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ORIGINAL RESEARCH

Impact of Positive Culture Reports of *E. coli* or *MSSA* on De-Escalation of Antibiotic Use in a Teaching Hospital in Pakistan and the Implications

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Background: Antibiotic de-escalation is a key element of antimicrobial stewardship programs that restrict the spread and emergence of resistance. This study was performed to evaluate the impact of positive culture sensitivity reports of *E. coli* or *Methicillin sensitive Staphylococcus aureus* (*MSSA*) on de-escalation of antibiotic therapy.

Methods: This prospective observational study was performed on 256 infected patients. The samples were obtained principally from the pus of infected sites for the identification of pathogens and culture-sensitivity testing. The data were collected from patient medical files, which included their demographic data, sample type, causative microbe and antimicrobial treatment as empiric or definitive treatment based on cultures. Data were analyzed using SPSS.

Results: Of 256 isolated microbes, 138 (53.9%) were *MSSA* and 118 were *E. coli* (46.1%). *MSSA* showed 100% sensitivity to cefoxitin, oxacillin, vancomycin, fosfomycin, colistin and more than 90% to linezolid (95.3%), tigecycline (93.1%), chloramphenicol (92.2%) and amikacin (90.2%). *E. coli* showed 100% sensitivity to only fosfomycin and more than 90% to colistin (96.7%), polymyxin-B (95.1%) and tigecycline (92.9%). The high use of cefoperazone+sulbactam (151), amikacin (149), ceftriaxone (33), metronidazole (30) and piperacillin + tazobactam (22) was seen with empiric prescribing. Following susceptibility testing, the most common antibiotics prescribed for *E. coli* were meropenem IV (34), amikacin (34), ciprofloxacin (29) and cefoperazone+sulbactam (25). For *MSSA* cases, linezolid (48), clindamycin (30), cefoperazone+ sulbactam IV (16) and amikacin (15) was used commonly. Overall, there was 23% reduction in antibiotic use in case of *E. coli* and 43% reduction in *MSSA* cases.

Conclusion: Culture sensitivity reports helped in the de-escalation of antimicrobial therapy, reducing the prescribing of especially broad-spectrum antibiotics. Consequently, it is recommended that local hospital guidelines be developed based on local antimicrobial susceptibility patterns while preventing the unnecessary use of broad-spectrum antibiotics for empiric treatment.

Keywords: antimicrobial resistance, antimicrobial stewardship, culture sensitivity reports, definitive treatment, empirical treatment, de-escalation, Pakistan

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Introduction

According to the 10th International Conference on Emerging Infectious Diseases (EID), emerging infections are responsible for approximately 15% of all human pathogens.[1] In most cases, antibiotic-resistant pathogens are responsible for nosocomial infections, which have risen due to excessive use of broad-spectrum antibiotics.[2–6] This is a concern as the development of new antibiotics and repositioning of old antibiotics has slowed.[3,7] Alongside this, the Centers for Disease Control and Prevention (CDC) recognized that 20–50% of all antibiotics prescribed to patients in critical care hospitals in the US are either redundant or inappropriate.[8] Consequently, optimizing the use of antibiotics is essential to minimize the increasing trend of nosocomial infections due to antibiotic-resistant pathogens.[9] The choice of appropriate antibiotics must be based on antibiotic susceptibility and microbiology profiling to optimize appropriate antibiotic prescribing within hospitals.[10,11] Consequently, any empirical use of broad-spectrum antibiotics must be based on local antibiograms and adjusted based on subsequent culture sensitivity reports.[12–14] The two approaches reported for the optimization of antibiotic therapy include de-escalation and surveillance of effective antibiotic treatment, with the potential to reduce costs.[15] Such monitoring can assist the hospital antibiotic stewardship team in deciding how to provide effective therapy and minimize the emergence and spread of antibiotic-resistant organisms.[8]

De-escalation of antibiotics is a key component of antibiotic stewardship to promote the rational use of antibiotics by narrowing the spectrum of suggested antibiotics or by selecting antibiotics for specific microorganism, thereby decreasing the possibility of antimicrobial resistance (AMR).[16–18] This approach also helps reduce inappropriate antibiotics prescribing, cost of hospitalization, length of stay and mortality.[19] Antibiotic de-escalation is considered a safe and effective strategy in many infectious diseases (ID) including pneumonia (hospital-acquired or community-acquired pneumonia), bacteremia, urinary tract infections (UTIs), sepsis with bloodstream infection (BSI), severe sepsis among neutropenic patients, and pneumococcal bacteremia.[20–25] However, due to multiple barriers, the practice of antibiotic de-escalation is not consistent among hospitals across countries. These barriers include a lack of diagnostic facilities, lack of education, lack of multidisciplinary collaboration, and hesitancy to de-escalate antibiotics in critically ill patients who are improving with broad-spectrum antibiotic therapy.[26–28]

