	481 (18)	1254 (37)	**<0.001**	353 (15)	272 (32)	**<0.001**	665 (21)	1606 (47)	**<0.001**	40 (13)	39 (30)	**<0.001**
4th gen. cephalosporins; J01DH	8 (0)	23 (1)	0.032	0 (0)	0 (0)		0 (0)	9 (0)		0 (0)	0 (0)	
Sulfonamide with timethoprime; J01E: J01EE	8 (0)	0 (0)		18 (1)	0 (0)		8 (0)	0 (0)		0 (0)	0 (0)	
Macrolides, lincosamides J01F	16 (1)	2 (0)	**<0.001**	4 (0)	6 (1)	0.025*	15 (0)	7 (0)	0.060	3 (1)	4 (3)	0.110[a]
Macrolides; J01FA	12 (0)	2	0.002	4 (0)	6 (1)		15 (0)	7 (0)		3 (1)	4 (3)	
Lincosamides; J01FF	4 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Aminoglycoside; J01G: J01GB	78 (3)	73 (2)	0.090	149 (6)	46 (5)	0.364	17 (1)	60 (2)	**<0.001**	11 (3)	9 (7)	0.102
Quinolones; J01M: J01MA	1031 (38)	301 (9)	**<0.001**	731 (31)	112 (13)	**<0.001**	1526 (48)	464 (13)	**<0.001**	126 (40)	37 (29)	0.030
Fixed dose combination of ABs; J01R: J01RA*	12 (0)	929 (28)	**<0.001**	31 (1)	170 (20)	**<0.001**	34 (1)	669 (19)	**<0.001**	6 (2)	17 (13)	**<0.01**
Other ABs; J01X	167 (6)	176 (5)	0.145	132 (6)	30 (4)	0.020	149 (5)	138 (4)	0.197	20 (6)	15 (12)	0.056
Glycopetide ABs; J01XA	15 (1)	176 (5)	**<0.001**	0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Imidazole derivatives; J01XD	152 (6)	0 (0)		132 (6)	30 (4)	0.020	149 (5)	137 (4)	0.176	20 (6)	15 (12)	0.056
Other ABs; J01XX	0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	1 (0)		0 (0)	0 (0)	
Drugs for treatment of tuberculosis; J04A	0 (0)	0 (0)		24 (1)	0 (0)		0	0 (0)		0 (0)	0 (0)	
Antibiotics; J04AB (Treatment for Tuberculosis)	0 (0)	0 (0)		6 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Hydrazides; J04AC	0 (0)	0 (0)		6 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Other drugs for treatment of tuberculosis; J04AK	0 (0)	0 (0)		12 (1)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Nitromidazole derivatives; P01AB (Oral Metronidazole)	201 (7)	0 (0)		81 (3)	3 (0)	**<0.001**	132 (4)	1 (0)	**<0.001**	15 (5)	0 (0)	

Abbreviations: n(%): Number of patients (percentage in antibiotic class), AB: antibiotics, ATC: WHO anatomic therapeutic chemical classification, NTH: non-teaching hospital, TH: teaching hospital. Significant p-values shown in bold. Pearson chi-square and [a]Fischer´s exact test were used to compare antibiotic prescribing details, gen-generation.

Third-generation cephalosporins (J01DD) constituted 47% and 30% of the prescriptions in sub-group 3 and 4 at the NTH, followed by FDCs (19% and 29% of the prescriptions respectively). Overall, antibiotic prescriptions were significantly more common for the patients in sub-group 3 than in the sub-group 1' ($p<0.001$). The type of malaria was verified by blood samples reports in some cases of sub-group 3 (TH: 4% and NTH: 7%). None of the records from the four sub-groups had requisition for sending samples for bacterial culture and susceptibility test.

Ciprofloxacin (J01MA02) was the most frequently prescribed antibiotic substance measured in DDD/1000 patients at the TH and ceftriaxone (J01DD04, Table 4) at the NTH. The highest number of prescribed DDDs/1000 patients was recorded for ciprofloxacin, followed by doxycycline and ceftriaxone in both hospitals (Figure 2).

Table 4: Most commonly prescribed antibiotics among the selected diagnoses groups presenting the prescribing occasions in DDDs/1000 patients at sixth level of the ATC classification

	Group (a): Cardiovascular diseases				Group (b): Malaria or Viral fever			
	Cardiovascular with no registered bacterial infection (Sub-group 1) n (%)		Cardiovascular with suspected bacterial infection (Sub-group 2) n (%)		Malaria or Viral Fever with no registered bacterial infection (Sub-group 3) n (%)		Malaria or Viral Fever with suspected bacterial infection (Sub-group 4) n (%)	
Name; ATC-code	TH	NTH	TH	NTH	TH	NTH	TH	NTH
Total DDDs/1000 patients	2062 (99)	1456 (100)	4514 (99)	3421 (100[#])	4480 (100[#])	3048 (100[#])	5432 (100[#])	5827 (100)
Doxycycline, J01AA02	491 (24)		1030 (23)		1463 (33)	296 (10)	2745 (51)	
Ampicillin, J01CA01	68 (3)		170 (4)					
Amoxicillin, J01CA04		81 (6)		435 (13)				
Amoxicillin + Clavulanic acid, J01CR02				566 (17)		88 (3)		
Piperacillin + Tazobactam, J01CR05						34 (1)		
Ampicillin + Cloxacillin, J01CR50	217 (11)		774 (17)				191 (4)	
Cefuroxime, J01DC02				95 (3)		136 (4)		
Cefprozil, J01DC10		75 (5)						
Cefotaxime, J01DD01	172 (8)	46 (3)	298 (7)	59 (2)	199 (4)	96 (3)	295 (5)	
Ceftriaxone, J01DD04	133 (6)	558 (38)	244 (5)	907 (27)	560 (13)	1052 (35)	164 (3)	1402 (24)
Azithromycin, J01FA10								476 (8)
Gentamicin, J01GB03	44 (2)		167 (4)	81 (2)				
Amikacin, J01GB06								321 (6)
Ofloxacin, J01MA01						202 (7)		
Ciprofloxacin, J01MA02	687 (33)	141 (10)	1057 (23)	527 (15)	1940 (43)	602 (20)	1185 (22)	2886 (50)
Norfloxacin, J01MA06			201 (4)				273 (5)	
Levofloxacin, J01MA12		73 (5)	202 (4)	129 (4)			145 (3)	
Cefoperazone + Sulbactam, J01RA*83		92 (6)		94 (3)		90 (3)		125 (2)
Ceftriaxone + Sulbactam, J01RA*84		228 (16)		277 (8)		199 (7)		
Ceftriaxone + Tazobactam, J01RA*85		162 (11)		156 (5)		162 (5)		250 (4)
Metronidazole, J01XD01	139 (7)		262 (6)	95 (3)	204 (5)	91 (3)	262 (5)	367 (6)
Metronidazole, P01AB01 (Oral)	111 (5)		109 (2)		114 (3)		172 (3)	

Abbreviations: n (%): Number of patients (percentage), AB: antibiotics, DDD: Defined Daily Dose, NTH: non-teaching hospital, TH: teaching hospital, [#] rounding off the percentages to nearest integer made the total more than 100%

Figure 2. Top 90% of prescription in the four selected groups measured in DDD/1000 patients, presented at fourth level of the ATC classification at one teaching and one non-teaching hospitals in Ujjain, India

DISCUSSION

To our knowledge this study is the first to investigate and present antibiotic prescription practices at medicine departments in Indian private sector hospitals by focusing on non-bacterial infectious diseases. This also leads to a limitation, as the results of the present study could not be compared with the findings of any other study. Thus the results of present study were compared with the most equivalent studies available globally.

Antibiotics were commonly prescribed to inpatients at both study hospitals. Irrespective of the indications, broad-spectrum antibiotics and third-generation cephalosporins that should be conserved for high risks co-morbidities and life-threatening bacterial infections were prescribed frequently. This study also highlights the high rates of antibiotic prescriptions used to treat the selected groups of non-bacterial infectious diseases such as cardiovascular disease, malaria, and viral fever.

Antibiotic prescriptions in the cardiovascular and fever groups

The average percentage of patients that were prescribed antibiotics in the medicine departments were similar (TH: 65% and NTH: 67%, $p<0.001$) in comparison to the rates in the medicine department of a public hospital at Bathalapalli, Andhra Pradesh, India (63%),[26]. With a few exceptions, such as rheumatic fever, endocarditis, pericarditis and myocarditis (bacterial or viral), cardiovascular diseases are primarily non-infectious. COPD and RHD are the common associated diseases in cardiovascular patients. Rheumatic fever is an immune response sequel to an infection and it may cause endocarditis,[23,27]. However, pericarditis and myocarditis most commonly develop from viral pathogens where antibiotic treatment is not a routine recommendation,[28,29].

Interestingly, more than 35% of inpatients among the 'cardiovascular group with no registered bacterial infection' were prescribed antibiotics at both hospitals. As per treatment guidelines and recommendations, only patients who have confirmed infectious diagnosis are expected to receive an antibiotic prescription,[30–32]. Nonetheless, empirical or presumptive antibiotic therapy is also accepted when the clinical diagnosis, based on the presence of a strong clinical suspicion of bacterial infection, is substantiated by relevant medical history and clinical findings,[30]. According to the WHO and the Indian National Treatment Guidelines for Antimicrobial Use; presumptive therapy is typically a one-time treatment given for clinically presumed infection while waiting for the culture report,[31,32]. In combination of clinical findings laboratory and radiological reports are considered to confirm the diagnosis and lead to the definitive therapy,[32].

