THE ECONOMIC BURDEN OF ANTIBIOTIC RESISTANCE BASED ON ANTI-MICROBIAL SUSCEPTIBILITY TESTS IN VARIOUS INFECTIONS IN A TERTIARY CARE HOSPITAL: A PROSPECTIVE STUDY

ABSTRACT

Introduction: Antibiotics are anti-microbial agents used for the treatment of various bacterial infections. Excessive use, inappropriate prescription pattern conduct to antibiotic resistance (AR). Antibiotic resistance leads to an increase in the cost of medical care. Our study assess the economic burden due to antibiotic resistance based on antimicrobial susceptibility testing in different infections.

Methods: The data for the study was collected prospectively and recorded in a data collection form specially designed for the study based on inclusion and exclusion criteria obtained from the Department of General Medicine, NIMS Hospital, Neyyattinkara, Thiruvananthapuram of patients with infectious diseases during the period of 6 months from April 2021 to September 2021.

Results: 128 patients were studied, 53.1% (n=68) were males and 46.9% (n=60) were females and the most frequent age range was between 46-60 years of age (35%, n=45).The most common infection seen in patients was urinary tract infection (20.3%, n=26). The socioeconomic status, (50%, n=64) belonged to lower- middle class. Antibiotic sensitivity test was done in (52.3%, n=67) and the patients with resistance (Rs.26530.81) had more mean cost than those without resistance (Rs.18412.01) showing highly significant difference (p=0.001). The resistant patients without antibiotic sensitivity testing had (Rs.30193.14).

Conclusion: Our study demonstrated that the resistant patients without antibiotic sensitivity testing had a significantly higher financial burden. Therefore, we strongly recommend to perform antibiotic sensitivity testing (AST) in patients with infectious diseases. Also, patient should be well-informed about the details and the results of antibiotic sensitivity testing to ensure medication adherence and to avoid self- medication.

Key words: Antibiotics, resistance, antibiotic sensitivity testing, economic burden

1.INTRODUCTION

The term antibiotic was derived from the word “antibiosis” meaning “against life” [1]. The introduction of antibiotics in the clinical field was one of the successful breakthroughs in the history of medicines. After discovering penicillin by Sir Alexander Fleming (a physician and microbiologist) in 1928, antibiotics have transformed into the era of modern medicine [2].

Antibiotic resistance is one of the major limitations of antibiotic use. Antimicrobial resistance occurs when bacteria change their response to the use of these medicines. The factors which lead to antibiotic resistance are antibiotic overuse, irrational prescribing of antibiotics and use of antibiotics in agricultural industry[2].

One of the major consequences of antibiotic resistance is the increase in cost for treatment (when first-line antibiotics are not effective, then, more expensive medicines are used). These increased costs are mainly due to prolonged length of hospital stay [3], increases in number of tests needed and increased medical and rehabilitation services provided. It also has an impact on morbidity and mortality, including significant increases in disease complications, increases side effects from the use of multiple and more powerful antibiotics[3].

The fundamental goal of the cost of illness study is to evaluate the economic burden that illness imposes on society as a whole [4]. It combines the cost of healthcare services (direct costs), the value of the patient's reduced or lost productivity (indirect costs), and the cost of pain and suffering (intangible costs)[4]. Hospitalization, medicine, emergency transport, and medical care are all direct costs in the health sector[4]. In addition, non-refunded payments for hospitalization, medical visits, and drugs; transportation of patient and family for health visits; transportation of family to visit the hospitalized patient; modifications at home as a result of illness; and costs for taking care of the patient at home are all costs directly related to the treatment of illness [5].Sickness, untimely mortality, side effects of illness or therapy, or time spent seeking treatment can all cause decreased or lost productivity.

Culture sensitivity test, also called susceptibility test, and helps to find out the most effective antibiotic to kill an infecting microorganism and to confirm whether the empirical antimicrobial agent is susceptible[6]. If antibiotics are prescribed based on culture sensitivity reports, economic burden can be reduced to an extent[6]. This is because effective antibiotics can be givenearly and shifting to costly antibiotics can be avoided[6]. All these reduce length of hospital staythus minimizing the cost of illness[6].

Biomarkers are biological characteristics that are objectively measured and used as an indicator of a physiological or pathological pathway or a pharmacologic response to therapeutic interventions and they assist physicians in triaging, diagnosing, stratifying risk, and monitoring clinical course and antibiotic response [6]. The most often investigated and used biomarkers are C-reactive protein (CRP) and pro-calcitonin (PCT). In comparison to normal care, PCT-guided antibiotic therapy reduces the number of antibiotic prescriptions without affecting the clinical success or increasing mortality.