There is generally high resistance to *Methicillin Sensitive Staphylococcus Aureus* (*MSSA*), the most common pathogen responsible for different infections in hospitals, making infections caused by these bacteria difficult to treat.[29] *MSSA* and *Escherichia coli* (*E. coli*) have been most common microbes isolated in orthopedic infections.[30] *MSSA* is also responsible for causing hospital acquired infections and community outbreak infections, with multidrug resistance making these infections difficult to treat.[31,32] *E. coli* is also a common pathogen among animals.[33] Different pathogenic strains of *E. coli* are responsible for different infections including UTIs and blood stream infections, wounds and other complications.[30] *E. coli* also causes nosocomial infections. Consequently, any de-escalation following empiric use based on local antibiograms needs to be implemented if pertinent after culture reports in order to prevent complications associated with resistant infections of *E. coli* and *MSSA*.[34] However, among health-care settings of Pakistan, there is currently excessive use of broad-spectrum antibiotics as empiric therapy.[35] This is a concern, especially as we believe there are currently no published data regarding the de-escalation of antibiotic therapy among hospitals in Pakistan. Having said this, there have been initiatives to improve antibiotic use using antibiotic stewardship program (ASP) in Pakistan.[36,37] In view of this, we sought to evaluate the impact of positive culture sensitivity reports of *E. coli* or *MSSA* on subsequent antibiotics use pattern within a leading teaching hospital in Pakistan. We believe the findings will not only be useful in this hospital but also in hospitals throughout Pakistan and wider as they seek to reduce AMR to these two leading organisms within hospitals as part of the National Action Plan to reduce AMR in Pakistan.[38]

Methods

Study Design and Study Setting

This prospective observational study was undertaken in the orthopedic ward of the Ghurki Trust Teaching Hospital (GTTH) to check the impact of positive culture reports of *MSSA* & *E. coli* on de-escalation of antimicrobial therapy from September 2020 to December 2020.

The Ghurki Trust Teaching Hospital, which is a 600 bed teaching hospital, is one of the largest charity hospitals in Pakistan certified by the Pakistan Center of Philanthropy and has a specialty in orthopedics. Consequently, if

stewardship programmes can be introduced in this hospital to enhance de-escalation, this can serve as an exemplar across Pakistan.

Ethics approval was taken from the administration department and ethical board of hospital Research Ethics Committee, Discipline of Pharmacy Practice, Faculty of Pharmacy, University of Lahore (REC/DPP/FOP/8-2020) before conducting the study. Informed consent was taken from patients or parents or legal guardians of patients under 18 years of age before collecting the data. The study was conducted in compliance with the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Patients with positive culture reports of *E. coli* and *MSSA* microbes during their stay in the orthopedic ward were included in this study. All patients had already been started on antibiotics empirically, and their therapies were changed if pertinent after the availability of culture reports. Patients with incomplete medical information, patients who died before the results of culture reports were known, patients who were discharged from the hospital before data collection, patients with positive culture reports of other microbes, patients with negative culture reports and patients with contaminated culture samples were excluded from the study. Patients who were admitted into other wards of the hospital were also excluded from the study.

Sample for Culture Sensitivity

Samples for the identification of microbes and for culture-sensitivity testing were obtained from infected sites of patients. The samples were subsequently enclosed within specialized containers and transported to the microbiological laboratory immediately at room temperature. Each culture-positive patient was followed regularly to determine their antibiotic prescribing pattern, and total length of hospital stay, as well as to check the sensitivity patterns of the prescribed antibiotics. All patients had only one culture report rather than multiple reports.

Data Collection

Data were collected on a pre-designed Performa from the patients in the orthopedic ward of the hospital. The data collection form included demographic characteristics, past surgical history, diagnosis, microbiological profiles and prescribed antibiotics empirically and for definitive treatment following the results of the sensitivity analysis. The data was collected by in-hospital staff following patient consent. The pre-designed Performa was based on the published literature and the considerable knowledge of the co-authors working in this area.

Antibiotic de-escalation was defined as switching from a broad-spectrum empiric antibiotic regimen to streamlining to a narrow-spectrum antibiotic regimen after the re-evaluation of the patient's condition combined with microbiological data and inflammatory markers.[39]

Statistical Analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS) version 21.0. Results were presented in the form of frequency and percentages as graphical and tabular presentations.

