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Compliance with the 4Ds of antimicrobial stewardship practice in a tertiary care centre

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Background: Antimicrobial stewardship describes the practice of promoting the selection of the right drug, dosage, delivery and duration of antimicrobial therapy (the 4Ds) in order to curtail the emergence of resistant organisms. It is important to quantify the inappropriate use of antimicrobials in terms of percentage adherence to each of the 4Ds mentioned.

Methods: We undertook a prospective review of medical records of patients admitted to the medical wards of a tertiary care centre in North India. All patients on antimicrobials were included and their records reviewed for indication, drug, dose, delivery and duration (or by asking the treating physician if not documented). Adherence to the 4Ds was determined by referring to updated literature-based standard treatment guidelines (STGs) for each specific disease.

Results: Of 304 patients, drugs were appropriate and matched STGs in 218 (72%) patients, with adherence to the right dose in 210 (69%), route of delivery in 216 (71%) and duration in 197 (65%). Full adherence to the 4Ds was observed in 196 (64.5%). Maximum adherence was observed in treating skin and soft tissue infections (100%), while minimum adherence was observed in administering medical prophylaxis (40%). WHO Access, Watch and Reserve categories comprised 29%, 63% and 8.5% of all prescribed antibiotics, respectively.

Conclusions: The right drug, dose, delivery and duration of therapy are prescribed in 72%, 69%, 71%, and 65% of patients, respectively. In order to increase the adherence to 100%, bedside stewardship practices in the form of prospective audits and feedback must be improved. There is a need to integrate WHO AWaRe classification of antibiotics into treatment guidelines.

Introduction

The discovery of antimicrobials has revolutionized the practice of medicine, making previously so-called 'lethal' infections readily treatable. Like any other drug, antimicrobials may have serious side effects of their own, including many difficult-to-treat conditions like *Clostridioides difficile* infection. Misuse of antimicrobials has contributed to antimicrobial resistance, which has become one of the most serious and growing threats to public health globally. Antimicrobial misuse is implicated from the fact that recently a superbug expressing the gene for NDM-1 has been found in the Arctic region.[1] The potential for the spread of resistant organisms means that their unjustified use can also affect the health of those who are not even exposed to them.

A growing body of evidence demonstrates that hospital-based programmes dedicated to optimizing antimicrobial use, commonly referred to as an antimicrobial stewardship programme (ASP), can both optimize the treatment of infections and reduce adverse events associated with antimicrobial use. This led CDC to force all hospitals in the USA to have ASPs from 2014.[2] However, ASPs are practised in only a few institutions in India, with the numbers even lower in public sector hospitals than those in the private sector.[3] One of the interventions of the ASP is prospective audit and feedback, which is important in guiding physicians to prescribe only appropriate antimicrobials, avoid unjustified prescriptions, reduce the emergence of resistant microbes and support high-quality clinical practice to minimize unnecessary expenses.[4] The implementation of evidence-based guidelines for antimicrobials has been shown to improve the overall patient outcome. However, many previous studies from outside India have shown that adherence to policy recommendations has been suboptimal, averaging 40%.[5] Even in India, prescription pattern monitoring studies conducted at various places have concluded inappropriate use of antimicrobials and lack of adherence to standard treatment guidelines (STGs).[6] Therefore, the first step towards ensuring the rational use of antimicrobials is

to understand prescribing patterns, which will aid in the identification of areas for potential interventions to improve use.

Prescription patterns are assessed to determine the adherence regarding the right drug, dose, delivery route, duration and de-escalation. This is a popular concept in ASPs—commonly known as the 5Ds of optimal antimicrobial therapy.[7] The present study aimed to measure the adherence (or compliance) of treating physicians' practising patterns towards these Ds based on the antimicrobial guidelines in a tertiary care hospital.

Materials and methods

Study setting and design

This study was a prospective review of medical records of the patients admitted to the general wards of the Department of Internal Medicine at a tertiary care hospital in North India. Patients admitted to the high dependency units and ICUs were not assessed. The study was conducted over 6 months, from September 2019 to February 2020.

Study population

A review of records was done for only those inpatients who were prescribed antimicrobials. We assumed the prevalence of antimicrobial prescribing in the medical wards to be 51% based on a 2014 Indian study.[8] Thus, it required a sample size of 304 with 95% confidence and a precision of 0.2.