Antibiotic resistance is a naturally occurring mechanism that can be slowed but not totally eliminated because resistance is an unavoidable result of medication selection pressure [7] and it can be prevented to a certain extent by practicing certain measures: using antibiotics only when prescribed by the physician, maintain hygienic environment by washing hands, discourage the use of leftover antibiotics, prescribe antibiotics after doing culture sensitivity test, strengthening policies and programs, prescribing antibiotic only when needed, giving antibiotics to animals only under veterinary supervision[8 and 9].

2. METHODS

Our study was carried out in 128 inpatients in the General medicine department of NIMS Medicity, Neyyattinkara, a tertiary care hospital in Trivandrum, Kerala. Data were obtained in a systematic manner utilizing a data collection form.

The data collection form includes details on patient's demographics, reason for admission, education, occupation, income, laboratory parameters Hb, PCV, RBC, WBC, Platelet, Neutrophils, Lymphocytes, Eosinophils, Basophils, Monocytes, ESR, CRP, MCV, MCH, MCHC, urine analysis, sensitivity test, expenses related to medical condition and other expenses.The data was collected from the patient’s files of inpatients with infection and were prescribed at least one antibiotic throughout their stay of more than three days.Information regarding the study (patient demographics, education, occupation, monthly income, transportation cost, cost of meals, loss of income due to hospitalization) was collected by interviewing the patients, and patient caregivers.

The Modified Kuppuswamy Socio-economic scale[27] was used to assess socioeconomic status. Cost of illness was calculated by interviewing the patients on direct medical and non-medical costs, including the cost of drugs, cost of laboratory test, cost of transportation, cost of rent, cost of food, and indirect non-medical costs like patient and bystander loss of wages. . The total mean value cost comparison is done with a *t-statistics*. After the collection of data, it was recorded and analyzed using an MS Excel spreadsheet and SPSS version 13.

This study is approved by the ethics committee of NIMS Medicity, Neyyattinkara and was certified by the Institutional Ethics Committee met and approved the proposal [ECR/218/Inst/Ker/2013/RR-16].

3. RESULTS

Table 1: Frequency and percentage distribution according to age.

AGE IN YEARS	FREQUENCY (n)	PERCENTAGE (%)
18-30	13	10
31-45	15	12
46-60	45	35
61-75	39	30
>75	16	13

Among 128 patients, age was categorized into five groups: 18-30 (10%, n=13), 31-45 (12%, n=15), 46-60 (35%, n=45), 61-75 (30%, n=39) and >75 (13%, n=16). The most frequent age range was between 46-60 years of age (35%, n=45). The mean age of patients involved in infection was 52 years.

Table 2: Frequency and percentage distribution according to gender.

GENDER	FREQUENCY (n)	PERCENTAGE (%)
Male	68	53.1
Female	60	46.9
Total	128	100.0

Out of 128 patients, 53.1% (n=68) were males and 46.9% (n=60) were females. Men were found to have a higher rate of infections than women.

Table 3: Frequency and percentage distribution according to Socio-economic status.

SOCIO-ECONOMIC STATUS	FREQUENCY (n)	PERCENTAGE (%)
Upper	3	2.3
Upper middle	29	22.7
Lower middle	64	50
Upper lower	24	18
Lower	8	6

Out of 128 patients, 2.3% (n=3), 22.7% (n=29), 50% (n=64), 18.8% (n=24) and 6.3% (n=8) were upper, upper middle lower middle, upper lower and lower middle respectively. The most of the patients presented with infection were from lower middle class (50%, n=64), followed by upper middle class (22.7%, n=29).

Table 4: Frequency and percentage distribution according to empirical therapy resistance.

EMPIRICAL THERAPY RESISTANCE	FREQUENCY (n)	PERCENTAGE (%)
Yes	53	41.4%
No	75	58.6%

Out of 128 samples, 41.4% (n=53) patients had empirical therapy resistance, while 58.6% (n=75) patients did not.

Table 5: Frequency and percentage distribution based on antibiotic sensitivity test conducted.

AST CONDUCTED	FREQUENCY (n)	PERCENTAGE (%)
Yes	67	52.3
No	61	47.7
Total	128	100.0

Among 128 patients, antibiotic sensitivity test (AST) was conducted in 52.3% (n=67) and was not conducted in 47.7% (n=61).

Table 6. Distribution of direct cost against empirical therapy resistance.

EMPIRICAL THERAPY RESISTANCE	FREQUENCY (n)	MEAN OF DIRECT COST	STANDARD DEVIATION	STANDARD DEVIATION ERROR MEAN	t/F	P VALUE
YES	53	17349.68	10162.33	1395.90	3.602	0.001
NO	75	10827.49	9984.70	1152.93		

The mean value of total cost for patients with resistance is Rs.17349.68 and the mean value of total cost for those without resistance is Rs.10827.49. The total mean value cost comparison is done with a t-statistics and it is found that the mean value difference according to empirical therapy resistance is statistically significant. t/F value =3.602 and significant value p=0.001.

