Research Article

A Multicentric, Prospective, Observational Antibacterial Utilization Study in Indian Tertiary Referral Centers

Nitin Bhagwan Mali, Siddharth P. Deshpande, Niteen D. Karnik, Nithya J. Gogtay, Renuka P. Munshi[1], Jigeeshu V. Divatia[2], Sanjay C. Wagle[3], Kannan Sridharan[4], Urmila Mukund Thatte

Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, [1]Department of Clinical Pharmacology, TNMC and BYL Nair Charitable Hospital, [2]Department of Anaesthesia, Critical Care & Pain, Tata Memorial Hospital, [3]Bombay Hospital and Medical Research Centre, Mumbai, Maharashtra, [4]Department of Pharmacology, Subharti Medical College and Chhatrapati Shivaji Subharti Hospital, Meerut, Uttar Pradesh, India

Abstract

Rationale: Antibacterials are largely prescribed to the intensive care unit (ICU) patients due to high prevalence of infections. However, appropriate use of antibacterials is imperative; since the misuse of antibacterials increases antibacterial resistance and ultimately, it has negative impact on health care and economic system. Hence, continuous antibacterials prescription assessments are very important to judge and improve prescription patterns. The present work was carried out at public and private hospitals to assess the differences in antibacterial prescribing pattern. **Methods:** The present study was conducted at three public and two private hospitals over the period of 14 months. Demographic and drug use details were captured daily from patients admitted to medical ICUs to assess the World Health Organization indicators. **Results:** A total of 700 patients were enrolled across the five centers (140 per center), among them 424 were male and 276 were female. Average number of drugs and antibacterials prescribed at public hospitals are significantly higher than the private hospital. However, percentage of antibacterial agents prescribed at public hospitals was significantly lower than the private hospitals ($P = 0.0381$). Private hospitals had significantly lower percentage of antibacterial agents prescribed by generic name ($P < 0.0001$). Differences in change of antibacterial agents required were not statistically significantly different ($P = 0.1888$); however, significant difference was observed in percentage of patients who received antibacterial treatment as per sensitivity pattern ($P = 0.0385$) between public and private hospitals. Significantly higher mortality was observed in public hospitals compared to private hospitals (<0.0001). **Conclusions:** More generic prescriptions and more number of prescriptions as per the sensitivity pattern are required at each public and private hospital.

Keywords: Antibacterial resistance, antibacterials, indicators, medical intensive care unit, public and private hospitals

Introduction

Patients admitted to the medical intensive care unit (MICU) of tertiary referral centers are critically ill and incidences of nosocomial infections are also very high.[1,2] Antibacterial agents are the most prescribed drugs for rapid control of serious infections to reduce the mortality and morbidity.[2-4] The burden of bacterial disease in India is among highest in the world and the inappropriate use of antibacterial agents leads to increase the development of antibacterial resistance.[1,5,6] Antibiotic resistance has been a low-priority area in most developing and many developed countries. To overcome the burden of infectious disease and rising antibiotic resistance prevalence in India, the Global Antibiotic Resistance Partnership-India Working Group have recommended important interventions which include surveillance of antibiotic use, distributing standard treatment guidelines, increasing the use of diagnostics tests, infection control interventions, educational approaches, and improving antibiotic supply chain and quality.[5]

A drug utilization study is a potential tool which not only assesses the current prescribing pattern of drugs but also assess the disease burden as well resistance pattern of microorganisms and recommends necessary interventions to be used to achieve rational prescribing practice.[7]

Resistance to important antibacterials such as vancomycin and colistin are increasing globally.[8,9] Majority of antibacterial

Access this article online

Quick Response Code:

Website: www.ijccm.org

DOI: 10.4103/ijccm.IJCCM_197_18

Address for correspondence: Dr. Urmila Mukund Thatte, Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai - 400 012, Maharashtra, India.
E-mail: urmilathatte@gmail.com

How to cite this article: Mali NB, Deshpande SP, Karnik ND, Gogtay NJ, Munshi RP, Divatia JV, *et al*. A multicentric, prospective, observational antibacterial utilization study in Indian tertiary referral centers. Indian J Crit Care Med 2018;22:723-9.

prescription data comes from single-center studies. In a developing country like India, there might be differences in prescription patterns between public and private hospitals due to differences in referral patterns, hospital resources, patients load, and availability of workforce. Hence, this prospective multicentric study was conducted at five centers across India to compare the prescription pattern of antibacterials and cost pattern of antibacterial treatment between three public and two private tertiary referral hospitals with special focus on vancomycin and colistin.