Aim

The aim of this study was to establish the adherence to antimicrobial guidelines used in clinical practice by treating physicians.

Objectives

The objectives were as follows: (i) to determine the adherence to the right antimicrobial drug, dose, delivery route and duration/de-escalation according to the current recommendations; and (ii) to estimate the prevalence of indications and types of antimicrobials used.

Ethics

The study was approved by the Institutional Ethics Committee, All India Institute of Medical Sciences, Rishikesh, India (Reference number—AIIMS/IEC/19/917). Informed consent was obtained from all study participants before data collection.

Methodology

After the institutional ethics committee approved the study, data on antimicrobials were collected from each patient's medical records and reviewed for the indication, drug name, dose, delivery route and duration of antimicrobial (or by asking the treating physician if not properly documented). The data were collected by a team of two data extractors which comprised one junior resident doctor and one undergraduate medical student in the final year of her training. The treating physician was also asked regarding the guidelines he/she had referred to for each patient and documented in the proforma. If a patient was prescribed more than a single antimicrobial, the whole prescription was taken as one and adherence was determined for the prescription as a whole, rather than for the individual drugs. The study flow followed is shown in Figure 1.

Adherence to the guidelines was determined by referring to the updated literature (local, national or international STGs and textbooks) for each specific disease condition. The investigators accepted the guidelines from the following sources as a standard reference: National Centre for Disease Control (India), Indian Council of Medical Research (ICMR), NICE, IDSA, AIIMS Antimicrobial Policy, Stanford Antimicrobial Stewardship Resources and Harrison's Textbook of Internal Medicine. The investigating team consisted of two doctors (Faculty in-charge and Junior Resident in the Infectious Diseases division) and one undergraduate medical student. A detailed discussion among investigators was done for each patient based on the literature review, and then adherence was entered in the proforma. Flexibility was kept regarding the choice of guidelines (as long as they were deemed to be from a reputed authority), and no single guideline was chosen as a reference as it was assumed that different clinicians might opt to refer to different guidelines for their patients.

The diagnoses formulated by the treating physicians were assumed right (100% adherence) for two reasons: firstly, if the diagnosis is not right, then there is no point in checking adherence for the other Ds; secondly, the diagnostic approach is different from physician to physician and the resources available at hand did not allow a re-evaluation of each patient. Moreover, assessment for the right duration and de-escalation of the antimicrobial were combined and assessed as the fourth D since both complement each other. Culture reports, clinical condition and surrogates for infection markers (like procalcitonin) were used to assess de-escalation. If

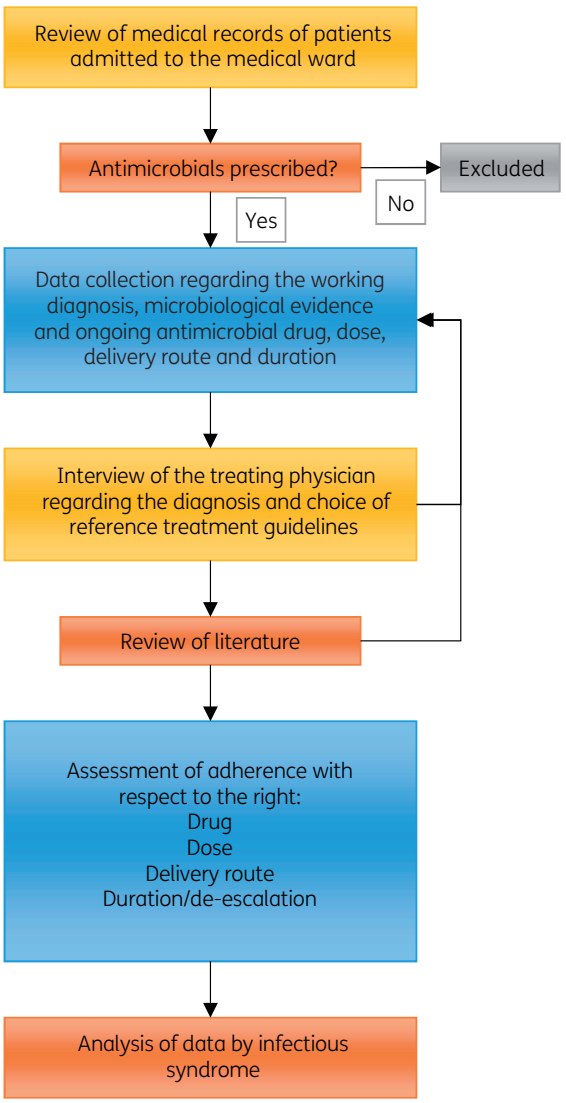

Figure 1. The study flow chart of antimicrobial prescription adherence.

