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A Study on Prescribing Pattern, Indications and Rationality of Restricted Antibiotic Use in a Tertiary Care Hospital

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Abstract

Background: Antibiotic stewardship aims to optimise restricted antibiotic use and thereby prevent the emergence of antibiotic resistance and improve treatment outcome. Resistance to conventional antimicrobial's is a major reason why restricted antibiotics are prescribed. ***Aim:*** To assess the prescribing pattern of restricted antibiotics, the indications for which restricted antibiotics were prescribed, the drug related problems associated and the sensitivity pattern of the isolated organisms. ***Results:*** Out of 340 patients included in the study, majority of patients was in the age group of 58-67(60.06 ±14.90) in both genders. There was a male (64.12%) dominance observed in the study populace and the minimum and maximum age observed was 18 and 93 years respectively. Most commonly prescribed antibiotic was Piperacillin tazobactum (31%) followed by Linezolid (16.06%). Empirically the most prescribed antibiotic was Piperacillin tazobactum (27.37%) while in definitive therapy it was Cefepime tazobactum (10.63%). The most common indication for which restricted antibiotics prescribed were for respiratory tract infection (n=116), followed by infection prophylaxis (n=114). Mean days of restricted antibiotic therapy was found to be 8.85 days ± 8.11. The maximum duration of antibiotic treatment was 62 days and minimum was 1 day. In 47% of cases IV to oral conversion was possible. When analysed retrospectively, in majority of the patients the duration of restricted antibiotic treatment was inappropriate (69.71%) while the inappropriateness in frequency and dose were 7.05% and 3.23% respectively. The total number of cultures collected were 292 in that 120 cultures were urine and found growth in 50.83%, followed by 84 cultures in sputum which accounted for 67.85% growth. The most common organism isolated was Klebsiella pneumoniae 39.73% cases followed by Pseudomonas aeruginosa 17.46% and Acinetobacter baumannii15.41. There was clinical cure in 91.47% of cases. ***Conclusion:*** When analysed retrospectively majority of the restricted antibiotics showed inappropriateness. This higher amount of inappropriateness could have been avoided to a certain extent, by the timely interventions of a clinical pharmacist. By implementing an effective antimicrobial stewardship program we could improve the rational use of restricted antibiotics and thereby prevent the future resistance and improve clinical outcome.
Keywords: Rational use; Restricted Antibiotics; Antimicrobial resistance; Appropriateness; Antibiogram; ADRs.

1. INTRODUCTION

Antibiotics are often defined as low molecular weight microbial metabolites that, at low concentrations inhibit the growth of other microorganisms (Lancini G *et al.*, 2013). The use of antibiotics made it possible for treating infections as well as many modern medical procedures like open heart surgery, organ transplant and cancer treatment (Hutchings MI *et al.*, 2019). The most common indications where antibiotics are prescribed includes Urinary Tract Infection (UTI), Lower Respiratory Tract Infection (LRTI), Tuberculosis (TB), meningitis, acute gastroenteritis etc. The bactericidal or bacteriostatic actions of antibiotics prove them effective in the treatment of infectious diseases (Gould K, 2016).

Resistance to antimicrobials stands as a major threat to public health. It often results in retardation of the onset of right antimicrobial therapy and further complicates the situation by leaving us very few choices, like the use of higher end antibiotics like colistin (Mobarki N *et al.*, 2019). This further increases the economic burden on the patient by increasing the length of hospital stay, adversely affects the quality of life of the patient and increases mortality (WHO, 2021).

Some of the reasons why antimicrobial resistance occurs are due to overuse and misuse of antibiotics. Some of the serious conditions like pneumonia, TB, gonorrhoea, food borne diseases becoming difficult to treat due to emergence of resistance .The patients who suffer with antibiotic resistant infections may experience ineffective therapy, delayed recovery and death may also follow. This threat to humanity is increasing day by day due to emergence of new strains of bacteria along with very few antibiotics being developed to treat the resistant strains (Yimenu DK *et al*., 2019).

Antibiotic stewardship programmes were implemented to tackle the issue of antimicrobial resistance. It aims to optimise antibiotic use and thereby prevent the emergence of antibiotic resistance and improve treatment outcome. Antibiotic resistance to an extent can be prevented by using antibiotics only when prescribed, never share or use leftover antibiotics, prevent infections by regularly washing hands, preparing food hygienically, avoiding close contact with sick people and taking vaccinations up to date (WHO, 2021). Irrational prescribing along with misuse, lead to antibiotic resistance towards the commonly encountered organisms which are otherwise very easily treatable with commonly used antibiotics (Mekonnen Sisay *et al*., 2017). Prevention of antibiotic resistance can be attained to some extend through rational drug use. However, irrational use of antibiotics is increasing day by day and it has significant adverse effects on health care costs, quality of pharmaceutical care and emergence of resistance (Nikhila Adla *et al*., 2018). Better clinical outcome and prevention of antibiotic resistance can be attained through the rational use of antibiotics (Abubakar Siddique *et al*., 2020). The primary aim of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms and the emergence of resistance (Timothy H Dellit *et al*., 2007). The need of the hour is to preserve the restricted antibiotics for serious infections and thereby save the mankind from fatal conditions where no drug proves useful. Thus, it is important to monitor and decrease the number of prescriptions with restricted antibiotics.

