Impact of Culture Sensitivity Reports on the Pattern of Antibiotics use and Cost of Therapy: A Prospective Observational study

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Abstract

Background: There are concerns with inappropriate prescribing of antibiotics in hospitals especially broad spectrum in Pakistan and the subsequent impact on antimicrobial resistance rates. One recognized way to reduce inappropriate prescribing is for empirical therapy to be adjusted according to the result of culture sensitivity reports.

Objective: To find the impact of culture sensitivity reports on the use of antibiotics and cost in a leading tertiary care hospital in Lahore.

Methods: This prospective observational study was carried out in Ghurki trust teaching hospital. A total of 465 positive culture patients were taken over an 8 month study period using convenient sampling techniques and immediately sent to the microbiology laboratory for pathogen identification and susceptibility testing using the Kirby-Bauer disc diffusion method. Additional data was collected from the patient medical file which included demographic data, sample type, causative microbe, anti-microbial treatment given in empirical and definitive treatment as well as medicine costs.

Results: Total of 497 isolates were detected from the 465 patient samples, which included 309 gram-negative rods and 188 gram-positive cocci. Out of 497 isolates, the most common Gram-positive pathogen isolated was *MSSA* (28.4%) and Gram-negative was *E. coli* (23.8%). Most of the gram-negative isolates were found to be resistant to ampicillin and co-amoxiclav. Most of the *A. baumannii* isolates were resistant to carbapenems. Gram-positive microorganism showed the maximum sensitivity to linezolid and vancomycin. The most widely used antibiotics in empirical therapy were cefoperazone+sulbactam, ceftriaxone, amikacin, vancomycin and metronidazole whereas high use of linezolid, clindamycin, meropenem and piperacillin + tazobactam was evidenced in definitive treatment. Empiric therapy was adjusted in 222 (71.8%) cases of Gram-negative infections and 131 (69.6%) cases of gram-positive infections (p-value <0.0001). Compared with empirical therapy, there was a 13.8% reduction in the number of antibiotics in definitive treatment. The average costs of antibiotics in definitive treatment was less than the empirical treatment (8.2%) and the length of hospitalization also decreased.

Conclusion: Culture sensitivity reports helped reduce antibiotic utilization, hospital stay and costs as well as helping select the most appropriate treatment. We also found an urgent need for implementing antimicrobial stewardship programs and the development of hospital antibiotic guidelines within the hospital to reduce future unnecessary prescribing of broad-spectrum antibiotics.

1. Introduction

The emergence of antimicrobial resistance (AMR) is a worldwide problem impacting on morbidity, mortality and costs [1–6]. Irrational use of broad-spectrum antibiotics is the most common cause of AMR [7–9]. Every year in the US, more than two million people get bacterial infections, which are mostly resistant to antibiotics that were previously considered effective for the types of bacterial infections [1], and currently approximately twenty-three thousand people die in a year in the US due to AMR [1]. There are similar figures in Europe [10]. The improved prescribing of antibiotics improves therapeutic outcomes with the minimum emergence of AMR [11–14]. However, it is well known that most of the restricted group of broad spectrum antibiotics are prescribed without proper indication potentially increasing AMR rates [15, 16]. Effective antimicrobial therapy depends on the early identification of causative microbes through culture sensitivity testing and the appropriate selection of antibiotics according to the results [11, 17, 18]. However, due to the threat of multidrug resistant hospital-acquired infections and for the coverage of multiple microbes, typically broad-spectrum are started as an empirical therapy [11, 19–21]. In order though to reduce unnecessary use of antibiotics and

treatment costs, as well as to avoid rising AMR rates, empirical therapy should subsequently be adjusted according to the result of culture sensitivity reports [11, 22–26].