the patient was improving but received a prolonged duration of antibiotics beyond recommended, it was considered non-adherent under duration/de-escalation.

The pattern of non-adherence was also identified and documented under four categories: over-prescription; under-prescription; choice not correct; and antimicrobial not indicated. Over-prescription and under-prescription were defined with respect to the dose/frequency or duration compared with the standard guidelines. At any time, the investigators' decision was not communicated to practising physicians (i.e. no feedback) to get real-life practice scenarios.

Data analysis

After recording the required data in a Microsoft Excel® sheet, they were evaluated for completeness, analysed and interpreted. Frequency and proportions were calculated. We followed the Strengthening the Reporting of

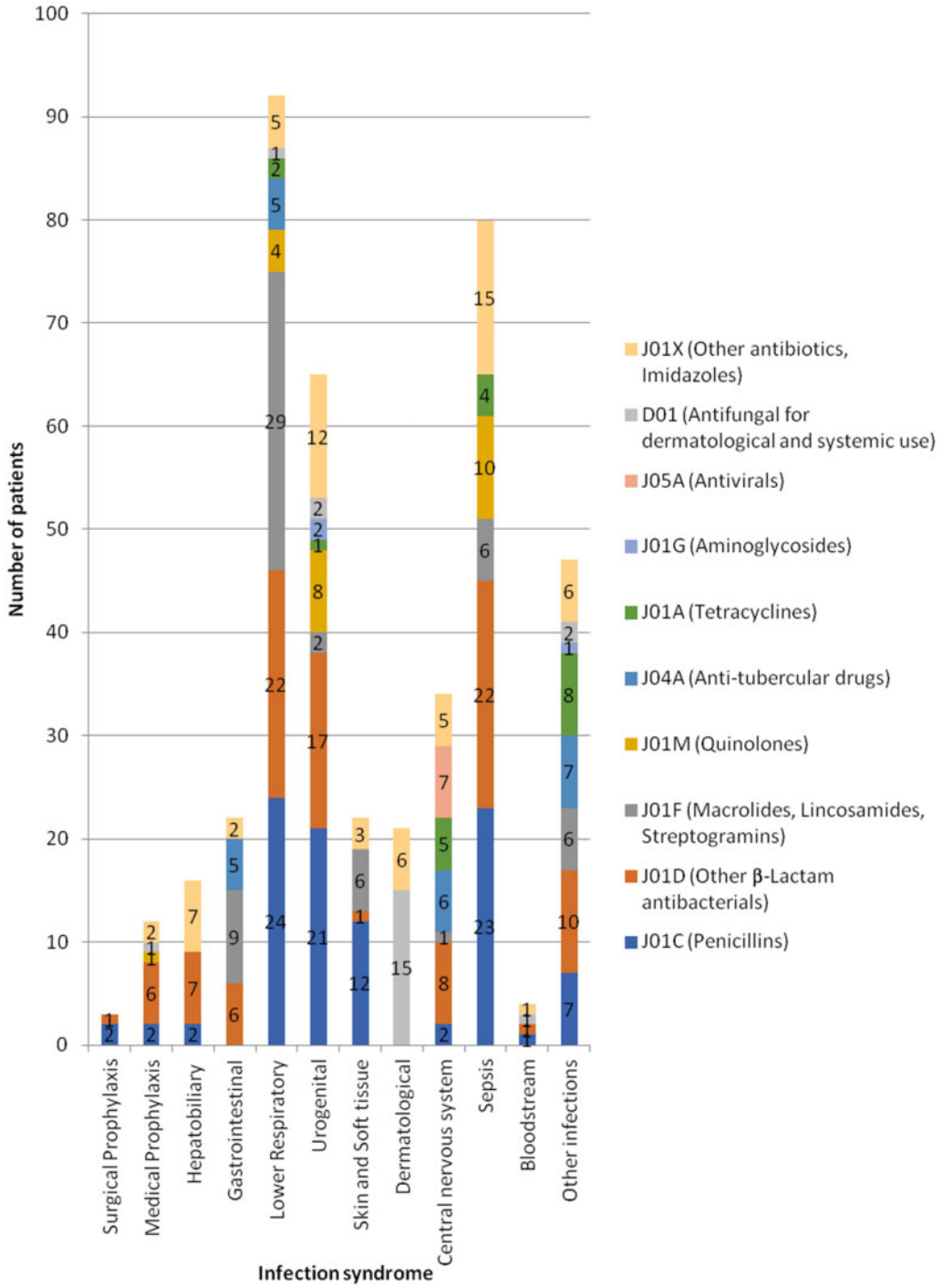

Figure 2. Distribution of antimicrobial prescriptions by indication.

Observational Studies in Epidemiology (STROBE) guidelines to report our findings.[9]

Results

Basic characteristics

Medical records of 304 hospitalized patients were assessed. All the prescriptions were initiated by medical officers (junior residents/senior residents/Faculty). Out of the 304 patients, 155 were female and 149 were male. The median age was 46.88 years. Indications of antimicrobial prescriptions were recorded as infection syndromes rather than individual diseases (Figure 2). Most physicians quoted the following guidelines: ICMR, NICE, IDSA, AIIMS Antimicrobial Policy and Harrison's Textbook of Internal Medicine. We used the 'Guidelines for Anatomical Therapeutic Chemical (ATC) classification and DDD assignment' by WHO to classify drugs.