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Correlation of Recommendations of Treatment Guidelines and Frequently Prescribed Antibiotics: Evaluation of Their Pharmaceutical Pack Size

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There are various factors that contribute to development of antimicrobial resistance. Overuse, inappropriate prescribing and extensive agricultural use of antibiotics are some of the factors which have been identified. Antibiotics are almost always universally packaged by manufacturers in packs that are heavily driven by cost of economies and convenience rather than by any scientific basis or duration of therapy. So, in this study, the correlation of the treatment guidelines with the choice of antibiotics and whether packing size contributes to leftover dosing units when used according to guideline recommendations were assessed.

The Standard Treatment Guidelines by DSPRUD 2015, Clinical Guidelines by MSF (Oct, 2016 Updated) and the Infectious Disease Society of America Guidelines 2007–2014 recommendations for various infections were compared and evaluated against the commonly prescribed antibiotics identified by prescription research. Number of branded generic products and their most commonly available pack size were also defined. For many antibiotics, multiple packs are required to complete a recommended course of therapy and these are likely to produce leftover medicines in case of 100% compliance or shortfalls when patients buy inadequate supply to complete the recommended regime of antibiotics. A simplified guideline on antibiotic use is required based on national data of antimicrobial resistance in different pathogens in the country. Pharmaceutical packing of antibiotics should be reviewed jointly by health policymakers and infectious disease physicians with representatives of the pharmaceutical industry to devise steps to reduce leftover antibiotic medications.

Antibiotic resistance is a global public health problem today [1], and the situation in India may be equally serious or worse [2]. New resistance mechanisms are emerging and spreading globally thereby hampering the ability to treat common infections, resulting in prolonged illness, disability and death [3]. The burden of bacterial disease in India is amongst the highest in the world [4]. It is a general belief that antibiotics play a critical role in limiting morbidity and mortality in the country. Antibiotic use has increased steadily in recent years. Data from IMS Health Information and Consulting Services India show that the units of antibiotics sold increased by about 40% between 2005 and 2009. Increased sales of cephalosporins was particularly striking, with sales (in units sold) increasing by 60% over that five-year period in private retail pharmacies [5] clearly supporting overuse.

The emergence of antibiotic resistance has been attributed to overuse, inappropriate prescribing and extensive agricultural use. In countries like India where regulation towards retail dispensing is lax and unregulated, prescription-only drugs are easily accessible to the patient without a prescription. Incorrectly prescribed antibiotics also contribute to the promotion of resistant bacteria [6]. Studies have shown that treatment indication, choice of agent or duration of antibiotic therapy is incorrect in 30–50% of cases [6,7].

Antibiotics are generally prescribed to a fixed regimen that involves a specific dose, dosage frequency and length of treatment [8]. Recent evidence indicates that extended regimens may be unnecessary as many clinical trials have shown that shorter courses of therapy are often just as effective as longer ones [7,9]. Despite evidence, guidelines still recommend relatively prolonged or imprecise treatment durations [9]. In India, national treatment guidelines have recently been published by the National Centre for Disease Control under the Ministry of Health and Family Welfare in 2016 and Treatment Guidelines for Antimicrobial Uses in Common Syndromes by the Indian Council of Medical Research in 2017. However, the Standard Treatment Guidelines prepared by the Delhi Society of Promotion of Rational Drug Use have been in use since 2003 and were the available guidelines during the current evaluation.

Some patients discontinue treatment when their symptoms improve, rather than finishing the entire course. This creates the possibility of reusing the balance medication for future use, increasing the likelihood of the medication's misuse to treat non-susceptible organisms [8]. In addition, antibiotics are almost universally packaged by manufacturers in packs that are heavily driven by cost of economies and convenience rather than by any scientific basis or duration of therapy [10].

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This prompted us to correlate the treatment guidelines with the choice of antibiotics and to assess whether packing size contributes to leftover dosing units when used according to guideline recommendations.

Materials and Methods

In this study, six common infections for which antibiotics are prescribed were selected viz., respiratory tract infections (upper & lower), urinary tract infections and skin and soft tissue infections. These infections make up a significant percentage of the total number of patients managed in primary care.

The following information sources were compared for recommendations on antibacterial treatment of these infections:

(1) Standard Treatment Guidelines (STG) by DSPRUD 2015, A Manual for Medical Therapeutics published by Delhi Society for Promotion of Rational Use of Drugs, Fourth Edition
(2) Clinical Guidelines by MSF (Oct, 2016 Updated)
(3) Infectious Disease Society of America Guidelines 2007–2014.