Microbiology laboratories were highly under-utilized in both study hospitals. None of the patient records in the selected four sub-groups included notes about sending samples for culture and susceptibility testing. Therefore, the practice of prescribing antibiotics to the patient groups with no registered bacterial infection in absence of laboratory confirmation could not be considered to be rational. Among the COPD and RHD patients the aetiology of the current episode of hospitalization could potentially be expected to be non-bacterial (e.g. viral infection). However, this could not be confirmed due to the absence of laboratory investigations. It is worth mentioning here that prolonged empiric antibiotic treatment without a clear evidence of infection is one of the causes of the development of antibiotic resistance.

More FDCs were prescribed to the cardiovascular patients at the NTH than at the TH. Rationality of the newer FDCs coded with ATC-code: J01RA* has not been established yet and these combinations are not listed in either the NLEMI or the WHOLEM,[18,19]. It is also

evident that the constituents of these combinations are often present in lower quantities than is recommended which might lead to the development of antibiotic resistance,[33].

The sub-group 'malaria or viral fever with suspected bacterial infection' was found to have the highest rate of antibiotic prescriptions among all the four sub-groups (TH: 96%, NTH: 75%). Our result also highlight that patients with fever were more likely to receive antibiotic prescriptions, than patients with cardiovascular diseases. Fever is a common symptom among malaria, viral fever and bacterial infection. Therefore, the doctors might have prescribed antibiotics as a 'prophylactic' treatment to treat bacterial infection, if any. In our study the rate of antibiotic prescriptions for the patients with fever was higher than, yet comparable with a study at primary and secondary health care settings in Uttar Pradesh, India where 85% of the fever patients were prescribed antibiotics,[34]. Additionally, in our study a high percentage of patients with fever (malaria or viral fever) with 'no registered bacterial infection' were prescribed antibiotics (TH: 82%, NTH: 71%). An out-patient study from Uganda, a malaria endemic country, showed that 42% of malaria patients were prescribed antibiotics without any registered indication,[25]. As the majority of the prescriptions in our study were empirical, the rationale for using the antibiotics cannot be evaluated. However, prescribing antibiotics to treat non-bacterial infections is considered to be an irrational practice. Thus it is imperative that this matter be addressed.

Adherence to the essential medicine lists and prescriptions by generic name

A higher proportion of prescribed antibiotics at the TH (77%) were from the NLEMI compared with the NTH (60%, $p<0.001$). This could be attributed to the presence of a management policy to purchase and supply medicines at the TH. However, there is a need to improve adherence to the NLEMI at both hospitals. According to WHO, prescribing by their generic name is; part of rational prescribing, cost effective and provides flexibility to buy the

available medicine of any company. This policy is equally applicable for both public and private healthcare settings. However, adherence to this policy is higher at public hospitals, followed by 'private non-profit' hospitals and by the 'private for-profit' hospitals,[13,14,35]. In the present study, significantly lower antibiotic prescriptions were made by generic names to the patients of sub-group 1 (TH: 6%, NTH: 1% p<0.001) or sub-group 2 (TH: 12% NTH: 5% p<0.001) at the NTH than at the TH. Third-generation cephalosporins (J01D, 29%) and FDCs (J01RA*, 23%) were the most commonly prescribed classes of antibiotics at the NTH while quinolones were most commonly prescribed at the TH (J01M, 37%, NTH: 13%). Previous studies from Uttar Pradesh, India and Madhya Pradesh, India have also shown similar results for academic and non-academic hospitals,[13,14,17]. The high incidence of prescribing these classes is further supported by Van Boeckel et al, who observed a significant increase in the consumption of fluoroquinolones and cephalosporins globally over the past decade. This increase was mainly attributed to the increased rates in India and China,[9]. At the NTH, prescriptions of FDCs varied between 19% and 28% among the selected sub-groups (TH: <2%) and the prescriptions of third-generation cephalosporins varied between 30% and 47% (TH: <22%). According to WHO, prescribing multiple antibiotics when not indicated, often combined in inadequate doses (smaller or larger quantity than recommended) and prescription of drugs other than local or national guidelines are all examples of actions deemed inappropriate,[36]. All these practices could be seen in prescribing newer FDCs (J01RA*); both of the study hospitals are from the private sector and are regulated by the same trust on a 'not for-profit' basis. The differences in the prescribing practices might be due to each hospital's policy and the fact that academic hospitals are part of the educational process, and regular educational activities conducted at these hospitals results in better adherence to the guidelines, as seen at the TH. Another reason for the frequent prescribing of broad-spectrum antibiotics, new FDCs and use of trade names at the NTH could be explained by the results of

a review conducted by Blumenthal et al,[37]. That review concluded that physicians who had received gifts or money from pharmaceutical companies were more likely to prescribe drugs produced by the brand names and less prone to use the generic names. The pressure from pharmaceutical companies could be anticipated on the doctors at the NTH, due to unrestricted visits from pharmaceutical company representatives,[37]. Moreover, these new FDCs of antibiotics are more expensive than the regular and generic formulations,[13,14,37]. The restriction of these visits and the management control over the purchase and supply of medicines can be seen as main reasons for low incidence of prescribing FDCs prescribing and high use of generic names at the TH.

Interestingly trade names were used as local abbreviations to prescribe four most commonly prescribed antibiotics; ciprofloxacin, doxycycline, gentamycin and metronidazole at the TH, as discussed in result section. However, only generic drugs were purchased and dispensed at the TH due to administrative control over the purchase and supply of the drugs. Thus even if these antibiotics were prescribed using an abbreviation similar to the trade name, they were included in adherence to the generic name prescribing category.

Duration of hospital stay and duration of antibiotic treatment

In the present study both the duration of hospital stay and the duration of antibiotic treatment were longer at the TH than the NTH among all inpatients groups. This could be due to the fact that the patients at the TH received free healthcare services and drugs, making their stay economically feasible. In contrast, at the NTH the patients had to pay for all the services and drugs they received. This association of longer duration of stay and antibiotic treatment at TH has also been observed in previous studies from India,[13,14,17]. However, it is evident that the treatment given for a time period that is either shorter or longer than recommended, is

inappropriate and it substantially contributes to the development of antibiotic resistance,[1,36].

STRENGTHS AND LIMITATIONS

A high number of patients were screened over a three year period this overcomes seasonal variations in infectious aetiology which would affect antibiotic prescribing. Same form was used for the data collection and the process was supervised and monitored by same person at both hospitals to improve the reliability of the data. The diagnoses were not verified externally being a limitation of the study. However, external verification is virtually inapplicable to studies that rely upon the routine collection of data. The results of the study were based on the notes included in the patient files. Extensive efforts were made to document all notes including diagnoses written in the patient files. However, the possibility of missing a few diagnoses and losing some data during the transition from the forms to the digital storage cannot be excluded.

CONCLUSION

A higher number of prescribing occasions were recorded at the TH, and not at the NTH, with regard to adherence to the guidelines. However, overall adherence was low. Fever was a risk factor to receive antibiotic prescription at both hospitals. Patients with non-bacterial infections such as malaria or viral fever or with cardiovascular diseases were prescribed antibiotics at both medicine departments which could not be justified. Broad spectrum antibiotics with irrational combinations of antibiotics were commonly prescribed in the study hospitals for non-indicated conditions. A large proportion of patients were categorised as suspected bacterial diagnoses (sub-groups 2 and 4). In the presence of confirmed aetiology, according to microbiology reports, some of these could have been categorised in non-bacterial group and could have contributed to higher antibiotic prescribing rates in the non-bacterial diagnoses

(sub-groups 1 and 3). However, this was unavoidable due to absence of confirmed aetiology and the nature of the study design (observational).

GENERALISABILITY AND FUTURE IMPLICATIONS

The data collection method used in the study is robust and reliable. In accordance with one of the WHO goals of "Global-action-plan" and in view of limited knowledge of antibiotic utilization and resistance patterns our study findings suggest that there is a need to conduct and share similar long term surveillance studies globally. The data collection method and tested tool used in the study could easily be adapted in other settings that lack computerized patient records. The management in the TH had a policy to control the purchase and supply of medicines. This control shows positive effects at the TH compared to the NTH; to minimise antibiotic prescribing, in better adherence to the NLEMI and in use of generic names. This control could be implemented and tested in other constrained settings. The recruitment of nursing staff for manual data collection who routinely work in the department would have helped to minimize the influence on the prescribers. High prescribing rates of antibiotics and use of FDCs among inpatients in these settings could broadly be considered as representative for similar health care settings in low-middle income countries. Lack of culture of sending cultures is another important issue raised by the study. The need to develop and implement local diagnosis specific prescribing guidelines in conjugation with continuous follow-up is also emphasized by our study. The physicians should be motivated to send samples for cultures before prescribing antibiotics. Improving hygiene practices is another recommendation to prevent spread of infection and to decrease in the 'prophylactic' use of antibiotics.

CONTRIBUTERSHIP STATEMENT

MS and CSL designed, visualized the research question and developed the data collection tool. MS conducted repeated training sessions for nursing personal for recording the data. MS was also responsible for coordination with the nursing staff, monitoring and supervision of the data collection and entry. CSL participated in planning the study design and the coordination of the study. KL, CSL and MS participated in the conception and design of the present study and revising the paper critically for substantial intellectual content. KL grouped and analyzed the data, performed the statistical analysis and contributed in drafting the manuscript along with MS, CSL, FJ and AS. KL, AS and MS were responsible for categorization of the patients. All authors read and approved the final version of the manuscript.

COMPETING INTERESTS

The authors have no competing interests to declare.