[10] β-Lactams were the most frequently prescribed antimicrobial category and were included in 197 prescriptions (64.8%). Amongst them, penicillins were prescribed in 96 cases (31.6%), and other β-lactam antimicrobials (cephalosporins, carbapenems and monobactams) were prescribed in 101 cases (33.2%). Macrolides and lincosamides were included in 59 (19.4%) prescriptions. Quinolones as well as first-line antitubercular therapy drugs (ATTs) were both included in 23 (7.5%) prescriptions each, followed by antifungals in 22 (7.2%) and tetracyclines in 20 prescriptions (6.6%). Antivirals were prescribed for seven (2.3%) patients and aminoglycosides in only three (1%) patients.

We also classified the prescribed antibiotics as per the WHO Access, Watch and Reserve (AWaRe) framework (Figure 3).[11] Of all the antibiotics prescribed (342), 99 (29%) were Access category, 214 (63%) were Watch category and 29 (8.5%) were Reserve category. The maximum prescription of Reserve antibiotics was in sepsis patients (26.4%).

Compliance with guidelines in antimicrobial prescribing

Out of 304 prescriptions, 196 (64.5%) were fully adherent (compliant). In three (1%) prescriptions, adherence could not be assessed due to the lack of STGs for the diagnosed indication. The choice of antimicrobials was appropriate and matched the guidelines in 218 prescriptions (72%). Out of those 218, adherence to the route of delivery was observed in 216 (71%), dose in 210 (69%) and duration in 197 (65%) prescriptions (Table 1). There were seven cases where the diagnosis/indication for starting antimicrobials was unclear even after interviewing the treating physician; hence, they