Typically though, the results of blood cultures are often ignored because the patients show a therapeutic response to empiric therapy; however, this is not always the case [20, 21, 25]. Against this, antimicrobial stewardship programmes (ASPs) have been developed in hospitals to improve future antibiotic utilization and reduce subsequent AMR rates [16, 27–29]. As part of these activities, ASPs generally encourage the de-escalation of therapy to improve the use of antibiotics [30, 31]. However to date, there is limited information regarding the extent to which culture sensitivity reports help physicians in the selection of the most appropriate antibiotic treatment especially in lower and middle income countries (LMICs) where resources are more limited [21, 32]. In one study in India, it was concluded that result of blood culture reports had a limited effect on the narrowing of antibiotics and the underutilization of culture sensitivity reports was observed in a study in England [20, 21] as well as Ghana where patients in the public system had to pay for sensitivity testing [33]. Choudhary et al also found that a change of therapy was only undertaken in 20.9% of positive culture patients. We are aware that there can be challenges with ordering culture reports among hospitals in LMICs with high rates of empiric prescribing [34–38]. However, we are aware that the results of culture reports can help reduce the number of antibiotics prescribed, with Berild et al demonstrating a 22% reduction consumption of antibiotics with definitive treatment [25]. To the best of our knowledge though, no such study has been conducted in Pakistan to review the impact of culture sensitivity testing on antimicrobial use. This is important as there are appreciable concerns with AMR in Pakistan driven by excessive use, leading to the recent publication of a national action plan and other suggestion to address the over use of antibiotics [39–43]. Consequently, we aimed to address this by ascertaining the resistance patterns of bacterial isolates and the subsequent impact of culture sensitivity tests on the subsequent use of antibiotics as well as the cost of therapy in a leading tertiary-care hospital in Pakistan. This builds on similar activities in other LMICs [44]. We believe the findings can guide subsequent utilization of antibiotics in this leading tertiary hospital in Pakistan and wider.

2. Methods

2. 1. Study design and study setting

This prospective observational study was conducted in Ghurki Trust Teaching Hospital (GTTH) between May 2018 and Dec 2018. The hospital is a charitable organization in Lahore, Pakistan, with a capacity of 600 beds. The hospital provides health care services from primary to tertiary health care. This hospital has all departments with a particular specialty in orthopedic medicine where the hospital has been awarded with the name of Center of excellence in Pakistan for arthroplasty and spinal surgery by Pakistan Orthopedic Association (POA), and POA fellows are being trained regularly in the hospital.

2.2. Study tool

A standardized paper data collection form was used to collect all information. The data collection form consisted of three main parts. The first part contained patient demographic data i.e. the patient's age, gender, the total length of hospitalization, ward, past surgical history and the treatment based on any biomarker data. The second part consisted of the type of the sample, causative agent, identification and the sensitivity pattern of antibiotics. The last part consisted of the brand name, generic name, route, frequency, duration, indication, treatment type and cost of the antibiotics used in empirical and in definitive therapy [25, 45].

2.3. Inclusion and exclusion criteria

Patients with positive culture reports during the study duration were included in this study. The patients with a negative culture report and ambulatory care patients were excluded from our study because we were principally concerned with in-patient care in this study. Patients who died prior to the index of culture report or discharged earlier prior to the availability of culture reports were also be excluded. Finally, patients with medication records that had irrelevant or incomplete information were also excluded from the study.

2.4. Data collection

A sample was taken from the patient infectious site for pathogen identification and antibiotic sensitivity testing. The samples were immediately transferred to the microbiological laboratory and subjected to bacteriological examination. Mostly the Blood agar and MacConkey agar were used for the identification of microorganisms. The antibiotic susceptibility pattern of all the bacterial pathogens was determined by Kirby-Bauer Disc Diffusion Technique according CLSI guidelines [46]. The interpretation of the test was performed according to CLSI guidelines as sensitive and resistant. In case of positive culture reports, patients were observed for their whole length of hospital stay (from the day of positive culture report to the last day of their treatment) to determine the consumption of antibiotics, length of hospital stay, and cost of antibiotics. Susceptibility patterns of microbes were noted in order to observe the pattern of culture guided definitive therapy.

2.5. Data Analysis

For Antibiotic consumption, data were analyzed by using the ATC/DDD methodology established by the WHO [47]. The ATC/DDD system is a tool for measurement of drug utilization and used for comparison purposes at regional, national and international levels [48, 49]. In the ATC classification system, medicines are classified into different groups based on the organ system upon which they act, as well as their chemical, pharmacological and therapeutic characteristics. Define Daily Dose (DDD) is a unit of measurement and it is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults. Only medicines with an ATC code can have DDD values. DDD value of drugs is defined by WHO and it is updated regularly [50].

DDD of commonly used antibiotics in empirical and definitive treatment are calculated separately. The antibiotic consumption at a certain period is calculated by 100 patient admissions and for 1000 patient days to provide data for comparative purposes.

2.6. Cost Analysis

The cost of antibiotics used in empirical and definitive treatment were calculated by calculating the per day cost of each antibiotic and then multiplied this by the total number of days that given patients received that antibiotic. The cost savings were calculated by subtracting the cost of definitive therapy from the cost of empirical therapy. We calculated the cost in Pakistani rupees and also in US Dollar for comparison purpose.

2.7. Ethical approval

Ethics Approval from the hospital ethical committee was taken before starting the study (Ref No 5574). The study was performed according to the ethics standards and data were collected according to the defined time duration.

