Appropriateness of antibiotic usage for gastrointestinal disorders in a tertiary care hospital

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ABSTRACT

Objective To assess antibiotic usage in gastrointestinal disorders with respect to appropriateness, pattern of resistance, and incidence of adverse drug reactions (ADRs).

Methodology Antibiotic prescribing in the gastroenterology department of a tertiary care hospital was evaluated using the Gyssens criteria and also by assessing drug related problems (DRPs) using the Pharmaceutical Care Network Europe V.6.2. A total of 173 patients were studied prospectively by a team of clinical pharmacists. Antibiotic susceptibility was prospectively studied; in addition, retrospective data on culture and sensitivity reports of commonly isolated organisms from 1 October 2012 to 30 September 2014 were collected to determine the resistance pattern in previous years. ADRs were evaluated using the Naranjo scale.

Results Antibiotic therapy was appropriate in 60% of patients and inappropriate in the remaining patients due to incorrect decision, choice, and use. A total of 184 DRPs and 30 ADRs of antibiotics were identified. In the study patients, the most commonly isolated organism was *Escherichia coli* (27.3%) followed by *Klebsiella pneumoniae* (16.7%). Both *E coli* and *K pneumoniae* exhibited 100% resistance towards cefotaxime. There was an increase in the resistance of *E coli* and *K pneumoniae* against various antibiotics tested in 2013–2014 as compared to the previous year. An empirical antibiotic policy was developed which was endorsed by the gastroenterology department.

Conclusions Although antibiotic therapy was appropriate in the majority of patients, irrational use occurred due to incorrect choice, improper dosage, and improper duration of therapy. *E coli* and *K pneumoniae* isolates showed an increase in resistance towards various antibiotics tested.

INTRODUCTION

Antibiotics play an important role in the management of various infections. However, over-utilisation of antibiotics is emerging as a major health problem.[1] In fact, the 2014 WHO report on global surveillance of antimicrobial use revealed antibiotic resistance as a public health concern putting at risk the ability to treat common infections in the community and hospitals. Even though the development of antibiotic resistance is a natural phenomenon, certain physician practices accelerate its emergence and dissemination. Antibiotic misuse constitutes the primary cause of increased antibiotic resistance. Irrational use of antibiotics not only results in the steady increase in resistance but also increases the incidence of adverse drug reactions (ADRs), cost of therapy, duration of hospital stay as well as drug interactions, all of which ultimately lead to the failure of therapeutic regimens.[2] Given the recent worldwide escalation in resistance and irrational use of antibiotics, the practical and essential approach is to control antibiotic use by developing and implementing antibiotic policies.

One of the areas where antibiotics are widely used as a prophylactic and treatment measure is in gastrointestinal (GI) disorders such as cholangitis, cholecystitis, gastroenteritis, pancreatitis, spontaneous bacterial peritonitis (SBP), and urinary tract infections (UTIs) associated with GI disorders. Hence, it would be worthwhile to assess antibiotic usage in these GI disorders with respect to appropriateness, pattern of resistance, and incidence of ADRs.

METHODS

A prospective observational study was conducted on 173 patients who were admitted to the gastroenterology department of a tertiary care hospital in India with the diagnosis of cholangitis, cholecystitis, gastroenteritis, pancreatitis, spontaneous bacterial peritonitis or UTIs associated with GI disorders. The study was approved by the Institutional Review Board and informed signed consent was obtained from the study patients. Demographic details of the patients, pertinent laboratory data, and drug treatment details were collected from the hospital's digital information system and by direct review of the medical records of the admitted patients as well as by direct interview of the patients and caregivers using a predesigned data collection form. Each case was meticulously examined and the patients were followed up on a daily basis from admission until discharge by a team of two dedicated clinical pharmacists. Assessments were made in terms of prescription pattern, appropriateness of antibiotic therapy, ADRs, and reasons for failure of initial therapy. The sensitivity pattern of organisms isolated was analysed. Systems involved in ADRs were classified according to the WHO System Organ Classification. Causality and severity assessment were performed by the Naranjo *et al* scale[3] and Modified Hartwig and Siegel scale,[4] respectively. For SBP, the initial antibiotic therapy was considered a failure when there was no improvement in clinical signs of infection and an inability to achieve at least a 25% decrease in ascitic fluid polymorphonuclear leucocytes after 48 h of antibiotic administration. For other indications, antibiotic therapy was considered a failure when there was no decrease in elevated inflammatory markers such as C-reactive protein (CRP) and no improvement in

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clinical signs of infection even after 48 h of antibiotic administration.