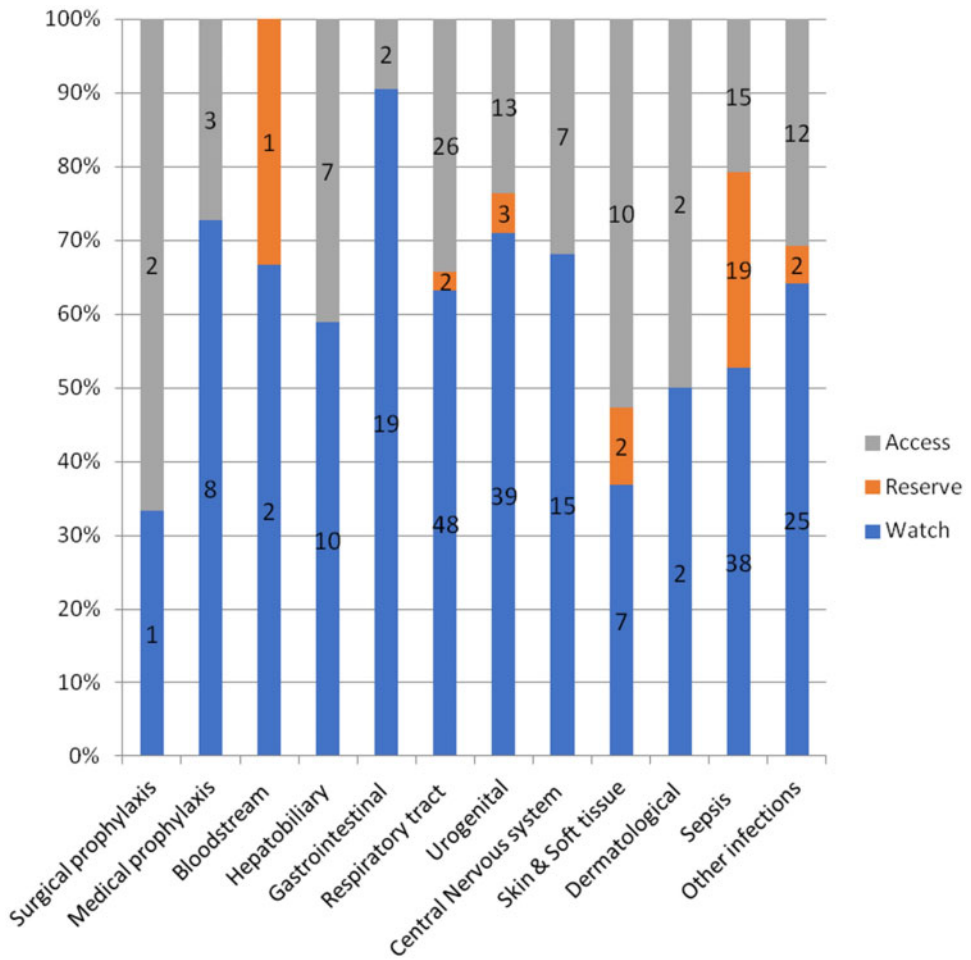

Figure 3. Distribution of antibiotic usage by WHO AWaRe classification.

have been included in the non-adherent category. In 10% of prescriptions, antimicrobials were not indicated but prescribed, while in 15% of prescriptions the choice was incorrect. Over-prescription and under-prescription were 3.3% and 3.9%, respectively (Table 2). Respiratory tract infections were the leading indication for antimicrobial prescribing, followed by urinary tract infections (both comprised one-third of prescriptions).

Discussion

This prospective record-based study reveals that the antimicrobial choice was appropriate and matched the guideline in the majority of admitted patients. Adherence was observed to the right drug, dose, route of delivery and duration/de-escalation, a fundamental principle of ASP. Full adherence to all the above-mentioned parameters was observed in two-thirds of prescriptions. One hundred percent adherence was seen for the treatment of bloodstream and skin and soft-tissue infections, while <50% was observed in medical prophylaxis.

WHO introduced the AWaRe classification of drugs with the aim of assisting antibiotic stewardship efforts.[12] The classification underlines that, wherever appropriate, narrow-spectrum antibiotics from the Access group should be preferred over broad-spectrum antibiotics from the Watch and Reserve groups.[13] In our study, only 29% of the prescribed antibiotics were from the Access group, which is much less than the WHO recommendation of 60% at the country level.[12] This is worrying since a recent systematic review found that 13 out of 16 studies reported ≥60% antibiotics prescribed from the Access group. The three studies with suboptimal usage of Access group antibiotics were from China, Mexico and Pakistan.[13]

Antimicrobial stewardship refers to interventions designed to promote the optimum use of antimicrobial agents and includes the 5Ds. To achieve this, the practising physician has to follow STGs. Along with the implementation of guidelines, adherence assessment is essential. A single centre study conducted in Namibia demonstrated compliance to the Namibia STGs to be 62%, while in Kuwait, full adherence was achieved only in 30.4% of

Table 1. Level of adherence to the guidelines by category of indication for antimicrobial prescription