2.8. Statistical analysis

Statistical Process for Social Sciences (SPSS version) program was selected to analyze data obtained. Results were presented in the form of frequency, percentages, mean and standard deviation in the form of tabular and graphical representation. Chi-square test was employed by using graph pad prism 5.0 to analyze the association among variables. $P < 0.05$ with 95% confidence interval was considered for statistically significant results.

3. Results

3.1. Demographic characteristics of selected patients

A total of 465 patients were identified with positive culture reports. Out of these patients, 299 (64.3%) were men and 166 (35.7%) were women. The majority of the patients were aged between 19-40 years (38.3%). Table **3.1** depicts the past surgical history of studied patients and it showed that majority of patients suffered from surgical site infections (62.8%). The parenteral route of administration was very prevalent (81.2%). Co-morbid conditions presented in majority of patients and mostly patients suffered from diabetes mellitus. The majority of the patients were admitted in the orthopaedic ward reflecting the fact that GTTH is a POA training hospital. Different samples were taken for microbiological identification and the majority of the samples were taken from pus.

Table 3.1
Demographic data of patients

Gender	Number	Percentage
Male	299	64.3%
Female	166	35.7%
Age group division		
Less than 18 year	95	20.4%
19–40 years	178	38.3%
41–60 years	140	30.1%
61–85 years	52	11.2%
Route of administration		
Oral	389	18.8%
Parenteral	1676	81.2%
Prescribing Trend		
Generic prescribing	73/2060	3.3%
Brand Prescribing	1987/2060	96.7%
Past surgical history		
Yes	292	62.8%
No	173	37.2%
Treatment Based On biomarkers		
ESR	67	14.4%
CRP	66	14.1%
Length of Hospitalization		
Average LOH before the availability of Culture reports (days)	12	60%
Average LOH after the availability of Culture reports (days)	8	40%
Ward		
Orthopedic	314	67.5%
ICU	69	14.9%
Medical	34	7.3%
Surgical	28	6%
Paeds	13	2.8%
Gynaecology	7	1.5%

ESR = Erythrocyte sedimentation rate, CRP = C-reactive protein, LOH = Length of Hospitalization, ICU = Intensive care unit, Others = High vaginal swab (3), Sputum (3), Cerebrospinal fluid (2).

Gender	Number	Percentage
Nature of the sample		
Pus	230	49.5%
Urine	86	18.5%
Tissue	50	10.7%
Wound Swab	42	9%
Bone	18	3.9%
Blood	10	2.1%
Sample from catheterization	21	4.5%
Others	8	1.6%
Co-morbidities		
Diabetes	101	21.7%
Hypertension	61	13.11%
Hepatitis C	54	11.6%
Tuberculosis	14	3%
Ischemic Heart Disease	13	2.7%
Quadriplegic	12	2.5%
ESR = Erythrocyte sedimentation rate, CRP = C-reactive protein, LOH = Length of Hospitalization, ICU = Intensive care unit, Others = High vaginal swab (3), Sputum (3), Cerebrospinal fluid (2).		

3.2. Microbiological finding of positive culture reports

A total of 497 isolates were detected from the 465 patient samples as 16 (3.4%) patients had polymicrobes. 62.2% gram-negative rods were isolated and 37.8% were gram-positive cocci. Table 3.2 showed that among the 188 isolated gram-positive microorganism, the most common pathogen was *Methicillin-sensitive Staphylococcus aureus* (MSSA) 141 (28.4%). Among the 309 isolated gram-negative microorganism, the most common pathogen was *E.coli* 118 (23.8%).

Table 3.2
Microbiological finding of positive culture reports

Organism	Number	Percentage
Gram-positive bacteria		
<i>Methicillin-sensitive Staphylococcus aureus</i>	141	28.4%
<i>Methicillin-resistant Staphylococcus aureus</i>	22	4.4%
<i>Streptococcus pyogenes</i>	12	2.4%
<i>Staphylococcus epidermidis</i>	8	1.6%
<i>Enterococcus faecalis</i>	4	0.8%
<i>Staphylococcus saprophyticus</i>	1	0.2%
Gram-negative bacteria		
<i>Escherichia coli</i>	118	23.8%
<i>Pseudomonas aeruginosa</i>	55	11.1%
<i>Klebsiella pneumoniae</i>	51	10.2%
<i>Acinetobacter baumannii</i>	39	7.9%
<i>Proteus mirabilis</i>	35	7%
<i>Citrobacter</i>	5	1%
<i>Enterobacter</i>	3	0.6%
<i>Salmonella typhi</i>	2	0.4%
<i>Serratia marcescens</i>	1	0.2%