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DATA SHARING STATEMENT

As per the institutional policy, the data is available with the Institutional ethics committee. This is to protect the patient's confidentiality and to ensure the electronic security of the data.

The data could be made available to all interested researchers upon request made to; The Chairman, Ethics Committee, R.D. Gardi Medical College, Agar Road, Ujjain, Madhya Pradesh, India 456006 (Email: iecrdgmc@yahoo.in, uctharc@sancharnet.in), giving all details of the article. The ethical approval number: 41/2007 needs to be quoted along with the request.

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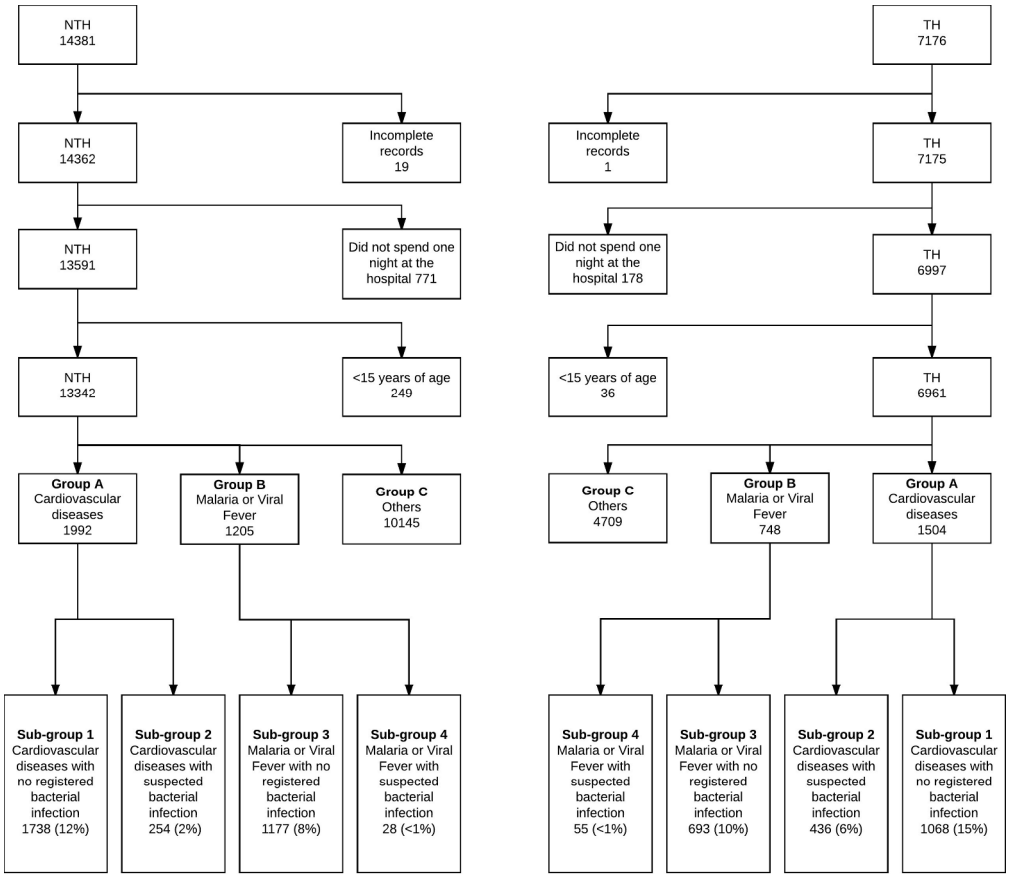

Figure 1. The process of selection and grouping of inpatients admitted in medicine departments of the TH and the NTH based on their diagnosis.

Figure 1. The process of selec
674x590mm (96 x 96 DPI)

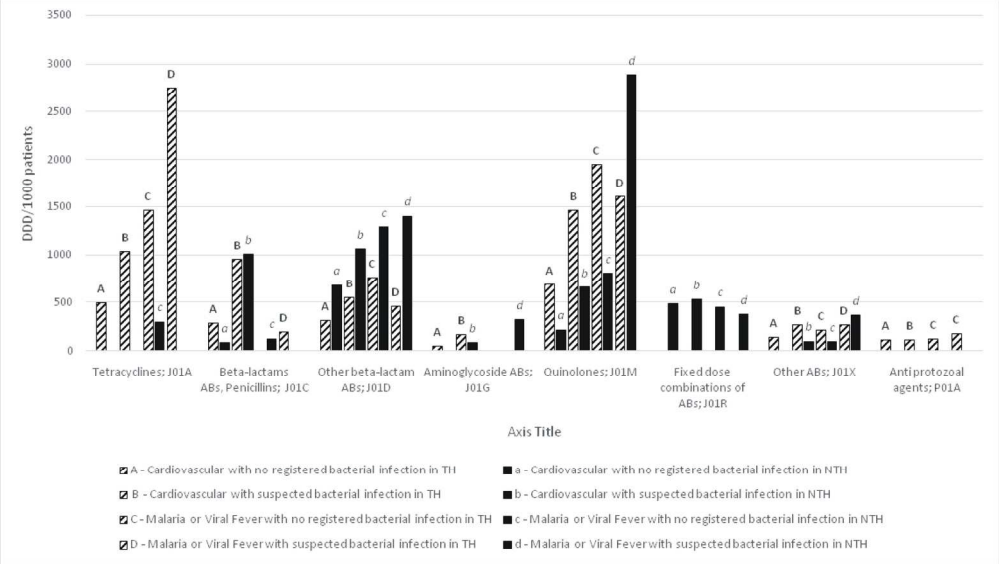

Figure 2. Top 90% of prescription in the four selected groups measured in DDD/1000 patients, presented at fourth level of the ATC classification at one teaching and one non-teaching hospitals in Ujjain, India
Figure 2. Top 90% of prescript
91x51mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2-3**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**5**
Objectives	3	State specific objectives, including any pre specified hypotheses	**6**
Methods			
Study design	4	Present key elements of study design early in the paper	**6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**6**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls ***Cross-sectional study***—Give the eligibility criteria, and the sources and methods of selection of participants	**7**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	***8***
Bias	9	Describe any efforts to address potential sources of bias	**9-10**
Study size	10	Explain how the study size was arrived at	**8**

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**8-10**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	**10**
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			Page Number
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**9,10**
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	**Figure 1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**09-11 Table 1**
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	**10-11, 14-15 Table 2**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**11-17 Table 2, 3 and 4 Figure 2**
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
		Discussion	
Key results	18	Summarise key results with reference to study objectives	**18**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**23**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**18-22**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**24**
		Other information	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**25**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Antibiotic prescriptions to the inpatients having non-bacterial diagnosis at medicine departments of two private sector hospitals in Madhya Pradesh, India: a cross sectional study

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Antibiotic prescriptions to the inpatients having non-bacterial diagnosis at medicine departments of two private sector hospitals in Madhya Pradesh, India: a cross sectional study

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Abstract

Objectives: To present and compare antibiotic prescribing among inpatients among most common non-bacterial diagnoses groups at medicine departments of a teaching (TH) and a non-teaching hospital (NTH) in Central India.

Setting: An observational cross-sectional study was conducted at two tertiary care settings at Ujjain district, Madhya Pradesh, India.

Participants: The data was collected manually, using a customized form. Complete records of all inpatients, who were >15 years of age and stayed at-least for one night in either of the hospitals during 2008-2011, were analysed.

Outcome measures: Inpatients were grouped based on the presence or absence of; a bacterial infectious diagnosis, viral/ malaria fever or cardiovascular diseases. Classes of antibiotics prescribed to these groups, and adherence to the available prescribing guidelines were compared between the hospitals using the notes from the patient files, and the diagnoses.

Results: Of 20303 inpatients included in the study, 66% were prescribed antibiotics. Trade name prescribing and use of broad spectrum antibiotics were more frequent at the NTH compared to the TH ($p<0.001$). At the TH significantly higher proportion of patients having fever without registered bacterial infection; were prescribed antibiotics (82%) compared with the NTH (71%, $p<0.001$). Patients admitted for cardiovascular diagnosis without registered bacterial infections received antibiotic prescriptions at both hospitals; (NTH- 47%and TH-37%); it was significantly higher at the NTH ($p<0.001$). None of the diagnoses were confirmed by microbiology reports.

Conclusions: Prescribing antibiotic including broad spectrum antibiotics to the inpatients without bacterial infections i.e. viral fever, malaria and cardiovascular diseases were common

at both hospitals which increase the risk for development of bacterial resistance, a global public health threat. Taking account of over prescribing of antibiotics, development and implementation of local prescribing guidelines, encouragement to use laboratory facilities, and prescription analysis, with antibiotic stewardship programs are the main recommendations for the settings.

Strengths and limitations

- Prospective study over a long time period of three years and inclusion of all patients, irrespective of their age and sex strengthens the representativeness of the results and overcome the seasonal variations.
- Data collecting tools were same at both study hospitals and the staff who collected the data was trained by the same person at both locations to minimize the variances.
- An observational non-interventional study design might have minimized the effect on the prescribers of being observed and audited.
- All possible efforts were made to minimize the risk of missing data by continuous monitoring and cross checking of the data. However, some data, for example few diagnoses might have been lost during translation from analogue to digital records.
- A big proportion of patients were categorised in the suspected bacterial diagnosis groups. Some of these diagnoses could have been categorised in non-bacterial diagnoses group if confirmed aetiology, i.e. microbiology reports, was present. This could have contributed to even higher antibiotic prescribing rates in the non-bacterial diagnoses group. However, due to absence of confirmed aetiology and observational study design this was indispensable.