Category of indication[a]	Total indicated cases	Proper adherence to the right: drug	dose	delivery route	duration	Percentage of full adherence in each category (*n*)
Indicated surgical prophylaxis	3	3	2	2	2	66.6% (2)
Indicated medical prophylaxis	15	8	6	8	6	40% (6)
Bloodstream infections	2	2	2	2	2	100% (2)
Infections involving						
hepatobiliary system	10	8	8	8	6	60% (6)
gastrointestinal system	20	17	17	17	17	85% (17)
respiratory tract infections	67	39	36	38	36	53.7% (36)
urinary tract infections	50	37	37	37	29	58% (29)
CNS	29	26	26	26	23	79.3% (23)
skin and soft tissue infections	16	16	16	16	16	100% (16)
other dermatological indications	14	12	12	12	11	78.5% (11)
others[b]	24	19	18	19	18	75% (18)
sepsis syndrome with a defined focus	47	31	30	31	31	63.8% (30)
Total[c]	304	218	210	216	197	64.5% (196)

[a]Details of the category of indication for antimicrobial prescription are as follows:
- indicated surgical prophylaxis: prophylaxis for snakebite and excisional biopsy;.
- indicated medical prophylaxis: prophylaxis for spontaneous bacterial peritonitis, acute rheumatic fever, active GI bleed and hospital-acquired infections in cases of severe pancytopenia;.
- hepatobiliary system: amoebic liver abscess and spontaneous bacterial peritonitis;.
- gastrointestinal tract infections: enteric fever, dysentery, worm infestation and abdominal TB;.
- respiratory tract infections: lower respiratory tract infections, aspiration pneumonia, acute exacerbation of COPD, atypical pneumonia, aspergillosis and pulmonary TB;.
- urinary tract infections: lower urinary tract infections, catheter-associated urinary tract infections, complicated and uncomplicated pyelonephritis and candiduria;.
- CNS infections: meningitis and encephalitis (bacterial/viral/listeria/scrub/tubercular) and neurocysticercosis;.
- skin and soft tissue infections: cellulitis and infected diabetic foot;.
- other dermatological indications: tinea, scabies, Hansen disease, oral candidiasis and bedsores.

[b]Includes infection of sinuses, rickettsia infections (scrub typhus), rheumatic heart disease, conditions involving febrile neutropenia, acute febrile illnesses, disseminated TB and histoplasmosis.

[c]Also includes antimicrobials for unclear diagnosis/conditions (where it could not be ascertained for what indication the antibiotic was started): $n = 7$.

prescriptions.[14,15] This lower level of compliance could be due to the lack of a formal monitoring system and outpatient ASP.

In a similar assessment done in North India, appropriateness of antibiotic prescription was seen in 66% of cases, which increased to 86% after an ASP (prospective audit and feedback) was implemented.[16] The pre-intervention adherence to the guidelines is comparable to our results of 64.5%. In another study from North India, 43% of patients referred to a tertiary care centre were prescribed antibiotics without any evidence of infectious aetiology.[17] This is significantly higher when compared with our results (10%), indicating that inappropriate over-prescription of antibiotics might be more prevalent in smaller (primary and secondary care) hospitals.

Although suboptimal, our adherence was higher than that reported by previous studies, usually around 40%.[5] This may be because we avoided sticking to any particular guideline for the choice of antimicrobials, as was done in most previous studies. We have included a wide range of clinical conditions in our study, and it would likewise be unfair to label a treatment as non-adherent to guidelines just because the guidelines used were different. We were flexible in our approach and asked the treating physician regarding their reference source and accepted the treatment as adherent as long as the guideline referred to was from a reputed source and confirmed by investigators.

Various studies across the globe show that 20%–50% of all antimicrobials prescribed are either unnecessary or inappropriate.[18,19] In studies conducted in China and Bangladesh, 63% and 50% of the antimicrobials selected to treat proven bacterial infections were deemed inappropriate.[20,21] Long treatment duration and subtherapeutic or suboptimal dosages have been correlated with an increase in selective resistance.[22]

In our study, the maximum non-adherence was found in the choice of antimicrobial. This is a cause of serious concern as, in these times of widespread internet access, all the guidelines are available at the touch of a button, and this non-adherence indicates a lack of awareness. The present study confirms 10% unnecessary antimicrobial use. This lower than expected non-indicated antibiotic prescription rate is probably because we included only inpatients (where proper assessment and discussion is feasible before initiating any treatment), unlike other studies that included outpatient prescriptions. It shows that physicians err on the side of over-prescription rather than under-prescription when in doubt or when the complete evaluation is not feasible, as in the outpatient department.

