Original Article

Utilization of antimicrobial agents in patients on ventilator in medical Intensive Care Unit at a tertiary care teaching hospital: A prospective study

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Abstract

Background: The burden of bacterial infections is huge and grossly underrepresented in the current health-care system. Inappropriate use of antimicrobial agents (AMAs) poses a potential hazard to patients by causing antibiotic resistance. In addition, the field of antimicrobials is witnessing constant development and introduction of new drugs for which holistic utilization, effectiveness, and side-effects studies are the need of the hour. The current study aims at studying the prescription pattern of AMAs in patients on ventilator and focuses on their prescribing trends.

Methodology: A prospective, observational study was conducted in Medical Intensive Care Unit (ICU) of a tertiary care hospital of Western India for 6 months. Prescription pattern of AMAs was analyzed using predesigned format.

Statistical Analysis: Descriptive statistics was used being an observational study

Results: Five-hundred and twenty patients who were on ventilator and were prescribed one or more AMAs were enrolled in the study with a mean patient age of 40.7 years. The intended purpose of the use of AMAs was prophylactic in 59% of patients. Empirical therapy was given in 92% of patients. β-lactams group of AMAs along with metronidazole were most frequently used. 73% required concurrent use of two or more AMAs. 9% of the patients required addition or substitution of one or more other AMAs on the basis of culture and sensitivity report or inadequate clinical response and expert opinion. The outcome of therapy with AMAs showed infection was effectively prevented in 34% of the patients.

Conclusion: This study provides a baseline data for improving the utilization of AMAs in ICU settings by rationalizing their use and also carrying out further studies on prescribing pattern of AMAs in a tertiary care unit.

Keywords: Antibiotic resistance, antimicrobials, Medical Intensive Care Unit, prescription pattern

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INTRODUCTION

To ascertain the role of drugs in the society, drug-utilization studies have been instrumental. They provide a sound sociomedical and health economic basis for health-care decision-making. Irrational use of drugs may lead to increased cost of treatment, antimicrobial resistance, adverse

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effects, and patient mortality.[1] Perhaps, drug-utilization studies have become a necessary tool for the evaluation of health-care systems.[2]

India contributes to the highest bacterial disease burden in the world, and consequently, one of the largest users of antimicrobial agents (AMAs). The use of AMAs has increased by more than 40% from 2005 to 2009, especially the use of cephalosporins and fluoroquinolones.[3] The reasons for this increase are mainly inappropriate use of AMAs which in turn has led to increased resistance with AMAs. Infection with multidrug-resistant pathogens adversely affects the quality of medical care. The Centers for Disease Control and Prevention (CDC) estimates more than 2 million people are infected with antibiotic-resistant organisms, resulting in approximately 23,000 deaths annually. It is a growing problem and developing new AMAs is not the solution for this.[4] Improving the use of AMAs is an important patient safety and public health issue as well as a national priority.[5]

One major area where AMAs can be used profoundly and needs a critical appraisal is in patients on ventilators in the Medical Intensive Care Unit (MICU). The total AMA consumption is approximately ten times higher in ICUs than in general hospital wards.[6] Widespread and excessive use of broad-spectrum AMAs, invasive medical devices, critically ill, and immunocompromized patients in ICU favor the spread of resistant organisms.

Hence, MICU is one of the ideal venues for screening, triage, and assessing morbidity in patients. The generated data and recommendations can be utilized in the future to prepare a local antibiogram that can aid clinicians to obtain the better clinical outcomes in intensive care setup and promote rational use of AMAs.

Objective

The main objective of this study is to evaluate the utilization and outcome of AMAs in patients on ventilator in MICU at tertiary care hospital in Baroda, India.

METHODOLOGY

This prospective, observational study was conducted in MICU of SSG Hospital, Vadodara, after the approval of the Institutional Ethics Committee. The study was conducted over a period of 6 months. A total of 520 patients were enrolled in the study as per the inclusion criteria. Written and verbal informed consent was taken from all the patients.

The inclusion criteria that were followed:

- Patients aged between 18 and 65 years of either gender admitted in the MICU on ventilatory support and receiving one or more AMAs.

