A STUDY OF ANTIMICROBIAL AGENT UTILIZATION AND THE RESISTANCE PATTERN OF PREDOMINANT MICROORGANISMS IN THE MEDICAL WARD OF A TERTIARY CARE CENTRE IN UTTAR PRADESH, INDIA

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Summary

The study was carried out in the context of rising trend of antibiotic resistance amongst microorganisms due to inappropriate and irrational misuse of anti-microbial agents (AMAs). The study aims at collecting information regarding AMAs prescribing patterns and the antibiotic resistance prevailing in the medical wards, which can serve as a basis for designing an appropriate intervention to improve the drug use profile. It was carried out over a 6-month period in the medical wards of a tertiary care centre in Uttar Pradesh, India. Only those patients who were prescribed AMAs were considered. The results of the study showed the defined daily dose per 100 bed-days of five most commonly prescribed anti-microbial agents were amoxicillin- 26.5, ampicillin- 18.5, metronidazole- 11.6, Co-amoxiclav- 9.65, and ciprofloxacin- 4.62, 3.53. The common organisms isolated were E.coli urine samples, P.aeruginosa in sputum samples and K. pneumoniae in blood samples. The AMAs (along with resistance rate [RR] %) effective against most of the E.coli in urine CST are amikacin (5.9%), tobramycin (11.2%), nitrofurantoin(12.8%) and meropenem (0%). The AMAs effective against most of the P.aeruginosa in sputum CST are ciprofloxacin (24.6%), amikacin (25.4%), piperacillin (21.8%) and meropenem (22.6%). The AMAs effective against most of the K.pneumoniae in blood CST are amikacin (28.6%), ceftriaxone (30.8%) and meropenem (0%).

Key words: anti-microbial agents, antibiotic resistance, defined daily dose, culture and sensitivity testing

Introduction

The study of prescribing patterns seeks to monitor, evaluate and suggest modifications in practitioners' prescribing habits so as to make the prescriptions more rational and cost effective. The inappropriate use of antimicrobial agents (AMAs) has been noticed all over the world. Even for trivial infections of viral etiology, an increasing trend is noticed for use of combinations, broad spectrum and newer generation antimicrobials[1-3]. This phenomenon is now posing serious negative impact in low economy countries where infectious diseases behold a major health challenge[4]. Information about antibiotic use patterns is necessary for a constructive approach to problems that arise from the multiple AMAs available[5]. Rational drug prescribing requires that a prescriber follow a standard process of prescribing and in accordance with standard treatment guidelines. Irrational drug use has been found to have definite impact on the quality of care, cost of therapy, and incidence of adverse drug reaction[6]. In developing countries the cost of health care is a matter of major concern[7]. Excessive and inappropriate use of anti-microbial agents in hospitals, health care facilities and the community contributes to the development of bacterial resistance. In India various regional reports on antibiotic utilization at an institutional level has been published on prescribing patterns.

To study the antimicrobial drugs consumption, the Anatomic Therapeutic Chemical (ATC) code and Defined Daily Dose (DDD) concept of World Health Organization (WHO) has been used in the hospital set up. The ATC classification assigns code letters and numbers to drugs[5,8]. The DDD concept was developed to overcome objections against traditional units of drug consumption. The DDD for a given drug is established on the basis of an assumed average use per day of the drug for its main indication in adults[8]. The DDD will be assigned only for drugs that already have an ATC code. DDD is a unit of measurement and may not reflect the prescribed daily dose; however they provide a fixed unit of measurement independent of price and formulation and enable the researcher to perform comparisons between population groups. DDD/100 bed-days provide a rough estimate of consumption of drugs among hospital in-patients.

The present study was carried out over 6 months (01.07.02 to 30.01.10) at a tertiary care hospital in northern Uttar Pradesh. The objectives of the study were to collect relevant information on duration of hospitalization of patients admitted to the

Medical ward and prescribed anti-microbial agents during the study and to obtain information on the antibiotic prescribing pattern and the disease conditions for which anti-microbial agents were prescribed. Also the common organisms isolated during culture and sensitivity testing and their antibiotic sensitivity patterns were pointed out. The ATC classification has been applied to the commonly used anti-microbial agents and their DDDs/100 bed-days were calculated.

