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Research Article

Pattern of use of antibiotics in hospitalized patients in the medicine department of a tertiary care hospital

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ABSTRACT

Background: (1) To assess pattern of antibiotic use among in-patients of medicine unit in a tertiary care hospital, (2) to determine the frequency of adverse drug reactions (ADR) among the inpatients receiving antibiotics in medicine unit.

Methods: The study was prospective and based on the daily review of patient records for 2 months (June, July) of study period, including all the inpatients of medicine unit 1 receiving antimicrobials. The general information of the patients, infection, antimicrobial use, culture and sensitivity reports, concomitant disease, concomitantly administered drugs, as well as clinical response were collected. The prescribed antimicrobials were correlated with the patient's culture and sensitivity report. The number of defined daily doses (DDDs) administered per patient was calculated for each antimicrobial prescribed as per WHO anatomical therapeutic chemical classification. The ADR observed during the study were assessed using WHO causality analysis. The economic burden of the antimicrobial used was analyzed using average cost of antimicrobial per patient. The study was approved by the Institute Ethics Committee.

Results: The antimicrobials that are commonly used as per total drug use (DDDs) are ceftriaxone followed by doxycycline and metronidazole. The antimicrobials account for 58.6% of cost spent on drugs for inpatients. Four antimicrobial related ADR were reported during the study period.

Conclusion: Ceftriaxone, doxycycline, and metronidazole are commonly used antibiotics and significant proportion of the cost of drugs is spent for antimicrobials in a medicine unit.

Keywords: Antibiotics, In patients, Rational use

INTRODUCTION

Antibiotics saving millions of lives all over the world are feared to enter post-antibiotic era in the near future owing to the development of resistance among microorganisms

following irrational use. Recently a new metallo- β -lactamase, named as New Delhi metallo- β -lactamase (*bla*_{NDM}), first identified in the clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae* from a Swedish patient who had traveled to India created a huge buzz globally.¹⁻³

The augmentation of antimicrobial resistance (AMR) is associated with increase in the overall health care costs due to prolonged hospitalizations following antimicrobial failures, additional investigations, alternative treatments, enhanced adverse-effects, reduced quality of life, decreased productivity, likelihood of death due to inadequate or delayed treatment and increased burden on family. As a result, antibiotic resistance increases the economic burden for both patient and the society.^{4,5} This was confirmed by a study that showed an association of 29.3% higher total hospital cost for each admission and a 23.8% increase in the length of stay among patients infected with hospital-acquired infection (HAI) caused by a resistant Gram-negative bacteria compared to those with HAIs caused by nonresistant pathogens.⁶ In addition the most common used antibiotics namely β -lactam antibiotics, fluoroquinolones, glycopeptides, antitubercular drugs, imidazoles, and other antimicrobials have been shown to contribute toward nearly 48.7% of all the reported adverse drug reactions (ADRs).⁷ As a consequence, assessment of the pattern of antimicrobial use in the hospital has become a priority with the increasing menace of AMR. Hence, this study aims to assess the pattern of antimicrobial use, associated ADR and the resultant economic as well as health burden of antibiotic overuse in a tertiary care hospital.

METHODS

The study was conducted prospectively from the information based on the daily review of patient records. The sample size was calculated to be 138, based on the assumption of ADR prevalence to be 10%, with 5% level of significance and 5% absolute precision. The study was conducted for a period of 2 months (June 2013-July 2013) with the inclusion of all the in-patients of medicine unit 1 who were receiving antimicrobials. The demographic information of the in-patients, date of admission, date of discharge, duration of stay, diagnosis, type of infection, antimicrobials used, indication for use, dose per administration, number of doses used per day, route of administration, duration of treatment, adverse effects, culture and sensitivity reports sent before starting antimicrobials, concomitant diseases as well as concurrently administered drugs were collected from the

patient record. Further, the clinical response to the prescribed antimicrobials and the patient's recovery was recorded toward discharge. The prescribed antimicrobials were correlated with the patient's culture and sensitivity report. The number of defined daily doses (DDD) administered per patient was calculated for each antimicrobial prescribed as per WHO anatomical therapeutic chemical (ATC) classification.⁸ The ADR observed during the study were assessed using WHO causality scale.⁹ The economic burden of the antimicrobials used was analyzed using average cost of antimicrobial per patient. The study was approved by the Institute Ethics Committee and was conducted as per ICMR ethical guidelines for biomedical research (2006). Waiver for obtaining informed consent from the study participants were granted by the IEC as the study involved only collection of information from the patient records.