The exclusion criteria that were followed:

- Patients aged below 18 years and above 65 years
- Terminally ill cancer patients
- HIV- and HBsAg-positive cases
- Patients who refuse to give the consent.

Following details were recorded from each prescription: (1) patient's demographic details; (2) details about patient's disease; (3) comorbid conditions; and (4) presumed site and nature of infection; (5) duration of stay on the ventilator; (6) intended purpose of AMA therapy, that is, curative or prophylactic; (7) criteria for selection of AMAs – whether empirical or definitive, based on laboratory investigations, and also to assess the pattern of AMA therapy; (8) the class of AMAs, the formulations, the dose, route, frequency, and duration of administration; (9) patients were monitored for the tolerability of AMAs, adverse drug reactions (ADR's), and interactions; (10) any change in AMA use during stay on ventilator and reason for the same, the results of laboratory investigations, their implications on the selection of AMAs, and possible influence on the outcome of patient.

All patients were enrolled in the study in alignment with the inclusion and exclusion criteria to avoid selection bias.

RESULTS

Five-hundred and twenty patients who were on ventilator and were prescribed one or more AMAs were enrolled in the study. Among the 520 patients, 164 (32%) were female and 356 (68%) were male. The mean age was 40.7 years. Majority of the patients were in the age group of 18–25 years (n = 124, 24%). Predominant system affected in patients was the central nervous system (n = 256, 51%) suffering with meningitis, hemorrhage, cerebrovascular accidents (CVA), etc., followed by respiratory tract conditions (n = 66, 13%) affected by pneumonia, pulmonary edema, ARDS, etc. The demographic details and reasons for hospitalization in ICU have been represented in Tables 1 and 2, respectively.

Prescription analysis

The intended purpose of AMAs use was prophylactic in 59% of patients followed by therapeutic in 192 patients. The criteria for initial selection of AMAs have been depicted in Table 3 and Figure 1. In most of the patients (n = 479, 92%), the AMAs were chosen empirically. Only in 16 patients (3%), it was definitive.

Among the AMAs prescribed, β-lactams were most frequently used, which mainly included ceftriaxone (38%), piperacillin + tazobactam (31%), followed by cefotaxime (19%) and co-amoxiclav (6%). Majority of the patients were treated with metronidazole (36%) [Table 4].

Table 1: Demographic details

Parameters	Number only/and Percentage
Number of patients (*n*)	520
Males (%)	356 (68)
Females (%)	164 (32)
Mean age of enrolled patients (years)	40.7
Mean age	
Males (*n*=356) (years)	41.1
Females (*n*=164) (years)	39.2

Table 2: Reasons for hospitalization in Medical Intensive Care Unit

Diagnosis	Number of patients (%)
CVA and encephalopathy*	137 (27)
Organophosphorus and other poisoning	80 (15)
Respiratory tract infections	56 (11)
Liver disease	45 (9)
Diabetic ketoacidosis	33 (6)
Renal dysfunction	57 (11)
CVS (corpulmonale, MI, and cardiac arrest)	16 (3)
Snakebite	42 (8)
Others	54 (10)

*Meningitis, seizures, hemorrhage, stroke, etc. Renal dysfunction: ARF, CKD, nephropathy. Others: Septicemia, anaphylactic shock, PPH, anemia, tetanus, etc., CVA=Cerebrovascular accidents, CVS=Cardiovascular system, MI=Myocardial infarction, ARF=Acute renal failure, CKD=Chronic kidney disease, PPH=Postpartum hemorrhage

Table 3: Criteria for initial antimicrobial agent selection

Criteria	Male (*n*=356), *n* (%)	Female (*n*=164), *n* (%)	Total (*n*=520), *n* (%)
Empirical[$]	331 (93)	148 (90)	479 (92)
Definitive*	10 (3)	6 (4)	16 (3)
Mixed[#]	15 (4)	10 (6)	25 (5)

χ^2=1.183, *P*=0.55 so *P*>0.5 (not significant)