Methods

Ethics

The study was initiated after obtaining approval from the Institutional Ethics Committee (IEC) of Public Hospital 1. Individual IEC approval of each four participating center was also obtained and the study was registered with the Clinical Trial Registry of India. Written informed consent was obtained from patient or legally acceptable representative of the patient only at Public Hospital 1 and waiver of consent were sought at other four participating centers and which was granted by each of IEC.

Study design and duration

This multicentric, prospective, observation antibacterial utilization study was carried out from May 20, 2014 to July 1, 2015.

Study sites

There were five centers across India. These included:

Public hospitals

1. Public Hospital 1 is a 2200-bedded hospital with capacity of 22 MICU beds
2. Public Hospital 2 is a 1623-bedded hospital with capacity of 23 MICU beds
3. Public Hospital 3 is a 600-bedded specialist cancer treatment and research center having a 14-bedded mixed medical–surgical ICU.

Private hospitals

1. Private Hospital 1 is a 725-bedded hospital having 18-bedded MICU
2. Private Hospital 2 is a 1044-bedded private hospital having 18-bedded MICU.

Study population

Consecutive patients admitted to the MICU regardless of previous admission history were enrolled in the study with day 1 of admission into MICU being considered as the 1st day of the study. Each admission was considered as a patient encounter[10] and all patients were followed up until death, discharge or transfer to the general ward.

Study procedure

Patient's medical records were scrutinized daily. Demographic details, clinical diagnosis, details of antibacterial use (name, dose, frequency, route and length of treatment, prescribed as generic or brand, change in antibacterial agent, fixed-dose combination [FDC]), total number of drugs prescribed, culture and sensitivity data, length of stay, and cost of antibacterial treatment was recorded in an online Google spreadsheet.

Cost calculation

The costs of antibacterials were obtained from hospital pharmacy price list (for those available on hospital schedule) and from the Monthly Index of Medical Specialties (MIMS_http://www.mims.com/assessed during the study period).

Definitions

For the purpose of the study, following definitions were considered:

1. Antibacterial: An agent that interferes with the growth and reproduction of bacteria. For the purpose of this study, antimalarials, antifungals, antifilarials, antischistosomals, antileprosy drugs, antituberculosis drugs, anti-amoebic, antigiardiasis drugs, antileishmaniasis drugs, and antitrypanosomal drugs were not considered as an antibacterial
2. Antibacterial use was classified into empiric use or definitive use:[11]
   A. Empiric use of antibacterial agent: It was defined as administration of an antibacterial agent within 72 h of admission in MICU, while microbiologic cultures results are pending or use of antibacterial agents in situations after 72 h of admission when microbiologic cultures do not yield a pathogen
   B. Definitive (therapeutic) use of antibacterial agent: It was defined as the use of any antibacterial agent at a time when microbiologic culture results and susceptibility data are available. This was at the time of initiation of therapy or after empiric antimicrobial use has been initiated once microbiological culture results are available.
3. FDC drug: The FDC of two or more active antibacterial agents was counted as separate antibacterial agents. If one of the agents in the FDC was inactive, that is, did not have direct antibacterial activity, then it was not counted as an antibacterial agent.[12]

World Health Organization indicators:[13,14] Below-mentioned indicators related to antibacterial use are divided into three main sections