Our study has its set of limitations as well. It was a single-centre study conducted in a single clinical department. Hence the number of cases in the different infection syndromes is very uneven (for example, some infection syndromes have only 2 cases whereas others have 67). Future studies that include a larger sample size may be more representative of the magnitude of the problem. Secondly, we did not evaluate the prescriptions for the correctness of the diagnosis. Since the study was conducted in the Internal Medicine department of a tertiary care institute, it was assumed that most diagnoses would be correct as per the available evidence. Also, the resources available at hand did not allow for a complete re-evaluation of each patient for the correctness of the diagnosis. Thirdly, there was no follow-up involved, and hence final treatment outcomes were not assessed.

Table 2. Frequency of non-adherent categories of antimicrobial prescription

Non-adherent category	Over-prescription[a]	Under-prescription[b]	Choice not correct[c]	Antimicrobial not indicated[d]
Indicated surgical prophylaxis	1			
Indicated medical prophylaxis	2	2		6
Bloodstream infections				
Hepatobiliary system infections	2		2	
Gastrointestinal system infections			2	1
Respiratory tract infections		5	19	9
Urinary tract infections	4	3	11	2
CNS infections		1		2
Skin and soft tissue infections				
Other dermatological indications			2	
Others[e]	1	1	2	2
Sepsis syndrome with a defined focus			8	8
Total	10	12	46	30

[a]Over-prescription: those prescriptions where the administered dose of a given antimicrobial was higher than that recommended by the guidelines and/or the total duration of antimicrobial therapy were greater than recommended by the guidelines.
[b]Under-prescription: those prescriptions where the administered dose of a given antimicrobial was lower than that recommended by the guidelines and/or the total duration of antimicrobial therapy was shorter than that recommended by the guidelines.
[c]Choice not correct: those prescriptions where there was a failure in choosing the correct choice of antimicrobial agent for that particular condition, partially or fully, and/or failure to review the antimicrobial treatment when microbiological culture data became available.
[d]Antimicrobial not indicated: those prescriptions where antimicrobial use was not warranted and/or those prescriptions where the patient had already completed the entire length of therapy during the hospital stay, but as a part of de-escalating therapy, antimicrobials were prescribed that were not required.
[e]Includes infection of sinuses, rickettsia infections (scrub typhus), rheumatic heart disease, conditions involving febrile neutropenia, acute febrile illnesses, disseminated TB and histoplasmosis.

The appropriate use of antimicrobials is an essential part of patient safety and deserves careful oversight and guidance. Given the association between antimicrobial use and the selection of resistant pathogens, the frequency of inappropriate antimicrobial use is often used as a surrogate marker for the avoidable impact on antimicrobial resistance (AMR). The combination of effective ASPs with a comprehensive infection control programme has been shown to limit the emergence and transmission of antimicrobial-resistant bacteria.

To improve adherence to antimicrobial guidelines, more efficient quality measures should be developed and implemented, including the availability of the guidelines on the hospital information system, monitoring antimicrobial misuse through repetitive audits and continuous education of the physicians to raise their awareness of proper prescription. Local institute protocol based on national/international guidelines and textbooks should be revised and periodically updated to cover all conditions treatable with antimicrobials.

Conclusions

The study demonstrates suboptimal compliance with the STGs on infectious diseases with respect to choosing the right drug, dose, delivery route and duration/de-escalation, although there was a lower prevalence of over-prescription, under-prescription, incorrect or unnecessary antimicrobial use when compared with studies from other developing countries. There is rampant use of the WHO Watch and Reserve group drugs. Thus, there is an urgent need to mandate prospective audits and feedback to improve ASPs and reduce AMR in the long run.

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Transparency declarations

None to declare.

Author contributions

Diksha Dixit and Rajat Ranka searched the literature, collected the data and drafted, reviewed and approved the study. Prasan K. Panda searched the literature, drafted the study statistically, critically reviewed and approved the study.

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