[$]Based on the site and severity of infection, comorbid conditions, and likely pathogen(s), *Based on culture and sensitivity report, [#]Initially treated empirically and also given definitive treatment for the specific infections, based on laboratory data and typical clinical features

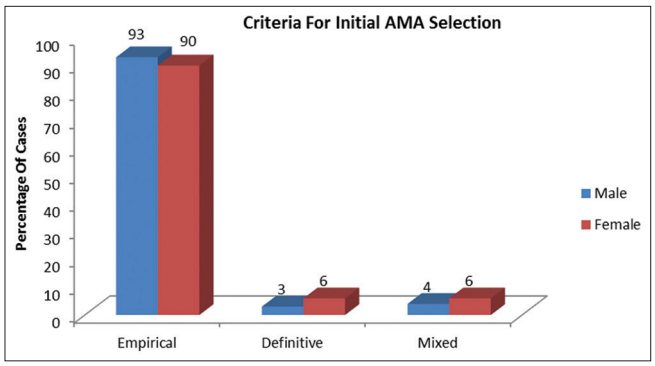

Figure 1: Criteria for initial antimicrobial agent selection in either sex

Monotherapy was prescribed in 144 prescriptions; rest all (73%) required concurrent use of two or more AMAs. The combinations used have been summarized in Table 5.

A total of 513 patients were given antibiotics by intravenous route followed by oral route (9%). Topical antibiotics use includes neosporin powder and ciprofloxacin eye ointment.

Figure 2 shows the duration of stay on mechanical ventilation (MV). Thirty-eight percent of patients (*n* = 196) were on MV support for 2–3 days; and about 20% of the cases for >5 days, most of them were associated with ventilator-associated pneumonia requiring culture and sensitivity report for definitive treatment.

Table 6 summarizes the changes in AMA therapy during their stay on ventilator. In 91% of the patients, the initially chosen AMAs for empirical therapy was continued throughout the course, whereas 9% of the patients required addition or substitution of one or more other AMAs. The change in AMAs use was based on culture and sensitivity report in 1.54% of total cases, and inadequate clinical response and expert opinion in 7% patients. Table 7 shows various ADR's encountered during the study.

The outcome of antimicrobial therapy showed that infection was effectively prevented in 34% of the patients (*n* = 176), 220 patients (42%) died during the AMAs course, because of other complications, whereas 24% of the patients were discharged against medical advice (DAMA) [Table 8].

DISCUSSION

The findings of the drug-utilization study conducted at a tertiary care hospital, Vadodara, provide information about the demographic data, prescribing patterns of AMAs use, reason for their use, criteria for selection, AMA susceptibility/resistance pattern based on clinical response of the patients and culture with sensitivity report, and the treatment outcome of medical intensive care management.

