

## APPROPRIATE EMPIRICAL MANAGEMENT OF MICROBIAL INFECTIONS IN A TERTIARY CARE HOSPITAL: A COST- EFFECTIVENESS APPROACH

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### ABSTRACT

**Objective:** Antibiotics are mostly prescribed empirically to decrease health-care costs. This has led to the misuse of antibiotics thereby making them inefficient in the treatment of infections. The aim of this study was to determine the appropriate, cost-effective drug for the empirical therapy in microbial infections.

**Methods:** A prospective observational study was conducted for a period of 6 months. Cost-effectiveness ratio (CER) of these antibiotics prescribed was calculated to determine the cost-effective drugs for the common microorganisms and common infections.

**Results:** In a population of 205 patients, 54.6% were treated based on antibiotic sensitivity pattern whereas 45.3% were treated empirically. In known microbial infections, the prevailing microorganism was extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* (14.3%), *Staphylococcus aureus* (10.6%), *Pseudomonas aeruginosa* (9.8%), *Klebsiella pneumoniae* (9.8%), and *K. pneumoniae* ESBL (6.81%). Based on the CER, the most cost-effective drugs for these organisms were found to be ciprofloxacin, clindamycin, ofloxacin, levofloxacin, and amikacin, respectively. In unknown microbial infection (empirical treatment), Diabetic Foot Infection (DFT) (25.8%), respiratory tract infection (RTI) (23.6%), and urinary tract infection (UTI) (16.1%) were the most common infections. The most cost-effective drugs for these infections were clindamycin, levofloxacin, and azithromycin, respectively. The predominant microorganism in DFT was found to be *S. aureus* (71%), in UTI was found to be *E. coli* ESBL (52%), and in RTI were found to be *P. aeruginosa* (42.4%) and *K. pneumoniae* (32.3%).

**Conclusion:** Appropriate empirical antibiotic treatment is associated with a lower medical cost and a better success rate in patients with microbial infections.

**Keywords:** Antibiotics, Cost-effectiveness analysis, Empirical therapy, Infection, Microorganisms, Sensitivity pattern.

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### INTRODUCTION

Infection is the invasion and multiplication of disease-causing microbes into a human's body tissue and the reaction of the host tissue to these microbes and the toxins they produce. Infection is a common occurrence that has required patients to seek medical care and for antibiotics to be prescribed [1]. Antibiotics have made a significant contribution to improving the health of patients with microbial infections [2]. The unnecessary prescribing of antibiotics have led to increased cost of care by increasing resistance, drug cost, and cost for laboratory test [3]. Hence, while prescribing the antibiotic, important considerations like the accurate diagnosis of infection, understanding the difference between empirical and definitive therapy, cost-effective oral agents for the shortest duration should be included.

Antibiotic resistance is a major worldwide problem, and its implication on public health is becoming overwhelming [4-6]. Culture test helps to identify the causative organism and the effective drugs against these organisms can be determined by susceptibility tests. Cost is one among the various factors to be considered [7]. Hence, the antibiotics are mostly prescribed empirically to decrease the health-care cost.

A vast majority of infections are treated empirically, therefore, the choice of an antimicrobial agent should be adjusted by local sensitivity pattern as the rising prevalence of multidrug-resistant infections cause more complexity in the empirical treatment of these infections. Awareness of local antimicrobial resistance trends among microbial isolates is important for the appropriate use of antibiotics and for the evidence-based recommendations in the empirical antibiotic treatment of infections [8]. Therefore, pharmaco-economic decision analysis is

a way to convey the relative value of beneficial treatments, and the choice must be directed to obtain maximum benefit to the society. The alternative with the lowest cost to effectiveness ratio (CER) is preferred for the microbial infections. This study determines the appropriate, cost-effective antibiotics for the empirical therapy for the infections based on the sensitivity pattern of prevailing microorganisms. There is need to improve our antibiotic prescribing practices and to strengthen research to identify cost-effective strategies for controlling resistance. This could ameliorate the care of the individual patient tremendously [9].