RESULTS

A total of 210 patients were admitted in unit 1 of medicine department over a period of 2 months. Of this, 136 (64.8%) patients including 80 males and 56 females were prescribed antimicrobials for various infections (Table 1). The mean length of hospital stay was 7.2 days and each patient on an average received 2.37 antimicrobials per prescription (Table 2). A total of 315 antimicrobials were prescribed for 136 patients and of this the most common prescribed antimicrobials were beta-lactams (32.81%), nitroimidazoles (11.68%), and aminoglycosides (9.46%) (Table 3). Among the beta-lactams, most commonly used agent was ceftriaxone (J01DD04) (19.87%), followed by metronidazole (P01AB01) (11.67%) of nitroimidazole group and amikacin (J01GB06) (8.83%) belonging to aminoglycosides. Based on DDD per 100 patient days, ceftriaxone (J01DD04) (45.96DDD/HPD) was the most common used antimicrobial followed by doxycycline (J01AA02) (14.17DDD/HPD) and metronidazole (P01AB01) (12.38DDD/HPD) (Table 4). This was calculated by dividing the total drug use of each antimicrobial by denominator of 20 beds multiplied by 60 days (1200 patient days). 78.1% of the antimicrobials prescribed were started empirically before obtaining culture and sensitivity report (Table 5). The most common antimicrobials that were started empirically include

Table 1: Age and genderwise distribution of inpatients receiving antibiotics during the study period.

| Patient characteristics | Total no of patients (n=210) | Number of patients receiving antimicrobials (n=136) | Percentage prescribed with antimicrobials |
|-------------------------|------------------------------|---|---|
| Age (years) | | | |
| <18 | 8 | 8 | 100 |
| 18-40 | 100 | 58 | 58 |
| 41-60 | 70 | 51 | 72.86 |
| >60 | 32 | 19 | 59.38 |
| Sex | | | |
| Males | 132 | 80 | 60.61 |
| Females | 78 | 56 | 71.79 |

Table 2: Demography and other characteristics of patients on antimicrobials.

| Parameter | n=136 Mean (SD) |
|---|--------------------|
| Age (years) | 41.9 (16.7) |
| Gender male/female | 80/56 |
| Mean duration of hospital stay (days) | 7.2 (4.2) |
| Average number of antimicrobials per prescription | 2.368 |

SD: Standard deviation

Table 3: Pattern of antimicrobials (n=315) among all patients (n=136).

| Class | Antimicrobials | n (%) |
|-------------------------|--------------------------|------------|
| Aminoglycosides | Amikacin | 28 (8.89) |
| | Gentamicin | 2 (0.63) |
| Anthelmintic | Albendazole | 4 (1.27) |
| | Mebendazole | 2 (0.63) |
| Antitubercular | Ethambutol | 6 (1.90) |
| | Isoniazid | 10 (3.18) |
| | Pyrazinamide | 10 (3.18) |
| | Rifampicin | 10 (3.18) |
| | Streptomycin | 7 (2.22) |
| | | |
| Azoles | Fluconazole | 7 (2.22) |
| Beta-lactams | Amoxicillin | 1 (0.32) |
| | Cefixime | 2 (0.63) |
| | Cloxacillin | 12 (3.81) |
| | Co-amoxiclav | 5 (1.59) |
| | Piperacillin+ tazobactam | 4 (1.27) |
| | Cefoperazone+ sulbactam | 6 (1.90) |
| | Cefotaxime | 4 (1.27) |
| | | |
| | Ceftazidime | 6 (1.90) |
| | Ceftriaxone | 63 (20.00) |
| | Cephalexin | 1 (0.32) |
| Carbapenems | Meropenem | 5 (1.59) |
| Glycopeptide | Vancomycin | 8 (2.54) |
| Lincosamide | Clindamycin | 1 (0.32) |
| Macrolides | Azithromycin | 19 (6.03) |
| Nitrofurans derivatives | Nitrofurantoin | 2 (0.63) |
| Nitroimidazoles | Metronidazole | 37 (11.75) |
| Quinolones | Ciprofloxacin | 20 (6.35) |
| | Levofloxacin | 5 (1.59) |
| Sulfonamides | Cotrimoxazole | 4 (1.27) |
| Tetracyclines | Doxycycline | 24 (7.62) |
| Total | | n=315 |

