Antibiotic prescribing among patients with severe infectious diseases in two private sector hospitals in Central India – A time series analysis over 10 years

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Abstract

Antibiotic resistance is an emerging problem, particularly in low- and middle-income countries, where mortality rates due to infectious diseases are highly associated with antibiotic resistance. Analyses of antibiotic prescribing practices is needed to develop strategies for improvement. The aim was to analyze antibiotic prescribing among patients with severe infections admitted to two Indian hospitals during 2007-2018. Methods Data from patients (>18 years-of-age), admitted to a teaching (TH) and a non-teaching hospital (NTH) in Ujjain, India, from 2008-2017 registered with one of the infectious diagnoses; epiglottitis, pneumonia, peritonitis, pyelonephritis, cellulitis, erysipelas, septic arthritis, endocarditis, meningitis or sepsis, were included. Antibiotic prescription data was analyzed using the 2019 Anatomical Therapeutic Chemical classification system and the Defined Daily Doses (DDD). Prescribing of antibiotics was calculated for DDD/1000 patient days. To compare data between the hospitals and patient groups, chi-square tests and t-tests were used. Time series analyses were conducted using linear regression. P-values <0.05 were considered significant. Results In total, 2571 patients were included (NTH: 1610, TH: 96, of which 92% respectively 89% were prescribed antibiotics). Antibiotics included in the World Health Organization's (WHO) access category; antibiotics that should be prescribed as first-choice treatment comprised 61% of the total antibiotic prescribing at the TH and 40% at the NTH ($P<0.05$). Prescribing of antibiotics categorized as the WHO's watch antibiotics (second-choice antibiotics) comprised 29% of the antibiotic prescribing at the TH and 40% at the NTH. Prescribing of fixed dose combinations (FDCs) of antibiotics comprised 8% of the antibiotic prescribing at the TH and 18% at the NTH ($P<0.05$). At the NTH, overall antibiotic prescribing as well as prescribing of access, watch and FDCs of antibiotics increased between 2008-2017 among all included patients and for patients with pneumonia, sepsis, cellulitis and peritonitis ($P<0.05$). At TH, prescribing of watch, reserve and FDCs of antibiotics increased among all included patients well as among patients with pneumonia, cellulitis and peritonitis ($P<0.05$). Conclusions High percentage of patients were prescribed antibiotics at both hospitals. Between 2008-2017, overall antibiotic prescribing increased at NTH and prescribing of watch, reserve and FDCs of antibiotics increased at both NTH and TH.

Background

Antibiotic resistance is an emerging global threat as it causes significant morbidity and mortality worldwide [1, 2]. In a publication of antibiotic surveillance report made in 22 countries worldwide between 2016-2017, some countries reported that up to 82% of the patients registered with suspected blood stream infections had bacteria that were resistant to at least one of the most commonly used antibiotics [3]. The World Health Organization (WHO) has stated that there is a need for global action against antibiotic resistance in order to keep the treatment effective for the future [4].

In low- and middle-income countries (LMICs), the infection burden is often high and antibiotic resistance is highly associated with mortality due to infectious diseases [2, 5]. However, it is difficult to state the exact burden of antibiotic resistance is in LMICs. It requires costly equipment for microbiological analyses, to determine the susceptibility of bacteria and these methods must be implemented and

reported [5, 6]. In LMICs, access to diagnostic methods is often limited. Consequently, antibiotics are commonly prescribed based on clinical suspicion of infection, and broad-spectrum antibiotics or fixed dose combinations (FDCs) of antibiotics are commonly used [7-10]. Mapping of antibiotic prescribing is highly valuable. Improper use of antibiotics contributes unnecessarily to development of antibiotic resistance, i.e. antibiotic should only be used for relevant indication, as targeted as possible, in correct doses, treatment duration and by suitable route of administration [11]. By analyzing the antibiotic prescribing practices, areas for improvement can be identified and handled. However, so far there are few long-term studies on antibiotic prescribing from LMICs, especially studies comparing various health care providers and settings [6].

Infectious diseases are the second most common cause of death in India, after diseases of the circulatory system [12]. In 2017, almost a million people died due to respiratory tract infections and almost 800,000 people died of enteric infections in India, which corresponds to approximately 10% respectively 8% of all deaths in India during that year [13]. Comparably, on a global basis approximately 7% of the people died of respiratory tract infections and 3% died of enteric infections [13]. Madhya Pradesh is one of the five Indian states where the mortality rates due to respiratory tract infections are the highest [14]. In order to battle the burden of infectious diseases and reduce development of antibiotic resistance in India, it is valuable to analyze the antibiotic prescribing practices among patients with severe infections admitted to Indian hospitals, to identify needs for improvements. The aim of this study was to present and compare the antibiotic prescribing among patients registered with severe infectious diseases at two hospitals with different settings in Ujjain, Madhya Pradesh, India [15], over a ten-year period. The secondary aim was to relate the antibiotic prescribing at the two hospitals to global recommendations for antibiotic treatment, and to evaluate any changes in prescribing during the study period.

Methods

Study settings

This prospective, observational study with time-series analysis was conducted at two tertiary care, private sector hospitals run by the same trust, located in Ujjain district of Madhya Pradesh, India, one teaching hospital (TH) and one non-teaching (NTH). The TH is in a rural area and has 570 beds. The NTH is centrally located and has 350 beds. At the TH, patients are provided medical services and medicines free of charge while medical services at the NTH are charged but at a reduced level [16]. At the NTH, the patients purchase their medicines also during hospital stay. Medical representatives are not allowed to visit the prescribers at the TH while they can do so at the NTH. A local essential medicines list was available at the TH, though it was not completely implemented but no local prescribing guidelines were available at the TH or NTH. As none of the hospitals had computerized prescribing records, data was manually registered in a form inserted in each patient's medical file at time of admission, and prospectively filled during the patients stay in the hospital. This was made by trained nursing staff that completed forms continuously, which has been described in detail earlier [9, 16].