BACKGROUND

Increasing morbidity and mortality due to infectious diseases, despite of the availability of the lifesaving antibiotics is an alarming situation, globally,[1]. These incidences of mortalities due to infections are higher in low- and middle-income countries than in high-income countries,[2–4]. The WHO has reported a high burden of communicable diseases in India, and infections are responsible for 28% of the total mortality in the country,[5,6]. Additionally, antibiotic resistance in India is reported to be high. However, figures cannot be generalized to all Indian settings as the bacterial resistance patterns widely vary between its regions and settings and most studies so far have been relatively limited in scope ,[7].

Irrational (both over- and under-) use of antibacterials, is of global concern. It results in unnecessary treatment costs, is a potential risk for the development of antibiotic resistance and side effects such as antibiotic associated diarrhoea caused by *Clostridium difficile* or gastroenteritis,[8]. According to a report, the global consumption of antibiotics increased by 36% between 2000 and 2010 of which five countries including India (Brazil, Russia, India, China and South Africa) accounted for 76% of this increase,[9]. Despite of the paucity of studies that describe antibiotic prescribing from India, Van Boeckel et al presented India on the top of the list of antibiotic consumption with $12.9x10^9$ units in 2010 where one unit indicates a pill, capsule or ampoule,[1,9]. However, this increase might also have meant that segments of the population that previously had no access to antibiotics can now access antibiotics yet it cannot be disregarded that antibiotic resistance is a sequel of antibiotic use,[10].

It is thus imperative to map the prescribing patterns of antibiotics on a local level to address the potential need of improvement and to counter the consequences of inappropriate prescription of antibiotics. Indian private sector are the major healthcare providers but little is known about prescribing patterns in this sector,[11–14].

OBJECTIVES

The study was conducted to present, analyse and compare antibiotic prescribing to the inpatients enrolled for most common non-bacterial diagnoses at the medicine departments of a teaching (TH) and a non-teaching hospital (NTH) in Central India.

METHODS

Study design

A cross sectional observational design was selected to conduct the study.

Setting

The study was conducted at the medicine departments of two tertiary care hospitals from private sector in Ujjain district, India. The hospitals are addressed as teaching hospital (TH) and non-teaching hospital (NTH). Both hospitals are run by the same trust. The TH is located in a rural area of Ujjain district and had 570 beds at the time of the study. The NTH is located in the central part of Ujjain city and had 350 beds at the time of the study. The TH provides medical services including medical treatment and free of charge medicines to all patients while the NTH charges for the medical facilities on a 'no profit-no loss' basis. Patients from the NTH have to buy prescribed medicines out-of-pocket from the pharmacies inside or outside the hospital. The physicians at the TH are salary paid and do not have any direct exposure to the sales representatives of pharmaceutical companies. Furthermore, the management at the TH is responsible for the purchase and supply of the drugs.

Hospital level Essential medicine list was available in written form at the TH but no specific implementation activities were conducted during the study period. Local prescribing guidelines were not present in any of the hospitals. Almost all physicians practicing at the NTH also had private practice and could be contacted by the representatives of pharmaceutical companies easily. The payments of the physicians at the NTH increase above

par according to the number of patients they admit in the hospital and the number of visits made to the inpatients. Both hospitals are tertiary care hospitals with a number of specialty departments such as; Pediatrics, Obstetrics and Gynecology, Surgery, Orthopedics, Pulmonary Medicine, and so on to treat specific patients. For example; patients presenting with complaints related to lungs and chest (other than heart) visit the Pulmonary Medicine department. A well-equipped microbiology laboratory was present to process the samples free of cost for all from the TH and with nominal charges from the NTH.

Participants

Inclusion and exclusion criteria

Patients who stayed for at least one night at medicine departments of either of the two hospitals were considered as inpatients and included in the study. Patients who had incomplete records or admitted to the medical intensive care units within the medicine departments were not included in the analysis. Treatment recommendations including dose and frequency is different for patients under 15 years of age and the DDD measurement is not applicable to them, thus they were also excluded,[15].

Variables

The patient information was analysed for age, sex, diagnosis, duration of hospitals stay, if they received antibiotic treatment, and duration of antibiotic treatment. The prescriptions were analysed for the type of antibiotics prescribed, its dose, and frequency. The antibiotics were classified according to the Anatomical Therapeutic Chemical (ATC) classification given by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC),[16].Defined Daily Doses (DDDs) were calculated for all prescribed antibiotics,[16]. DDD is a technical unit for comparative purposes and is the average daily dose of the specific drug for its main indication in adults,[15]. Fixed dose combinations of antibiotics (FDCs) that did not have an ATC code assigned by WHOCC were assigned the code 'J01RA*' according to Sharma et

al,[17]. FDCs that did not have a DDD were assigned one by examining the constituents and the proportions in which they were found in one unit dose. DDD was then calculated on the basis of number of units and converted to dose in gram. Total number of antibiotics prescribed during hospital stay was counted per patient and was termed as prescribing occasions.

The List of Essential Medicines of India (NLEMI) is based on the WHO list of essential medicines (WHOLEM) and adapted to the disease panorama of India,[18]. These lists serve as guidelines to promote the prescribing of safe, cheap and effective drugs to the population,[18,19]. Adherence to these lists was evaluated for all prescriptions.

Data sources and considerations

The data collection process is described in detail elsewhere,[13,14]. In brief, the study was conducted prospectively between April 1st, 2008 and March 31st, 2011. Patient throughput in the TH and the NTH amounted to 29026 and 41561 patients respectively. The data were manually collected by the nurses using a specially designed form attached to the patient's file at the medicine department of the TH and the NTH. All patients were included to minimize the possibility of selection bias. Every admission in the department was considered as a new patient. The nurses and new recruits were trained regularly for the data collection by the last author (MS). The data collection form was updated daily based on patient's day to day progress. All notes written in the patient files by the treating consultant were recorded and included for the analysis. It was possible that a patient could have more than one diagnosis. Therefore all indications, diagnoses and/or symptoms recorded in the patient files, were transferred to the data collection form. The data was translated to digital data files using EPI Info 3.1 and Microsoft Excel. Two specifically trained data entry operators translated the diagnoses as per 'International Classification of Diseases' (ICD-10 codes) and the generic

names of the prescribed antibiotics were translated to WHO assigned ATC-codes and Defined Daily Doses (DDDs) per day,[15,20,21].

In order to exclude all clinically suspected cases of bacterial infection and following the aim of the study, best possible efforts were made to distinguish the patients who had any indications even for secondary antibiotic prophylaxis from those who did not,[22–24]. The patients were categorized into three main groups using the diagnoses registered in the patient files and the ICD-10 codes; Group (a) cardiovascular diseases, (b) non-bacterial fevers and (c) all diagnoses other than Group (a) and (b) including all types of bacterial infections. Sixty seven percent of patients in the TH and 75% in the NTH were included in Group (c). All cases of chronic obstructive pulmonary disease (COPD) were also included in Group c. Although aetiology of the disease was seldom specified in the records but these patients should receive less restricted antibiotic treatment.

Groups (a) and (b) were selected for detail study of the antibiotic prescribing for non-bacterial diagnoses as per the study aim. In 'Group (a)', hypertension, acute myocardial infarction and valvular heart disease were the most common diagnoses. In 'Group (b)' different types of malaria and cases of viral fever (ICD code- B34.9) were included. These non-bacterial fevers were common in both study settings. It has previously been reported that antibiotics are prescribed to a high extent to patients having malaria or viral fever in malaria endemic countries like Uganda (Figure 1),[25]. Moreover, Groups (a) and (b) comprised the largest homogenous patient groups in our study settings.

Figure 1. The process of selection and grouping of inpatients admitted in medicine departments of the TH and the NTH based on their diagnosis.

These groups were further divided into four sub-groups to identify and analyse the patients exclusively having non-bacterial diagnoses corresponding to our study aim. The cardiovascular group (Group a) was divided in two sub-groups; 'cardiovascular diseases with

no registered bacterial infection' (sub-group 1), 'cardiovascular diseases with suspected bacterial infection' (sub-group 2). Similarly, the non-bacterial fever group (Group b) was divided 'malaria or viral fever with no registered bacterial infection' (sub-group 3) and 'malaria or viral fever with suspected bacterial infection' (sub-group 4, Figure 1).

All patients with rheumatic heart disease (RHD) were categorized in sub-group 2 or in sub-group 4 to rule out all possible bacterial infection as a confounder, since the WHO guidelines for secondary prevention after rheumatic fever sets the duration of preventive antibiotic treatment from five years up to life-long, depending on a number of factors e.g. time since the last episode of rheumatic fever and severity of valve engagement and supports an individual assessment of every case,[22,23].

An antibiotic prescribed for a day was considered as one prescribing occasion. Prescribed DDDs were calculated per 1000 patients. According to WHOCC, oral metronidazole (P01AB01) is coded as an antiprotozoal drug, but is coded as an antibacterial in the NLEMI. Therefore it was considered as an antibacterial in this study,[18].

Ethics statement

Being an observational study, the data collection did not interfere with the treatment or caused any extra risks for the patients. Moreover, the names of the prescribers were not recorded to minimize the effect of being observed. All patients were assigned a unique code during the data entry to maintain anonymity of the inpatients. This unique code was used to compare details of patient information and antibiotic prescriptions for the analysis. The data was collected at individual level for all inpatients and was linked per patient with the assigned unique codes instead of; for example social security number. However, the analysis was conducted at group level to maintain the confidentiality.

The ethics committee of Ruxmaniben Deepchand Gardi Medical College, Ujjain, approved the study with approval number: 41/2007.