There were differences/variations in terminologies and inclusion or exclusion of several distinct entities in each of the three guidelines that were considered for comparison (table 1). For example, the STG considers the term acute suppurative otitis media while MSF termed it as acute otitis media. The Infectious Diseases Society of America does not consider it as a separate entity but have clubbed it along with acute bacterial rhinosinusitis.

The Strategic Marketing Solutions and Research Centre (SMSRC), Kolkata, India, is a contract research organization that works with various sponsors offering strategic marketing solutions and prescription research. The authors obtained the overall antibiotic usage pattern in general and hospital practice in urban and semi-urban areas in India. The data for the quarter from November 2015 to February 2016 were made available and analysed to indicate how closely the prescribers were following a treatment guidance (personal communication of Dr. Sanjoy Mitra).

The information regarding the number of brands and the most common pack size of various preparations/brands of antibiotics was collected from the quarterly formulation listing publication 'Drug Today India' (corresponding July–September 2015 issue) [11]. Information and availability regarding the most common pack size were identified. The choice of antibiotics, their doses and duration for common infections were used to calculate the number of unit formulations required to complete therapy for each drug. Number of doses of antibiotic required (milligram strength, frequency and duration) was based on the recommendations for each antibiotic and compared with the number of doses provided in a single standard pharmaceutically packaged antibiotic. Whether surplus antibiotics would remain at the end of therapy was calculated after comparison to the available pack size.

All quantitative data collected were subjected to descriptive statistics, which included analysis of range, calculation of mean, standard deviation and mode.

Results

A comparison of the recommendations of antibiotic use in six common indications for prescribing antibiotics from three guidelines viz. STG, MSF and IDSA was made and is presented in table 2.

For the six major indications focused in this study, a total of fifteen antibiotics were recommended. Of these 15 drugs, 14 drugs were listed as available in India in the drug list referred for the study (table 3). While MSF and IDSA proposed one to three alternative antibiotics for managing common bacterial infections, two in most cases (Mean 1.83 recommendations per indication), STG recommended two to four alternative antibiotics for the same indications, with a mean (±S.D.) of three (±0.89) alternatives. For 'Tonsillitis & Pharyngitis' although penicillin V was included for long-term prevention of streptococcal infections, it was not listed in the drug catalogue available in India, though an Internet search revealed online pharmacies selling packs of 100 tablets of 500 mg strength.

Twenty-four different regimens were recommended involving 14 antibiotics for management of the six infections. Only six of these 24 regimens would be completed using one available pack of the corresponding drug, all for treatment of UTI. At an average of 2.167 (S.D. – 0.963, range of 1–4), available packs would be required for completion of therapy. Of the 14 antibiotics available in India and recommended for the treatment of common infection, 11 would have doses in surplus after completion of the antibiotic therapy/course when administered according to the guidelines referred to in the present study. Using antibiotics according to STG, only four drugs would have no leftover units of antibiotics after completion of therapy with 100% compliance of the patient. Hence, a significant number of mismatches were found between the number of doses and the duration mandated by standard packaging sizes and that of the recommended guidelines.

Data received from SMSRC, amongst the top 10 prescribed antibiotics, four drugs (cefixime, cefpodoxime, levofloxacin and cefixime + ofloxacin) did not feature in any of the treatment guidelines and these four drugs were contained in 25.5% of the prescriptions. Also, cefixime, a third-generation

Table 1.
Differences in terminology when describing common infections by various treatment guidelines and equivalence used in the present article.

STG (2015)	MSF (2016)	IDSA
Cellulitis & erysipelas	Cellulitis and erysipelas – 2016 update	Cellulitis/erysipelas: skin & soft tissue infections: 2014 update
Acute rhinosinusitis	Acute sinusitis	Acute bacterial rhinosinusitis in adult: 2012 update
Acute tonsillitis	Acute pharyngitis	Streptococcal pharyngitis (pharyngotonsillitis): 2012 update
Acute suppurative otitis media (ASOM)	Acute otitis media (AOM)	Along with rhinosinusitis
Pneumonia (community-acquired pneumonia) in adults	Acute pneumonia in adults	Community-acquired pneumonia in adults: 2007 update
Acute uncomplicated cystitis in women	Acute cystitis	Acute uncomplicated cystitis in women: 2010 update

Table 2.
Antibacterial drugs, recommended by treatment guidelines with their doses, frequency and duration, number of packs required for a complete treatment course and number of units as leftover in case of 100% compliance.