A. Prescribing indicators: Average number of drugs prescribed per patient, percentage of antibacterial agents prescribed, percentage of patients who received an antibacterial agent, average number of antibacterial agents prescribed per patient, percentage of antibacterial agents prescribed by generic name, percentage of antibacterial agents prescribed by intravenous route, percentage of antibacterial agents available in hospital pharmacy, percentage of patients in whom a change of antibacterial agent was made, percentage of antibacterial

agents prescribed as FDC, average length of antibacterial treatment, average length of empirical use of antibacterials, and average antibacterial treatment cost per patient

B. Patient care indicators: Average length of MICU stay and percentage of patients died during MICU stay

C. Supplemental indicators: Percentage of patients who received antibacterial treatment as per the sensitivity pattern.

Sample size calculation

Sample size was calculated using nMaster 1.0, Department of Biostatistics, CMC, Vellore, Tamilnadu, India. Vancomycin use in Indian population varies between 3% and 10%. No data were available on the prevalence of use of colistin. Hence, keeping the prevalence of vancomycin use as 10%, with alpha error and precision as 5%, we have enrolled 140 patients per center; collectively 700 patients were enrolled from five centers.

Statistical analysis

Descriptive statistics was used and data were expressed using measures of central tendency. Numerical data were tested for normality using the Kolmogorov–Smirnov test. Unpaired *t*-test, Fisher exact test, and Chi-square test (nonparametric) were used to compare the data between the centers and $P \leq 0.05$ was considered statistically significant. All analyses were done with Statistical Package for the Social Sciences (SPSS) 20, IBM, Armonk, NY, United States of America and GraphPad version 3.06, (GraphPad Software, California, USA).

Results

Demographics

A total of 700 patients were enrolled across the five centers (140 per center). The median age of the patients across the centers was 48 (13, 92), of which 424 (60.57%) were male and 276 (39.43%) were female. Demographic details and study length of individual center are depicted in Table 1.

More number of patients with respiratory disease, central nervous system disease, heart disease, and fever were admitted to Public Hospital 1 and 2. At Public Hospital 3, patients with respiratory disease, postoperative infections, heart disease, and central nervous system disease contributed most of the ICU admissions. Where at Private Hospital 1 and 2, more number of patients with heart disease, respiratory disease, central nervous system disease, and trauma were admitted to ICU.

Indicators

In public hospitals, the average number of drugs and average number of antibacterials prescribed were significantly higher compared to private hospitals; the values are depicted in Table 2.

Percentage of antibacterial agents prescribed at public hospitals was significantly lower than the private hospitals ($P = 0.0381$). The individual values of each participating center are depicted in Table 3. Percentage of patients received antibacterials was significantly different between public and private hospitals ($P = 0.0016$) and between the individual centers ($P = 0.0003$). Private hospitals had significantly lower percentage of antibacterial agents prescribed by generic name ($P < 0.0001$). There was no significant difference in intravenous use ($P = 0.4095$) of antibacterials and the FDCs ($P = 1.0000$). At private hospitals, none of the patients received antibacterial from the hospital pharmacy.

Differences in change of antibacterial agents required were not statistically significantly different ($P = 0.1888$); however, significant difference was observed in percentage of patients who received antibacterial treatment as per sensitivity pattern ($P = 0.0385$) between public and private hospitals. Public hospitals had a longer average length of antibacterial treatment and empirical use of antibacterials as well as longer duration of MICU stay as compared to private hospitals. Antibacterial treatment cost was not significantly different between public and private hospitals; significantly higher mortality was observed in public hospitals compared to private hospitals (<0.0001). Details of the prescribed antibacterials are presented in Figure 1.