Statistical Methods

All frequency and percentage of categorical values were calculated. Sum, median, mean, range and standard deviation were calculated for continuous numerical values. Values were rounded off to the closest whole number for percentage, prescription tables and in the text. The independent t-test was used for comparison of normally distributed and continuous variables. The chi-square test was used for comparison of categorical values. Fischer's exact test was used for expected values below 5 and Pearson chi-square test was used for expected values above 5. Bonferroni's correction for multiple comparisons was used and p- values <0.001 were chosen for significance level to minimize the risks of type one errors. The data were analysed with Excel, SPSS version 22 (SPSS Inc., Chicago, IL, USA) and STATA version 13.1 (Stata Corp, College station, TX, USA).

RESULTS

During the study period, totally 21557 patients were admitted to the two medicine departments, 7176 patients in the TH and 14381 in the NTH (Figure 1). Of the admitted patients, records of 20 patients were incomplete, 949 (5%) stayed less than one night and 285 patients (1%) were aged <15 years. Therefore, as per the inclusion criteria 1254 patient records were excluded and 20303 (94%) records were included for further analysis (6961 at the TH and 13342 at the NTH, Figure 1).

Most common diagnoses in the TH were chronic obstructive pulmonary disease (COPD, 10%), viral fever (7%) and hypertension (5%) while in the NTH were viral fever (10%), malaria (6%) and COPD (5%, Table 1). Antibiotics were prescribed to 4540/6961 inpatients (65%) in the TH and 8900/13342 (67%) in the NTH (Table 2). An average of eight and five

prescribing occasions was found per patient at the TH and the NTH respectively. Overall a significantly higher proportion of the antibiotics prescribed in the TH adhered to the NLEMI; 77% prescriptions (27649/35732) than in the NTH; 60% (24683/41068, p<0.001).

Seven percent of antibiotics in the TH were prescribed using generic names it was significantly higher compared to the NTH (2%, p<0.001). Some antibiotics were prescribed using trade names at the TH e.g., "Cipro", "Doxy", "Genta"' and "Metrogyl". However, these were local abbreviations devised by the staff for ciprofloxacin, doxycycline, gentamycin and metronidazole respectively. Even though these four antibiotics were prescribed using trade names, generic antibiotics were dispensed from the hospital pharmacy. A longer duration of stay and longer duration of antibiotic treatment was observed at the TH (mean days; 6 and 6 respectively) compared to the NTH (mean days; 3 and 4 respectively, p<0.001).

Distribution of inpatients in Groups a and b, and antibiotic prescription patterns

Cardiovascular diseases accounted for 48% of patients in Group (a) and (b) at the TH and 30% at the NTH. In the non-bacterial fever group, malaria was significantly more common at the NTH (74%) and viral fever was significantly more common at the TH (66%, p<0.001, Table 1).

Broad-spectrum antibiotics such as third-generation cephalosporins (J01DD) and FDCs (J01RA*) comprised 52% of the prescribing occasions at the NTH of which FDCs accounted for approximately half (Table 3). These classes accounted for 13% of total prescribing occasions and <1% FDCs. At the NTH, cephalosporins (third-generation cephalosporins J01DD, >30%) were most commonly prescribed for the cardiovascular diseases (>35%), followed by FDCs (>20%). Fluoroquinolones (J01M) was the most commonly prescribed antibiotic class in the TH in both (a) and (b) groups (>30% and >40% respectively).

Table 1: Diagnoses of the four groups of inpatients at medicine departments at one teaching and one non-teaching hospitals in Ujjain, India

Group (a): Cardiovascular diseases						Group (b): Malaria or Viral fever					
Cardiovascular with no registered bacterial infection Sub-group 1			Cardiovascular with suspected bacterial infection Sub-group 2			Malaria or Viral Fever with no registered bacterial infection Sub-group 3			Malaria or Viral Fever with suspected bacterial infection Sub-group 4		
Diagnosis group	**TH**	**NTH**	**Diagnosis group**	**TH**	**NTH**	**Diagnosis group**	**TH**	**NTH**	**Diagnosis group**	**TH**	**NTH**
	n(%)	**n(%)**		**n(%)**	**n(%)**		**n(%)**	**n(%)**		**n(%)**	**n(%)**
Total	**1068**	**1738**	**Total**	**438**	**254**	**Total**	**693**	**1177**	**Total**	**55**	**28**
Hypertension	328(31)	470(27)	COPD	209(48)	77(30)	**Malaria**	237(34)	872(74)	COPD	10(18)	5(18)
Cerebro vascular accident	126(12)	383(22)	Rheumatic Heart Disease	130(30)	102(40)	Cerebral malaria caused by *P. falciparum*	4(1)	11(1)	Urinarytrac tinfection	5(9)	7(25)
Acute Myocardial Infarction	28(3)	202(12)	Pulmonary Tuberculosis	19(4)	18(7)	Malaria caused by *P. falciparum* UNS	9(1)	9(1)	Tyfoid fever	8(15)	2(7)
Chronic Ischemic Heart Disease	17(2)	189(11)	Urinarytract infection	17(4)	15(6)	Malaria caused by *P. vivax* UNS	16(2)	61(5)	Acute gastroenteritis	4(7)	6(21)
Coronary Artery Disease	98(9)	101(6)	Acute Gastroenteritis	14(3)	12(5)	Malaria UNS	208(30)	791(67)	Disease of airways UNS	8(15)	0(0)
Left Ventricle Failure	44(4)	69(4)	Lower airway infection UNS	13(3)	0(0)	**Viral fever**	456(66)	305(26)	Disease of upper airways UNS	7(13)	0(0)
Congestive Heart Failure	56(5)	39(2)	Sepsis	0(0)	5(2)				Pulmonary Tuberculosis	4(7)	2(7)
Dilated Cardiomyopathy	79(7)	6(<1)	HIV with infection	8(2)	1(<1)				HIV with infection	2(4)	0(0)
Unspecified Cardiomyopathy	21(2)	54(3)	Rheumatic Fever	1(<1)	4(2)				Rheumatic Heart Disease	2(4)	1(4)
Multiple Valve Disease	61(6)	7(<1)	Endocarditis	0(0)	4(2)				Pelvic Inflammatory Disease	2(4)	0(0)
Angina Pectoris	10(1)	35(2)	Pneumonia	1(<1)	4(2)				Pneumonia	0(0)	1(4)
Acute Ischemic Heart Disease	31(3)	11(1)	Others	26(6)	12(5)				Other diagnoses	3(5)	4(14)
Deep Vein Thrombosis UNS	13(1)	19(1)									
Mitral Stenosis	21(2)	2(<1)									
Hypertensive Heart Disease	20(2)	1(<1)									
Cardiac arrest	2(<1)	16(1)									
Other	113(11)	134(8)									

Abbreviations: n (%): Number of patients (percentage in that diagnosis group), NTH: non-teaching hospital, TH: teaching hospital, COPD: chronic obstructive pulmonary disease, UNS: unspecified, *P.-plasmodium*, HIV: human immunodeficiency virus.

Table 2: Demographic details and antibiotic prescribing information of the inpatients at medicine departments at one teaching and one non-teaching hospitals in Ujjain, India

	Group (a): Cardiovascular diseases									Group (b): Malaria or Viral Fever					
	Medicine Department			Cardiovascular with no registered bacterial diagnosis (Sub-group 1)			Cardiovascular with suspected bacterial infection (Sub-group 2)			Malaria or Viral Fever with no registered bacterial diagnosis (Sub-group 3)			Malaria or Viral Fever with suspected bacterial infection (Sub-group 4)		
	TH	NTH	p-value	TH	NTH	p-value	TH	NTH	p-value	TH	NTH	p-value	TH	NTH	p-value
Inpatients; n	6961	13342		1068	1738		438	254		693	1177		55	28	
Age; mean years (SD)	45(17)	43 (18)	**<0.001**	53 (14)	55 (15)	**<0.001**	49 (17)	51 (17)	0.222	36 (15)	35 (16)	0.387	37 (14)	40 (20)	0.440
Inpatients prescribed AB; n (%)	4540 (65)	8900 (67)	0.034	392 (37)	808 (47)	**<0.001**	299 (68)	179 (71)	0.545	569 (82)	831 (71)	**<0.001**	53 (96)	21 (75)	0.006[a]
Duration of hospital stay; mean days (SD)	6 (5)	3 (3)	**<0.001**	6 (5)	3 (3)	**<0.001**	7 (5)	4 (3)	**<0.001**	4 (4)	3 (2)	**<0.001**	5 (3)	4(2)	0.796
Duration of AB treatment; mean days (SD)	6 (4)	4 (2)	**<0.001**	6 (4)	4 (2)	**<0.001**	7 (4)	4 (2)	**<0.001**	5 (3)	4 (2)	**<0.001**	5 (2)	5(2)	0.419
Total AB prescription; n	35732	41068		2741	3366		2388	855		3210	3451		316	128	
Prescriptions per patient	7.8	4.6		7	4		8	4.8		5.6	4.2		6	6.1	
AB prescriptions by generic name; n (%)	2341 (7)	685 (2)	**<0.001**	175 (6)	47 (1)	**<0.001**	282 (12)	46 (5)	**<0.001**	61 (2)	52 (2)	0.214	19 (6)	5 (4)	0.374[a]
Prescriptions of AB found in NLEMI; n (%)	27640 (77)	24683 (60)	**<0.001**	-	-	-	-	-	-	-	-	-	-	-	-

Abbreviations: AB: antibiotics, NTH: non-teaching hospital, SD: standard deviation, TH: teaching hospital. Significant p-values are shown in bold. Independent sample t-test was used to compare age, duration of hospital stay and duration of antibiotic treatment. Pearson chi-square was used to compare prescription details with expected value >5. [a]Fischer´s exact test was used to compare expected values <5.