Results

Demographic Characteristics of Patients

The patient's base-line demographics are shown in Table 1. In this study, 256 patients were included, the majority were males (N=159, 62.1%) with a mean age of 65 years old. The majority of the patients suffered from surgical site infections (59.4%), and the co-morbid condition present in majority of patients was diabetes mellitus (N=57, 22%). Different samples were taken from patient infected site with most of samples taken from pus (N=171, 66.8%). Of 256 isolated microbes, 118 were *E. coli* (46.1%) and 138 were *MSSA* (53.9%).

Table 1 Demographic Characteristics of Selected Patients

Characteristics	Frequency (N)	Percentage (%)
Gender		
Male	159	62.1
Female	97	37.9
Age group		
Less than 18 years	28	11.0
19–40 years	32	12.7
41–60 years	39	15.4
61–85 years	161	63.1
Sample		
Pus	171	66.8
Urine	54	21.1
Tissue	17	6.6
Dead Bone	6	2.3
Blood	4	1.6
Tracheal secretion	3	1.2
CSF	1	0.4
Isolated microbes		
MSSA	138	53.9
E.coli	118	46.1
Past surgical history		
Yes	152	59.4
No	104	40.6
Ward		
Orthopedic	256	100
CRP		
No	216	84.4
Yes	40	15.7
ESR		
Yes	39	15.2
No	217	84.8
OTHER COMPLICATIONS		
Diabetes	57	22.2
Hepatitis C	35	13.6
Hypertension	30	11.7
TB	8	3.1
IHD	6	2.3
Hepatitis B	4	1.5

Abbreviations: CSF, Cerebro Spinal Fluid; *MSSA*, Methicillin-sensitive Staphylococcus aureus; E. coli, Escherichia coli; NICU, Neonatal intensive care units, CRP, C-reactive protein; ESR, Erythrocyte Sedimentation rate, TB, tuberculosis, IHD, Ischemic Heart Disease.

Sensitivity Pattern of Antibiotics

The sensitivity to prescribed antibiotics is shown in Table 2. Fosfomycin (100%) was the most effective antibiotic against *E. coli*, followed by colistin (96.7%), polymyxin-B (95.1%), tigecycline (92.9%) and chloramphenicol (80.5%). However, *MSSA* showed 100% sensitivity to cefoxitin, oxacillin, fosfomycin, vancomycin and colistin. Resistant strains of linezolid were identified against *MSSA,* which is a concern.

Table 2 Antibiotic Sensitivity Pattern of *E. coli* and *MSSA* Isolates

Antibiotics	***E.coli* Sensitivity n (%)**	***MSSA* Sensitivity n (%)**
Cephalosporin		
Cefoxitin	NT	130/130(100)
Cefazolin	NT	(85.7)
Cefuroxime	5/88(5.7)	30/47(63.8)
Cefoperazone + Sulbactam	18/30(60)	NT
Ceftriaxone	8/100(8)	26/45(57.8)
Ceftazidime	9/29(31)	6/16(37.5)
Cefipime	11/52(21.2)	5/16(31.3)
Cefixime	2/58(3.5)	5/17(29.4)
Cefoperazone	1/23(4.4)	NT
Quinolones		
Levofloxacin	28/82(34.2)	32/45(71.1)
Ciprofloxacin	17/74(23)	49/92(53.3)
Norfloxacin	10/44(22.7)	26/55(47.3)
Ofloxacin	6/29(20.7)	6/11(54.5)
Nalidixic	7/40(17.5)	NT
Penicillin		
Oxacillin	NT	8/8(100)
Piperacillin + tazobactam	71/111(71)	10/17(58.8)
Co-Amoxiclav	12/86(14)	13/25(52)
Penicillin	NT	30/104(28.9)
Ampicillin	7/104(6.7)	12/46(26.1)
Carbapenems		
Imipenem	81/101(80.2)	12/17(70.6)
Ertapenem	49/69(71)	NT
Meropenem	81/108(75)	18/24(75)
Macrolide		
Clarithromycin	NT	16/19(84.2)
Erythromycin	NT	89/133(66.9)
Aminoglycoside		
Amikacin	87/103(84.5)	101/112(90.2)
Gentamicin	51/96(53.1)	85/108(78.7)
Tobramycin	30/59(50.9)	39/59(66.1)
Oxalidone		
Linezolid	NT	121/127(95.3)

(*Continued*)

Table 2 (Continued).