### METHODS

A prospective observational study was conducted over a period of 6 months from March 2016 to August 2016 in a multispecialty tertiary care hospital in Coimbatore, India. The study was approved to be conducted in PSG Institute of Medical Science and Research by the Institutional Human Ethics Committee (IHEC) (ref no: 16/092 dated on 14/03/2016). Patients receiving only one antibiotic who were treated either empirically or with culture sensitivity tests were included in the study. During this period 205 patients were enrolled in the study based on inclusion and exclusion criteria. Non-hospitalized, patients with incomplete and insufficient data/record and who received antibiotic as prophylaxis were excluded in the study. Data were collected using data collection form from the sources; laboratory tests and patient case file. The patients enrolled in the study were reviewed for 2 weeks. The total cost of each antibiotic was calculated based on the unit cost of drug, frequency and the number of days of administration.

Total cost=Unit cost×frequency×number of days.

Study subjects were grouped based on the culture test; known microorganisms (sensitivity pattern therapy group) and unknown microorganisms (empirical therapy group). The cost-effectiveness analysis by CER was performed for common antibiotics used in both groups.

$$\text{CER} = \frac{\text{Total cost of antibiotic (INR)}}{\text{Outcome (success rate \%)}}$$

The outcome was calculated as the percentage of successful treatments. CER was calculated for antibiotics prescribed in both the groups. From this analysis, the drug with the least CER was the most cost-effective drug of choice.

## RESULTS

During the study period, 205 subjects met the criteria. Out of these 205 patients, 66.83% were male patients, and 33.17% were female patients. 40% of these patients were hospitalized for 6–10 days.

The study population was divided into two groups based on the culture test: Culture test with known microorganisms (sensitivity pattern therapy group) and culture test with the unknown microorganism (empirical therapy group). Table 1 summarizes the antibiotics mostly prescribed for the common microorganisms and infections.

Cost-effectiveness analysis of antibiotics for most commonly known organisms and unknown microorganisms were done, and a decision tree was prepared based on CER. In *Escherichia coli* extended-spectrum beta-lactamase (ESBL) infection, the most common cost-effective drug was found to be amikacin (CER=29.03) followed by ceftriaxone (CER=44.92) as shown in Table 2.

Likewise, the cost-effectiveness analysis was performed for the other known microorganism as reported in Table 3.

Similarly, a cost-effectiveness analysis was performed for microbial infection with unknown microorganism and reported in Table 4.

The predominant microorganism in diabetic foot infection (DFT) was found to be *Staphylococcus aureus* (71%), *E. coli* ESBL (52%) in urinary tract infection (UTI) then *Pseudomonas aeruginosa* (42.4%),

and *Klebsiella pneumonia* (32.3%) in respiratory tract infection (RTI).

Comparison of antibiotics of preference suggested in both known and unknown microbial infections showed that clindamycin was the best drug of choice for DFI and infections caused by *S. aureus*. It is also evident from the study that levofloxacin is the best drug of choice for RTI and infections caused by *K. pneumonia*, which is one of the common causative organisms for RTI. *P. aeruginosa* was also a predominant isolate in RTI, and the best drug of choice was ciprofloxacin. In UTI, the most common causative agent was *E. coli* ESBL, and nitrofurantoin was found to be the best alternative Table 5 represents the above data.

## DISCUSSION

In this study, demographic characteristics of the participants involved in the study were categorized based on gender and age distribution. A study conducted by Thomas *et al.* in South India indicated the majority of the patients were male 68.5%, the age distribution of these patients was between 41 and 60 years (43.6%). Their study also showed that cephalosporins (73.0%) are the most prescribed class of antibiotics followed by fluoroquinolones (53.9%) which are in accordance with our study [10]. As per the study conducted by Dominick *et al.*, it was reported that amikacin, piperacillin+tazobactam, cefepime, and nitrofurantoin were the most preferred drug in *E. coli* and *K. pneumonia* ESBL infection to avoid resistance to beta-lactams (meropenem and imipenem) which were expensive and could be used for more severe infections instead [11]. As stated by Rayner and Munchhof in their study conducted in Poland, penicillinase-resistant penicillins (flucloxacillin and dicloxacillin) were the best drugs in the treatment of severe infections of *methicillin-sensitive S. aureus* and acute infections, the first generation cephalosporins, and clindamycin could be used [4].