Table 3: Class wise distribution of prescribed antibiotics in four selected diagnoses groups at one teaching and one non-teaching hospitals in Ujjain, India

	Group (a): Cardiovascular diseases						Group (b): Malaria or Viral fever					
	Cardiovascular with no registered bacterial infection (Sub-group 1)			Cardiovascular with suspected bacterial infection (Sub-group 2)			Malaria or Viral Fever with no registered bacterial infection (Sub-group 3)			Malaria or Viral Fever with suspected bacterial infection (Sub-group 4)		
Name of AB; ATC-code	**TH**	**NTH**	**p-value**	**TH**	**NTH**	**p-value**	**TH**	**NTH**	**p-value**	**TH**	**NTH**	**p-value**
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Total prescriptions	2741	3366		2388	855		3210	3451		316	128	
Tetracyclines; J01A: J01AA	284 (10)	5 (0)	**<0.001**	243 (10)	0 (0)		553 (17)	75 (2)	**<0.001**	83 (26)	0 (0)	
Beta-lactam ABs, penicillin; J01C	458 (17)	498 (15)	0.041	622 (26)	184 (22)	0.009	111 (3)	245 (7)	**<0.001**	12 (4)	7 (5)	0.431
Extended-spectrum penicillins; J01CA	83 (3)	99 (3)	0.843	122 (5)	99 (12)	**<0.001**	19 (1)	51 (1)	**<0.001**	0 (0)	2 (2)	
Combination of penicillin incl. Beta-lactamase AB; J01CR	373 (14)	399 (12)	0.040	500 (21)	85 (10)	**<0.001**	92 (3)	194 (6)	**<0.001**	12 (4)	5 (4)	1.0[a]
Other Beta-lactam; J01D	488 (18)	1391 (41)	**<0.001**	353 (15)	304 (36)	**<0.001**	665 (21)	1792 (52)	**<0.001**	40 (13)	39 (30)	**<0.001**
1st gen. cephalosporins; J01DB	7 (0)	16 (1)	0.163	0 (0)	5 (1)		0 (0)	9 (0)		0 (0)	0 (0)	
2nd gen. cephalosporins; J01DC	0 (0)	98 (3)		0 (0)	27 (3)		0 (0)	168 (5)		0 (0)	0 (0)	
3rd gen. cephalosporins; J01DD	481 (18)	1254 (37)	**<0.001**	353 (15)	272 (32)	**<0.001**	665 (21)	1606 (47)	**<0.001**	40 (13)	39 (30)	**<0.001**
4th gen. cephalosporins; J01DH	8 (0)	23 (1)	0.032	0 (0)	0 (0)		0 (0)	9 (0)		0 (0)	0 (0)	
Sulfonamide with timethoprime; J01E: J01EE	8 (0)	0 (0)		18 (1)	0 (0)		8 (0)	0 (0)		0 (0)	0 (0)	
Macrolides, lincosamides J01F	16 (1)	2 (0)	**<0.001**	4 (0)	6 (1)	0.025*	15 (0)	7 (0)	0.060	3 (1)	4 (3)	0.110[a]
Macrolides; J01FA	12 (0)	2	0.002	4 (0)	6 (1)		15 (0)	7 (0)		3 (1)	4 (3)	
Lincosamides; J01FF	4 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Aminoglycoside; J01G: J01GB	78 (3)	73 (2)	0.090	149 (6)	46 (5)	0.364	17 (1)	60 (2)	**<0.001**	11 (3)	9 (7)	0.102
Quinolones; J01M: J01MA	1031 (38)	301 (9)	**<0.001**	731 (31)	112 (13)	**<0.001**	1526 (48)	464 (13)	**<0.001**	126 (40)	37 (29)	0.030
Fixed dose combination of ABs; J01R: J01RA*	12 (0)	929 (28)	**<0.001**	31 (1)	170 (20)	**<0.001**	34 (1)	669 (19)	**<0.001**	6 (2)	17 (13)	**<0.01**
Other ABs; J01X	167 (6)	176 (5)	0.145	132 (6)	30 (4)	0.020	149 (5)	138 (4)	0.197	20 (6)	15 (12)	0.056
Glycopetide ABs; J01XA	15 (1)	176 (5)	**<0.001**	0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Imidazole derivatives; J01XD	152 (6)	0 (0)		132 (6)	30 (4)	0.020	149 (5)	137 (4)	0.176	20 (6)	15 (12)	0.056
Other ABs; J01XX	0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	1 (0)		0 (0)	0 (0)	
Drugs for treatment of tuberculosis; J04A	0 (0)	0 (0)		24 (1)	0 (0)		0	0 (0)		0 (0)	0 (0)	
Antibiotics; J04AB (Treatment for Tuberculosis)	0 (0)	0 (0)		6 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Hydrazides; J04AC	0 (0)	0 (0)		6 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Other drugs for treatment of tuberculosis; J04AK	0 (0)	0 (0)		12 (1)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Nitromidazole derivatives; P01AB (Oral Metronidazole)	201 (7)	0 (0)		81 (3)	3 (0)	**<0.001**	132 (4)	1 (0)	**<0.001**	15 (5)	0 (0)	

Abbreviations: n(%): Number of patients (percentage in antibiotic class), AB: antibiotics, ATC: WHO anatomic therapeutic chemical classification, NTH: non-teaching hospital, TH: teaching hospital. Significant p-values shown in bold. Pearson chi-square and [a]Fischer´s exact test were used to compare antibiotic prescribing details, gen-generation.

Third-generation cephalosporins (J01DD) constituted 47% and 30% of the prescriptions in sub-group 3 and 4 at the NTH, followed by FDCs (19% and 29% of the prescriptions respectively). Overall, antibiotic prescriptions were significantly more common for the patients in sub-group 3 than in the sub-group 1' ($p<0.001$). The type of malaria was verified by blood samples reports in some cases of sub-group 3 (TH: 4% and NTH: 7%). None of the records from the four sub-groups had requisition for sending samples for bacterial culture and susceptibility test.

Ciprofloxacin (J01MA02) was the most frequently prescribed antibiotic substance measured in DDD/1000 patients at the TH and ceftriaxone (J01DD04, Table 4) at the NTH. The highest number of prescribed DDDs/1000 patients was recorded for ciprofloxacin, followed by doxycycline and ceftriaxone in both hospitals (Figure 2).

Table 4: Most commonly prescribed antibiotics among the selected diagnoses groups presenting the prescribing occasions in DDDs/1000 patients at sixth level of the ATC classification

	Group (a): Cardiovascular diseases				Group (b): Malaria or Viral fever			
	Cardiovascular with no registered bacterial infection (Sub-group 1) n (%)		Cardiovascular with suspected bacterial infection (Sub-group 2) n (%)		Malaria or Viral Fever with no registered bacterial infection (Sub-group 3) n (%)		Malaria or Viral Fever with suspected bacterial infection (Sub-group 4) n (%)	
Name; ATC-code	**TH**	**NTH**	**TH**	**NTH**	**TH**	**NTH**	**TH**	**NTH**
Total DDDs/1000 patients	2062 (99)	1456 (100)	4514 (99)	3421 (100[#])	4480 (100[#])	3048 (100[#])	5432 (100[#])	5827 (100)
Doxycycline, J01AA02	491 (24)		1030 (23)		1463 (33)	296 (10)	2745 (51)	
Ampicillin, J01CA01	68 (3)		170 (4)					
Amoxicillin, J01CA04		81 (6)		435 (13)				
Amoxicillin + Clavulanic acid, J01CR02				566 (17)		88 (3)		
Piperacillin + Tazobactam, J01CR05						34 (1)		
Ampicillin + Cloxacillin, J01CR50	217 (11)		774 (17)				191 (4)	
Cefuroxime, J01DC02				95 (3)		136 (4)		
Cefprozil, J01DC10		75 (5)						
Cefotaxime, J01DD01	172 (8)	46 (3)	298 (7)	59 (2)	199 (4)	96 (3)	295 (5)	
Ceftriaxone, J01DD04	133 (6)	558 (38)	244 (5)	907 (27)	560 (13)	1052 (35)	164 (3)	1402 (24)
Azithromycin, J01FA10								476 (8)
Gentamicin, J01GB03	44 (2)		167 (4)	81 (2)				
Amikacin, J01GB06								321 (6)
Ofloxacin, J01MA01						202 (7)		
Ciprofloxacin, J01MA02	687 (33)	141 (10)	1057 (23)	527 (15)	1940 (43)	602 (20)	1185 (22)	2886 (50)
Norfloxacin, J01MA06			201 (4)				273 (5)	
Levofloxacin, J01MA12		73 (5)	202 (4)	129 (4)			145 (3)	
Cefoperazone + Sulbactam, J01RA*83		92 (6)		94 (3)		90 (3)		125 (2)
Ceftriaxone + Sulbactam, J01RA*84		228 (16)		277 (8)		199 (7)		
Ceftriaxone + Tazobactam, J01RA*85		162 (11)		156 (5)		162 (5)		250 (4)
Metronidazole, J01XD01	139 (7)		262 (6)	95 (3)	204 (5)	91 (3)	262 (5)	367 (6)
Metronidazole, P01AB01 (Oral)	111 (5)		109 (2)		114 (3)		172 (3)	

Abbreviations: n (%): Number of patients (percentage), AB: antibiotics, DDD: Defined Daily Dose, NTH: non-teaching hospital, TH: teaching hospital, [#] rounding off the percentages to nearest integer made the total more than 100%

Figure 2. Top 90% of prescription in the four selected groups measured in DDD/1000 patients, presented at fourth level of the ATC classification at one teaching and one non-teaching hospitals in Ujjain, India

DISCUSSION

To our knowledge this study is the first to investigate and present antibiotic prescription practices at medicine departments in Indian private sector hospitals by focusing on non-bacterial infectious diseases. This also leads to a limitation, as the results of the present study could not be compared with the findings of any other study. Thus the results of present study were compared with the most equivalent studies available globally.