Material & Methods

The study was carried out over a six-month period at a tertiary care centre in northern Uttar Pradesh, India, after approval from institutional ethics committee. Patients admitted to the medical ward who were prescribed anti-microbial agents were included in the study. The age, sex, clinical diagnosis, duration of hospitalization, antibiotic information (name, dose, route of administration and frequency) and the results of culture and sensitivity testing, if done were recorded. The anti-microbial agents were used on empirical basis (Non- CST based) or after culture sensitivity testing (CST based). The CST based use of antibiotic was noted with details. The DDD/100 bed-days of the 10 most commonly prescribed anti-microbial agents in the Internal Medicine ward, was calculated. The DDD/100 bed-days of the individual anti-microbial agents were added together to get the total antibiotic consumption. The ciprofloxacin has two DDDs, one for oral use of the antibiotic and the other for parenteral use. The 2 DDDs/100 bed-days were calculated separately and then were added to measure the total consumption of ciprofloxacin in DDDs/100 bed-days.

The DDD/100 bed-days were calculated by the formula:

$$\textbf{DDD/100 bed days} = \frac{\textbf{No. of units administered in a given period (mg) x 100}}{\textbf{DDD (mg) x no. of days in that period x no. of beds x bed occupancy}}$$

Results

Four hundred and eighty eight patients were prescribed anti-microbial agents during the six month study period in the medical wards. Out of the total of 488 patients, 274 were male. 249 were above the age of 60 years.

235 patients were prescribed a single antibiotic, while 146 patients were prescribed two anti-microbial agents. 92 patients were prescribed 3 anti-microbial agents, while 4 anti-

microbial agents were prescribed to 15 as shown in Table 1. The duration of hospitalization of the 488 patients was recorded. 268 were hospitalized for a time period ranging from 3 to 7 days. The median duration of hospitalization was 5 days. The most common type of infection for which an antibiotic was prescribed was respiratory infections 49.6 % (242) (COPD-141, 28.9 %; LRTI-101, 20.7 %), urinary tract infections (UTI) (67, 13.7%) and abdominal infections (46, 9.4 %). Out of Four hundred and eighty eight patients, who received AMAs, 466 patients were discharged, 9 patients died, 8 patients were discharged at request and 5 were transferred to the Intensive Care Unit (ICU).

Table1. Percentage of Prescription with number of antibiotics.

No. of Antibiotics	No. of Patients (n)	% of Total Prescription
One	235	48.15
Two	146	29.91
Three	92	18.85
Four	15	3.07
Total	488	

Table 2 shows the frequency of prescribing of the 5 most commonly prescribed anti-microbial agents. The route of administration in 51% of AMA was parenteral. Amoxycillin was the most commonly prescribed anti-microbial agent, prescribed in 194 (26.8%) prescription, followed by ampicillin (18.8%), ciprofloxacin (15.3%), metronidazole (14.8%) and lastly co-amoxiclav (14.4%).

Table 2: Anti-microbial agents prescribed during hospital stay

Name of antibiotic	Number of prescriptions (percentage)
Amoxicillin	194 (26.5)
Ampicillin	138 (18.8)
Co-amoxiclav	106 (14.4)
Metronidazole	109 (14.8)
Ciprofloxacin	112 (15.3)
Others	86 (11.7)
Total	745

Table 3 shows the ATC codes and the DDDs/100 bed days of the 10 most commonly used anti-microbial agents in the Internal Medicine ward. The study was carried out for a period of 180 days, the number of beds in the Internal Medicine ward was 120 and the average occupancy index during the study period was 0.7.

Table 3: ATC codes and DDD/100 bed-days of the ten most commonly used AMAs in the Internal Medicine ward

Name of antibiotic	ATC code	DDD/100 bed-days
Amoxicillin	J01CA04	26.5
Ampicillin	J01CA01	18.5
Metronidazole	J01XD01	11.6
Ciprofloxacin*	J01MA02	4.62, 3.53
Gentamicin	J 01GB03	7.25
Co-amoxiclav	J01CR02	9.65
Ceftriaxone	J01DA13	4.56
Cefixime	J01DD08	2.26
Azithromycin	J01FA10	1.89
Piperacillin	J01CA12	3.18
Levofloxacin	J01MA12	2.92

* Two DDDs have been defined one for oral use and the other for parenteral use

Anti-microbial agents used on CST basis in 180 and on empirical basis in 308 patients.