Sr. no.	Drug	Indication	Guidance	Dose	Frequency per day	Duration	Common pack size	No. of packs required	Extra units
1	Cephalexin	SSTI	STG	500	4	7	10	3	2
		Tonsillitis/pharyngitis	IDSA	500	2	10	10	2	Nil
2	Cloxacillin[1]	SSTI	STG	500	4	7	15	2	2
3	Amoxicillin	ASOM	MSF	500	3	5	10	2	5
		Bacterial rhinosinusitis/ tonsillitis/pharyngitis	STG	500	3	5	10	2	5
		Tonsillitis/pharyngitis	MSF	500 × 2	2	6	10	3	6
		CAP	MSF	500 × 2	3	5	10	3	Nil
4	Amoxycillin + clavulanate	ASOM	MSF	625	3	7	10	3	9
		Bacterial rhinosinusitis/ tonsillitis/pharyngitis	STG	625	3	5	10	2	5
5	Ciprofloxacin	Bacterial rhinosinusitis	STG	250	2	5	10	1	Nil
		UTI	MSF	500	2	3	10	1	4
6	Azithromycin	Tonsillitis/pharyngitis	STG	500	1	5	3	2	1
		CAP	STG	500	1	10	3	4	2
		CAP	IDSA	500	1	5	3	2	1
7	Clarithromycin	CAP	STG	500	2	10	10	2	Nil
8	Erythromycin	CAP	STG	500	4	10	10	4	Nil
9	Cefadroxil	Tonsillitis/pharyngitis	IDSA	500 × 4	1	10	10	4	Nil
10	Doxycycline	CAP	STG	100[1]	1	10	10	2	9
11	Nitrofurantoin	UTI	STG	100	4	5	10	2	Nil
		UTI	IDSA	100	2	5	10	1	Nil
		UTI	MSF	100 × 3	3	5	10	2	5
12	Cotrimoxazole	UTI	STG, IDSA	160 + 800	2	3	10	1	4
13	Norfloxacin	UTI	STG	400	2	3	10	1	4
14	Ofloxacin	UTI	STG	200	2	3	10	1	4

[1]Loading dose of two tablets.

Table 3.
Antibacterial drugs, either recommended by treatment guidelines or commonly used with their drug content, number of brands, common pack sizes (with range).

Sr. no.	Drug	Content (mg)	Top 10 rank	No. of brands	Pack size (range)	Common pack size
Drugs recommended by treatment guidelines						
1	Cephalexin	500	–	65	4–10	10
2	Cloxacillin[1]	250	–	1	15	15
3	Amoxicillin	500	8	130	6–15	10
4	Amoxycillin + clavulanate	625	2	307	6–10	10
5	Ciprofloxacin	500	9	200	2–10	10
6	Azithromycin	500	3	67	3–10	3
7	Clarithromycin	500	–	27	4–10	4
8	Erythromycin	500	–	7	10	10
9	Cefadroxil	500	–	61	4–10	10
10	Doxycycline	100	–	22	6–10	10
11	Nitrofurantoin	100	–	5	10	10
12	Cotrimoxazole	160 + 800	–	10	10–20	10
13	Norfloxacin	400	–	26	4–10	10
14	Ofloxacin	200	6	411	5–10	10
Drugs, not recommended by treatment guidelines but in top 10 list						
15	Cefixime	100/200	1	471	4–10	10
16	Cefpodoxime	100/200	4	275	4–10	10
17	Levofloxacin	250/500	5	96	5–10	10
18	Cefixime + ofloxacin	200 + 200	7	142	10	10
19	Ceftriaxone Na inj.	250, 500, 1000	10	265	–	–

Data obtained from Drug Today, September 2015. Top 10 ranks provided by SMSRC (courtesy of Dr. Mitra).
[1]Cloxacillin in combination with ampicillin (250 + 250 mg) is available in 28 brands with pack sizes ranging between 4 and 10 with 10 being the most common pack size; cloxacillin in combination with amoxicillin (250 + 250 mg) is available in 140 brands with pack sizes ranging between 4 and 10 with 10 being the most common pack size.

cephalosporin, was prescribed more frequently in India appearing in 10.2% of prescriptions with 471 brands on the market (table 3). Cefpodoxime, another oral third-generation cephalosporin, was found in 5.8% of the prescriptions and 275 brands listed as available.