The pattern of prescription was ranked based on the number of antimicrobials (315) prescribed for 136 patients. The denominator for percentage calculation was taken as 315

Table 4: Pattern of antimicrobial use based on DDDs.

| Antimicrobial | ATC classification | Total drug use in DDD (g) | DDD/100 patient day |
|--------------------------|--------------------|---------------------------|---------------------|
| Albendazole | P02CA03 | 5 | 0.42 |
| Amikacin | J01GB06 | 86.95 | 7.25 |
| Amoxicillin | J01CA04 | 13.5 | 1.13 |
| Azithromycin | J01FA10 | 101.7 | 8.48 |
| Cefixime | J01DD08 | 3 | 0.25 |
| Cefoperazone+ sulbactam | J01DD62 | 27 | 2.25 |
| Cefotaxime | J01DD01 | 24 | 2 |
| Ceftazidime | J01DD02 | 32.75 | 2.73 |
| Ceftriaxone | J01DD04 | 551.5 | 45.96 |
| Ciprofloxacin | J01MA02 | 37 | 3.08 |
| Clindamycin | J01FF01 | 2 | 0.17 |
| Cloxacillin | J01CF02 | 39.5 | 3.29 |
| Cotrimoxazole | J01EE01 | 8 | 0.67 |
| Co-amoxiclav | J01CR02 | 29 | 2.42 |
| Doxycycline | J01AA02 | 170 | 14.17 |
| Ethambutol | J04MA06 | 12 | 1 |
| Fluconazole | J02AC01 | 51.5 | 4.29 |
| Gentamicin | J01GB03 | 4.3 | 0.36 |
| Isoniazid | J04MA06 | 31 | 2.58 |
| Levofloxacin | J01MA12 | 38 | 3.17 |
| Mebendazole | P02CA01 | 3 | 0.25 |
| Meropenem | J01DH02 | 29.5 | 2.46 |
| Metronidazole | P01AB01 | 148.5 | 12.38 |
| Nitrofurantoin | J01XE01 | 3 | 0.25 |
| Piperacillin+ Tazobactam | J01CR05 | 12.6 | 1.05 |
| Pyrazinamide | J04MA06 | 18 | 1.5 |
| Rifampicin | J04MA06 | 11.35 | 0.95 |
| Streptomycin | J01GA01 | 9.68 | 0.81 |
| Vancomycin | J01XA01 | 51.9 | 4.33 |

Antimicrobial use was expressed as total drug use in DDD. Total drug use in DDD=(Dose×frequency×duration of treatment)/WHO DDD. The denominator was taken as 20 patients (study setting) *60 days (total study period), ATC: Anatomical therapeutic chemical, DDD: Defined daily doses

Table 5: Percentage of antimicrobial used based on culture and sensitivity report.

| Antimicrobial therapy | Number of antimicrobials | Percentage |
|-----------------------|--------------------------|------------|
| Empirical* | 246 | 78.1 |
| Non-empirical | 69 | 21.9 |
| Total | 315 | 100 |