Anti-microbial agents were prescribed at the time of discharge in 392 patients with amoxicillin (134 patients) being most commonly prescribed. The other commonly prescribed anti-microbial agents on discharge were ampicillin (78 patients), ciprofloxacin (68 patients), ampicillin (56 patients) and metronidazole (60 patients). 98(58 %) of the 180 patient, the anti-microbial agents used on CST basis, were prescribed by the parenteral route.

Culture and sensitivity testing was carried out in 302 patients (61.9 %) and a total of 346 specimens were sent for testing. Two hundred and sixty five patients had single specimen sent for culture and sensitivity testing, 30 patients had two specimens, and 7 patients, three specimens. Sputum was the most frequent specimen (124) followed by urine (118) and blood (104). The results were negative in 89 specimens while in 68, a normal flora was grown. A total 189 organisms were isolated.

The predominant organisms obtained in sputum culture were P. aeruginosa (n=23), in urine culture (n=42), and K. pneumoniae (n=13) in blood culture as shown in Table 4.

Table 4. Percentage of microbial isolates from respective samples

Organism	**Urine (118)**	**Sputum (124)**	**Blood (104)**
E.coli	42	4	6
P.aeruginosa	5	23	4
HI	-	9	-
HPI	-	12	-
SPn	-	21	-
SgrpA	-	20	-
KP	13	10	13
SA	3	-	4

Table 5 shows the antibiotic resistance patterns of the commonly isolated organisms. The AMAs effective against most of the E.coli are amikacin, tobramycin, nitrofurantoin and meropenem. The AMAs effective against most of the P.aeruginosa are ciprofloxacin, amikacin, piperacillin and meropenem. The AMAs effective against most of the K.pneumoniae are amikacin, ceftriaxone and meropenem.

Table 5. Antimicrobial agent resistance pattern of the most commonly isolated organism

Antimicrobial agent	E.coli in n=42 Urine sample (%)	P.aeruginosa in n=23 Sputum (%)	K. pneumoniae in n=13 Blood (%)
Ampicillin	92.9	-	92.4
Amoxycillin	90.5	-	84.6
Co-amoxiclav	88.1	98.8	70.8
Ciprofloxacin	66.7	**24.6**	43.1
Co-trimoxazole	69.1	-	57.8
Gentamicin	40.5	57.5	35.4
Amikacin	**5.9**	**25.4**	**28.6**
Tobramycin	**11.2**	58.4	-
Nitrofurantoin	**12.8**	-	-
Piperacillin	57.2	**21.8**	38.5
Ceftriaxone	81.0	84.2	**30.8**
Ceftazidime	-	50.8	-
Meropenem	**0**	**22.6**	**0**

Discussion

The inappropriate use of antimicrobial agents (AMAs) has been noticed all over the world[1]. This phenomenon is now posing serious negative impact in low economy countries where infectious diseases behold a major health challenge[4]. Information about antibiotic use patterns is necessary for a constructive approach to problems that arise from the multiple AMAs available[5].The present study was carried out over 6 months (01.07.2010 to 30.01.2011) at a tertiary care hospital in northern Uttar Pradesh. The study focused on the collection of relevant information regarding prescribed anti-microbial agents and the organisms isolated during culture and sensitivity testing and their antibiotic resistance pattern patterns. The ATC classification has been applied to the commonly used anti-microbial agents and their DDDs/100 bed-days were calculated.

In 48.15% of prescription only one antibiotic was prescribed and in 51.85% of prescription 2 or more than 2 antibiotics were prescribed. The most common type of infection for which an antibiotic was prescribed was respiratory infections 49.6 % (242)

(COPD-141, 28.9 %; LRTI-101, 20.7 %), followed by urinary tract infections (UTI) (67, 13.7%) and abdominal infections (46, 9.4 %).