Sensitivity analysis is a test that determines the "sensitivity" of the bacteria to an antibiotic. It also determines the ability of the drug to kill the bacteria. It is often used to find the right antibiotic for an infection and to monitor changes in bacterial resistance to antibiotics which are crucial in treatment. In most cases many bacteria are resistant to common antibiotics this means that the antibiotic will no longer be effective in killing the organism. Sensitivity analysis is a useful tool that helps in quickly identifying if the bacteria are resistant to certain drugs. It can be ordered if the infection does not respond to the given treatment. The main aim of antimicrobial stewardship program is to improve patient outcomes, to reduce health care expenditures and limiting the unintended consequences of drug resistance and superinfections (Laura M King, 2013). A good antimicrobial stewardship involves selecting an appropriate drug and optimizing its dose and duration to cure an infection while minimising toxicity and conditions for selection of resistant bacterial strains. Preventing the overuse, misuse and abuse is another objective of the program. Execution of antimicrobial stewardship program through surveillance, performing basic research and developing newer generation antimicrobial agents can to a certain extend prevent and control the antimicrobial resistance by decreasing the disease burden related to drug resistant microorganisms.

2. METHODOLOGY

2.1. Study Design

A Retrospective cross-sectional single centre study was done for a period of 6 months (November 2020 to May 2021), by taking details of patients from the medical records available in the hospital for a period of five years (01-06-2015 to 31- 05-2020).

2.2 Inclusion Criteria

In patients who were prescribed with restricted antibiotics (Cefepime, Cefipime+Tazobactum, Colistin, Linezolid, Piperacillin+Tazobacum, Tigecycline, Sulbactum and Vancomycin or their combinations)

In Patients ≥ 18years of age.

2.3 Exclusion Criteria

Patients whose medical records are incomplete

Patient's who got discharged against medical advice.

2.4 Sample size

The sample size was calculated by the formula

$n = Z^2 P(1-P) / d^2$

Where n is the sample size, Z is the statistic corresponding to level of confidence, P is expected prevalence 31.7% (Kadir Alam *et al*., 2013), d is the allowable error = 5%. The sample size calculated was 333. A total of 340 cases were collected during the study period.

2.5 Data Collection

The data were collected using specially designed data collection form. Retrospective patient demographic details, pertinent laboratory as well as treatment details were extracted from medical records.

2.6. Data collection tools- Specially designed data collection form

2.7 Data collection methods

Data was collected with the help of mediware software which was available in the hospital. It was done by selecting the patients who were prescribed with restricted antibiotics for a period of five years (01-06-2015 to 31-05-2020). The restricted antibiotics selected were Cefepime, Cefipime+Tazobactum, Colistin, Linezolid, Piperacillin+Tazobacum, Tigecycline, Sulbactum and Vancomycin or their combinations as per the hospital antibiotic policy. The selected cases were then analysed by obtaining those files from medical records department and subsequently entered into data collection forms. The data entered were subsequently entered into Microsoft excel and further analysis was done.

2.8 Statistical Analysis

The collected data were compiled using Microsoft Excel and were presented using tables. The data were tabulated, analysed and compared with relevant studies using IBM SPSS Statistics software version 20. Descriptive statistics, including percentage, mean and standard deviation were calculated for all variables. Proportions were compared using correlation and P-value less than 0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

A total of 340 cases were collected during the study period. There was a male (64.12%) dominance observed in the study populace. The minimum age observed was 18 years and maximum age observed was 93 years. The Mean age ± SD was found to be 60.06±14.90.

The prescribing pattern of restricted antibiotics

Antibiotics most commonly prescribed were Piperacillin tazobactum (137; 31%) followed by Linezolid (71; 16.06%). Empirically the most prescribed antibiotic was Piperacillin tazobactum (121; 27.37%) while in definitive therapy it was Cefepime tazobactum (47; 10.63%). 61.99% (274/442) of the restricted antibiotics were prescribed empirically during a 3017 days of treatment (DOT). Michael Samarkos *et al*., (Michael Samarkos *et al*., 2021) found out that 172 (67.2%) were empirical prescriptions of restricted antibiotics and accounted for a total of 1316 days of treatment (DOT) which is closely similar to our study.