The patients with resistance have more direct cost than those without resistance and this difference is highly significant. This financial burden faced by the empirical therapy resistance patient was due to the shifting of antibiotics from low cost to high cost or use multiple antibiotics for the same infection [10].

Table 7 Distribution of indirect cost against empirical therapy resistance.

EMPIRICAL THERAPY RESISTANCE	FREQUENCY (n)	MEAN OF INDIRECT COST	STANDARD DEVIATION	STANDARD DEVIATION ERROR MEAN	t/F	P VALUE
YES	53	9184.53	5223.25	717.47	1.79	0.077
NO	75	7632.44	4231.81	488.65		

The mean value of total cost for patients with resistance is Rs.9184.53 and the mean value of total cost for those without resistance is Rs.7632.44. The total mean value cost comparison is done with a t-statistics and it is found that the mean value difference according to empirical therapy resistance is statistically significant. t/F value =1.79 and significant value p=0.077.

The patients with resistance has more indirect cost than those without resistance and this difference is highly significant. The patient who is resistant to treatment may have to stay in the hospital or be sick for a longer period of time [11 and 12]. As a result, the number of productive days is reduced. This will have an impact on their pay. The age group impacted by resistance in our study was 46-60 years old and male. Furthermore, the majority of these patients were from the lower middle class. Normally, these people rely on their daily salaries to keep their families

operating smoothly. They are facing a financial burden of indirect costs as a result of the loss of their primary source of income.

Table 8. Distribution of total cost against empirical therapy resistance.

EMPIRICAL THERAPY RESISTANCE	FREQUENCY (n)	MEAN OF TOTAL COST	STANDARD DEVIATION	STANDARD DEVIATION ERROR MEAN	t/F	P VALUE
No	75	18412.01	12443.386	1436.838	3.468	0.001
Yes	53	26530.81	13859.107	1903.695		

The total cost for patients without resistance is Rs.18412.01 and the total cost for those with resistance is Rs.26530.81. The total cost comparison is done with a t-statistics and it is found that the mean value difference according to empirical therapy resistance is statistically significant. t/F value =3.46 and significant value p=0.001.

The patients with resistance has more mean cost than those without resistance and this mean difference is highly significant.

Table 9. Distribution of hospital stay against cost.

HOSPITAL STAYS	TOTAL COST				
	Frequency (n)	Mean	SD	t/F	P-value
3-6 days	46	11078.35	5252.088	42.03	0.001
7-10 days	55	23488.13	11459.117		
11-14 days	15	32431.60	9924.438		
>15 days	12	41592.42	13283.479		
HOSPITAL STAYS	**DIRECT COST**				
	Frequency (n)	Mean	SD	t/F	P-value
3-6 days	46	5974.39	4416.108	30.46	0.001
7-10 days	55	14809.07	9578.358		
11-14 days	15	20293.73	7788.747		
>15 days	12	28155.67	11355.174		
HOSPITAL STAYS	**INDIRECT COST**				
	Frequency (n)	Mean	SD	t/F	P-value
3-6 days	46	5186.00	1696.182	22.43	0.001
7-10 days	55	8679.05	4292.395		
11-14 days	15	12137.87	4776.998		
>15 days	12	13436.75	5903.540		

The total cost were Rs.11078.35(n=46), Rs.23488.13 (n=55), Rs.32431.60(n=15), Rs.41592.42 (n=12) for patients with 3-6, 7-10,11-14 and more than 15 days of hospital stay. The direct cost were Rs.5974.39(n=46), Rs.14809.07 (n=55), Rs.20293.73(n=15), Rs.28155.67 (n=12) for patients with 3-6, 7-10, 11-14 and more than 15 days of hospital stay. The indirect cost were Rs.5186.00 (n=46), Rs.8679.05(n=55), Rs.12137.87(n=15) and Rs.13436.75(n=12) for patients with 3-6, 7-10, 11-14 and more than 15 days of hospital stay respectively. The relationship between hospital stay and cost is highly significant.

A similar result was found in the study conducted by *Mauldin,etal*[17] where increased hospital stay attributed to an increased hospital cost (23%, P=0.0003). Similarly, a research by *Zhen et al*[25] found that increased overall costs ($77 billion) were associated with an increase in length of stay (95 percent, n=15105) owing to antibiotic resistance.

Patients who were in the hospital for a longer period of time had a higher mean total cost. This is because the cost of therapy, medicine, administration fees, laboratory costs, room rent, and other expenses rise when patients are admitted to the hospital for extended periods of time[4,5 and 13].

Table 10. Distribution of test done and empirical therapy resistance against direct cost.