Another interesting observation was regarding fixed-dose combinations (FDCs) of antibiotics. The FDC of cefixime 200 mg and ofloxacin 200 mg was present in 4.2% of prescriptions and listed 142 brands. India-specific FDCs containing antibiotics like cefixime + ofloxacin, cefixime + azithromycin, cefpodoxime + clavulanate and cefixime + clavulanate account for 10.2% of prescriptions. Cloxacillin is recommended by STG as a single-agent therapy for the treatment of SSTI; however, all formulations of cloxacillin listed were combination products with either ampicillin or amoxicillin.

Discussion

Treatment guidelines are prepared to develop consensus and to simplify clinical management of infections based on prevailing microbiological sensitivity patterns of most common causative organisms to available antibiotics. STG is a manual for medical therapeutics with an aim to promote rational use of all drugs, not only antibiotics, which was updated in 2015 and served as a reference point for the current research. The international perspective was provided by the comparison with the guidance of MSF for use in field and hospitals all over the world. The reason for higher number of recommendations by STG could be related to unavailability of reliable data of sensitivity patterns in India. Reliable Indian data on antimicrobial resistance for important pathogens of public health importance is an essential prerequisite for developing appropriate guidelines for use of antimicrobials. Currently, many microbiology laboratories (in both the public as well as the private sector) perform routine antibiotic susceptibility testing (AST) of bacterial pathogens; the data are neither analysed regularly nor disseminated for use by clinicians, public health experts and programme managers.

Medicines dispensed in the original fixed packaging may result in under- or oversupply of antibiotics leading to either suboptimal duration of treatment or 'leftover' antibiotics. A recent WHO survey found that a quarter of patients would share the leftover antibiotics [12]. There is significant probability that these leftover antibiotics, whose use would be uncontrolled, unsupervised and possibly inappropriate, contribute to development of antimicrobial resistance [13]. Pharmaceutical packing of antibiotics should be reviewed jointly by health policymakers, infectious disease physicians with representatives of the pharmaceutical industry to devise steps to reduce leftover antibiotic medications. Evaluating the pharmaceutical packaging in Australia, McGuire *et al.* [10] opine that there are no easy solutions to the leftover antibiotics problem as individualized packaging adds to the healthcare cost, especially when medicines are out-of-pocket expense for patients.

All calculations in the present study for leftover pills presumed 100% compliance of the patients. However, patient compliance is a confounding variable. Non-compliance may lead to incomplete and inadequate therapy without any leftover medicines if multiple packets of medicines are not bought by the patients to complete the treatment regimen. On the other hand, full compliance towards treatment regimen may lead to leftover pills. In either case, the excess or inadequate medicines will enhance the chances of development of antimicrobial resistance [10].

Prescription data reviewed by a contract research organization in India (SMSRC) showed few interesting observations when the prescription data were matched with the STG. Cefixime was the most commonly prescribed antibiotic in 2015, which did not feature in the STG [14]. Most of the third-generation cephalosporins are injectables, and cefixime and cefpodoxime are a few drugs of this class available for oral route of delivery. Cefixime appears in the World Health Organization's 'List of Essential Medicines' and is approved for a number of indications by regulatory bodies around the world. However, the absence of cefixime in any of the treatment guidelines reviewed in the current study is significant. There are alternative drugs which are equally effective and safe and are recommended by experts preparing guidelines for the treatment of conditions for which cefixime is approved.

The present data of antibiotic use, provided by SMSRC and obtained from prescription research conducted in hospital and primary care of urban and semi-urban areas in India, are similar to the earlier findings of Kotwani and Holloway (2011). In Australia, Fredericks *et al.* (2017) reviewed data on repeat antibiotic prescriptions from community pharmacies and reported the most frequently used (% prescriptions) antibiotics. The usage pattern there, matched with the recommendations of IDSA.

Frequent use of any antibiotic by healthcare professionals result in an increased commercial opportunity, which is reflected by the number of generic products of the drug listed as available in the country. India allows branding of generic versions of drugs, and proof of bioequivalence *in vivo* is required only for new drugs marketed for less than 4 years in the country [15]. Thus, more than 100 manufacturers produced frequently prescribed drugs like cefixime, cefpodoxime, amoxicillin, amoxicillin + clavulanic acid, ofloxacin, ciprofloxacin and combination of cefpodoxime and ofloxacin. Several fixed-dose antibiotic combinations were observed, and some of them have been made available based on *in vitro* data and these warrant critical evaluation in randomized, controlled clinical trials [16,17].

A sustained and concerted effort is required to highlight the contribution of universal pack sizes and leftover antibiotics or inadequate treatment towards development of antimicrobial resistance to the healthcare professionals.

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