Categorization of antibiotics

Prescribed antibiotics were classified using the 2019 year Anatomical Therapeutic Chemical classification system (ATC) and the Defined Daily Doses (DDD) classification according to the WHO [17]. Further, the WHO has adopted a classification of antibiotics, the so-called *access*, *watch* and *reserve* antibiotics (Table 1). The aim for the categorization of antibiotics is to sort antibiotics according to how they should be used, based on the risk of development of antibiotic resistance in order to preserve the effectiveness of antibiotic treatment and to improve clinical outcomes [4, 18, 19]. *Access* antibiotics should be widely available, affordable and of good quality, *watch* antibiotics include most of the highest priority, critically important medicines and should be used only for specific and limited indications and *reserve* antibiotics should only be used when all alternative antibiotics have been unsuccessful for the treatment [4, 18, 19]. Some of the prescribed antibiotics are categorized only up to antibiotic-groups level, these antibiotics were added to the relevant category as per their antibiotic-groups. For example; cefuroxime was not categorized by the WHO but second generation cephalosporins were categorized as *access* antibiotic, then we added cefuroxime to the *access* category for the analysis [20]. The following antibiotics were added in *access* group: first generation cephalosporins: cefadroxile, cefradine, second generation cephalosporins: cefuroxime, cefaclor, aminoglycosides: netilmicin, streptomycin, kanamycin, tobramycin as well as ornidazole, tinidazole, piperacillin and tazobactam. *Watch*: third generation cephalosporins: cefoperazone, cefodoxime, quinolones and fluoroquinolones: ofloxacin, gemifloxacin, gatifloxacin, pazufloxacin, prulifloxacin and macrolids: roxithromycin. Since FDCs consist of at least two antibiotics, often from different antibiotic-groups, we added “FDCs” as a category beside the *access*, *watch* and *reserve* antibiotics. Antibiotics categorized in the respective categories are presented in Table 1.

Table 1. Antibiotics categorized in *access*, *watch*, *reserve* and fixed dose combinations of antibiotics.

ATC-code	Antibiotic group	Specific antibiotics	Antibiotic category
J01A	Tetracyclines	Doxycycline	<i>Access</i>
		Tigecycline	<i>Reserve</i>
J01B	Amphenicols	Chloramphenicol	<i>Access</i>
J01 group 1: J01CA, J01CE, J01CF, J01CG	Penicillins with extended spectrum, Beta-lactamase sensitive penicillins, beta-lactamase resistant penicillins, beta-lactamase inhibitors	Amoxicillin, ampicillin, benzathine benzylpenicillin, benzylpenicillin, cloxacillin, phenoxymethylpenicillin, procaine benzylpenicillin, piperacillin, tazobactam	<i>Access</i>
J01CR	Combinations of penicillins including beta-lactamase inhibitors	Amoxicillin with clavulanic acid	<i>Access</i>
		Piperacillin with tazobactam	<i>Watch</i>
J01D	Beta-lactam antibiotics	Cefalexin, cefazolin, cefadroxile, cefradine, cefuroxime	<i>Access</i>
		Cefixime, ceftriaxone, cefotaxime, cefoperazone, cefodoxime, ceftazidime, meropenem, imipenem, cilastin, faropenem	<i>Watch</i>
		Aztreonam, cefepime, ceftaroline	<i>Reserve</i>
J01E	Sulfonamides and trimethoprim	Sulfamethoxazole with Trimethoprim	<i>Access</i>
J01F	Macrolides	Clindamycin	<i>Access</i>
		Azithromycin, clarithromycin, erythromycin, lincomycin, roxithromycin	<i>Watch</i>
J01G	Aminoglycosids	Gentamicin, netilmicin, kanamycin, tobramycin, streptomycin, amikacin	<i>Access</i>
J01M	Quinolones and fluoroquinolones	Ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, gemifloxacin, pazufloxacin, gatifloxacin, prulifloxacin	<i>Watch</i>
J01R	Combinations of antibiotics	Ampicillin with Cloxacillin. Amoxicillin with Cloxacillin Azithromycin with Ambroxol Cefixime with Ornidazole Cefoperazone with Sulbactam Ceftriaxone with Sulbactam Ceftriaxone with Tazobactam Norfloxacin with Tinidazole Ofloxacin with Ornidazole Ofloxacin with Tinidazole	FDCs of antibiotics

		Cefixime with Clavulanate Potassium Cefixime with Clavulanic Acid Cefixime with Cloxacilline Cefixime with Ofloxacin Cefixime with Tazobactam Cefotaxime with Sulbactam Cefpodoxime with Clavulanic Acid Cefpodoxime with Cloxacillin Cefpodoxime with Dicloxacillin Meropenem with Sulbactam Ceftazidime with Tazobactam Cefuroxime with Clavulanic Acid Ciprofloxacin with Ornidazole Ciprofloxacin with Tinidazole Efoperazone with Sulbactam Levofloxacin with Ornidazole Cefixime with Azithromycin Cefpodoxime with Potassium Clavulanate Ceftriaxone with Clavulanic Acid	
J01X	Other antibiotics	Metronidazole (J01XD01), nitrofurantoin, tinidazole, ornidazole, spectinomycin Teicoplanin, vancomycin Polymyxin B, colistin, fosfomycin, linezolid, daptomycin	Access (P01AB01 Metronidazole included) Watch Reserve

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification; FDC, fixed dose combination.

To analyze adherence to prescribing guidelines, existing international guidelines for empiric antibiotic prescribing were used. The WHO has developed international guidelines for empirical treatment of cellulitis and pneumonia [18]. For peritonitis, the World Society of Emergency Surgery has published guidelines for empirical antibiotic treatment and likewise, the Surviving Sepsis Campaign has published international guidelines for sepsis [21, 22]. The guidelines from the World Society of Emergency Surgery are developed by an international panel of experts and aim to provide an international, evidence-based

consensus position on the management of intra-abdominal infections such as peritonitis, and state that empirical antibiotic therapy, should be initiated upon suspicion of peritonitis [21]. The guidelines from the Surviving Sepsis Campaign have been developed by 55 international experts from 25 international organizations, to be used by clinicians caring for adult patients with sepsis or septic shock [22]. The “Surviving sepsis campaign” for sepsis and septic shock states that the initial empiric treatment for sepsis or septic shock should cover most pathogens isolated in healthcare-associated infections and that the broad-spectrum antibiotics are rational to use [22]. As soon as the pathogen has been identified and susceptibility report is established and/or clinical improvement is noted, antibiotic therapy should be narrowed down, adjusted to site of infection and knowledge about local microbiologic etiology.