Pooled data

Patients in MICU received as many as 10.90 (±6.83) drugs, of which only 1.98 ± 1.36 (16.11%) were antibacterials. Over

Table 1: Study length and demographic details

	Public hospitals			Private hospitals	
	Public hospital 1	Public hospital 2	Public hospital 3	Private hospital 1	Private hospital 2
			Study length		
	3 months, 24 days (May 20, 2014-September 11, 2014)	7 months, 17 days (June 9, 2014-January 22, 2015)	4 months, 27 days (November 18, 2014-April 14, 2015)	7 months, 20 day (November 13, 2014-July 01, 2015)	6 months, 13 days (June 10, 2014-December 20, 2014)
Total number of patients	140	140	140	140	140
Male (%)	74 (52.85)	78 (55.71)	96 (68.57)	85 (60.72)	91 (65)
Female (%)	66 (47.15)	62 (44.28)	44 (31.42)	55 (39.28)	49 (35.00)
Age (years), median (range)	30 (13-86)	32 (13-78)	54 (18-86)	60 (23-91)	55 (19-92)
Number of deaths	45	48	42	7	31

Table 2: World Health Organization indicators (public vs. private hospitals)

Indicator	Statistics	Public hospitals	Private hospitals	*P*
Average number of drugs prescribed per patient	Mean±SD	12.73±8.17	8.77±4.05	<0.0001
	Median (range)	11.00 (2-71)	8.00 (2-27)	
Average number of antibacterial agents prescribed per patient	Mean±SD	2.23±1.62	1.81±0.98	0.0080
	Median (range)	2 (1-18)	2 (1-6)	
Percentage of antibacterial agents prescribed	Percentage	15.52	17.46	0.0381
Percentage of patients who received an antibacterial agent	Percentage	93.33	86.07	0.0016
Percentage of antibacterial agents prescribed by generic name	Percentage	51.82	16.59	<0.0001
Percentage of antibacterial agents prescribed for intravenous use	Percentage	94.07	93.48	0.4095
Percentage of antibacterial agents available in hospital pharmacy	Percentage	86.15	0.00	<0.0001
Percentage of patients in whom a change of antibacterial agent was made	Percentage	33.67	28.63	0.1888
Percentage of antibacterial agents prescribed as fixed dose combination	Percentage	2.98	4.34	0.9079
Average duration of MICU stay (days)	Mean±SD	7.08±8.27	5.30±4.24	0.0020
	Median (range)	5 (1-80)	4 (1-35)	
Average duration of antibacterial treatment (days)	Mean±SD	7.02±8.97	5.33±4.09	0.0063
	Median (range)	4 (1-80)	4 (1-32)	
Average duration of empirical use of antibacterials (days)	Mean±SD	6.47±6.10	5.00±3.55	0.0011
	Median (range)	5 (1-47)	4 (1-28)	
Percentage of patients who received antibacterial treatment as per sensitivity pattern	Percentage	13.26	7.88	0.0385
Average cost of antibacterial treatment per patient	Mean±SD	7792.46±4434.01	7765.205±6830.09	0.9490
Percentage of patients died during MICU stay	Percentage	47.36	15.70	<0.0001

MICU: Medical intensive care unit; SD: Standard deviation

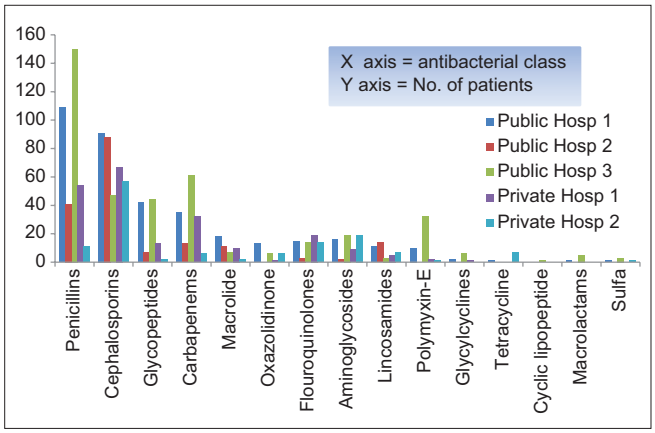

Figure 1: Class-wise distribution of antibacterials

the study period, 92.42% patients received antibacterials of which 41% antibacterials were prescribed by generic name. A total of 93.89% antibacterials were prescribed intravenously. Only 46.01% antibacterials were prescribed from the hospital pharmacy. Change of antibacterial agent was made in 31.75% patients and only 3.54% antibacterials were prescribed as FDCs. The average length of MICU stay was 6.33 days (±7.31), average length of antibacterial treatment was 6.38 days (±7.54), and average duration of empirical treatment was 5.94 days (±5.35). Across the centers, average antibacterial cost per patient was INR 7781.58 (±4636.054). A total of 88 culture tests were positive among 212 patients, from which 71 (80.68%) patients received antibacterials as per sensitivity pattern. Pooled data indicators have been presented below in Table 4.