The appropriateness of antibiotic therapy was evaluated using the method developed by Gyssens *et al*[5] and also by assessing drug related problems (DRPs) of antibiotics as per the Pharmaceutical Care Network Europe (PCNE)[6] V.6.2. DRPs due to drug interactions were analysed using the Lexicomp drug interaction checker (UpToDate (http://www.uptodate.com), and category C (monitor the therapy), D (consider therapy modification) and category X (avoid combinations) interactions were considered.

The antibiotic consumption was calculated to defined daily dose (DDD)/100 bed days according to the anatomic therapeutic chemical/DDD index from the WHO collaborating centre for drug statistics methodology.[7] Antibiotic susceptibility was prospectively studied during the study period from 1 October 2014 to 31 May 2015. In addition, in order to study any change in the resistance pattern of most commonly isolated organisms in the previous 2 years, retrospective data of culture and sensitivity reports of commonly isolated organisms during 1 October 2012 to 30 September 2014 were collected. All the collected data were compiled using Microsoft Excel and analysed using the Statistical Package for the Social Sciences (SPSS) software V.20. Descriptive statistics such as frequencies, mean±SD and median with range were calculated for relevant parameters. Pearson's χ^2 test was used to calculate the p values and a value of $p<0.05$ was taken as significant.

RESULTS

A total of 173 patients received antibiotic therapy for 183 indications. Antibiotics were administered to the inpatients for the treatment of cholangitis and cholecystitis (9, 4.9% each), gastroenteritis (3, 1.6%), pancreatitis (10, 5.5%), spontaneous bacterial peritonitis (51, 27.9%) and UTIs associated with GI disorders (101, 55.2%). Eighty-eight (48%) of total indications were treated with 2–3 antibiotics and 111 (60.6%) indications were treated with parenteral therapy. The duration of hospital stay (16.6±8.1 days) and duration of administration of antibiotics (15±7.9 days) were higher in cases of cholangitis. For the various indications treated, antibiotic use was appropriate in 55.5% cases of cholangitis, 44.5% cases of cholecystitis, 33.3% cases of gastroenteritis, 50% cases of pancreatitis, 80.4% cases of SBP, and 64.4% of UTI cases. The most commonly prescribed empirical antibiotic class was the cephalosporins for all the indications, but in the case of gastroenteritis combinations of fluoroquinolones and nitroimidazoles were most commonly used.

The mean age of the patients was 54.8±13.2 years (median age 57 years, range 17–85 years) and 74% of the total study patients were males. One hundred and forty-three (82.7%) patients were discharged with oral antibiotics. The initial antibiotic therapy was a failure in 106 (61.3%) patients. Antibiotic therapy was appropriate only in 104 (60%) patients as judged by the Gyssens criteria[5] (table 1). Among the factors contributed to inappropriate antibiotic use, incorrect use was the major factor.

One hundred and eighty-four DRPs of antibiotics were identified during the study period. The major cause of DRP was inappropriate drug selection followed by inappropriate dose selection (table 2). More than half (117, 59.2%) of the DRPs occurred in patients with UTIs.

A total of 31 ADRs caused by antibiotics were identified in 30 patients. Ten (33.3%) of the ADRs were classified under the WHO SOC criteria 'investigations' (figure 1). Most of the ADRs (24, 80%) were 'moderate' in severity. Seventeen (56.7%) ADRs were 'probable', 11 (36.6%) 'possible', and 2 (6.7%) 'definite'. Eighteen (60%) ADRs were caused by cephalosporins followed by penicillins (4, 13.3%). In 20 (66.6%) cases of ADRs, treatment with the antibiotic causing the ADR was continued with conservative management.