Data analysis

The WHO has listed the following infectious diseases as indications for empirical treatment with antibiotics; epiglottitis, pneumonia, peritonitis, pyelonephritis, cellulitis, erysipelas, septic arthritis, endocarditis, meningitis and sepsis [18]. For this study, antibiotic prescribing data has been collected prospectively from the records of all patients above 18 years of age, admitted to the TH and the NTH from 2008 to 2017 and were registered with one of the infectious diseases listed as indications for empiric antibiotic treatment. A unique code was generated for each patient record, without identifying the patients individually, thus all data were anonymized. Patient data were analyzed for gender, duration of hospital stay and if antibiotics were prescribed or not during hospital stay. The antibiotic prescription data were analyzed for type of antibiotic, dose, treatment duration, frequency and route of administration. For categorical variables, frequencies and percentage were calculated. For numerical variables, sum and mean with its 95% confidence interval (CI) were calculated. To compare data between the two hospitals and between the patient groups, chi-square test (for categorical variables) and t-test (for continuous numerical variables) were used. Pearson chi-square was used for expected values > 5 and Fischer’s exact test for expected values < 5.

Prescribed antibiotics were grouped for their first 4-5 characters of their ATC-code: J01A, J01B, J01C group 1 (containing all antibiotics starting with J01CA to J01CG), J01CR, J01D, J01E, J01F, J01G, J01M, J01R (containing FDCs that has been listed in the ATC/DDD classification system until June 2019) and J01X [17] (Table 1). Prescribed antibiotics were also classified for: *access*, *watch*, *reserve* and FDCs of antibiotics [4, 18, 19] (Table 1). Antibiotic prescribing was calculated for in DDDs and DDD per 1000 patient days according to following formulas:

DDD per prescription = *dose in grams* × *frequency*

WHO DDD for the antibiotic prescribed

$$DDD \text{ per } 1000 \text{ patient days} = \frac{DDD_{total} * 1000}{365}$$

N

Where DDD_{total} is total antibiotic prescribing (in DDDs) prescribed during one year among a patient group and N is total number of patients in that patient group during that year.

Time series analyses were conducted using linear regression for antibiotic prescribing in DDD per 1000 patient days during 2008-2017. Time series analysis were made for different patient groups; all included patients at the NTH and the TH respectively and patients with cellulitis, peritonitis, pneumonia and sepsis at the NTH and the TH respectively, as these were the most common infectious diagnoses among patients at both hospitals. Analyses were done both for total antibiotic prescribing among these groups and for prescribing of *access*, *watch*, *reserve* and FDCs of antibiotics. Linear regression was used with DDD per 1000 patient days as outcome (dependent variable) and year as independent variable to obtain a slope for the trend during 2008-2017. P-values < 0.05 were considered statistically significant. Data was entered manually in EPI Info 3.1 and analyzed using STATA software version 15.1 (Stata Corp. College Station. Texas. USA).

Results

Data from 2,571 patients analyzed, 1,610 patients from the NTH and 961 patients from the TH (Table 2). Antibiotics were commonly prescribed at both hospitals, although a significantly higher percentage of patients were prescribed antibiotics at the NTH (89% at the TH, 92% at the NTH, $P < 0.05$) (Table 2). Among each individual diagnosis group, there were no differences in percentage of antibiotic prescribing between the hospitals except for meningitis, where 90% of the patients were prescribed antibiotics at the NTH and 70% at the TH ($P < 0.05$). The number of antibiotic prescriptions per patient was higher at the TH compared to the NTH, among all patients the average number of antibiotic prescriptions (i.e. prescription of one specified antibiotic with stated dose, frequency and duration in days) per patient were 22 at the TH and 8 at the NTH (Table 2). Also, duration of hospital stay was higher among the patients at the TH compared to the NTH (mean 4.4 days at the NTH and 10.1 days at the TH, $P < 0.05$).

Table 2. Clinical characteristics and antibiotic prescribing among patients with severe infections at two private sector hospitals.

Patients	Number of patients, n (%)		Patients prescribed AB, n (%)		Difference among patients prescribed AB, OR (CI) p P-value	Prescriptions n (n of prescriptions per patients prescribed AB)	
	NTH	TH	NTH	TH		NTH	TH
All included patients	2504 (100)	1262 (100)	2294 (92)	1122 (89)	1.36 (1.08, 1.72) <0.05	18751 (8)	24956 (22)
Female	894 (36)	301 (24)	809(90)	259(86)	1.54 (1.01, 2.32) 0.03		
Male	1610 (64)	961 (76)	1485(88)	863(90)	1.35 (1.01,1.80) 0.03		
Cellulitis	388 (15)	402 (32)	354 (91)	362 (90)	1.15 (0.69, 1.91) 0.57	3505 (10)	8608 (24)
Endocarditis	7 (0)	2 (0)	6 (86)	1 (50)	6 (0.04, 547.49) 0.28	33 (6)	54 (54)
Epiglottitis	12 (0)	1 (0)	11 (92)	1 (100)	-	57 (5)	2 (2)
Meningitis	186 (7)	38 (3)	167 (90)	27 (71)	3.58 (1.37, 8.93) <0.05	1126 (7)	442 (16)
Peritonitis	431 (17)	252 (20)	402 (93)	233 (92)	1.13 (0.58, 2.14) 0.69	4909 (12)	6715 (29)
Pneumonia	761 (30)	410 (32)	692 (91)	366 (89)	1.21 (0.78, 1.83) 0.36	4686 (7)	6179 (17)
Pyelonephritis	71 (3)	3 (0)	68 (96)	2 (67)	11.33 (0.14, 262.11) 0.16	518 (8)	89 (45)
Septic arthritis	3 (0)	38 (3)	3 (100)	29 (76)	-	15 (5)	1159 (40)
Sepsis	645 (26)	116 (9)	591 (92)	101 (87)	1.6 (0.82, 3.0) 0.11	3902 (7)	1708 (17)