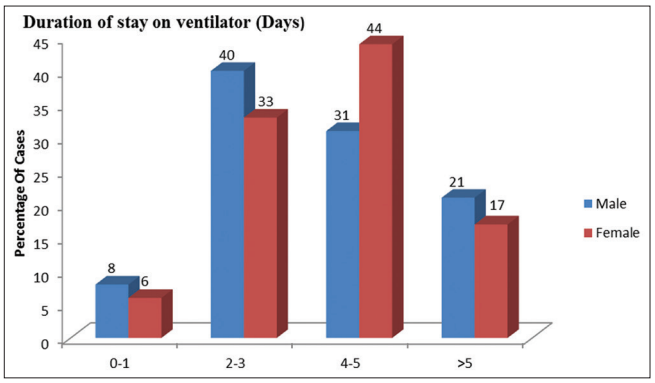

Figure 2: Duration of stay on mechanical ventilation

Table 4: Antimicrobial agents used in patients on ventilator

Generic name and dose*	Male, *n* (%)	Female, *n* (%)	Total, *n* (%)
Beta-lactams			
Piperacillin + tazobactam, 4.5-13.5 g IV	92 (25)	68 (41)	160 (31)
Meropenem, 1-2 g IV	8 (2)	9 (3)	17 (3)
Ceftriaxone, 2 g IV	122 (34)	74 (45)	196 (38)
Cefixime, 400 mg oral	2 (0.5)	3 (2)	5 (0.9)
Cefoperazone + sulbactam, 3-4.5 g IV	10 (3)	6 (4)	16 (3)
Cefotaxime, 2-3 g IV	73 (21)	27 (16)	100 (19)
Amoxicillin + clavulanate, 2.4-3.6 g IV	21 (6)	11 (7)	32 (6)
Sulfonamides			
Co-trimoxazole, 480 mg oral	3 (0.8)	1 (0.6)	4 (0.8)
Macrolides			
Azithromycin, 0.5-1 g oral	5 (1)	2 (1)	7 (1.3)
Glycopeptides			
Vancomycin, 1-2 g IV	40 (11)	24 (15)	64 (12)
Lincosamides			
Clindamycin, 0.6-0.9 g IV	2 (0.5)	7 (4)	9 (1.7)
Anthelmintics			
Albendazole, 400 mg oral	2 (0.5)	5 (3)	7 (1.3)
Nitroimidazoles			
Metronidazole, 1-1.5 g IV	127 (36)	61 (37)	188 (36)
Aminoglycosides			
Neosporin powder	12 (3)	5 (3)	17 (3)
Fluoroquinolones			
Levofloxacin, 0.5-1 g IV	67 (19)	25 (15)	92 (18)
Ciprofloxacin, 1-1.5 g IV	7 (2)	4 (2)	11 (2)
Ciprofloxacin eye ointment	1 (0.3)	0	1 (0.2)
Sparfloxacin eye drops	2 (0.5)	1 (0.6)	3 (0.6)
Antitubercular drugs			
Standard antitubercular drugs#	15 (4)	7 (4)	22 (4)
Antimalarial drugs			
Artesunate, 120 mg IV	10 (3)	9 (5)	19 (3.5)
Antiviral drugs			
Acyclovir, 0.5 mg IV	20 (6)	8 (5)	28 (5)
Miscellaneous			
Rifaximin, 550 mg oral	2 (0.5)	0	2 (0.4)
Linezolid, 0.6-1.2 g IV	5 (1)	2 (1)	7 (1.3)

*Total daily dose; #Rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin

Table 5: Combinations of antimicrobial agents used

Antimicrobial agents	Number of patients prescriptions
Ceftriaxone + metronidazole	32
Cefotaxime + metronidazole	26
Piperacillin + tazobactam + levofloxacin	25
Piperacillin + tazobactam + metronidazole	20
Piperacillin + tazobactam + metronidazole + acyclovir	19
Piperacillin + tazobactam + vancomycin	16
Ceftriaxone + metronidazole + AKT	13
Ceftriaxone + levofloxacin	9
Piperacillin + tazobactam + vancomycin + metronidazole	8

*Co-amoxiclav, piperacillin+tazobactum, and cefoperazone + sulbactam were considered as single drug. AKT=Anti-Koch's therapy

Majority of the patients were male and the age of onset was middle age. A study conducted by Biswal *et al*. in India has reported male predominance, in agreement with our study.[7]

In our study, the most common causes for admission in ICU requiring ventilatory support were CVA and encephalopathies such as seizures, stroke, and meningitis (27%), followed by poisoning (15%) and respiratory tract infections (11%). Organophosphorus (OP) poisoning was the most common poisoning encountered, usually suicidal, requiring ventilatory support. Septicemia was seen in 8% of patients, which was almost similar to other studies. In both studies, septicemia was least encountered indication, while in our study, urinary tract infection was the least common because of prophylactic use of AMAs and aseptic precautions.[6,8]

Ninety-two percent of the AMAs were used empirically based on the site and severity of infection, comorbid conditions, anticipated pathogens, and the prevalent trends rather than using broad spectrum AMAs as the only criteria. Definitive therapy was possible only in 3% of patients based on culture and sensitivity, in accordance to a study where 93% of cases[9] and contrary to study where 64% of cases were treated empirically.[10] Thus, it may be suggested that selection of specific AMAs for definitive therapy may not be possible unless the