TEST DONE	EMPIRICAL RESISTANCE	FREQUENCY (n)	DIRECT COST			t/F	P VALUE
			Mean	Standard Deviation	Standard Error		
Yes	Yes	17	12239.82	9346.34	2266.82	0.545	0.590
	No	50	10774.30	10213.04	1444.31		
No	Yes	36	19762.67	9738.049	1623.01	3.49	0.001
	No	25	10933.88	9716.72	1943.34		

The direct cost for patients with test done and resistance developed is Rs.12239.82 and the cost for patients with resistance but had not subjected to antibiotic sensitivity test is Rs.19762.67. It is found that the mean value difference according to empirical therapy resistance and test done against direct cost is statistically significant. For patients with test done and resistance developed, t/f value=0.545 and p value =0.590.And for resistant patients without test done, t/f value=3.49 and significant p value=0.001.

The resistant patients without antibiotic sensitivity testing have a significantly higher direct cost. In most patients, clinical evidence of increased CRP and ESR is taken into account rather

than antibiotic sensitivity test during antibiotic treatment [15, 16 and 17]. The physician may alter antibiotics based on clinical judgment if the patient's condition does not improve significantly. As a result, the cost of therapy, laboratory fees and drugs will rise and thus the direct cost also increased. Therefore we recommend antibiotic susceptibility testing prior to antibiotic therapy.

Table 11. Distribution of test done and empirical therapy resistance against indirect cost.

TEST DONE	EMPIRICAL RESISTANCE	FREQUENCY(n)	INDIRECT COST			t/F	P VALUE
			Mean	Standard Deviation	Standard Error		
Yes	Yes	17	6546.06	5287.62	1282.44	0.726	0.475
	No	50	7575.96	4287.51	606.35		
No	Yes	36	10430.47	4772.26	795.38	2.320	0.024
	No	25	7745.40	4203.06	840.61		

The indirect cost for patients with test done and resistance developed is Rs.6546.06 and the cost for patients with resistance but had not subjected to antibiotic sensitivity test is Rs.10430.47. It is found that the difference according to empirical therapy resistance and test done against indirect cost is statistically significant. For patients with test done and resistance developed, t/f value=0.726 and p value =0.475.And for resistant patients without test done, t/f value=2.320and significant p value=0.024.

The resistant patients without antibiotic sensitivity testing have a significantly higher indirect cost. There was a significant association between total cost and resistance to empirical therapy [18 and 19]. This might be due to a longer hospital stay, higher therapy cost before and after switching over of antibiotics, higher medication cost, transportation cost, laboratory fees and administration fees [20, 23 and 26].

Table 12. Distribution of test done and empirical therapy resistance against total cost.

TEST DONE	EMPIRICAL RESISTANCE	FREQUENCY (n)	TOTAL COST			t/F	VALUE
			Mean	Standard Deviation	Standard Error		
Yes	Yes	17	18775.29	13464.11	3265.53	0.114	0.910
	No	50	18350.26	12519.64	1770.55		
No	Yes	36	30193.14	12628.77	2104.79	3.560	0.001
	No	25	18535.52	12545.09	2509.02		

The cost for patients with test done and resistance developed is Rs.18775.29 and the cost for patients with resistance but had not subjected to antibiotic sensitivity test is Rs.30193.14. The total cost comparison is done with a t-statistics and it is found that the mean value difference according to empirical therapy resistance and test done is statistically significant. For patients with test done and resistance developed, t/f value=0.114 and p value =0.910.And for resistant patients without test done, t/f value=3.560 and significant p value=0.001.

The resistant patients without antibiotic sensitivity testing have a significantly higher mean total cost. An antibiotic sensitivity test is used to determine which antibiotic will be most successful against the bacteria or fungus infecting a given person[21 and 22].A "susceptible" result means that the patient's organism should react to treatment with that antibiotic at the usual dosage for that kind of infection and species. In contrast, an organism that is considered as "resistant" means that the organism in patient should not react to treatment with the antibiotic[24]. This is an essential component of antibiotic therapy since it can minimize the expense and toxicity of antibiotics while also preventing the spread of antimicrobial resistance in the population[6].

4. CONCLUSION

Antibiotics were undoubtedly the biggest medical breakthrough of the twentieth century, with their development and introduction into clinical usage. Despite their importance in preventing and treating infectious diseases, antibiotic misuse and overuse have led in an alarming rise in antibiotic resistance around the world[2,3]. The study demonstrated that the resistant patients without antibiotic sensitivity testing had a significantly higher mean total cost. We strongly recommend the need to perform antibiotic sensitivity test in patients with various infectious disease and to inform the patients about the importance of antibiotic sensitivity testing, including its indications and patient management.

CONSENT

Informed consent of the participants was collected.

ETHICAL APPROVAL

The study was approved by the ethics committee of NIMS Medicity, Neyyattinkara and was certified by the Institutional ethics committee met and approved the proposal.

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