Notes: Statistically significant p-values are marked in bold font. Abbreviations: AB, antibiotic; CI, confidence interval; n, number; NTH, non-teaching hospital; OR, odds ratio; TH, teaching hospital

The overall antibiotic prescribing among all included patients increased from 2008 to 2017 at the NTH ($P < 0.01$) but did not significantly change at the TH ($P = 0.07$, Figure 1, Table 3). Antibiotics included in the *access* category comprised 61% of the total antibiotic prescribing at the TH and 40% at the NTH. Prescribing of *access* antibiotics increased at the NTH from 2008 to 2017 ($P < 0.01$, Figure 2, Table 3). Prescribing of antibiotics categorized as *watch* antibiotics comprised 29% of the total antibiotic prescribing at the TH and 40% at the NTH. Prescribing of *watch* antibiotics increased at both hospitals from 2008 to 2017 ($P < 0.01$ for both hospitals, Figure 2, Table 3). *Reserve* antibiotics comprised less than one percent of the antibiotic prescribing at both hospitals, however prescribing of *reserve* antibiotics increased from 2008 to 2017 at the TH ($P < 0.01$, Figure 2, Table 3). Prescribing of FDCs of antibiotics comprised 8% of the antibiotic prescribing at the TH and 18% at the NTH. Prescribing of FDCs of antibiotics increased at both hospitals from 2008 to 2017 ($P < 0.01$ for both hospitals, Figure 2, Table 3).

Table 3. Description of trends in antibiotic prescribing among patients with severe infections in Ujjain between 2008-2017.

	NTH	TH
Antibiotic prescribing among specific diagnoses		
All antibiotics	13.84 (< 0.01)	1.82 (0.07)
Cellulitis	5.72 (< 0.01)	6.52 (< 0.01)
Peritonitis	14.59 (< 0.01)	18.52 (< 0.01)
Pneumonia	4.87 (< 0.01)	7.30 (< 0.01)
Sepsis	2.18 (0.03)	-21.91 (< 0.01)
Antibiotic prescribing among all included patients		
<i>Access</i> antibiotics	11.52 (< 0.01)	1.78 (< 0.07)
<i>Watch</i> antibiotics	9.63 (< 0.01)	6.49 (< 0.01)
<i>Reserve</i> antibiotics	-0.76 (0.45)	2.54 (< 0.01)
FDCs of antibiotics	14.28 (< 0.01)	7.31 (< 0.01)
Antibiotic prescribing among sepsis patients		
<i>Access</i> antibiotics	1.49 (0.14)	-16.89 (< 0.01)
<i>Watch</i> antibiotics	3.02 (< 0.01)	-11.38 (< 0.01)
<i>Reserve</i> antibiotics	-9.32 (< 0.01)	Too few prescriptions
FDCs of antibiotics	3.78 (< 0.01)	-9.93 (< 0.01)

Notes: All values are presented with a value for the slope: t (obtained from linear regression analysis), followed by P-value in parenthesis. A positive t shows a positive trend and a negative t shows a negative trend. Statistically significant p-values are marked in bold font. Abbreviations: FDC, fixed dose combination; NTH, non-teaching hospital; TH, teaching hospital.

The most common diagnosis groups were cellulitis, peritonitis, pneumonia and sepsis that comprised 88% of the included patients at the NTH and 93% of the included patients at the TH. At both hospitals, there were few patients in the diagnosis groups: endocarditis, epiglottitis, meningitis pyelonephritis and septic arthritis (Table 2). The antibiotic groups comprising at least 75% of antibiotic prescribing within each of the four most common diagnoses; cellulitis, peritonitis, pneumonia or sepsis, as presented in Table 4. Total antibiotic prescribing among patients with cellulitis, peritonitis and pneumonia increased between 2008-2017 at both the NTH and the TH ($P < 0.01$ respectively, for both hospitals, Figure 1, Table 3). Total antibiotic prescribing among patients with sepsis increased from 2008 to 2017 at the NTH ($P = 0.03$), while it decreased at the TH ($P < 0.01$, Figure 1, Table 3). Prescribing of *access*, *watch*, *reserve* and FDCs of antibiotics among patients with sepsis is presented in Figure 3 and Table 3, since sepsis was the only of these diagnoses where the consumption decreased at one of the hospitals.

Table 4. Antibiotics prescribed among patients with severe infections at two private sector hospitals from 2007-2018.