Table 6: Change in antimicrobial agent therapy in patients on ventilator[#]

	Males, *n* (%)	Females, *n* (%)	Total, *n* (%)
AMAs			
Change/substituted	33 (9)	12 (7)	45 (9)
No change	323 (91)	152 (93)	475 (91)
χ^2=0.3227, *P*=0.57 so *P*>0.05 (not significant)			
Antimicrobial agents added/substituted			
Piperacillin + tazobactam	7 (2)	2 (1.2)	9 (1.7)
Meropenem	2 (0.6)	2 (1.2)	4 (0.8)
Linezolid	3 (0.8)	1 (0.6)	4 (0.8)
AKT	7 (2)	2 (1.2)	9 (1.7)
Acyclovir	3 (0.8)	0	3 (0.6)
Cefoperazone + sulbactam	2 (0.6)	1 (0.6)	3 (0.6)
Levofloxacin	5 (1.4)	2 (1.2)	7 (1.3)
Metronidazole	4 (1.1)	2 (1.2)	6 (1.2)
χ^2=2.610, *P*=0.92 so *P*>0.5 (not significant)			

[#]Either substituted or added with one or more AMAs. AMAs=Antimicrobial agents, AKT=Anti Koch's therapy

Table 7: Adverse drug reactions encountered during antimicrobial agent therapy

Drug	ADR	Number of patients
Piperacillin + tazobactam	Thrombophlebitis	10
Ceftriaxone	Thrombophlebitis and hypersensitivity	6
Amoxicillin + clavulanate	Thrombophlebitis	3
Levofloxacin	Diarrhea	5
Metronidazole	Severe allergic reaction	7
Vancomycin	Rash	2

ADR=Adverse drug reaction

Table 8: Age group and outcome of antimicrobial agents therapy

Age group (years)	Improved, *n* (%)	Died, *n* (%)	DAMA, *n* (%)	Total, *n* (%)
18-25	56 (45)	50 (40)	18 (15)	124 (100)
26-35	40 (44)	38 (41)	14 (15)	92 (100)
36-45	34 (36)	40 (41)	22 (23)	96 (100)
46-55	30 (27)	54 (48)	28 (25)	112 (100)
56-65	16 (17)	38 (39)	42 (44)	96 (100)
Total	176 (34)	220 (42)	124 (24)	520 (100)
χ^2=41.987, *P*<0.0001 (highly significant)				

DAMA=Discharge against medical advice

causative pathogen is isolated. Moreover, antibiogram for MICU of this institution was not available at time of conduct of this study.

In the present study, the AMAs used were mainly ceftriaxone followed by β-lactam antibiotics, mainly piperacillin + tazobactam and metronidazole either as a monotherapy or combination therapy. These were preferred because of their wider antimicrobial spectrum covering most of the common pathogens. Metronidazole was commonly used as adjuvant for effective coverage on anaerobic organisms in 36% of cases, as also reported in other studies.[11,12] Carbapenems were used in 3% of patients as reserve drugs. Apart from this, specific chemotherapy was required in few patients like ceftriaxone was being prescribed for hepatic encephalopathy, altered sensorium, tubercular meningitis; levofloxacin for lower respiratory tract infection; piperacillin + tazobactam or cefotaxime for OP poisoning; amoxicillin + clavulanate for cases of snake bite; piperacillin + tazobactam for PPH and CKD; and vancomycin in stroke.

The prescribing frequency of AMA combinations in our study was very high (73%) when compared to multicentric study.[13] Piperacillin or ceftriaxone-based combinations were prescribed most frequently, often with metronidazole. Levofloxacin was added in case of Gram-negative infections and to increase the synergistic prolongation of the postantibiotic effect of β-lactams. Most of the combinations can be considered as rational.