A study conducted by Suleiman *et al.* revealed Ciprofloxacin to be the most cost-effective treatment for sensitive isolates of *P. aeruginosa* when compared to ceftazidime and gentamicin. In resistant isolates, amikacin was dominantly more cost-effective when compared to meropenem and imipenem [6]. As per Canadian study conducted by Chow *et al.*, showed clindamycin dominated other drugs such as cephalixin, cloxacillin, levofloxacin, and amoxicillin+clavulanate with the lowest CER in the treatment of DFT [12]. Radji *et al.* conducted a study in Indonesia found that the most common infecting microorganisms on pus culture to be

**Table 1: Antibiotics mostly prescribed for the common microorganisms and infections**

Groups	Organisms/infections (%)	Antibiotics prescribed (%)
Sensitivity pattern therapy group (known microorganisms)	<i>E. coli</i> ESBL (14.39)	Amikacin (22) Ceftriaxone (17) Cefoperazone+sulbactam (17)
	<i>S. aureus</i> (10.6)	Amoxicillin+clavulanate (59) Piperacillin+tazobactam (24) Clindamycin (19)
	<i>P. aeruginosa</i> (9.84)	Piperacillin+tazobactam (36) Clindamycin (23) Ofloxacin (23)
	<i>K. pneumoniae</i> (9.84)	Levofloxacin (31) Ceftriaxone (31) Piperacillin-tazobactam (23)
	<i>K. pneumoniae</i> ESBL (6.81)	Piperacillin+tazobactam (36) Meropenem (22) Amikacin (21)
Empirical therapy group (infections)	DFI (25.80)	Amoxicillin+clavulanate (44.18) Clindamycin (25.58)
	RTI (23.65)	Ceftriaxone (41.17) Azithromycin (17.64) Levofloxacin (14.75)
	UTI (16.12)	Cefoperazone+sulbactam (21.05) Piperacillin+tazobactam (20.1)

*E. coli*: *Escherichia coli*, ESBL: Extended-spectrum beta-lactamase, *S. aureus*: *Staphylococcus aureus*, *P. aeruginosa*: *Pseudomonas aeruginosa*, *K. pneumoniae*: *Klebsiella pneumoniae*, DFI: Diabetic foot infection, RTI: Respiratory tract infection, UTI: Urinary tract infection

Table 2: CEA of Antibiotics in *E. coli* ESBL infection

Antibiotic	Total cost (INR)	Mean cost per patient (INR)	Success (%)	CER
Amikacin	2257.95	250.88	77.7	29.03
Ceftriaxone	3850.80	550.11	85.7	44.92
Cefoperazone+sulbactam	41445.62	5920.8	100	414.45

CER: Cost-effectiveness ratio

Table 3: Choice of antibiotic in common organisms based on CER

Microorganism	Antibiotic of first preference	CER	Antibiotic of 2 <sup>nd</sup> preference	CER
<i>E. coli</i> ESBL	Amikacin	29.03	Ceftriaxone	44.92
<i>Pseudomonas aeruginosa</i>	Ofloxacin	24.4	Clindamycin	90.9
<i>Klebsiella pneumoniae</i>	Levofloxacin	3.19	Ceftriaxone	33.15
<i>Klebsiella pneumoniae</i> ESBL	Amikacin	16.09	Amoxicillin+clavulanate	38.7
<i>Staphylococcus aureus</i>	Clindamycin	145.6	Amoxicillin+clavulanate	286

*E. coli*: *Escherichia coli*, ESBL: Extended-spectrum beta-lactamase, *S. aureus*: *Staphylococcus aureus*, *P. aeruginosa*: *Pseudomonas aeruginosa*, *K. pneumoniae*: *Klebsiella pneumoniae*, CER: Cost-effectiveness ratio