3.3. Sensitivity pattern of antibiotics

Antibiotic sensitivity testing showed that *E. coli* was sensitive for more than 75% cases in fosfomycin (100%), colistin (95.8%), polymyxin-b (93.7%), tigecycline (92.8%), amikacin (86%), Imipenem (82.5%), chloramphenicol (79.4%) and in meropenem (78%). *P. aeruginosa* showed more than 75% sensitivity in chloramphenicol and fosfomycin (100%), polymyxin-b (96%) and in colistin (95.8%). *K. pneumoniae* showed more than 75% sensitivity in meropenem (80%), imipenem (90.3%), chloramphenicol (94.7%) and 100% in fosfomycin, polymyxin-b, colistin and in tigecycline. *A. baumannii* showed more than 75% sensitivity in polymyxin-b and in colistin (96.2%). *P. mirabilis* showed more than 75% sensitivity in meropenem (85.1%), piperacillin+tazobactam (84%) and 100% in cefoperazone+sulbactam and in tigecycline. *MSSA* showed more than 75% sensitivity in ceftiofloxacin (100%), vancomycin (100%), linezolid (95.7%), tigecycline (95.4%), clindamycin (94.1%), amikacin (90.1%), minocycline (89.7%), rifampicin (88.5%), co-amoxiclav (80%) and in gentamicin (75.9%). Ampicillin and co-amoxiclav showed high level of resistance in Gram-negative microorganisms. Cephalosporins and fluoroquinolones also exhibited high levels of resistance in all Gram-negative microbes and even in *MSSA*. All the *A. baumannii* isolates showed high levels of resistance to all antibiotics even for carbapenems. Some resistant strains of linezolid also observed in *MSSA*, which is alarming and needs to be

addressed. Overall, there are serious concerns surrounding the extent of AMR which need to be urgently addressed (Table **3.3**).

Table 3.3
Sensitivity pattern of antibiotics

Antibiotics	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Klebsiella pneumoniae</i>	<i>Acinetobacter baumannii</i>	<i>Proteus mirabilis</i>	<i>Methicillin sensitive staphylococcus aureus</i>
Ampicillin	6/94(6.3%)	4/13 (30.7%)	NA	NA	NA	6/29 (20.6%)
Co – amoxiclav	11/74 (14%)	6/11 (54.5%)	9/34 (36.4%)	NA	3/20 (15%)	8/10 (80%)
Piperacillin + Tazobactam	62/94 (65.9%)	22/31(70%)	19/27 (70.3%)	9/27 (33.3%)	21/25 (84%)	NA
Penicillins	NA	NA	NA	NA	NA	24/113(21.1%)
Cefepime	8/37 (21.6%)	8/22 (36.3%)	5/12 (41.6%)	3/20 (15%)	5/11 (45.4%)	NA
Cefixime	2/44 (4.5%)	NA	1/9 (11.1%)	NA	NA	NA
Cefuroxime	4/75 (5.3%)	3/9 (33.3%)	2/28 (7.1%)	NA	2/21 (9.5%)	27/45 (60%)
Ceftriaxone	8/84 (9.5%)	6/16 (37.5%)	7/31 (22.5%)	NA	5/21 (23.8%)	21/28 (75%)
Cefazolin	NA	NA	NA	NA	NA	21/35 (60%)
Cefoxitin	NA	NA	NA	NA	NA	107/107(100%)
Ceftazidime	10/23 (43%)	13/28 (36.4%)	9/20 (45%)	NA	4/7 (57.1%)	NA
Cefoperazone + Sulbactam	12/21 (57.1%)	4/6 (66.6%)	3/6 (50%)	4/14 (28.5%)	6/6 (100%)	NA
Meropenem	78/100 (78%)	18/34 (52.9%)	28/38 (80%)	9/32 (28.1%)	23/27 (85.1%)	NA
Imipenem	71/86 (82.5%)	16/26 (61.5%)	28/31 (90.3%)	7/18 (38.8%)	13/22 (59%)	NA
Ertapenem	44/60 (73.3%)	4/6(66.6%)	9/16 (56.2%)	3/13 (23.0%)	11/15 (73.3%)	NA
Ciprofloxacin	15/64 (23.4%)	19/32 (5.9%)	11/26 (42.3%)	1/14 (7.1%)	10/21 (47.6%)	45/99(44.4%)
Norfloxacin	9/39 (23%)	2/9 (22.2%)	1/5 (20%)	NA	NA	21/54 (46.2%)
Levofloxacin	21/69 (30.4%)	12/26 (46.1%)	9/24 (37.5%)	10/22 (45.4%)	8/17 (47%)	19/27 (70.3%)
Erythromycin	NA	NA	NA	NA	NA	84/132 (63.6%)
NA = Not available						