	Antibiotic prescribing in DDDs per 1000 patient days										%	t ^a	P-value
Year	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017			
Cellulitis NTH													
J01CR	4.12	4.44	0.73	4.78	3.17	4.90	5.77	4.33	3.24	7.11	16	2.32	0.02
J01D	13.11	9.01	1.98	11.52	5.09	4.28	12.50	7.54	14.18	3.06	32	6.33	<0.01
J01R	6.53	5.60	3.12	2.60	4.70	3.46	3.01	6.78	6.12	1.84	17	6.97	<0.01
J01X	9.25	15.76	3.68	3.34	1.30	1.05	1.62	1.08	1.42	1.48	15	3.31	<0.01
Cellulitis TH													
J01CR	10.84	7.45	4.24	7.14	9.47	8.99	10.07	8.03	16.29	13.33	19	4.91	<0.01
J01D	4.48	6.01	9.32	6.22	4.76	4.66	6.87	6.53	9.98	2.10	12	5.58	<0.01
J01G	9.33	13.53	9.11	9.26	14.55	10.47	10.01	6.37	15.64	5.45	21	0.44	0.66
J01M	10.20	8.70	3.35	5.66	9.00	4.51	4.30	3.31	9.11	6.22	13	2.66	<0.01
J01X	6.53	3.70	7.38	6.50	6.86	10.22	7.89	3.84	9.17	3.91	13	2.27	0.02
Peritonitis NTH													
J01CR	3.71	4.26	3.85	10.23	3.06	5.70	4.45	5.89	5.67	4.40	16	4.98	<0.01
J01D	26.28	6.43	4.54	4.34	10.36	7.35	1.41	7.78	8.04	5.06	25	1.34	0.18
J01R	8.58	6.14	5.29	5.55	5.01	1.14	3.09	5.02	6.19	1.40	15	8.67	<0.01
J01X	16.03	11.72	11.64	9.09	4.57	2.49	1.58	1.81	3.54	1.97	20	10.95	<0.01
Peritonitis TH													
J01CR	5.84	4.39	6.68	5.55	10.92	9.13	16.54	13.44	13.36	5.35	15	10.16	<0.01
J01D	4.00	4.95	9.63	9.44	6.87	2.76	6.04	7.64	15.87	7.73	12	17.55	<0.01
J01G	10.08	4.65	11.08	9.94	11.84	6.49	11.43	11.87	8.64	4.08	15	8.13	<0.01
J01M	16.05	10.72	3.27	6.40	11.99	5.83	11.60	12.86	15.42	3.56	16	2.92	<0.01
J01X	15.75	9.55	16.85	17.73	15.44	13.92	22.64	17.30	23.05	5.24	26	8.69	<0.01
Pneumonia NTH													
J01CR	11.54	5.01	4.05	4.27	4.95	4.61	5.96	5.79	8.79	8.17	29	-0.91	0.36
J01D	7.75	6.92	4.22	8.53	3.24	2.95	1.37	4.44	4.23	4.18	22	-1.38	0.17
J01M	1.00	0.49	0.47	0.50	2.41	0.83	3.98	7.34	3.47	1.18	10	2.54	0.01
J01R	5.74	4.61	3.51	2.55	4.21	4.76	5.27	4.61	3.72	4.82	20	5.65	<0.01
Pneumonia TH													
J01A	16.44	11.85	14.23	8.45	13.76	10.18	7.21	2.91	2.25	18.79	25	1.81	0.07
J01CR	8.45	12.64	10.66	1.91	8.26	15.71	20.02	19.21	15.38	13.27	30	6.65	<0.01
J01D	3.85	6.01	5.04	10.91	7.24	4.65	3.94	3.81	15.31	20.74	19	12.87	<0.01
J01M	15.87	9.36	8.72	5.72	3.88	2.04	1.61	1.77	4.65	7.44	14	1.89	0.06
Sepsis NTH													
J01CR	5.05	3.90	2.13	1.97	2.23	2.55	3.01	6.90	3.47	6.66	21	1.10	0.27
J01D	10.74	7.47	1.19	3.27	4.63	3.86	4.77	6.37	4.29	1.70	27	-4.67	<0.01
J01R	7.55	3.66	1.71	1.33	2.09	3.36	1.84	3.07	2.63	2.76	17	3.17	<0.01
J01X	12.22	6.54	4.51	0.99	0.79	0.00	1.28	1.02	0.72	0.00	16	-6.07	<0.01
Sepsis TH													
J01A	14.61	7.67	9.59	1.83	4.31	2.95	4.26	0.00	0.00	3.13	11	-5.50	<0.01
J01CR	1.84	11.18	27.87	2.76	5.09	1.83	8.04	7.09	7.79	7.09	19	-5.07	<0.01
J01D	1.37	5.48	8.48	3.03	5.87	3.79	12.27	5.57	7.21	4.89	13	-5.20	<0.01
J01M	11.51	1.75	14.45	11.32	3.13	0.11	4.75	0.91	2.81	3.62	13	-8.49	<0.01

J01X	8.95	12.93	15.34	7.08	9.18	6.36	12.60	0.91	6.00	4.07	19	-15.48	<0.01
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Notes: Antibiotics presented comprise $\geq 75\%$ of the total antibiotic prescribing within each diagnosis group. Numbers are presented in total antibiotic prescribing of antibiotic groups for each year, measured in DDD/1000 patient days and percentage of the total prescribing of antibiotic groups for each diagnosis and hospitals during the study period. ^a t obtained by linear regression. Statistically significant p-values are marked in bold font. Abbreviations: DDD, defined daily doses; NTH, non-teaching hospital; TH, teaching hospital.

Cellulitis

The WHO's recommendations for empirical antibiotic treatment for cellulitis are combination of amoxicillin with clavulanic acid (J01CR) or cloxacillin (J01CF) as first choice and cefalexin (J01D) as second choice treatment [18]. At the NTH, the two most commonly prescribed antibiotics were of second choice treatment; J01D and J01R (FDCs of antibiotics). J01D antibiotics comprised 32% of antibiotic prescribing and J01R comprised 17% of the prescribing among patients with cellulitis. Prescribing of both J01D and J01R increased during the study period, and so did prescribing of recommended treatment J01CR and J01D ($P < 0.05$ for all, Table 4). At the TH the most commonly prescribed antibiotics among patients with cellulitis were from the J01CR (19%) and J01G group (21%), prescribing of J01CR increased from 2008 to 2017 ($p < 0.01$, Table 4). At the NTH, prescribing of *access*, *watch* and FDCs of antibiotics increased from 2008 to 2017 while at the TH, prescribing of *access*, *watch*, *reserve* and FDCs of antibiotics increased ($P < 0.01$ for all categories, at both hospitals).