*Empirical antimicrobial therapy is antimicrobial therapy commenced before the identification of the causative microorganism is available

ceftriaxone (24.8%) followed by metronidazole (9.35%) and amikacin (8.94%). The empirical treatment was changed to definitive treatment as per culture and sensitivity report in all the patients except for two cases where empirically started ceftriaxone was continued even after the culture reports showed resistance to the antimicrobial used. The routes of administration of the antimicrobials were parenteral (59.31%) and oral (40.69%) with the parenteral route including both intravenous as well as intramuscular routes. The most common indication for antimicrobial use based on ATC classification was found to be anti-infective for systemic use (33%) as shown in Table 6. Among the study group, the gastrointestinal system was found to be the organ system being the most common foci of infection as given in Table 7.

Out of the 136 patients whose records were assessed, ADRs were reported in 6 patients. Most of the ADRs were related to the skin and subcutaneous tissues with pruritus, itching and edema being the commonly reported ADRs (n=3) followed by gastrointestinal system related ADRs including abdominal pain, diarrhea and stomatitis (n=2). The classes implicated with ADRs were antimicrobials

(n=4), calcium channel blockers (n=1) and anticancer drugs (n=1). The antimicrobials associated with the ADRs were ceftriaxone (J01DD04), vancomycin (J01XA01) and azithromycin (J01FA10) (Table 8). In addition to this a patient on vinblastine and dacarbazine developed chemotherapy-induced febrile neutropenia. The ADRs recorded in this study were classified according to WHO causality assessment scale. The total hospital expenditure on drugs for these patients (n=136) was estimated to be nearly Rs 68939.70 with antimicrobials contributing to 58.6% of the total costs. The parenteral formulations of antimicrobials alone contributed to 56.6% of the total costs. The average cost of antimicrobial per patient was found to be Rs 296.84 (Table 9).

DISCUSSION

Among the 210 patients admitted in unit 1 medicine department during the study period, 64.8% (n=136) were prescribed antimicrobials. In a similar North Indian study

Table 6: Indication for antimicrobial use based on ATC classification.

| Indication | Frequency of antimicrobial use (n=317) | n (%) |
|--|--|-------|
| J Antiinfectives for systemic use | 278 | 89.4 |
| A01AB Antiinfectives and antiseptics for local oral treatment | 13 | 4.2 |
| Others (P, D, S) | 26 | 6.4 |

Others include P: Antiparasitic products, insecticides and repellants, D: Dermatologicals, S: Sensory organs, ATC: Anatomical therapeutic chemical

Table 7: Infections as per organ system as an indication for antimicrobial use.

| System diagnosed as focus of infection | Number of patients receiving antimicrobials (n=136) | Percentage |
|--|---|------------|
| Gastrointestinal | 33 | 24.26 |
| Renal | 11 | 8.09 |
| Central nervous | 12 | 8.82 |
| Respiratory | 11 | 8.09 |
| Cardiovascular | 12 | 8.82 |
| Generalized | 25 | 18.38 |
| Others | 32 | 23.54 |

Others include poisoning, snake bites, leukemia, etc.

Table 8: ADR among the study patients (n=136).

| Suspected drug | ADR | WHO causality assessment |
|-----------------------------|---------------------------|--------------------------|
| Related to antimicrobials | | |
| Vancomycin | Pruritus | Certain |
| Ceftriaxone | Stomatitis | Possible |
| Ceftriaxone | Itching | Certain |
| Azithromycin | Stomach ache and diarrhea | Probable |
| Unrelated to antimicrobials | | |
| Amlodipine | Pedal edema | Certain |
| Vinblastine and dacarbazine | Febrile neutropenia | Certain |

ADR: Adverse drug reactions

Table 9: Top ten commonly prescribed antimicrobials, use (DDD) and costs (Rs).