Antibiotics were commonly prescribed to inpatients at both study hospitals. Irrespective of the indications, broad-spectrum antibiotics and third-generation cephalosporins that should be conserved for high risks co-morbidities and life-threatening bacterial infections were prescribed frequently. This study also highlights the high rates of antibiotic prescriptions used to treat the selected groups of non-bacterial infectious diseases such as cardiovascular disease, malaria, and viral fever.

Antibiotic prescriptions in the cardiovascular and fever groups

The average percentage of patients that were prescribed antibiotics in the medicine departments were similar (TH: 65% and NTH: 67%, $p<0.001$) in comparison to the rates in the medicine department of a public hospital at Bathalapalli, Andhra Pradesh, India (63%),[26]. With a few exceptions, such as rheumatic fever, endocarditis, pericarditis and myocarditis (bacterial or viral), cardiovascular diseases are primarily non-infectious. COPD and RHD are the common associated diseases in cardiovascular patients. Rheumatic fever is an immune response sequel to an infection and it may cause endocarditis,[23,27]. However, pericarditis and myocarditis most commonly develop from viral pathogens where antibiotic treatment is not a routine recommendation,[28,29].

Interestingly, more than 35% of inpatients among the 'cardiovascular group with no registered bacterial infection' were prescribed antibiotics at both hospitals. As per treatment guidelines and recommendations, only patients who have confirmed infectious diagnosis are expected to receive an antibiotic prescription,[30–32]. Nonetheless, empirical or presumptive antibiotic therapy is also accepted when the clinical diagnosis, based on the presence of a strong clinical suspicion of bacterial infection, is substantiated by relevant medical history and clinical findings,[30]. According to the WHO and the Indian National Treatment Guidelines for Antimicrobial Use; presumptive therapy is typically a one-time treatment given for clinically presumed infection while waiting for the culture report,[31,32]. In combination of clinical findings laboratory and radiological reports are considered to confirm the diagnosis and lead to the definitive therapy,[32].

Microbiology laboratories were highly under-utilized in both study hospitals. None of the patient records in the selected four sub-groups included notes about sending samples for culture and susceptibility testing. Therefore, the practice of prescribing antibiotics to the patient groups with no registered bacterial infection in absence of laboratory confirmation could not be considered to be rational. Among the COPD and RHD patients the aetiology of the current episode of hospitalization could potentially be expected to be non-bacterial (e.g. viral infection). However, this could not be confirmed due to the absence of laboratory investigations. It is worth mentioning here that prolonged empiric antibiotic treatment without a clear evidence of infection is one of the causes of the development of antibiotic resistance.

More FDCs were prescribed to the cardiovascular patients at the NTH than at the TH. Rationality of the newer FDCs coded with ATC-code: J01RA* has not been established yet and these combinations are not listed in either the NLEMI or the WHOLEM,[18,19]. It is also

evident that the constituents of these combinations are often present in lower quantities than is recommended which might lead to the development of antibiotic resistance,[33].

The sub-group 'malaria or viral fever with suspected bacterial infection' was found to have the highest rate of antibiotic prescriptions among all the four sub-groups (TH: 96%, NTH: 75%). Our result also highlight that patients with fever were more likely to receive antibiotic prescriptions, than patients with cardiovascular diseases. Fever is a common symptom among malaria, viral fever and bacterial infection. Therefore, the doctors might have prescribed antibiotics as a 'prophylactic' treatment to treat bacterial infection, if any. In our study the rate of antibiotic prescriptions for the patients with fever was higher than, yet comparable with a study at primary and secondary health care settings in Uttar Pradesh, India where 85% of the fever patients were prescribed antibiotics,[34]. Additionally, in our study a high percentage of patients with fever (malaria or viral fever) with 'no registered bacterial infection' were prescribed antibiotics (TH: 82%, NTH: 71%). An out-patient study from Uganda, a malaria endemic country, showed that 42% of malaria patients were prescribed antibiotics without any registered indication,[25]. As the majority of the prescriptions in our study were empirical, the rationale for using the antibiotics cannot be evaluated. However, prescribing antibiotics to treat non-bacterial infections is considered to be an irrational practice. Thus it is imperative that this matter be addressed.

Adherence to the essential medicine lists and prescriptions by generic name

A higher proportion of prescribed antibiotics at the TH (77%) were from the NLEMI compared with the NTH (60%, $p<0.001$). This could be attributed to the presence of a management policy to purchase and supply medicines at the TH. However, there is a need to improve adherence to the NLEMI at both hospitals. According to WHO, prescribing by their generic name is; part of rational prescribing, cost effective and provides flexibility to buy the

available medicine of any company. This policy is equally applicable for both public and private healthcare settings. However, adherence to this policy is higher at public hospitals, followed by 'private non-profit' hospitals and by the 'private for-profit' hospitals,[13,14,35]. In the present study, significantly lower antibiotic prescriptions were made by generic names to the patients of sub-group 1 (TH: 6%, NTH: 1% p<0.001) or sub-group 2 (TH: 12% NTH: 5% p<0.001) at the NTH than at the TH. Third-generation cephalosporins (J01D, 29%) and FDCs (J01RA*, 23%) were the most commonly prescribed classes of antibiotics at the NTH while quinolones were most commonly prescribed at the TH (J01M, 37%, NTH: 13%). Previous studies from Uttar Pradesh, India and Madhya Pradesh, India have also shown similar results for academic and non-academic hospitals,[13,14,17]. The high incidence of prescribing these classes is further supported by Van Boeckel et al, who observed a significant increase in the consumption of fluoroquinolones and cephalosporins globally over the past decade. This increase was mainly attributed to the increased rates in India and China,[9]. At the NTH, prescriptions of FDCs varied between 19% and 28% among the selected sub-groups (TH: <2%) and the prescriptions of third-generation cephalosporins varied between 30% and 47% (TH: <22%). According to WHO, prescribing multiple antibiotics when not indicated, often combined in inadequate doses (smaller or larger quantity than recommended) and prescription of drugs other than local or national guidelines are all examples of actions deemed inappropriate,[36]. All these practices could be seen in prescribing newer FDCs (J01RA*); both of the study hospitals are from the private sector and are regulated by the same trust on a 'not for-profit' basis. The differences in the prescribing practices might be due to each hospital's policy and the fact that academic hospitals are part of the educational process, and regular educational activities conducted at these hospitals results in better adherence to the guidelines, as seen at the TH. Another reason for the frequent prescribing of broad-spectrum antibiotics, new FDCs and use of trade names at the NTH could be explained by the results of

a review conducted by Blumenthal et al,[37]. That review concluded that physicians who had received gifts or money from pharmaceutical companies were more likely to prescribe drugs produced by the brand names and less prone to use the generic names. The pressure from pharmaceutical companies could be anticipated on the doctors at the NTH, due to unrestricted visits from pharmaceutical company representatives,[37]. Moreover, these new FDCs of antibiotics are more expensive than the regular and generic formulations,[13,14,37]. The restriction of these visits and the management control over the purchase and supply of medicines can be seen as main reasons for low incidence of prescribing FDCs prescribing and high use of generic names at the TH.

Interestingly trade names were used as local abbreviations to prescribe four most commonly prescribed antibiotics; ciprofloxacin, doxycycline, gentamycin and metronidazole at the TH, as discussed in result section. However, only generic drugs were purchased and dispensed at the TH due to administrative control over the purchase and supply of the drugs. Thus even if these antibiotics were prescribed using an abbreviation similar to the trade name, they were included in adherence to the generic name prescribing category.

Duration of hospital stay and duration of antibiotic treatment

In the present study both the duration of hospital stay and the duration of antibiotic treatment were longer at the TH than the NTH among all inpatients groups. This could be due to the fact that the patients at the TH received free healthcare services and drugs, making their stay economically feasible. In contrast, at the NTH the patients had to pay for all the services and drugs they received. This association of longer duration of stay and antibiotic treatment at TH has also been observed in previous studies from India,[13,14,17]. However, it is evident that the treatment given for a time period that is either shorter or longer than recommended, is

inappropriate and it substantially contributes to the development of antibiotic resistance,[1,36].

Absence of computerized record systems in hospitals, absence of personal identification number, untrained staff and high staff turnover makes a detailed study like this, time consuming and onerous exercise and delays the analysis. We are aware that extensive manual checking and working with the data like adding the ICD codes and the ATCs for the new FDCs to the data has prolonged the analysis process and has delayed the presentation. However, use of man power is the only option to conduct such detailed studies at resource constrained settings but at the same time lead to relatively more accurate description of the prescribing patterns.

STRENGTHS AND LIMITATIONS

A high number of patients were screened over a three year period this overcomes seasonal variations in infectious aetiology which would affect antibiotic prescribing. Same form was used for the data collection and the process was supervised and monitored by same person at both hospitals to improve the reliability of the data. The diagnoses were not verified externally being a limitation of the study. However, external verification is virtually inapplicable to studies that rely upon the routine collection of data. The results of the study were based on the notes included in the patient files. Extensive efforts were made to document all notes including diagnoses written in the patient files. However, the possibility of missing a few diagnoses and losing some data during the transition from the forms to the digital storage cannot be excluded.