The predominant organisms obtained in sputum culture were Pseudomonas aeruginosa (n=23) followed by Streptococcus Pneumoniae (n=21); in urine culture it was Escherichia Coli (n=42) followed by Klebsiella Pneumoniae, and in blood culture K. pneumoniae (n=13) followed by Escherichia Coli (n=6) were the predominant organisms.
The AMAs effective against most of the E.coli in urine CST in our study are amikacin, tobramycin, nitrofurantoin and meropenem. The AMAs effective against most of the P.aeruginosa in sputum CST are ciprofloxacin, amikacin, piperacillin and meropenem. The AMAs effective against most of the K.pneumoniae in blood CST are amikacin, ceftriaxone and meropenem.
Many studies in the past few decades have reported higher incidence of gram negative organisms among culture positive pneumonia[9,10]. In another study on community acquired pneumonia, the most common organism cultured from sputum was Streptococcus pneumoniae followed by Pseudomonas aeruginosa[11]. Barrett Conner *et al* have reported that only in 18.75% patients organism isolated from sputum culture were consistent with those isolated from blood culture[12]. The rates of antimicrobial resistance of pseudomonas isolates in an another study were 6.73% to amikacin, 12.9% to gentamicin, 10.1% to netilmicin, 10.9% to ceftazidime, 11.3% to ciprofloxacin, 9.9% to imipenem, 10.8% to piperacillin, 9.4% to piperacillin-tazobactam[13]. In our study we found a resistance rate of 24.6% ciprofloxacin, 25.4 % amikacin, 21.8% piperacillin and 22.6% meropenem.

The major organism isolated in urine culture in our study is E.coli. The AMAs which were found to be very effective against E.coli in our study are amikacin with resistance rate (RR) of 5.9%, tobramycin with RR of 11.2%, nitrofurantoin with RR of 12.8% and meropenem with RR of 0%. In one large sample study in Nigeria comprising of 1814 urine samples, the commonest isolates were Escherichia coli (in 46.3% samples), followed by Staphylococcus aureus[14]. E. coli showed a resistance rate of 48% to aminoglycosides, 88% to amoxicillin and 87% to cotrimoxazole, which is almost similar to our study where we found that E.coli showed a resistance rate of 40.5% to gentamicin,

90.5 % to amoxicillin, and 69.1% to cotrimoxazole. It was found to be highly sensitive to nitrofurantoin, only 24% resistance rate found (12.8% in our study). In a similar study conducted in Nepal, E.coli was the most prevalent organism isolated (49%) and it showed a 100% susceptibility to Nitrofurantoin and considerable resistance to amoxicillin and ciprofloxacin[15]. In a previous study at Seychelles, E. coli isolates from urine samples of UTI patients showed a 78.6% resistance against ampicillin and amoxicillin and a 54.8% resistance against Cotrimoxazole. The same E. coli isolates showed a 25% resistance rate to Gentamicin, Nalidixic acid and Nitrofurantoin[16].

In blood culture K. pneumoniae (n=13) followed by Escherichia Coli (n=6) were the predominant organisms isolated in our study and the AMAs effective against most of them are amikacin (28.6% resistance rate{RR}), ceftriaxone (30.8% RR) and meropenem (0% RR). The blood culture positivity rate in north Indian studies, in the clinically suspected septicaemia cases was 20.5%. Overall, 67.5% of septicaemia was caused by Gram negative bacilli and remaining 32.5% by Gram-positive bacteria[17,18].In one north Indian study, the most frequent pathogenic microorganisms in the medical wards in blood culture samples (total = 118) were Klebsiella pneumoniae = 16, 13.56%, Pseudomonas 16, 13.56 %, Acinetobacterspp. = 16, 13.56% followed by staphylococcus aureus 12, 10.17% and E.coli 9, 7.63 %[19]. The RR in this study to various AMA were- Gentamicin 44.8%, Ceftriaxone 30.4%, Ampicillin 78.4%, Amoxycillin-clavulanic acid 74.4%, Amikacin 29.6%, Ciprofloxacin 42.5% which is very similar to our study. In a similar type of study on 567 blood samples Pseudomonas aeruginosa (19.75%) followed by Escherichia coli (15.17%) and Klebsiella pneumoniae (14.99%) were the most frequently isolated bacteria. Among the antibiotics amikacin showed higher activity (RR = 23.39%) against Enterobacteriaceae and ciprofloxacin (RR = 34.83 %) against non-fermenters, which further supports our results[18].

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