In 248 cases restricted antibiotics were prescribed empirically, in that 233 cases it was given parenterally and 30 cases restricted antibiotics was initiated orally. Tashi Tobgay *et al*., found out that a total of 51.1% prescriptions were prescribed antibiotics on the first day of their visit and only 2.7% of the prescriptions were prescribed after a culture sensitivity test (Tashi Tobgay *et al*., 2010). Similarly in our study (248) 65.60% were given as empirical therapy and (130) 34.39% was given as definitive therapy after a culture report. Ambili Remesh *et al*., found out that most commonly used dosage form for antibiotics were injections 89 (60%) and our study showed similar results in which restricted antibiotics were given parenterally 356 (89.67%) (Ambili Remesh *et al*., 2013).

Days of restricted antibiotic therapy the Mean ± SD was found to be 8.85 days ± 8.11. The maximum duration of antibiotic treatment was 62 days and minimum was 1 day. Helma R et al. found the Average duration of prescribed antimicrobial treatment to be 5.57 ± 2.42 days while our study showed a slightly greater duration of antimicrobial treatment of 8.85 ± 8.11 days (Rejoice Abimiku Helma *et al*., 2020).

Zeina M Shrayteh *et al*., found out that it was possible to convert one thirds of the prescribed intravenous therapy to oral therapy (Zeina M Shrayteh *et al*., 2014),while in our study around half (47%) of the intravenous prescriptions were converted to oral therapy whenever possible.

In 83.6 % cases 1-5 number of antibiotics were prescribed during hospital stay. While in 14.7 % of cases 6-10 number of antibiotics were prescribed also in 1.8% cases 11-15 number of antibiotics were prescribed. Most of the cases DOT were between 1-25 days ie, 62.35%. The Average duration of restricted antibiotic therapy after discharge was found to be 6.6 days.

Table 1: Indications for restricted antibiotics prescription

Indications	Number of patients (n=340)	Percentage
RTI	116	29.29
UTI	21	5.30
Skin and soft tissue	37	9.34
Infection prophylaxis	114	28.78
Sepsis	54	13.63
Meningitis	20	5.05
Others	34	8.58

Ambili ramesh *et al*., found out that the commonest indication that led to antibiotics prescription was respiratory tract infections (30%) which is similar to our findings RTI (29.29%) (Ambili Remesh *et al*., 2013). The respiratory tract infections were further sub classified into pneumonia (35.6%), LRTI (22.72%), URTI (2.27%), COPD (12.12%), respiratory failure (7.57%), bronchiectasis (3.78%), cough (6.81%) and others (9.09%). Rune Aabenhus *et al.*, found that acute respiratory tract infections accounted for 456 in 532 antibiotic prescriptions (Rune Aabenhus *et al*., 2017). Pneumonia was the most common indication with 178,354 prescriptions (39%), followed by acute tonsillitis and acute otitis media which was similar to our study where pneumonia accounted for 35.6% of patients followed by LRTI 22.72%.

Appropriateness of antimicrobial therapy

Table 2: Appropriateness of restricted antibiotic therapy

Appropriateness	Yes	No
Right antimicrobial	339	1
Right Dose	329	11
Right frequency	316	24
Right duration	103	237

In 329 cases the dose was appropriate in 11 cases dose was inappropriate as listed in Table 2, 3.23% of the restricted antibiotic dose was inappropriate among this colistin (0.9%) and sulbactum (0.9%) was predominantly inappropriate. Patricia Tarcea Bizo *et al*., found out that 49.82 % the dose was incorrect from 664 prescriptions (Patricia Tarcea Bizo *et al*., 2015), while our study found a 3.23% inappropriateness in dose from 340 prescriptions analysed. Right frequency was observed in 316 cases. In 7.05% cases frequency was inappropriate in that sulbactum (40%) and colistin (36%) was predominantly inappropriate.

In 103 cases the antibiotics were given in the Right duration and the inappropriate cases accounted for 237 cases., Sanjeev Singh *et al*., found out that wrong duration was the most common reason for inappropriateness and found to be 29% (806 cases) (Sanjeev Singh *et al*., 2019) . Our study had 69.70 % (237 cases) of inappropriateness in duration and in that Piperacillin tazobactum (32.20%) and colistin (18.30%) were mostly predominant. Tashi Tobgay *et al*., did a study and in that, 47.1% of the prescriptions had appropriate indication, 12.9% marginally appropriate, and 40.0% inappropriate (Tashi Tobgay *et al*., 2010). Their study showed 55.9% of the prescriptions had inappropriate higher generation antibiotics prescribed, while in our study 71% of the restricted antibiotics were prescribed inappropriately.

Antimicrobial susceptibility

Number of culture specimens collected per patient were as follows:

At least 1 culture was taken in (98 cases) 62.42% of cases and upto 10 cultures were taken in (1 case) 0.63% cases. There is a significant association between number of cultures and length of hospital stay with a p <0.001.