Discussion

The World Health Organization defines drug utilization as "the marketing, distribution, prescription, and use of drugs in a society with special emphasis on the resulting medical, social, and economic consequences.[10] To the best of our knowledge, this is the first study which has assessed and compared the prescribing pattern of antibacterials between public and private tertiary care hospitals of India. At all five centers, the majority of patients were male was also seen in most reported literature.[15-18] Respiratory disorders are a common problem faced in the ICUs, and at our centers also a large number of patients with respiratory disease were admitted to MICU.[19-23] The mean number of drugs received by patients at public hospitals (12.73 ± 8.17) was comparatively higher than the private hospitals and study conducted at various regions of India.[16,18,24] Extensive polypharmacy (100%), that is, more than five drugs were prescribed at all the centers; since ICU patients require more drugs due to multiple comorbidities and prophylaxis needs. However, it is also essential to keep a balance between the number of drugs and effective pharmacotherapy. Our findings are closely similar with the study conducted by Sireesha *et al*. (100%), Hussain *et al*. (97.27%), and Badar and Navale (83.00%) but lower than with the study conducted by Pandiamunian and Somasundaram (57%).[15,16,18,23] Patients admitted to tertiary referral centers are critically ill and are needs to be treated with antibacterials for prophylactic, suspected or proven bacterial infections; majority of patients of public as well private hospitals had received antibacterials during their ICU stay. Cephalosporin antibacterials were largely prescribed at

Table 3: World Health Organization indicators (individual)

Indicator	Statistics	Public hospitals			Private hospitals		*P*
		Public Hospital 1	Public hospital 2	Public hospital 3	Private hospital 1	Private hospital 2	
Prescribing indicators							
Average number of drugs prescribed per patient	Mean±SD	14.60±9.95	11.17±5.07	11.79±6.96	10.40±4.65	7.90±2.30	<0.0001
	Median (range)	12.00 (2-71)	10.00 (2-32)	10.50 (2-32)	9.00 (2-27)	6.00 (2-14)	
Average number of antibacterial agents prescribed per patient	Mean±SD	2.93±2.12	1.28±0.53	2.32±1.24	2.01±1.10	1.61±0.80	<0.0001
	Median (range)	3 (1-18)	1 (1-3)	2 (1-6)	2 (1-5)	2 (1-3)	
Percentage of antibacterial agents prescribed	Percentage	18.23	11.44	17.62	15.16	21.11	<0.0001
Percentage of patients who received an antibacterial agent	Percentage	90.71	100	89.28	85.71	86.42	0.0003
Percentage of antibacterial agents prescribed by generic name	Percentage	41.92	73.66	59.33	19.25	13.63	<0.0001
Percentage of antibacterial agents prescribed for intravenous use	Percentage	94.33	94.55	93.23	93.13	93.87	0.5259
Percentage of antibacterial agents available in hospital pharmacy	Percentage	68.96	100.00	100.00	0.00	0.00	<0.0001
Percentage of patients in whom a change of antibacterial agent was made	Percentage	48.81	10.00	44.80	30.83	26.44	<0.0001
Percentage of antibacterial agents prescribed as fixed dose combination	Percentage	3.57	0.00	4.16	3.85	4.54	0.9656
Average length of antibacterial treatment (days)	Mean±SD	10.07±14.61	5.33±3.67	5.24±4.69	6.08±4.22	4.58±3.83	<0.0001
	Median (range)	6 (1-80)	4 (1-30)	3 (1-31)	5 (1-31)	4 (1-32)	
Average length of empirical use of antibacterials (days)	Mean±SD	8.42±9.61	4.99±2.80	4.89±4.22	5.54±3.42	4.49±3.42	0.0001
	Median (range)	5 (1-47)	4 (1-18)	5 (1-31)	5 (1-18)	4 (1-28)	
Average antibacterial treatment cost per patient	Mean±SD	7415.54±21738.43	3558.94±8975.24	12402.90±21544.11	12594.81±22154.21	2935.60±3745.01	<0.0001
	Median (range)	10.42-170528.7	19.18-21532.14	80.70-91340.16	23.10-70899.87	16.34-20549.20	
Patient care indicators							
Average length of MICU stay	Mean±SD	10.55±14.69	5.95±3.96	5.05±4.55	6.00±4.582	4.6±3.14	<0.0001
	Median (range)	-	-	-	-	-	
Percentage of patients died during MICU stay	Percentage	32.14	34.28	30.00	5.00	22.15	<0.0001
Supplemental indicators							
Percentage of patients who received antibacterial treatment as per sensitivity pattern	Percentage	11.42	4.28	21.43	12.14	1.43	<0.0001