Antibiotics	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Klebsiella pneumoniae</i>	<i>Acinetobacter baumannii</i>	<i>Proteus mirabilis</i>	<i>Methicillin sensitive staphylococcus aureus</i>
Clarithromycin	NA	NA	NA	NA	NA	12/22 (54.5%)
Amikacin	80/93 (86%)	26/35 (74.2%)	28/40 (70%)	9/26 (34.6%)	15/27 (55.5%)	101/112 (90.1%)
Gentamicin	47/82 (55.2%)	14/30 (46.6%)	16/31 (51.6%)	6/24 (25%)	24/78 (43.5%)	82/108 (75.9%)
Tobramycin	22/44 (50%)	15/25 (60%)	3/9 (33.3%)	7/22 (31.8%)	2/8(25%)	37/54 (68.5%)
Tetracycline	13/72 (18%)	2/7 (28.5%)	8/22 (36.3%)	2/15 (13.3%)	3/12 (25%)	41/83 (49.3%)
Minocycline	16/36 (44.4%)	6/8 (75%)	4/9 (44.4%)	20/29 (68.9%)	2/8 (25%)	35/39 (89.7%)
Tigecycline	39/42 (92.8%)	3/5 (60%)	8/8 (100%)	18/25 (72%)	6/6 (100%)	42/45 (95.4%)
Co-trimoxazole	9/65 (13.8%)	1/9 (11.1%)	4/12 (33.3%)	NA	2/16 (12.5%)	17/79 (21.5%)
Clindamycin	3/6 (50%)	NA	NA	NA	NA	97/129(75.1%)
Chloramphenicol	31/39 (79.4%)	9/9 (100%)	18/19 (94.7%)	4/10 (40%)	6/16 (37.5%)	81/86 (94.1%)
Nalidixic Acid	7/39 (17.9%)	1/7 (14.2%)	NA	NA	NA	NA
Fosfomycin	44/44 (100%)	6/6 (100%)	3/3 (100%)	NA	NA	NA
Polymyxin-b	45/48 (93.7%)	24/25 (96%)	14/14 (100%)	26/27 (96.2%)	2/7 (28.5%)	NA
Colistin	46/48 (95.8%)	23/24 (95.8%)	13/13 (100%)	27/28 (96.2%)	3/9 (33.3%)	NA
Vancomycin	NA	NA	NA	NA	NA	121/121 (100%)
Teicoplanin	NA	NA	NA	NA	NA	44/66 (66.6%)
Linezolid	NA	NA	NA	NA	NA	114/119 (95.7%)
Rifampicin	NA	NA	NA	NA	NA	54/61 (88.5%)
NA = Not available						

2.4. Calculation of the number of DDDs for commonly used antibiotics, for 100 patient admission, for 1000 patient days

The high use of parenteral co-amoxiclav (149.66 DDS), cefoperazone + sulbactam (1100.25 DDS), ceftriaxone (519 DDS), amikacin (830.59 DDS), vancomycin (256.15 DDS) and parenteral metronidazole (375.11 DDS) were observed with empirical treatment. In comparison with definitive treatment, the most common antibiotics prescribed were piperacillin + tazobactam (372.53 DDS), meropenem (260.31 DDS), oral levofloxacin (194 DDS), oral clindamycin (187.5 DDS) and oral linezolid (407.68 DDS). Compared with empirical treatment, antibiotic consumption decreased by 13.8% with definitive treatment.

Table 3.4

Calculation of No of DDD for commonly used antibiotics, for 100 patient admission, for 1000 patient days