Table 1 Appropriateness of antimicrobial therapy (AMT) based on the Gyssens criteria[5]

Criteria	No. (%) of patients (n=173)
Appropriate AMT	104 (60.1)
Inappropriate AMT	69 (39.9)
Incorrect decision	
No infection and no AMT needed but AMT given	10
No AMT given for prophylaxis but AMT needed	3
Incorrect choice	21
Incorrect use	
Improper dosage	20
Improper timing	2
Improper administration	3

The most commonly isolated organism was *Escherichia coli* (41, 27.3%) followed by *Klebsiella pneumoniae* (25, 16.7%). *E coli* showed 100% sensitivity towards nitrofurantoin and colistin during the prospective study period. Sensitivity of *K pneumoniae* isolates ranged from 4–62% among the antibiotics commonly administered. Both *E coli* and *K pneumoniae* exhibited 100% resistance towards cefotaxime. Even though there was a general increase in the resistance of *E coli* and *K pneumoniae* against various antibiotics tested, a significant increase was seen in the case of *E coli* towards amikacin, cotrimoxazole, levofloxacin, piperacillin–tazobactam, cefoperazone–sulbactam, and nitrofurantoin (see online supplementary table S1), and in the case of *K pneumoniae* towards piperacillin–tazobactam, cefoperazone–sulbactam, cotrimoxazole, and ciprofloxacin (see online supplementary table S2) in 2013–2014 as compared to the previous year.

In our study the departmental antibiotic consumption was estimated to be 117.04 DDDs/100 bed days and the total antibiotic consumption was 2208.6 DDDs. In 26.4% of cases, reason for the failure of initial antibiotic therapy was resistance towards these agents (figure 2). Based on the outcome of evaluation and the local sensitivity pattern, an empirical antibiotic policy was developed by the clinical pharmacists in consultation with the physicians of the department.

DISCUSSION

The major consideration for the proper use of antibiotics is to select an agent with optimal activity at the proper dose and dose interval for the appropriate duration of time. In this study, however, 69 (40%) patients received inappropriate antibiotic therapy as per the criteria developed by Gyssens *et al*.[5] SBP, cholangitis, and UTIs associated with GI disorders were the clinical conditions most linked with inappropriate antibiotic use. During this study, a considerable number of DRPs and ADRs were identified.

Another important problem in antibiotic use was resistance of the organisms towards various antibiotics. *E coli* and *K pneumoniae* accounted for the majority of the Gram-negative organisms isolated during the study period. Analysis of the sensitivity and resistance pattern showed *E coli* was fully susceptible to colistin

Table 2 Drug related problems (DRPs) based on the Pharmaceutical Care Network Europe (PCNE) V.6.2 classification scheme

Classification of DRPs	DRP code V 6.2	Cause	No. (%) of DRPs (n=184)
Drug selection	C1.1	Inappropriate drug	39 (21.1)
	C1.2	No indication for drug	19 (9.6)
	C1.3	Inappropriate combination of drug, drugs and food	30 (15.2)
	C1.4	Inappropriate duplication of therapeutic group or active ingredient	3 (1.6)
	C1.8	Synergistic/preventive drug required and not given	5 (2.6)
Drug form	C2.1	Inappropriate drug form	30 (15.2)
Dose selection	C3.1	Drug dose too low	5 (2.5)
	C3.4	Dosage regimen too frequent	4 (2)
	C3.7	Deterioration/improvement of disease state requiring dosage adjustment	34 (17.1)
Treatment duration	C4.1	Duration of treatment too short	4 (2)
	C4.2	Duration of treatment too long	11 (5.9)

and nitrofurantoin. On the other hand, susceptibility of *K pneumoniae* isolates ranged from 4–62% among the commonly administered antibiotics. Both the bacteria exhibited 100% resistance towards cefotaxime. Data collected retrospectively showed that there was an increase in the resistance pattern of *E coli* and *K pneumoniae* towards most of the antibiotics tested.

Though UTI is not a GI disorder, approximately 50% of the patients had UTI in conjunction with other GI conditions such as SBP (11.8%), cholangitis (2.9%), cholecystitis (2.9%), pancreatitis (0.9%), and cirrhosis (81.4%). Hence it was decided to evaluate antibiotic usage in these UTI patients.

Usually females are more prone to UTI and cholecystitis,[8 9] but in our study there was a male predominance for all the indications of antibiotic therapy, which may be due to there being more male patients in our study. Parenteral antibiotic therapy was prescribed for the majority of infections; however, when the patient's condition improves and he or she is able to tolerate oral medications it is possible to convert parenteral medications into oral form, which can reduce the cost of treatment and the complications resulting from parenteral therapy.[10 11] This was reflected in our study in which the majority of our patients were switched from parenteral to oral therapy.