Antibiotics	*E.coli* Sensitivity n (%)	*MSSA* Sensitivity n (%)
Glycopeptide		
Vancomycin	NT	122/122(100)
Teicoplanin	NT	46/66(69.7)
Lincomycin		
Clindamycin	NT	96/125(76.8)
Phosphonic acid Antibiotics		
Fosfomycin	48/48(100)	3/3(100)
Polymyxin		
Colistin	58/60(96.7)	11/11(100)
Polymyxin B	58/61(95.1)	11/12(91.7)
Antimycobacterials		
Rifampicin	NT	51/58(87.9)
Tetracycline		
Tigecycline	52/56(92.9)	54/58(93.1)
Minocycline	20/44(45.5)	33/38(86.8)
Tetracycline	17/80(21.3)	43/80(53.7)
Sulfonamide		
Nitrofurantoin	13/14(76.5)	NT
Co-Trimoxazole	12/81(14.8)	21/83(25.3)
Others		
Chloramphenicol	33/41(80.5)	71/77(92.2)

Abbreviation: NT, Not Tested.

Antibiotic Prescribing Trend

In total, for *E. coli* and *MSSA*, there was high use of cefoperazone+sulbactam (151), amikacin (149), ceftriaxone,[33] metronidazole[30] and piperacillin + tazobactam.[22] After getting the results of susceptibility test, the most common antibiotics prescribed for *E. coli* were meropenem IV,[34] amikacin,[34] ciprofloxacin[29] and cefoperazone+sulbactam.[25] In *MSSA* cases, linezolid,[48] clindamycin,[30] cefoperazone+ sulbactam IV[16] and amikacin[15] were the most commonly prescribed antibiotics following sensitivity analyses. Overall, there was 23% reduction in antibiotic use in case of

Table 3 De-Escalation of Antibiotics

Antibiotics	*E.coli*			*MSSA*			Total		
	Before	**After**	**% Change**	**Before**	**After**	**% Change**	**Before**	**After**	**% Change**
Inj. Cefoperazone+Sulbactam[a]	53	25	↓**53**	98	16	↓**84**	151	41	↓**73**
Inj. Amikacin[a]	54	34	↓**37**	95	15	↓84	149	49	↓**67**
Inj. Ceftriaxone[a]	19	7	↓**63**	14	8	↓**43**	33	15	↓**55**

(*Continued*)

Table 3 (Continued).

Antibiotics	*E.coli*			*MSSA*			Total		
	Before	**After**	**% Change**	**Before**	**After**	**% Change**	**Before**	**After**	**% Change**
Inj. Metronidazole[b]	21	6	↓**71**	9	4	↓**56**	30	10	↑*67*
Inj. Piperacillin+Tazobactam[c]	22	19	↓**14**	0	0	0	22	19	↓**14**
Inj. Meropenem[c]	12	34	↑*183*	8	3	↓**63**	20	37	↑*85*
Inj. Vancomycin[d]	7	0	↓**100**	9	7	↓**22**	16	7	↓**56**
Inj. Ciprofloxacin[a]	9	8	↓**11**	5	3	↓**40**	14	11	↓**21**
Tab. Co-amoxiclav[a]	2	2	0	11	5	↓**55**	13	7	↓**46**
Inj. Moxifloxacin[a]	8	2	↓**75**	5	1	↓**80**	13	3	↓**77**
Tab.Ciprofloxacin[a]	3	21	↑*600*	8	11	↑*38*	11	32	↑*191*
Inj. Cefotaxime[a]	10	1	↓**90**	0	0	0	10	1	↓**90**
Inj. Linezolid[d]	2	0	↓**100**	5	9	↑*80*	7	9	↑*29*
Inj. Co-amoxiclav[a]	4	1	↓**75**	2	3	↑*50*	6	4	↓**33**
Inj. Ampicillin[a]	4	0	↓**100**	2	0	↓**100**	6	0	↓**100**
Tab. Linezolid[d]	2	0	↓**100**	4	39	↑*875*	6	39	↑*550*
Inj. Clindamycin[a]	2	0	↓**100**	4	6	↑*50*	6	6	0
Inj. Imipenem + Cilastatin[c]	3	5	↑*67*	2	2	0	5	7	↑*40*
Inj. Levofloxacin[a]	2	9	↑*350*	1	6	↑*500*	3	15	↑*400*
Tab. Clindamycin[a]	0	0	0	3	24	↑*700*	3	24	↓**700**
Fosfomycin Sachet[a]	1	11	↑**1000**	1	1	0	2	12	↑*500*
Total	240	185	↓**23**	286	163	↓**43**	526	348	↓**34%**

Notes: [a]Broad Spectrum, [b]Narrow Spectrum, [c]Extended Spectrum, [d]Broad Spectrum only for Gram Positive microbes, otherwise Narrow Spectrum, ↓; Reduce, ↑; Increase, Bold; Reduce, Italic; Increase.