Antibiotics (ATC code)	No of DDD		For 100 Patient Admission		For 1000 Patient days	
	Empirical treatment	Definitive treatment	Empirical treatment	Definitive treatment	Empirical treatment	Definitive treatment
Piperacillin + tazobactam (J01CR05)	246.82	372.53	1.00	1.52	2.87	4.34
Parenteral Amoxicillin and clavulanic acid (J01CR02)	149.66	37.66	0.61	0.15	1.74	0.43
Oral Amoxicillin and clavulanic acid (J01CR02)	53.7	32	0.21	0.13	0.62	0.37
Cefoperazone + sulbactam (J01DD62)	1100.25	349.87	4.49	1.42	12.83	4.08
Ceftriaxone (J01DD04)	519	135	2.11	0.55	6.05	1.57
Meropenem (J01DH02)	174.86	260.31	0.71	1.06	2.04	3.03
Amikacin (J01GB06)	830.59	298.56	3.39	1.21	9.69	3.48
Vancomycin (J01XA01)	256.15	137.10	1.04	0.55	2.98	1.59
Parenteral Ciprofloxacin (J01MA02)	138	116.63	0.56	0.47	1.60	1.36
Oral Ciprofloxacin (J01MA02)	359	344.75	1.46	1.40	4.18	4.02
Parenteral Moxifloxacin (J01MA14)	132	70	0.53	0.28	1.53	0.81
Oral Moxifloxacin (J01MA14)	20	10	0.08	0.04	0.23	0.11
Parenteral Levofloxacin (J01MA12)	66.5	106.83	0.27	0.43	0.77	1.24
Oral Levofloxacin (J01MA12)	96	194	0.39	0.79	1.11	2.26
Tigecycline (J01AA12)	29	140	0.11	0.57	0.33	1.63
Parenteral Clindamycin (J01FF01)	95.33	80.33	0.38	0.32	1.11	0.93
Oral Clindamycin (J01FF01)	17.75	187.5	0.07	0.76	0.20	2.18
Parenteral Metronidazole (J01XD01)	375.11	147.10	1.53	0.60	4.37	1.71
Oral Metronidazole (P01AB01)	12.4	23.4	0.05	0.09	0.14	0.27
Parenteral Linezolid (J01XX08)	56.05	129.62	0.22	0.52	0.65	1.51

DDD = Define Daily Dose, ATC = Anatomical Therapeutic Chemical Classification System of the World Health Organization

Antibiotics (ATC code)	No of DDD		For 100 Patient Admission		For 1000 Patient days	
Oral Linezolid (J01XX08)	60.53	407.68	0.24	1.66	0.70	4.75
Colistin (J01XB01)	0.88	23	0.003	0.09	0.01	0.26
DDD = Define Daily Dose, ATC = Anatomical Therapeutic Chemical Classification System of the World Health Organization						

3.5. Cost Analysis

The average per day cost of the antibiotics used in definitive treatment was 8.2% less than that with empiric treatment. The total average duration of patient hospitalization was 20 days, and the average duration after the availability of culture sensitivity reports was 8 days. This showed that the culture sensitivity reports helped in the reduction of the total length of hospitalization and ultimately reduced the overall costs related to the treatment of patients into his hospital. We calculated the cost in Pakistani rupees and also in US dollars for comparison purpose as shown in Table 3.5.

Table 3.5
Cost

Variables	Before the Availability of Culture Report (A)	After the Availability of Culture Report (B)	Difference in cost (A-B)
Per Day Average Cost of Antibiotics (In Pakistani Rupees)	PKR = 9,225	PKR = 8,467	PKR = 758 (8.2%)
Per Day Average Cost of Antibiotics (In US Dollar)	60\$	55\$	5\$
PKR = Pakistan rupees			

3.6. Adjustment of empirical therapy after the availability of culture sensitivity reports

At the time of culture report, empiric therapy was given to 93.1% patients. The antibiotics administered were subsequently adjusted in 222 (71.8%) cases of Gram-negative microorganism followed by 131 (69.6%) in Gram-positive microorganism following the results of culture sensitivity test (p-value <0.0001). The rates of the adjustment of antibiotics after the availability of culture reports are given in Fig 1.

4. Discussion

In our current study, most common microorganism isolated from the patient's sample was gram-positive MSSA, with similar results seen in other studies [20, 21, 51]. However, in other studies, gram negative bacteria appear more common than gram-positive bacteria [32]. This may well reflect different bacteria seen in different hospital care settings with different patient populations. In our study, most of the patients were suffering from bone diseases and

mostly MSSA or gram-positive bacteria were involved in osteomyelitis and in bone infections [52]. The second most common bacteria found in our study was *E. coli*, similar to another study conducted in a tertiary care hospital in India [20] but different from another study conducted in England [21].

A high proportion of patients in our study received antibiotics before the availability of culture results, similar to other studies [53]. However, different to a recent study in South Africa where 83% of antibiotics were modified following sensitivity reports [54]. Consequently, prescribing behavior may be due to a desire to prevent patients getting severe infections without waiting for sensitivity reports. However, the empiric therapy can subsequently be adjusted according to the culture sensitivity reports to help reduce unnecessary prescribing of particularly broad spectrum antibiotics and associated costs. The most commonly used antibiotics for empiric treatment in our study were cefoperazone + sulbactam followed by amikacin. This is in contrast with the high use of piperacillin+tazobactam and meropenem as empiric therapy in other studies [20], as well as the high use of ceftriaxone in the recent point prevalence study in Pakistan [55]. This may be due to the ready availability of cefoperazone + sulbactam in GTTH and less resistance against microbes, and the use of amikacin may be due to the high prevalence of *E. coli* with amikacin have good therapeutic coverage against *E. coli*. However, this needs further analysis. We are aware that the main reasons for selecting antibiotics for empiric treatment needs to be investigated further to improve future antimicrobial use in this and other hospitals in Pakistan [56].