Peritonitis

The World Society of Emergency Surgery's recommendations (2017) for empirical antibiotic treatment of peritonitis are separate for community acquired or health care-associated peritonitis [21]. The first- and second choice antibiotics for community acquired peritonitis are presented in Table 5. At the NTH, the two most commonly prescribed antibiotics were of first choice treatment for community acquired peritonitis; J01D antibiotics comprised 25% of antibiotic prescribing and J01X 20% of the prescribing among patients with peritonitis, prescribing of J01X increased during the study period ($P < 0.01$, Table 4). At the TH, the two most commonly prescribed antibiotics were of first choice treatment for community acquired peritonitis; J01M (16%) and J01X group (26%), prescribing of both J01M and J01X increased from 2008 to 2017 ($P < 0.01$ for both antibiotic groups, Table 4). Further, prescribing of J01CR (first choice treatment for community acquired peritonitis), also increased during the study period at both hospitals. At both hospitals, prescribing of *access*, *watch*, *reserve* and FDCs of antibiotics increased from 2008 to 2017 ($P < 0.01$ for all categories mentioned at both hospitals).

Table 5. The World Society of Emergency Surgery's recommendations for empirical antibiotic treatment of peritonitis.

	First choice antibiotics	Second choice antibiotics
Community acquired peritonitis	<p>Amoxicillin with clavulanic acid,</p> <p>ceftriazone with metronidazole,</p> <p>cefotaxime with metronidazole,</p> <p>ciprofloxacin with metronidazole,</p> <p>moxifloxacin.</p> <p>For patients with risk of infection with extended spectrum beta lactamase (ESBL)-producing enterobacteriaceae: ertapenem or tigecycline.</p>	<p>Meropenem,</p> <p>doripenem,</p> <p>imipenem with cilastatin,</p> <p>ceftolozane with tazobactam and metronidazole, ceftazidime with avibactam and metronidazole plus additional vancomycin and teicoplanin. In patients at risk for infection with vancomycin-resistant enterococci: linezolid or daptomycin.</p>
Health care associated peritonitis	<p>Piperacillin with tazobactam,</p> <p>meropenem with ampicillin,</p> <p>doripenem with ampicillin,</p> <p>imipenem with cilastatin,</p> <p>tigecycline or amikacin.</p>	<p>Piperacillin with tazobactam,</p> <p>cefepime with metronidazole.</p> <p>In patients at risk for infection with ESBL-producing enterobacteriaceae: meropenem, doripenem or imipenem with cilastatin.</p>

Abbreviations: ESBL, extended spectrum beta lactamase.

Pneumonia

The WHO's recommendations for empirical antibiotic treatment for pneumonia are presented in Table 6 [18]. At the NTH, the two most commonly prescribed antibiotics were of first choice treatment for community acquired pneumonia (J01D) and of second choice treatment for community/first choice treatment of health care acquired pneumonia (J01CR, Table 4). J01CR antibiotics comprised 29% and J01D 22% of the prescribing among patients with pneumonia, the prescribing did not change from 2008 to 2017. At the TH, the most commonly prescribed antibiotics among patients with pneumonia were of second choice treatment for community acquired pneumonia (J01A, 25%) and of second choice treatment for community/first choice treatment of health care acquired pneumonia (J01CR, 30%), prescribing J01CR increased from 2008 to 2017 ($P < 0.01$, Table 4). At the NTH, prescribing of *access*, *watch* and FDCs of antibiotics increased from 2008 to 2017. At the TH, prescribing of *access* and *watch*

antibiotics increased from 2008 to 2017, while the prescribing of FDCs of antibiotics decreased ($P < 0.01$ for all categories at both hospitals).

Table 6. World Health Organization's recommendations for empirical antibiotic treatment of pneumonia.

	First choice antibiotics	Second choice antibiotics
Community acquired peritonitis	Ampicillin, benzylpenicillin, cefotaxime, ceftriaxone, clarithromycin, gentamicin	Amoxicillin with clavulanic acid, doxycycline
Health care associated peritonitis	Amoxicillin, amoxicillin with clavulanic acid, ampicillin, benzylpenicillin, cefotaxime, ceftriaxone, phenoxymethylpenicillin, piperacillin-tazobactam	

Sepsis

The “Surviving sepsis campaign’s” international guidelines for empirical antibiotic treatment for sepsis and septic shock (2016) recommends: carbapenems (meropenem, imipenem/cilastatin or doripenem) or extended-range penicillin/ β -lactamase inhibitor combination (piperacillin/tazobactam or ticarcillin/clavulanate) and third, or higher-generation cephalosporins can also be used [22]. At both hospitals, piperacillin with tazobactam from the J01CR group, were commonly prescribed, which is adherent to guidelines [22]. At the NTH, J01CR antibiotics comprised 21% of antibiotic prescribing and J01D 27% of the prescribing among patients with sepsis, prescribing of J01D decreased from 2008 to 2017 ($P < 0.01$, Table 4). At the TH, the most commonly prescribed antibiotics among patients with sepsis were from the J01CR (19%) and J01X group (19%), prescribing of both J01CR and J01X decreased from 2008 to 2017 ($P < 0.01$ for both antibiotic groups, Table 4). At the NTH, prescribing of *watch* and FDCs of antibiotics increased from 2008 to 2017 while prescribing of *reserve* antibiotics decreased. At the TH, prescribing in DDDs per 1000 patient days, of *access*, *watch* and FDCs of antibiotics decreased from 2008 to 2017 (Figure 3, Table 3).

Discussion

According to our knowledge, this is the first study that present and compare antibiotic prescribing over a ten years period in two Indian private sector hospitals. From this study, we conclude that patients were commonly prescribed antibiotics at both hospitals. The overall antibiotic prescribing among all included patients as well as separately for patients with cellulitis, pneumonia, peritonitis and sepsis from the NTH increased from 2008 to 2017. At the TH, the overall antibiotic prescribing among all patients did not change but antibiotic prescribing among patients with cellulitis, pneumonia and peritonitis increased during the study period, and decreased among patients with sepsis. From 2008 to 2017, prescribing of *access*, *watch* and FDCs of antibiotics increased at the NTH while *watch*, *reserve* and FDCs of antibiotics increased at the TH.