Table 4: Choice of antibiotics in common infections based on CER

Microbial infection	Antibiotic of first preference	CER	Antibiotic of second preference	CER
UTI	Azithromycin	3.15	Nitrofurantoin	4.71
DTI	Clindamycin	208.25	Cefoperazone+sulbactam	315.77
RTI	Levofloxacin	3.47	Cefpodoxime	6.15

CER: Cost-effectiveness ratio, DFI: Diabetic foot infection, RTI: Respiratory tract infection, UTI: Urinary tract infection

Table 5: Comparison of antibiotics of preferences for both groups

Infection	Organism	Drug of choice
DTI	<i>Staphylococcus aureus</i>	Clindamycin
RTI	<i>Klebsiella pneumoniae</i>	Levofloxacin
	<i>Pseudomonas aeruginosa</i>	Ciprofloxacin
UTI	<i>E. coli</i> ESBL	Nitrofurantoin

DFI: Diabetic foot infection, RTI: Respiratory tract infection, UTI: Urinary tract infection, *E. coli*: *Escherichia coli*, ESBL: Extended-spectrum beta-lactamase, *S. aureus*: *Staphylococcus aureus*, *P. aeruginosa*: *Pseudomonas aeruginosa*, *K. pneumoniae*: *Klebsiella pneumoniae*

*Staphylococcus* spp. 47.5%, *Pseudomonas* spp. 16.9%, and *E. coli* 10.2%, *Streptococcus* spp. 8.5%. Overall, 37.2% of DFI was caused by a single organism, and 62.8% had polymicrobial infections [13]. Commonly administered antibiotics were ceftriaxone 40.0%, ciprofloxacin 11.4%, and meropenem 8.6%. The empiric antibiotic regimen of clindamycin and ciprofloxacin covered 85% of *S. aureus* and 78% of Gram-negative species of DFI in a study conducted by de Vries *et al.* in Netherlands [14].

An Egyptian study by Harwan *et al.* reported that respiratory fluoroquinolone such as Levofloxacin should be regarded as a first line antimicrobials in admitted and outpatients due to their association with increased clinical response, faster resolutions, greater improvement of signs and symptoms and shorter hospital length of stay [15]. According to a study conducted in Nigeria by Egbe *et al.*, *Klebsiella pneumoniae* was reported to be the predominant isolate fluoroquinolones, beta-lactams, and Gentamicin showed moderate to high activity [16]. Varotto, Maria found the four most frequent isolates in RTI to be *P. aeruginosa* 24%, *Streptococcus pyogenes* 18%, *Staphylococcus* spp. 17%, and *Klebsiella* spp. 8%.

IDSA guidelines state that the first line treatment for UTI is nitrofurantoin and fluoroquinolones. Dudas *et al.* reported that 80% of UTI was caused by *E. coli* in Northern California. Most patients were treated empirically using beta-lactams, nitrofurantoin, fosfomycin tromethamine, fluoroquinolones, and trimethoprim eradicate Gram-negative flora, hence, provide best long-term cures [17]. In the USA, Bouza *et al.* found *E. coli* to be the main etiological agent of UTI [18].

A study in Turkey on the evaluation of empirical treatment by Yüksel *et al.* reported that the most common causative agent was *E. coli* 87%, *Klebsiella* 10%. Nitrofurantoin was the most active agent against *E. coli* followed by amikacin and ceftriaxone [19].

This study had some limitations. First, it was conducted for a short period (6 months), therefore, the sensitivity pattern could not be thoroughly assessed. Second, the cost focused on only antibiotics; other medical expenses were not included. Finally, the data were analyzed from one of the tertiary care hospitals in Southern India.

## CONCLUSION

Appropriate empirical antibiotic treatment is associated with a lower medical cost and a better success rate in patients with microbial infections. Efforts to improve the appropriateness of empirical antibiotic treatment should be dictated by the benefit inherent inappropriate treatment. The choice of antimicrobial agent should be adjusted by local sensitivity pattern as there might be geographic differences in sensitivity patterns. In addition, prudent use of available antibiotic drugs, improved methods of prediction, and rapid detection of resistance is clearly needed.

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