For definitive treatment, the most common antibiotic prescribed was linezolid, which contrasts with meropenem in another published study [20]. This may well be due to the high prevalence of MSSA in our study and that linezolid is seen to have good coverage against MSSA. However, again this needs further investigation [56]. In this study, the highest use of antibiotics was seen in ICU which was similar to the results observed in Kenya and Switzerland [35, 57], with high rates of antibiotic use in ICUs seen in the recent PPS study in Pakistan [37]. Overall, the extensive use of broad-spectrum antibiotics in definitive treatment could be explained by high bacterial resistance rates [58]. Antibiotic resistance may be reversed if the over-use of antibiotics among hospitals in Pakistan can be decreased.

Encouragingly in our study, empiric therapy was adjusted in 68.9% of the patients greater than the study conducted by Chuodhary et al (47.27%) [20]; however, this is less than the study conducted by Berild et al (88%) [25]. Adjustments were mostly undertaken in gram-negative microorganism compared with gram-positive microorganism similar to the study by Berild et.al [25]. We do not know why the results of culture reports were ignored by some physicians in our study. This may be because physicians mostly rely on the apparent clinical situation of the patient rather than the result of culture reports [32]. However, this will be investigated further in future studies as this is a concern.

In our study, it was observed that no national or international guidelines were available in hospital to guide empiric therapy [59]. This again needs to be urgently addressed as the high use of unnecessary antibiotics increases AMR rates [60], with adherence to guidance known to improve future antibiotic use and is increasingly considered as a robust measure of the quality of prescribing [13, 38, 61-64]. Our results suggest the urgent need to develop guidelines as well as instigate antimicrobial stewardship programmes (ASPs) in this hospital to reduce the unnecessary use of antibiotics [65]. This also applies to other hospitals in Pakistan to help improve future antimicrobial prescribing in hospitals [66].

Another major concern in our study was the high use of parenteral antibiotics (81.8%) similar to other studies [67]. High use of parenteral antibiotics may well reflect physician and patients' views that the IV route is more effective compared with the oral route [68]. Whilst the parenteral route was more preferable in critically ill patients such as ICU patients where patients are often unable to take oral medicines, or in life threatening indication where no oral equivalent is available [68], the oral route is generally preferable where possible as it reduces the risk of cannula related infection and thrombophlebitis as well as reducing length of stay and ultimately the overall cost of treatment [62, 68-

72]. This is helped by the fact that many antibiotics are now available for switching as they have more than 90% bioavailability in their oral form. These include linezolid, fluoroquinolones, doxycycline, metronidazole and rifampicin [68].

The consumption of antibiotics decreased by 13.8% with definitive treatment compared with empirical treatment, similar to findings of Berild et al [73]. Encouragingly as well, the cost of antibiotics used in definitive therapy was 8.2% less than empiric therapy, again similar to findings of Berild et al [25]. The true cost savings may well be higher as the early availability of culture sensitivity reports decreased the length of stay, which would ultimately decrease overall cost of patient care similar to the findings of Stevenson et al in 2012 [74].

It was also encouraging to see that only 3.3% of the antibiotics were prescribed by their brand name as generic medicines tend to be considerably less expensive [75-78]. The rates of INN prescribing in this hospital are considerably less than seen in studies conducted in Karachi (12.26%), Hyderabad (12%), Bangladesh (78%) and in Islamabad (23%) [79-82]. Higher rates can be achieved through more stringent bioequivalent studies given some of the concerns as well as generally encouraging INN names to be taught in medical and pharmacy schools similar to the UK and continued post qualification [83-86].

In this study, the most common gram-negative microbe was *E. coli*. Encouragingly, antibiotic sensitivity test showed that *E. coli* showed maximum (more than 75%) sensitivity to fosfomycin (100%), colistin (95.8%), polymyxin-b (93.7%), tigecycline & nitrofurantoin (92.8%), amikacin (86%), imipenem (82.5%), erythromycin (80%), chloramphenicol (79.4%) and meropenem (78%). However, Nirangan et al (2014) showed a maximum sensitivity of imipenem (98.9%), amikacin (82.6%), nitrofurantoin (82.1%), and Piperacillin + tazobactam (78.2%) for *E. coli* [87] and Gales et al showed a maximum sensitivity to aztreonam (78.8%), ceftazidime (82.1%), cefepime (84.1%), gentamicin (81.2%), tobramycin (75.7%) and more than 90% in piperacillin+tazobactam (90.5%), imipenem (99.6%), meropenem (99.9%), amikacin (98.6%) and colistin (99.8%) for *E. coli* [88]. We will be monitoring this closely in the future to help further guide antibiotic choices.