In our study mostly collected specimen was urine 120 cultures in that 50.83% had growth, followed by sputum 84 cultures in that 67.85% had growth and blood in 84 cultures in that 36.88% had cultures. Michael Samarkos *et al*., did a study (Samarkos M, 2021), and blood cultures were obtained for 97.5%, urine cultures for 61.3% while other types of cultures (pus, sputum, etc.) were obtained for less than 5% of prescriptions. The most common organism causing infections was Klebsiella pneumoniae 39.73% cases followed by Pseudomonas aeruginosa 17.46%, Acinetobacter baumannii 15.41%, E coli 7.19%, Staphylococcus aureus 5.82%. Patricia Tarcea Bizo *et al*., found out that the most common bacteria responsible for infections was Staphylococcus aureus, found in 26.4% cases (Patricia Tarcea Bizo *et al*., 2015).

Antibiogram

Organisms with 10-30 isolates have been included for antibiogram. Only antimicrobials that are routinely tested are included. Both percentage susceptibility and intermediate susceptibility are included.

Table 3: Susceptiblity pattern of gram negative organisms

Gram negative		K.pneumoniae	Pseudomonas aeruginosa	Acinetobacter baumanii	E. coli
Total number of isolates		116	51	45	21
Penicillins	Ampicillin	0	0	0	12.5
	Amoxiclav	7.07	0	25	60
	Piperacillin tazobactum	8.92	53.65	11.11	57.89
Aminoglycoside	Amikacin	47.78	48	100	95
	Gentamycin	24.34	50.90	37.77	55
Cephalosporins	Ceftazidime	0	47.05	0	-
	Cefepime	5.71	54.16	9.75	50
	Cefotaxime	4.62	0	0	15
	Ceftriaxone	5.26	20	6.89	14.28
	Cefuroxime	3.63	0	-	5.26
	Cefoxitin	100	-	-	-

	Cefoperazone sulbactum	10.52	50	53.33	59.09
Carbapenem	Imipenem	36.36	34.88	9.30	83.33
	Meropenem	18.51	43.18	13.04	88.88
	Ertapenem	41.66	-	-	100
	Doripenem	-	60	-	-
Fluroquinolones	Levofloxacin	0	73.91	57.14	-
	Clindamycin	50	-	-	-
Others	Linezolid	100	-	-	-
	Teicoplanin	100	-	-	-
	Vancomycin	100	-	-	-
	Cotrimoxazole	22.12	7.69	55.55	42.10
	Nitrofurantoin	2.38	0	0	100
	Colistin	88.88	100	100	100
	Tigecycline	86.56	0%	100	87.5

Table 4: Susceptibility pattern of gram positive organisms

Gram positive		**Staphylococcus aureus**
Penicillins	No of isolates	17
	Penicillin	6.25
	Ampicillin	9.09
	Cloxacillin	35.29
	Amoxiclav	37.5
Macrolide	Erythromycin	30.76
Others	Clindamycin	64.7
	Minocycline	100
	Linezolid	100
	Rifampicin	100
	Tigecycline	100
	TMP/SMX	53.33
	Vancomycin	100
	Teicoplanin	100
	Nitrofurantoin	100
	Imipenem	25
	Meropenem	25
Aminoglycoside	Gentamycin	35.29
	Amikacin	100
Cephalosporins	Cefazolin	35.29
	Cefuroxime	35.29
	Cefoxitin	80
	Cefotaxime	40
	Ceftriaxone	55.55
	Ceftazidime	25

Treatment outcome

There was clinical cure in 91.47 % of cases and 29 cases were with clinical failure, 1 case therapy failed yet the patient was stable, in all the other 28 cases the patients expired. There are more cases of failure found between age group 71-90 (19.7%). Among the 18-30 age group there is 100% in clinical cure therefore there is a significant association between age and clinical cure/failure with a $p < 0.001$.

4. CONCLUSION

In this study most commonly prescribed antibiotic was Piperacillin followed by Linezolid and the most common indication for which restricted antibiotics were prescribed was for respiratory tract infection, followed by infection prophylaxis .When analysed retrospectively 71 % of the restricted antibiotics showed inappropriateness. This may be due to the fact that most restricted antibiotics prescribed empirically were converted to definitive therapy. Antibiogram was prepared for most commonly isolated organisms like E.coli, K. Pneumoniae, P. Aeruginosa, A.baumannii, S.aureus and most of the organisms were sensitive to colistin. All restricted antibiotic prescriptions should be reassessed by a clinical pharmacist for appropriateness before administration. By implementing an effective antimicrobial stewardship program we could improve the rational use of restricted antibiotics and thereby prevent the future resistance and improve clinical outcome.

Declaration of Interest: The authors report no conflicts of interest.

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