However, the combined use of ceftriaxone with piperacillin and piperacillin with carbapenems in few patients and other combinations such as piperacillin with linezolid and carbapenems with linezolid may not be considered rational as there is no documented advantage. No difference exists in clinical outcomes between the two treatment strategies (combination AMA therapy and monotherapy) for definitive management of infections with Gram-negative bacteria, but there are well-documented increased toxicities with combination therapy. This suggests that patients with infections with Gram-negative bacteria are served best by receiving definitive treatment with a single appropriate AMA.[14]

The initial empirical AMAs were continued in 91% of patients, while in 9% of cases, AMAs were either added or substituted, based on laboratory report or inadequate clinical response or both. This data are not similar to other studies which demonstrated that in 37.6% of cases, AMAs had to be changed or added based on culture and sensitivity report.[9] This can be attributed to various factors:

- Delay in sending culture and sensitivity report
- Delay in receiving culture and sensitivity report
- Limitation of effective system of reporting
- Lack of antibiograms for the disease
- Relying upon empirical therapy largely
- Poor monitoring of AMA therapy.

The AMAs were used within the recommended range of therapeutic dose and further adjusted depending on the site and severity of infection.[15] The duration of AMAs administration for most of the patients was <1 week, with an average of 4.12 days/patient. This strategy may help in reducing the rate of nosocomial infections, as longer duration of AMAs therapy predisposes the patient to

infection with resistant bacteria.[16] Very few patients were administered AMAs for >5 days, particularly those who responded inadequately to initial empirical therapy. Similar observations have been recorded in other studies.[11,12] The AMAs used were well-tolerated with few ADR's which were not serious. There were no drug interactions observed.

Infections were effectively prevented or controlled in 34% of the patients who showed a favorable outcome with AMAs. The effectiveness of AMA therapy could not be assessed in 24% patients who got discharged against medical advice. The overall mortality rate was 42%, which was 23% more when compared to a study by Vincent *et al*., in which it was only 19%.[17] This can be explained due to underlying disease states, comorbid conditions or complications, multiorgan failure, and probably contributed by uncontrolled infection like septicemia.

Higher mortality was found in cases of hepatic encephalopathy, tubercular meningitis, OP poisoning, and snake bite. Forty-five percent patients had one or more comorbid conditions requiring drug therapy. Diabetes mellitus and hypertension were the most common comorbid conditions requiring intensive care monitoring, followed by chronic obstructive pulmonary disease and neurological disorders. All these conditions could influence the choice and dose of AMAs, prolong ventilatory support, or increase the risk of nosocomial infections, thereby mortality. Similar comorbidities were also noted in the study conducted by Vincent *et al*.[17] Remaining 55% of patients, requiring intensive care monitoring were of OP poisoning, snake bite, malaria, tetanus, etc. Higher DAMA cases in this study can be attributed to debilitating conditions not responding to treatment; dissatisfaction with treatment and care provided by physicians and other medical staff; and poor environmental conditions of tertiary care hospitals of India. DAMA cases increase the economic burden on health-care system due to increase disease relapse ultimately leading to readmission.

Limitations

Our study was a preliminary study to understand the pattern of AMAs used in an ICU setting, hence we did not touch upon severity of the patients at the time of hospitalization in terms of advanced ICU outcome methods and cost of AMA therapy. Further extensive multicentric studies involving patients of all age groups can be useful to formulate appropriate cost-effective strategies, local antibiogram of ICU, and guidelines for effective infection control.

CONCLUSION

The pattern of use of AMAs in patients on ventilator in MICU was found to be primarily based on extended-spectrum penicillins and third-generation cephalosporins. The initial choice of AMAs was empirical but modified depending on the clinical response or laboratory reports. AMAs were used for medical/surgical prophylaxis and for treatment of bacteriologically proven infections.

Increased use of AMAs is at an alarming rate due to irrational prescribing habits of clinicians. This has made India a pill-popping country, resulting in increased mortality and morbidity along with increased economic burden. Policy-makers and health-care professionals need to understand the urgency of restricting their use and form stringent rules for using AMAs. This study can act as a torchbearer emphasizing the need of local antibiograms and implementing antibiotic stewardship program in hospitals, thereby optimizing clinical outcome in patients on ventilator. This will help to rationalize their use to combat AMA resistance.

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Conflicts of interest

There are no conflicts of interest.

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