E. coli and 43% reduction in *MSSA* cases. Details of antibiotics use in empiric and definitive treatment following susceptibility testing are described in Table 3.

Discussion

Prompt diagnosis and appropriate antibiotic administration are essential to reduce morbidity and mortality with infectious diseases.[40] Despite recommendations, clinical practice regarding requesting culture reports are often inadequate, exacerbated by habit, clinical judgement, available personnel, facilities and costs, especially among low- and middle-income countries.[41–44] This is a concern as inappropriate utilization of antibiotics will increase resistant strains and associated morbidity, mortality and costs.[45–47] Alongside this, due to increasing resistance rates, broad-spectrum antibiotics are preferred in definitive treatment.[48] However, this is not always the case with a study in South Africa reporting that 83% of antibiotic therapy was changed following culture sensitivity results where these data were recorded.[49] Implementation of antibiotic stewardship programs is considered as an essential approach to restrict inappropriate use of antibiotics.[50,51] Therefore, there is an urgent need for the implementation of antibiotic stewardship programs in Pakistan,[52] building on the goals of the NAP in Pakistan.[38]

We believe this is the first study in Pakistan to estimate the effect of *E. coli* or *MSSA* positive culture sensitivity reports on antibiotic de-escalation. The culture reports of most of the patients in our study were positive for *E. coli* and *MSSA* for orthopedic infections, which is contrary to a study conducted in South India where *Methicillin-resistant Staphylococcus aureus* (*MRSA*) was the predominant cause of orthopedic infection.[53] These differences may exist due to the prevalence of different pathogens and their resistance in different geographical regions.

In our study, fosfomycin exhibited 100% sensitivity to *E. coli* isolates. This compares to a study conducted in Ethiopia documented that *E. coli* isolates exhibited high level of sensitivity to nitrofurantoin (96.4%), norfloxacin (90.6%) and gentamicin (79.6%).[54] Alongside this, *MSSA* showed a high level of sensitivity in our study to cefoxitin, oxacillin, fosfomycin and colistin. However, in a previous study in Pakistan, *MSSA* isolates were highly sensitive to vancomycin (100%), linezolid (98.9%), rifampicin (95.7%) and chloramphenicol (94.7%), respectively.[55] Oxacillin was

100% sensitive in our study with comparison to the national data (91.7%), which may be because of the decreased use of oxacillin nowadays.[55,56] Co-trimoxazole and nitrofurantoin showed the least sensitivity for *MSSA*.[57]

The most common antibiotics prescribed as empiric therapy in our study were cefoperazone + sulbactam, amikacin and ceftriaxone. However, a study conducted in India documented the utilization of piperacillin + Tazobactam in orthopedic patients as empiric therapy.[41] This difference may be due to the high availability of cefoperazone + sulbactam in GTTH and sensitivity against microbes, and the use of amikacin has good therapeutic coverage against *E. coli*. For definitive therapy, the most prescribed antibiotic in our study was meropenem and amikacin. Similar findings have been documented in another study.[41]

We are aware that this study has some limitations. Firstly, as this was an observational study, the pharmacist could not intervene with physician prescribing trends in the selection of antibiotics. Secondly, we included patients with positive culture reports of only *MSSA* and *E. coli* so our sample size was limited. Third, there are no guidelines currently available in Pakistan with a special focus on culture sensitivity reports and antibiotic prescribing. Consequently, we were unable to compare our results with any such guidelines. However, we believe that our findings are robust as this study documented the impact of culture sensitivity reports on de-escalation of therapy and has also reduced antibiotic prescribing and hospital stay. Furthermore, this study also accentuates the need for antibiotic guidelines for initiating effective treatment and reducing unnecessary antibiotic prescribing.

Conclusion

Our study reported that sensitivity reports help narrow antibiotic therapy. Consequently, antibiotic de-escalation practice is increasingly required for all medical and surgical patients to reduce the overuse of antibiotics and minimize the spread of resistance. Guidelines for appropriate use of antibiotics and narrowing the level of health-care professionals who can prescribe antibiotics are also needed. We will be following this up in future projects.

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Disclosure

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