Adherence was analyzed to the WHO's recommendations for empirical antibiotic treatment for cellulitis and pneumonia, to the recommendations of empiric antibiotic treatment from the "Surviving sepsis campaign" for sepsis and to the World Society of Emergency Surgery for peritonitis [18, 21, 22]. Among patients with cellulitis, NTH prescribed mostly antibiotics recommended as second line treatment, which also increased over the study period. At the TH, both first- and second line antibiotics dominated the prescribing, however prescribing of first line antibiotics increased over the study period but second line did not. Among patients with peritonitis, first line antibiotics were most commonly prescribed at both hospitals and prescribing of recommended antibiotics increased during the study period at both hospitals. The antibiotic prescribing among patients with pneumonia was dominated by both first- and second line antibiotics at the NTH but only of second line antibiotics at the TH, however, at the TH, prescribing of recommended antibiotics increased during the study period. Patients registered with sepsis were most commonly prescribed recommended antibiotics at both hospitals. Conclusively, prescribing of antibiotics recommended by international guidelines was more commonly increasing at the TH compared to the NTH during the study period, especially among patients with peritonitis and pneumonia.

Guidelines for empirical antibiotic treatment are often based on whether the infection is healthcare associated or community acquired. Since both bacterial flora and susceptibility patterns vary throughout the world, it is important to choose antibiotic as far as possible for the most probable bacteria, the patient's clinical status, allergies to specific antibiotics and knowledge of current or previous antibiotic resistance and response for antibiotic treatment [1, 21, 22]. In this study, most patients did not have cultures sent for analysis since use of microbiological analyses was limited at both hospitals which is a constraint to comment on the rationality of the antibiotic prescriptions. However, prescribing of broad-spectrum antibiotics was high at both hospitals, which is in line with previous Indian studies reporting high prescribing of broad-spectrum antibiotics [15, 23]. As patients were charged for their treatment at the NTH, they might have put pressure on the physicians to prescribe broad-spectrum antibiotics. In a qualitative study including 36 Indian prescribers, Kotwani et al. presented that the prescribers describe high demands from their patients to describe "strong" antibiotics, and that they sometimes prescribe antibiotics because they do not have time to argue with the patients due to overcrowding at the health care facilities [24]. These factors might have contributed to high prescribing of broad-spectrum antibiotics to avoid re-consultation.

FDCs of antibiotics (J01R) were commonly prescribed at the NTH and increased during the study period, among all included patients as among patients with cellulitis, peritonitis, pneumonia and sepsis. On the contrary, FDCs of antibiotics were less commonly prescribed at the TH. However, the overall prescribing of FDCs of antibiotics at the TH increased during the study period but decreased among the patients with pneumonia and sepsis. Prescribing FDCs of antibiotics is not recommended as they have been shown to drive antibiotic resistance forward, as common consequences are unnecessarily prescribed antibiotics in possible wrong doses [25]. For rationally prescribed antibiotics, the dose should be individually adapted for the patient which is not often possible when prescribing FDCs of antibiotics. FDCs of antibiotics, sometimes including unapproved formulations, are known to be widely used in India [26-29]. In March 2016, the Indian Government banned around 330 FDCs of which 63 (19%) were antibiotics but there are

still over 118 FDCs of antibiotics available on the Indian market [30]. Presence of medical representatives and lack of local essential medicines lists at the NTH are factors that might have contributed to the high prescribing of FDCs of antibiotics at the NTH compared to the TH, where medical representatives were forbidden, and a local essential medicines list was available. Pressure from pharmaceutical companies has been described to influence physicians to prescribe FDCs of medicines in India [31].

By categorizing antibiotics based on the risk of antibiotic resistance development, the so called *access*, *watch* and *reserve* antibiotic categories have been arranged by the WHO [20]. Regardless of country or setting, *access* antibiotics should primarily be used to save, *watch* and *reserve* antibiotics for specific and limited indications in critically ill patients or patients with infections caused by bacteria with known antibiotic resistance. At both hospitals, *reserve* antibiotics comprised less than one percent of the total antibiotic prescribing. At the TH, *access* antibiotics were most commonly prescribed (61% of prescribing) while *watch* antibiotics were less prescribed (29%) but at the NTH, *access* and *watch* antibiotics were equally prescribed (40% each). The results indicating that the antibiotic prescribing at the NTH was comprised of a higher percentage of watch antibiotics compared to the antibiotic prescribing at the TH. Further, prescribing of *watch* and *reserve* antibiotics increased during the study period among patients with cellulitis or peritonitis at both hospitals but decreased among sepsis-patients at the TH. Even if it is difficult to determine whether the prescribing of antibiotics at the hospitals in study was rational or not, the antibiotic prescribing can be related to international recommendations for antibiotic use to reduce the emergence of antibiotic resistance. Consequently, greater adherence to international guidelines for empirical antibiotic treatment is needed at both hospitals to optimize the antibiotic use. The *access*, *watch* and *reserve* categorization for antibiotics is customized to be a feasible guide for proper antibiotic prescribing and can provide a basis in the development of local prescribing guidelines.

According to the total number of patients that were admitted to the hospitals during the study period, in total 243,790 patients, very few patients were diagnosed with infective endocarditis (n=9), epiglottitis (n=13), meningitis (n=224) pyelonephritis (n=74) and septic arthritis (n=41). The definite incidence of these diagnoses is hard to predict, since incidence data from India are scarce [32]. According to the latest census-data (2011), the district of Ujjain had approximately 2 million inhabitants [33]. Thus, the average incidence of infective endocarditis is 1.0 cases per year, based on the number of patients diagnosed with infective endocarditis at the NTH and the TH. For the Ujjain district, the annual incidence of infective endocarditis from 2008 to 2017, is approximately 1 per 2,000,000 people, i.e. 0.05 cases per 100,000 people. This is much less compared to global incidence data, presenting incidence of infective endocarditis ranging from 14-17 cases per 100,000 people [34]. The low incidence of some infectious diseases such as infective endocarditis at the NTH and the TH, might be explained by underdiagnosing, which is a considerable problem previously described in a study of infective endocarditis in India [32]. In many health care facilities in LMICs, microbiological tests and imaging methods are seldom used, due to lack of access to such diagnostic methods or lack of time and money [8, 24]. A very small amount of the patients included in this study had samples sent for microbiological analyses, despite that such analyses were easily accessible at both hospitals. Insufficient use of microbiological analysis might have contributed to underdiagnosing of infectious diseases at the hospitals. Previously described reasons why

culture tests are not taken are: the patients cannot afford the tests or the extra time spent at hospital waiting for the result, the prescribers does not have time to wait for the lab results due to overcrowding of hospitals or they are paid for the number of patients they admit to the hospital and want to keep each patients time at hospital short [15, 24, 35]. Implementation of routinely use of diagnostic methods such as microbiological analysis and imaging methods for patients with suspected infections might contribute to better management and guidance of antibiotic treatment for infectious diseases.