| Drug | Drug use in DDD (g) | Cost (Rs) |
|---------------|---------------------|-----------|
| Ceftriaxone | 551.5 | 8351.15 |
| Doxycycline | 170 | 126.13 |
| Metronidazole | 148.5 | 3406.40 |
| Azithromycin | 101.7 | 402.95 |
| Amikacin | 86.95 | 1346.28 |
| Vancomycin | 51.9 | 3600 |
| Fluconazole | 51.5 | 37.45 |
| Cloxacillin | 39.5 | 261.64 |
| Levofloxacin | 38 | 226.47 |
| Ciprofloxacin | 37 | 1473.60 |

DDD: Defined daily doses

conducted by Pathak et al. it was reported that 92% of the inpatients were prescribed antimicrobials for various infections.¹⁰ This contradicts results of a study in Turkey showing only 30.2% of the total inpatients were started on antimicrobial therapy.¹¹ These findings suggest the diverse nature of antimicrobial prescription in various parts of the regions. In addition, variation in antimicrobial prescribing according to age groups was also observed in this study. 42.6% of the study patients fell under the adult category which was in accordance with the study by Pathak et al.¹⁰

It was observed that on an average 2.34 antimicrobials were prescribed per antimicrobial containing prescription as shown in previous Indian study.¹² In our study, the most common prescribed antimicrobials were the beta-lactams (33.01%) followed by nitroimidazoles (11.75%) and aminoglycosides (9.52%). This is in accordance with similar studies by Khan et al.^{12,13} The most common used agents among these classes were found to be ceftriaxone (J01DD04), metronidazole (P01AB01) and amikacin (J01GB06). In a study by Khan et al., amoxicillin with clavulanic acid combination was mostly prescribed, followed by ceftriaxone in the β -lactam group, levofloxacin, metronidazole and amikacin.¹² Based on DDDs per 100 patient days, ceftriaxone (J01DD04) (45.96DDD/HPD) was the most commonly used antimicrobial followed by doxycycline (J01AA02) (14.17DDD/HPD) and metronidazole (P01AB01) (12.38DDD/HPD). The increased DDD/HPD of doxycycline can be attributed to the longer duration of treatment. The higher rate of antimicrobial use in our study could be attributed to the tertiary center hospital set up. Studies have shown that unnecessary use of antimicrobials that eliminate anaerobes promote intestinal overgrowth of nosocomial pathogens. Substitution of anti-anaerobic antimicrobials with equally efficacious alternatives with minimal anti-anaerobic activity would further reduce the unnecessary use of this spectrum of activity.^{14,15} However in our setting, antimicrobials with minimal anti-anaerobic activity namely ceftriaxone, amikacin and metronidazole were preferred over co-amoxiclav.

The present study found that empirically started antimicrobials accounted for 78.1% of the total number of antimicrobials prescribed. This is in accordance with an earlier study that showed empirically started antimicrobials contributing toward 79% of therapeutic antimicrobial use. The study also demonstrated that appropriate antimicrobial use was highest when prescribed based on culture and sensitivity reports.¹¹ Changing empirical therapy to definitive treatment based on culture reports have shown to improve health and economic outcomes.¹⁶ In our study, two patients on empirically started ceftriaxone were continued even after the culture reports showed resistance to the antimicrobial. However, we were not able to trace the reason for this as the data was taken from patient records.

The reason for the higher percentage of the patients receiving injectable antimicrobials (59.3%) in our set up

could be attributed to the physician's concerns about the drugs including bioavailability, food - drug interactions, tissue distribution, non-adherence etc.¹⁷ Further, the most common prescribed antimicrobial ceftriaxone is available only as parenteral preparation. However, as increased use of parenteral preparations is associated with increased hospital costs, measures should be taken to promote the use of oral formulations where both oral and parenteral antimicrobials are available unless contraindicated.

The study found that gastrointestinal tract infection accounted for 33% of antimicrobial use. This was on the higher side compared to the study by Ozgen et al. that revealed nearly half of all antimicrobial use is attributed to lower respiratory tract (27%) and urinary tract infections (15%) followed by gastrointestinal tract infections (10%).¹¹ The reason for this variation is attributed to the referral of patients with lower respiratory tract infection and urinary tract infection to Pulmonary Medicine and Urology respectively in our hospital.