A study by Berrington[12] in the UK showed that antibiotic consumption in the gastroenterology department of a 950-bed secondary care hospital was 438.5 DDDs/1000 bed days; however, in our study the antibiotic consumption was 2.6 times more than this study. 'Inappropriate antibiotic selection' was the major DRP according to PCNE classification. One of 'the inappropriate selections' observed in the majority of the patients was the prescribing of linezolid after the culture and sensitivity reports, in spite of the availability of other antibiotics to which the isolated organism was sensitive. Being a reserved antibiotic, linezolid is recommend[13 14] only in cases of vancomycin–ampicillin resistance. Linezolid is now restricted to consultants in our institution after the feedback of this study.

Arribas *et al*[15] conducted a study to measure appropriateness of antibiotic therapy in patients with UTI in an emergency ward of a tertiary care hospital. Approximately 20.5% of patients had inappropriate empirical antibiotic therapy as judged by the culture and sensitivity tests; however, inappropriate antibiotic use was higher in our patients, which may be due to changes in the methodology. Arribas *et al*[15] measured appropriateness with only one criterion which specifies that the empiric antibiotic therapy was appropriate if the isolated organism was susceptible to the antibiotic administered. In our study appropriateness was judged using the Gyssen *et al* criteria.[5] The major factors influencing inappropriate antibiotic therapy were improper dosage, timing, administration, and duration of therapy. About 57% of the cases of incorrect use were due to incorrect dosage, mainly attributed to failure of dosage adjustment in renal failure patients. Hence, physician education is extremely important to reduce irrational use of antibiotics.

The documented adverse effects of antibiotics mainly affect the GI system and skin,[16 17] but in our case the majority of antibiotics caused 'investigation-related' adverse effects. For example, cefoperazone–sulbactam caused elevation of

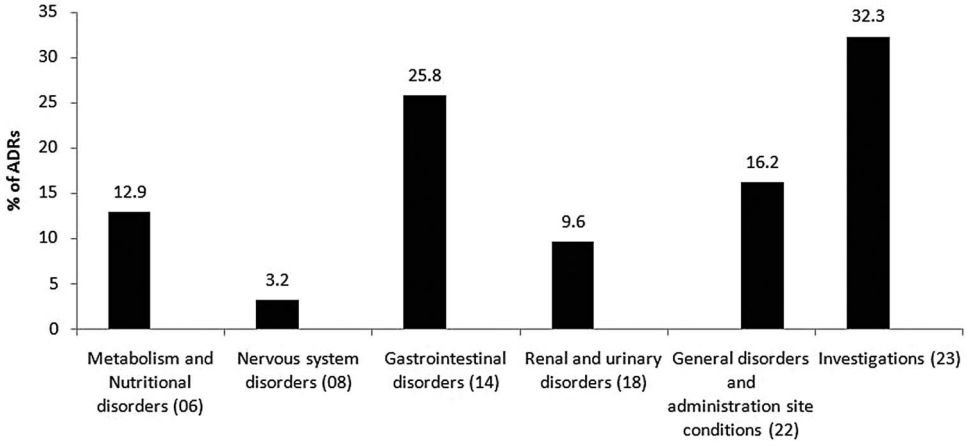

Figure 1 Adverse drug reactions (ADRs) of antibiotics in the study patients based on WHO System Organ Classification (31 ADRs in 30 patients).

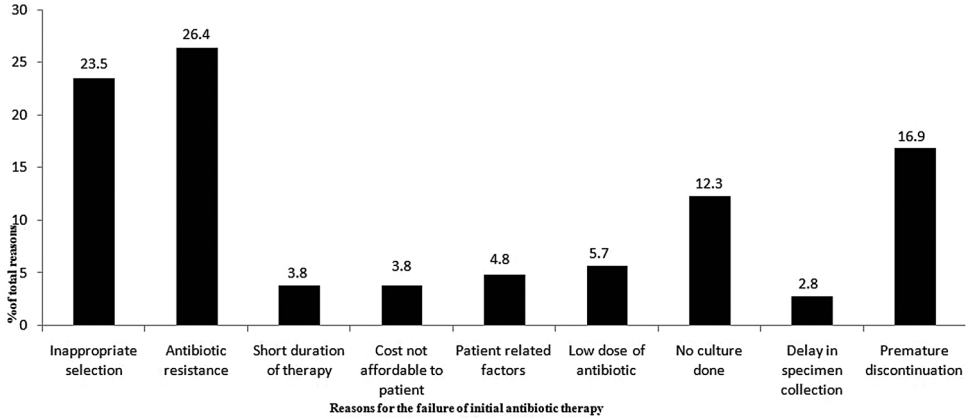

Figure 2 Reasons for failure of initial antibiotic therapy in the study patients (106 failures occurred in 106 patients).

prothrombin time/international normalised ratio (PT/INR) in the majority of patients (figure 1).