The most common gram-positive microbe was MSSA with antibiotic sensitivity testing showed that MSSA had maximum (more than 75%) sensitivity to ceftazidime (100%), vancomycin (100%), linezolid (95.7%), tigecycline (95.4%), chloramphenicol (94.1%), amikacin (90.1%), minocycline (89.7%), rifampicin (88.5%), gentamicin (75.9%), clindamycin (75.1%) and ceftriaxone (75%). However, Mir et al (2016) showed a maximum sensitivity of vancomycin, linezolid, rifampicin, chloramphenicol, clindamycin, amikacin, fusidic acid and gentamicin in the case of MSSA i.e. 100%, 98.9%, 95.7%, 94.7%, 86.2%, 84%, 83% and 76.6% respectively [89]. Our findings are a concern especially with some strains of MSSA showing resistance to linezolid which may well be due to the overuse of linezolid, and we will also be investigating this further.

We are aware of a number of limitations with this study. Firstly, no standard antibiotic guidelines were available for the selection of appropriate empiric and definitive therapy in the hospital. Consequently, it was impossible to determine physician adherence with hospital guidelines. Nonetheless, we believe this study was the first step to identifying the prescribing pattern of physicians after the availability of culture sensitivity reports. Secondly, our study was an observational study; consequently, we did not interfere with physician prescribing trends in the selection of antibiotic treatment. However, in the future, the impact of the involvement of a pharmacist or other key stakeholders actively involved in guiding antibiotic selection in hospitals will be investigated. Lastly, to the best of present knowledge, we believe no such research has been undertaken to date in Pakistan with a special focus on culture sensitivity reports; consequently, we were unable to compare our results with any existing studies in Pakistan.

In spite of these limitation, we believe our findings are robust with this study highlighting the impact of culture sensitivity reports on the antibiotic use as well as the significance of culture guided therapy on definitive versus empiric treatment in Pakistan. In addition, this study highlighted the need for antibiotic guidelines for the selection of appropriate antibiotics in empiric and in definite treatment which will be helped by the instigation of ASPs in this hospital and wider.

5. Conclusions

Overall, culture sensitivity reports helped reduce antibiotic utilization in this hospital, decreasing hospital stay and reducing the costs of the antibiotics prescribed. However, there were concerns at the high rates of antimicrobial resistance patterns observed. Consequently, there is an urgent need for the implementation of ASPs and the development of hospital antibiotic guidelines in this hospital, and potentially wider in Pakistan, to reduce unnecessary prescribing of broad-spectrum antibiotics and improve the rationality of antibiotics through culture sensitivity reports. We will be monitoring these developments in the future.

Declarations

Ethics approval and consent to participate

The study was approved and registered from Ethics committee on human research, University College of Pharmacy, University of the Punjab, Lahore, Pakistan under the registration number (HEC/1000/PUCP/1925I). Because the manuscript does not contain any individual person's data in any form (including any individual details, images or videos), so the ethics committee has granted an exemption from requiring consent to participate. The head of departments of various wards and their staff physicians and nurses were informed about the study and they allowed the principal investigators to conduct the study in respective wards.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interest

The authors declare that they have no competing interests.

Funding

Not applicable

Contributions of Authors

Ummara Altaf is the leader of project. She facilitated the launch and smooth running of project by coordinating among all partners. Zikria prepared the detailed work plan, monitoring and evaluation system. The compilation and interpretation of factual materials of the research paper was done by Furqan K Hashmi, Hamid Saeed and Brian Godman. Ummara and Hassan Mehmood Yasir collected data. Bashir Ahmed and Muhammad Furqan Akhtar supervised and helped in the analysis of the results. Brian Godman reviewed the paper and approved the paper

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Figures

Figure 1

Adjustment of empirical therapy after the availability of culture sensitivity reports E. coli= Escherichia coli, P. aeruginosa = Pseudomonas aeruginosa, K. pneumoniae = Klebsiella pneumoniae, A. baumannii = Acinetobacter baumannii, P. mirabilis = Proteus mirabilis, MSSA= Methicillin-sensitive staphylococcus aureus, MRSA= Methicillin-

resistant staphylococcus aureus, Others= Citrobacter, Enterobacter, Salmonella typhi, Serratia marcescens, Streptococcus pyogenes, Staphylococcus epidermidis, Enterococcus faecalis, Staphylococcus saprophyticus