MICU: Medical intensive care unit; SD: Standard deviation

Table 4: Pooled data indicators

	Mean±SD
A. Prescribing indicators	
Average number of drugs prescribed per patient	10.90±6.83
	Median: 9 (2-71)
Average number of antibacterial agents prescribed per patient	1.98±1.36
	Median: 2 (1-18)
Percentage (%) of antibacterial agents prescribed	16.11
Percentage (%) of patients who received an antibacterial agent	92.42
Percentage (%) of antibacterial agents prescribed by generic name	41.00
Percentage (%) of antibacterial agents prescribed for intravenous use	93.89
Percentage (%) of antibacterial agents available in hospital pharmacy	46.01
Percentage (%) of patients in whom a change of antibacterial agent was made	31.75
Percentage (%) of antibacterial agents prescribed as fixed dose combination	3.54
Average length of antibacterial treatment	6.38±7.54
	Median: 4 (1-80)
Average length of empirical use of antibacterials	5.94±5.35
	Median: 5 (1-47)
Average cost of antibacterial treatment per patient over the study period	INR 7781.58±4636.054
	Median: 756.21 (20-35549)
B. Patient care indicators	
Average length of MICU stay	6.33 days±7.31
	Median: 4 (1-80)
Percentage (%) of mortality during MICU stay	24.42
C. Supplemental indicators	
Percentage (%) of patients who received antibacterial treatment as per sensitivity pattern among the 88 culture-positive cases	80.68

MICU: Medical intensive care unit; SD: Standard deviation; INR: International normalized ratio

each center and these findings are similar to some reported studies.[24-28] Very low proportion of generic prescription at private centers was observed and among our participating centers, therefore, there is need to increase the prescription of antibacterials by generics at every center to reduce the antibacterial treatment cost. Some of the antibacterial cost was taken from MIMS and this is one of the limitations of the present study. The intravenous use of antibacterial was very high among the centers, and at each center, more than 90% of the antibacterials were administered intravenously possibly to reduce the mortality and morbidity in an emergent situation since these all are tertiary referral centers and most of the patients come with a fairly advanced disease requiring emergent action.

An antibacterials need to be prescribed as per the sensitivity pattern; since inappropriate use of antibacterials increases the risk of bacterial resistance.

Conclusions

The number of antibacterials and drugs prescribed at public hospitals are significantly higher than the private hospitals. Generic prescriptions are very low at private hospitals; however, more generic prescriptions are suggested at each public and private hospital. In addition, more number of prescriptions as per the sensitivity pattern is required to reduce prolonged empirical use of antibacterials.

Acknowledgments

The authors would like to thank Dr. Avinash Supe, director (Medical Education & Major Hospitals) and dean of Seth G.S. Medical College & KEM Hospital for granting permission to publish this manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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