CONCLUSION

A higher number of prescribing occasions were recorded at the TH, and not at the NTH, with

regard to adherence to the guidelines. However, overall adherence was low. Fever was a risk factor to receive antibiotic prescription at both hospitals. Patients with non-bacterial infections such as malaria or viral fever or with cardiovascular diseases were prescribed antibiotics at both medicine departments which could not be justified. Broad spectrum antibiotics with irrational combinations of antibiotics were commonly prescribed in the study hospitals for non-indicated conditions. A large proportion of patients were categorised as suspected bacterial diagnoses (sub-groups 2 and 4). In the presence of confirmed aetiology, according to microbiology reports, some of these could have been categorised in non-bacterial group and could have contributed to higher antibiotic prescribing rates in the non-bacterial diagnoses (sub-groups 1 and 3). However, this was unavoidable due to absence of confirmed aetiology and the nature of the study design (observational).

GENERALISABILITY AND FUTURE IMPLICATIONS

The data collection method used in the study is robust and reliable. In accordance with one of the WHO goals of "Global-action-plan" and in view of limited knowledge of antibiotic utilization and resistance patterns our study findings suggest that there is a need to conduct and share similar long term surveillance studies globally. The data collection method and tested tool used in the study could easily be adapted in other settings that lack computerized patient records. The management in the TH had a policy to control the purchase and supply of medicines. This control shows positive effects at the TH compared to the NTH; to minimise antibiotic prescribing, in better adherence to the NLEMI and in use of generic names. This control could be implemented and tested in other constrained settings. The recruitment of nursing staff for manual data collection who routinely work in the department would have helped to minimize the influence on the prescribers. High prescribing rates of antibiotics and use of FDCs among inpatients in these settings could broadly be considered as representative for similar health care settings in low-middle income countries. Lack of culture of sending

cultures is another important issue raised by the study. The need to develop and implement local diagnosis specific prescribing guidelines in conjugation with continuous follow-up is also emphasized by our study. The physicians should be motivated to send samples for cultures before prescribing antibiotics. Improving hygiene practices is another recommendation to prevent spread of infection and to decrease in the 'prophylactic' use of antibiotics.

CONTRIBUTERSHIP STATEMENT

MS and CSL designed, visualized the research question and developed the data collection tool. MS conducted repeated training sessions for nursing personal for recording the data. MS was also responsible for coordination with the nursing staff, monitoring and supervision of the data collection and entry. CSL participated in planning the study design and the coordination of the study. KL, CSL and MS participated in the conception and design of the present study and revising the paper critically for substantial intellectual content. KL grouped and analyzed the data, performed the statistical analysis and contributed in drafting the manuscript along with MS, CSL, FJ and AS. KL, AS and MS were responsible for categorization of the patients. All authors read and approved the final version of the manuscript.

COMPETING INTERESTS

The authors have no competing interests to declare.

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DATA SHARING STATEMENT

As per the institutional policy, the data is available with the Institutional ethics committee. This is to protect the patient's confidentiality and to ensure the electronic security of the data. The data could be made available to all interested researchers upon request made to; The Chairman, Ethics Committee, R.D. Gardi Medical College, Agar Road, Ujjain, Madhya Pradesh, India 456006 (Email: iecrdgmc@yahoo.in, uctharc@sancharnet.in), giving all details of the article. The ethical approval number: 41/2007 needs to be quoted along with the request.

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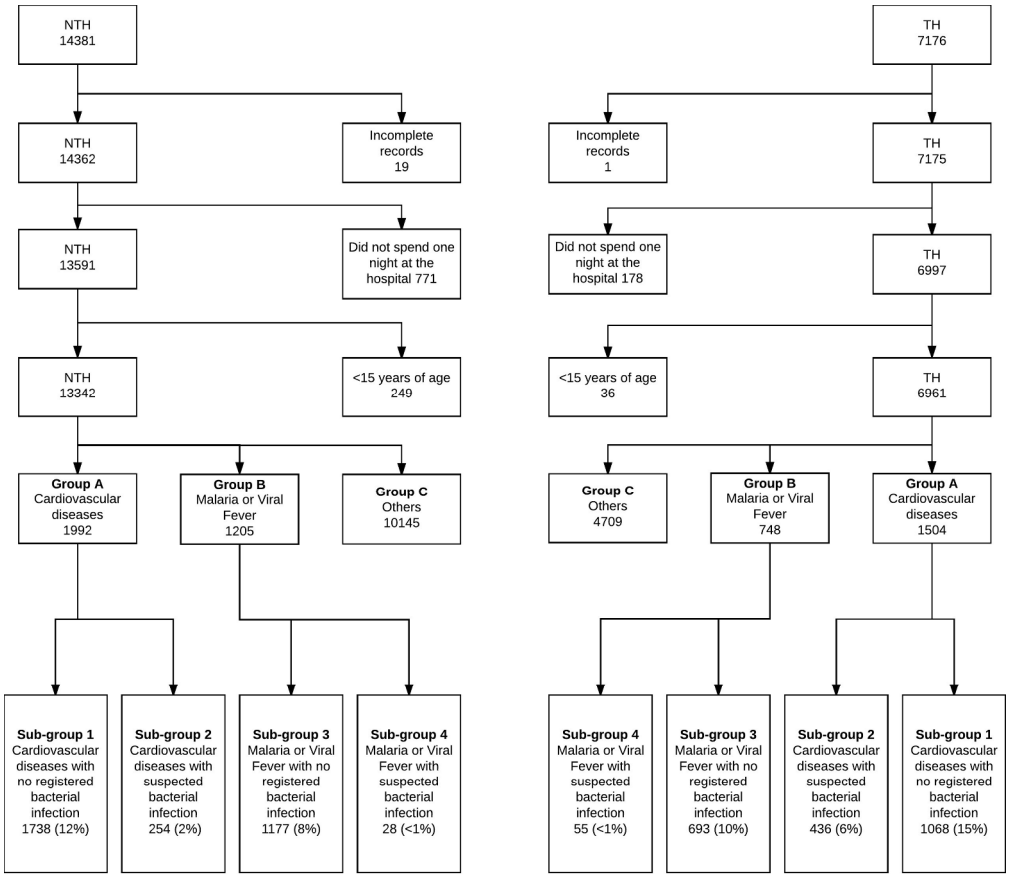
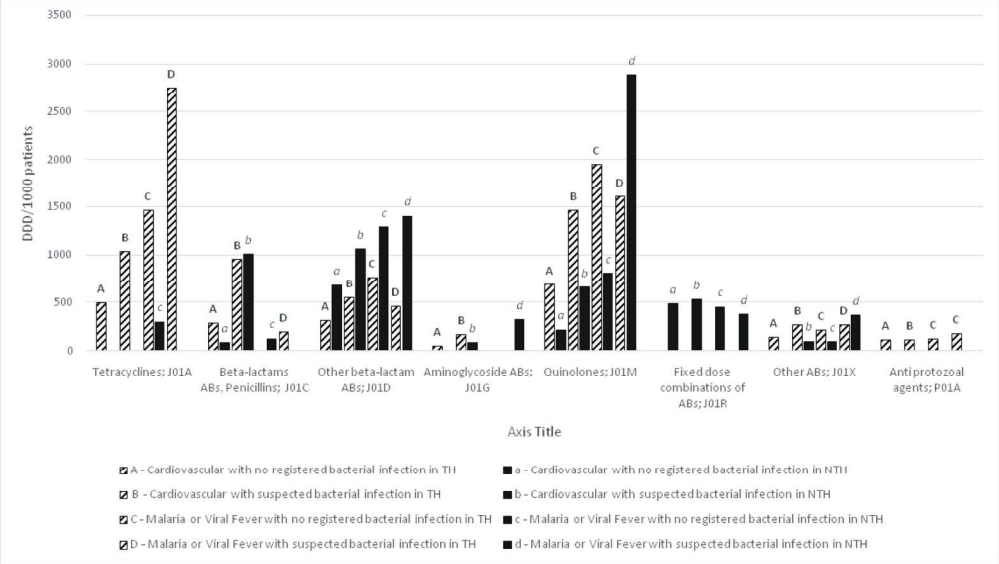
Figure 1. The process of selection and grouping of inpatients admitted in medicine departments of the TH and the NTH based on their diagnosis.

Figure 2. Top 90% of prescription in the four selected groups measured in DDD/1000 patients, presented at fourth level of the ATC classification at one teaching and one non-teaching hospitals in Ujjain, India



The process of selection and grouping of inpatients admitted in medicine departments of the TH and the NTH based on their diagnosis

674x590mm (96 x 96 DPI)



Top 90% of prescription in the four selected groups measured in DDD/1000 patients, presented at fourth level of the ATC classification at one teaching and one non-teaching hospitals in Ujjain, India

91x51mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2-3**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**5**
Objectives	3	State specific objectives, including any pre specified hypotheses	**6**
Methods			
Study design	4	Present key elements of study design early in the paper	**6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**6**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls ***Cross-sectional study***—Give the eligibility criteria, and the sources and methods of selection of participants	**7**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	***8***
Bias	9	Describe any efforts to address potential sources of bias	**9-10**
Study size	10	Explain how the study size was arrived at	**8**

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**8-10**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	**10**
		(e) Describe any sensitivity analyses	

Continued on next page

Results			Page Number
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**9,10**
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	**Figure 1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**09-11 Table 1**
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	**10-11, 14-15 Table 2**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**11-17 Table 2, 3 and 4 Figure 2**
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
		Discussion	
Key results	18	Summarise key results with reference to study objectives	**18**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**23**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**18-22**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**24**
		Other information	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**25**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.