The antimicrobial resistance pattern might increase or decrease with time. In our study, *E coli* and *K pneumonia* had developed 100% resistance towards cefotaxime since 2012 when the GI disorders of the gastroenterology department were taken separately. But our hospital-wide antibiotic susceptibility pattern showed 27% and 24% sensitivity, respectively, for 3714 isolates of *E coli* and 3757 *K pneumoniae* isolates towards cefotaxime. Sheikhbahaei *et al*[18] conducted a study on SBP patients in 2014 and noticed a significant increase in the resistance of organisms towards cefotaxime, from 62.5% to 85.7%. In our study, *E coli* and *K pneumoniae* isolates showed increased resistance to meropenem (see online supplementary tables S1 and S2). A study[19] conducted in India showed a significant increase in meropenem resistance towards *K pneumoniae* isolates. Another study[20] also showed 22.1% of total isolates as being resistant to meropenem.

The current American[21] and European guidelines[22] recommend third generation cephalosporins, especially cefotaxime, as the first-line treatment for SBP. Recent studies[23 24] have reported the emergence of resistance to third generation cephalosporins at rates of 21–41%. In contrast, a study[25] conducted in India suggested that cefotaxime could still be the choice of primary empiric antibiotic therapy for SBP. Due to high resistance, ascitic fluid isolates are not commonly tested for cefotaxime sensitivity currently in our institution, and those isolates which are tested occasionally have shown complete resistance to cefotaxime. Other cephalosporins (ceftriaxone, cefoperazone, and cefixime) show susceptibility of <6% towards most of the *E coli* isolates. So we recommend cefoperazone–sulbactam as first line and piperacillin–tazobactam as second line for the treatment of SBP in our clinical setting; this is because 65% of *E coli* isolates were found to be susceptible to cefoperazone–sulbactam and 53% of isolates were susceptible to piperacillin–tazobactam. Even though colistin is 100% susceptible, it was not recommended as it is a reserved antibiotic.

Our study led to the development of an empirical antibiotic policy (see online supplementary table S3) which was developed by the clinical pharmacists in consultation with the physicians based on sensitivity patterns of bacterial isolates and was endorsed by the gastroenterology department. It is recommended to conduct an antibiotic stewardship programme to evaluate the effectiveness of the policy and an interventional study using a locally established guideline for increasing appropriateness of antibiotic therapy. Addition of a dedicated 'antibiotic pharmacist' to the healthcare team has shown to be of benefit to patients by reducing medication errors, reducing length of hospital stay, increasing savings on antibiotic costs, encouraging the use of oral medications, and ensuring the appropriate choice of drugs.[26] Our study also suggests that clinical pharmacists can play an active role in monitoring the appropriateness of antibiotic use and help to develop guidelines for antibiotic use.

A limitation of our study is that the outcome of antibiotic therapy was not assessed.

CONCLUSION

Though antibiotic therapy was appropriate in the majority of patients in our study, irrational use occurred due to incorrect decision, choice, and use. There was an increase in the resistance of *E coli* and *K pneumoniae* in the year 2013–2014 as compared to the previous year. Although cefotaxime is recommended as the drug of choice for SBP by the American Association for the Study of Liver Diseases, in our setting cefoperazone–sulbactam is a better choice because of the development of 100% resistance towards cefotaxime by the causative bacteria. Rational use of antibiotics is needed to prevent further development of antibiotic resistance.

Key messages

What is already known on this subject

- Misuse of antibiotics can increase adverse drug reactions, duration of hospital stay, and cost of therapy.
- Irrational use of antibiotics results in a steady increase in antibiotic resistance.

What this study adds

- Inappropriate use of antibiotics continues to occur and monitoring of antibiotic usage by clinical pharmacists can help identify irrational use.
- Incorrect use of antibiotics such as improper dosage, timing, administration, and duration of treatment are factors contributing to inappropriate use of antibiotics.
- Even those antibiotics recommended as drugs of choice in certain infections can become ineffective due to development of resistance by the causative bacteria.
- Our study led to the development of an empirical antibiotic policy which was endorsed by the gastroenterology department.

Contributors GM collected the data. EJ, RPV and GM were involved in analysis and interpretation of results and preparation of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Institutional Review Board of AIMS.

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