Methodological considerations

One strength of this study is the data collection. For this study, data have been collected manually in the same way for a long period of time, in an area that lacks computerized medical record systems. At the time of this study, none of the hospitals used microbiological analysis (cultures) consistently and consequently, a majority of the diagnoses were based on clinical suspicion. Since almost all antibiotic prescriptions were empirical, it was not possible to make an actual assessment whether antibiotics were rationally prescribed or not. By applying the WHO's categories of *access*, *watch* and *reserve* antibiotics and existing guidelines for empirical prescribing for each diagnosis, it was possible to assess the rationality of the antibiotic prescribing. For time series analysis, we chose to look at the overall trend from 2008 to 2017.

Conclusions

The antibiotic prescribing rates for the patients included in the study were high at both hospitals. At the NTH, prescribing of *access* and *watch* antibiotics was most common, comprising 40% each of the total antibiotic prescribing, followed by FDCs of antibiotics comprising 18% of the prescribing. At the TH, prescribing of *access* antibiotics was most common, comprising 61% of the total antibiotic prescribing, followed by *watch* antibiotics (29%) and FDCs (8%). From 2008 to 2017, the overall antibiotic prescribing among all included patients from the NTH increased, and so did prescribing of *access*, *watch* and FDCs of antibiotics. At the TH, overall antibiotic prescribing among all included patients did not significantly change although *watch*, *reserve* and FDCs of antibiotics increased from 2008 to 2017. Overall prescribing of antibiotics increased between 2008-2017 among patients with pneumonia, peritonitis and cellulitis at both hospitals, although among sepsis patients, antibiotic prescribing decreased at the TH but increased at the NTH. The results indicate that there are areas for improvement at both hospitals. However, the TH generally prescribe more recommended treatments, less FDCs of antibiotics and tend to improve the prescribing of recommended treatment during the study period. The NTH have high prescribing of *watch* antibiotics and FDCs, which tend to have increased during the study period. Factors contributing to extensive prescribing of FDCs at the NTH could be pressure from pharmaceutical companies and patients as well as lack of essential list of medicines. Implementation of antibiotic stewardship programs based on the *access*, *watch* and *reserve* antibiotic categorization as well as implementation of locally adapted lists of essential medicines could contribute to improve the use of antibiotics and thus limit the development of antibiotic resistance.

The results of this study further suggest that there might be underdiagnosing of some severe infectious diseases, such as infective endocarditis. Implementation of routines for diagnostic methods such as microbiological analysis could be a possible improvement in the management of infectious diseases and a guide for antibiotic therapy decisions in order to improve antibiotic use.

List Of Abbreviations

ATC Anatomical Therapeutic Chemical classification system

CI Confidence interval

DDD Defined Daily Doses

ESBL Extended spectrum beta lactamase

GLASS Global Antimicrobial Surveillance System

LMIC Low- and middle-income countries

NTH Non-teaching hospital

TH Teaching hospital

VRE Vancomycin-resistant enterococci

WHO World Health Organization

Declarations

Ethics approval and consent to participate

Data was collected by specially trained nurses at the NTH and the TH. The forms containing patient data were collected regularly and the information was entered to a computerized registry. The forms are kept in security by the research group in Ujjain. Data was registered anonymously, since there were no personal identity numbers entered in the forms. For anonymizing, a unique code was given for each form, with no possibility to track the data to an individual person's identity.

The patients were informed about the research project at the time of admission to the hospitals and were able to refuse their participation without consequences. The study did not affect or cause any changes in the patients' treatment. The study was approved by the ethics committee of Ruxmaniben Deepchand Gardi Medical College, Ujjain (approval numbers 41/2007. 114/2010. 311/2013).

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study are available from Ruxmaniben Deepchand Gardi Medical College in Ujjain, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Institutional ethics committee of the Ruxmaniben Deepchand Gardi Medical College, Ujjain, India.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MS and CSL conceptualized the study. AD, MS, CSL designed the study. MS was responsible for training the nurses, data collection, and supervised the process. AD analyzed the data under supervision of GM. AD, GM and MS interpreted the data. AD drafted the manuscript, MS, GM and CSL revised it. All authors approved the final manuscript.

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Figures

Figure 1

Title Prescribing of antibiotics among patients with severe infections from 2008 to 2017. Legend Notes: Each line is presented with t (obtained from linear regression analysis), followed by p-value. Abbreviations: DDD, defined daily dose; NTH, non-teaching hospital; TH, teaching hospital.

Figure 2

Title Prescribing of antibiotics categorized by access, watch, reserve and FDCs of antibiotics from 2008-2017. Legend Notes: Each line is presented with t (obtained from linear regression analysis), followed by p-value. Abbreviations: DDD, defined daily dosis; FDC, fixed dose combinations; NTH, non-teaching hospital; TH, teaching hospital.

Figure 3

Title Prescribing of access, watch and reserve antibiotics, and FDCs of antibiotics during 2008-2017 among sepsis-patients. Legend Notes: Each line is presented with t (obtained from linear regression analysis), followed by p-value. Abbreviations: DDD, defined daily dosis; FDC, fixed dose combination; NTH, non-teaching hospital; TH, teaching hospital.