Out of the 136 patients whose records were assessed, ADRs were mentioned in the records of only 6 patients. The skin and subcutaneous tissues followed by gastrointestinal system were the most common involved systems in the recorded ADRs (n=4). The antimicrobials associated with ADRs were ceftriaxone (J01DD04), vancomycin (J01XA01) and azithromycin (J01FA10). According to the prospective study on ADR monitoring by Dang et al.⁷ the β -lactam antibiotics were associated with the maximum number of ADRs (20.37%), followed by fluoroquinolones (13.2%). Antimicrobials have been shown to be responsible for more than 50% of drug related ADRs, both in adults and children.¹⁸ This may be due to the fact that antimicrobials are the most frequent and often irrationally prescribed drugs among the hospitalized patients. Though ADR prevalence was assumed to be 10% for calculating the sample size of the present study, we could show a prevalence of only 4%. This is low compared to the results of a meta-analysis conducted by Lazarou et al., which reported that 15.1% of hospitalized patients develop drug-related adverse events.¹⁹ This is considered as one of the limitations of the study as the patients were not interviewed regarding the occurrence of ADRs. The other possible reason could be under reporting or non-reporting of ADRs.^{20,21} This shows that the culture of spontaneous reporting of ADRs needs to be cultivated among the physicians. The total wholesale price of all the drugs prescribed for the study patients was estimated to be Rs. 68939.70. Of this antimicrobials alone accounted for Rs. 40370.494 (58.6%) of the total estimate for study patients. Average cost of antimicrobial per patient was estimated to be Rs.294.84 and this was similar to the reports of earlier studies.¹² The annual assessment of drug costs done in a Canadian hospital showed that antimicrobials alone account for 20-40% of total drug costs thus constituting one of the major components of the hospital pharmacy budget.²² This increased cost could be due to the prescription of drugs before obtaining the microbiological reports or continuation of necessary

regimens ahead of the required duration recommended by standard guidelines. Change over to appropriate treatment based on culture results, choosing a cost effective, as well as efficacious agent, sequential antimicrobial therapy and change from parenteral to oral formulation as well as combination to monotherapy in a timely manner are considered as valuable measures to improve both health and economic outcomes.^{16,23,24} In our study only, the apparent cost of drugs was considered and other indirect costs related to hospital stay, drug administration, ancillary supplies, and laboratory investigations were not included. Most of the patients included in the present study showed improvement symptomatically at the end of completion of antibiotic course on which they were discharged. Three patients diagnosed as cases of acute myeloid leukemia, chronic lymphoid leukemia, and autoimmune hemolytic anemia expired on an average of 4th day of hospitalization and was related to the disease outcome.

This major limitations of the study includes, it was conducted in a single unit of medicine department for a period of 2 months owing to time constraint as it was undergraduate student project. Sample size was small and intensive care unit patients were not included. The severity of the illness was not evaluated in the patients. An important measure of quality of care and treatment including the data on outcome, health status, disability, impairment, quality of life, etc., could not be collected which is considered a drawback of the study. In addition, a greater number of ADRs might have been identified if the patients were interviewed and examined. However, the main strength of this study is that unlike the previous surveillance studies that simply collected the dispensing data at aggregate levels, we collected information on individual patients as well as the antimicrobials actually administered to them. Nevertheless further, studies including interventions to limit unnecessary use of antimicrobials are needed to provide a more accurate assessment of the rational use of antimicrobials on clinical and economic outcomes.

CONCLUSION

Our study found that 64.8% of in-patients of medicine ward receive antimicrobials with ceftriaxone (J01DD04), doxycycline (J01AA02) and metronidazole (P01AB01) being the most common prescribed drugs. The antimicrobials account for 58.6% of the cost spent on drugs for inpatients of medicine unit in a tertiary care hospital.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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