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ORIGINAL ARTICLE

A Pattern of Antimicrobial Sensitivity and Resistance in Large Series of Indoor Patients at a Tertiary Care Hospital

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ABSTRACT

Objective: In the era of increasing antibiotic resistance, associated with increasing hospital stay and morbidity, the purpose was to define guidelines for antibiotics in different clinical situations.

Patients and Methods: This study was conducted at Khan Research Laboratories Hospital, Islamabad, Pakistan, from July 2014 to December 2016. 3277 patients admitted in Medical, Surgical, Gynaecology & Obstetrics, ENT, Eye and Dental departments were included. Positive cultures from different sources including blood, urine, pus, central venous lines, bronchial washings and cervical swabs were taken. Age, gender, common pathogens, their sensitivity and resistance to 27 antimicrobial drugs were taken into account. Statistical Package for Social Sciences (SPSS) version 20 was used for data analysis.

Results: 53.1% (n=1738) were females while 46.9% (n=1539) were males.2800 samples were available for analysis. Majority of the patients belonged to Medical ward, 56.9% (n=1864). Major source of culture was urine, 38.3% (n=1073). Escherichia coli (E. coli) was the most common isolate 51.3% (n=1436) followed by Staphylococcus aureus 19.9% (n=558). E. coli showed maximum sensitivity to Imipenem i.e. 94% (n=1349) followed by Amikacin, 93% (n=1335). It was resistant to ceftriaxone (77%).Staphylococcus aureus showed maximum sensitivity to Linezolid and Vancomycin i.e. 98% (n=548) followed by Chloramphenicol 84% (n=470), while being resistant to ciprofloxacin and levofloxacin (54%). Klebsiella pneumoniae showed maximum sensitivity to Imipenem i.e. 75%, while showing resistance to Amoxicillin/Clavulanic Acid (95%) and Ceftriaxone (80%).Staphylococcus epidermidis showed maximum sensitivity to Linezolid i.e.99%. Pseudomonas aeruginosa showed maximum sensitivity to Piperacillin and Tazobactam i.e. 76% . Acinetobacter baumannii showed maximum sensitivity to Colistin i.e. 91%.Salmonella typhi showed maximum sensitivity to Ceftriaxone i.e. 99% while resistance to Ciprofloxacin (94%).Enterococcus faecalis showed maximum sensitivity to Linezolid i.e.100% and Salmonella Paratyphi A showed maximum sensitivities to Cefixime and Ceftriaxone i.e 100%

Conclusion: Antibiotic resistance is emerging. Rationale use of antibiotics is required to curtail the surge of antibiotic resistance. There is also a need to modify treatment guidelines in different clinical situations based on local sensitivity and resistance patterns in order to reduce hospital stay, morbidity and mortality.

Key words: Antimicrobials, Bacteria, Blood culture, Culture, E. coli; Imipenem, Resistance, Sensitivity, Urine culture.

Author`s Contribution
[1] Conception, synthesis, planning of research and manuscript writing Interpretation and discussion
[2] Data analysis, interpretation and manuscript writing, [3] Active participation in data collection.

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Introduction

Antimicrobial resistance is recognized as one of the greatest threats to human health worldwide.[1] Drug-resistant infections take a staggering toll in the United States (US) and across the globe. Just one organism, methicillin-resistant *Staphylococcus aureus* (MRSA), kills more Americans every year (~19,000) than emphysema, HIV/AIDS, Parkinson's disease, and homicide combined.[2] Antibiotic resistance is an increasing crisis as both the range of microbial antibiotic resistance in clinical settings expands and the pipeline for development of new antibiotics contracts.[3] The first isolation of a bacterium, enables the design of experimental models to analyze virulence and to complete Koch's criteria, thereby establishing a link between microorganisms and infectious diseases.[4] Antimicrobial agents have been greatly important cornerstones of clinical medicine since the second half of the 20th century and have saved a great number of people from life-threatening bacterial infections. However, the last decade of 20th century and the first decade of the 21th century have witnessed the emergence and spread of antibiotic resistance in pathogenic bacteria around the world, and the consequent failure of antibiotic therapy, especially in intensive care units (ICUs), which has led to hundreds of thousands of deaths annually.[5] A pure bacterial culture remains essential for the study of its virulence, its antibiotic susceptibility, and its genome sequence in order to facilitate the understanding and treatment of caused diseases.

The first culture conditions empirically varied incubation time, nutrients, atmosphere, and temperature; culture was then gradually abandoned in favor of molecular methods. The rebirth of culture in clinical microbiology was prompted by microbiologists specializing in intracellular bacteria.[6] Bacterial culture also enables the study of the antibiotic susceptibility of bacteria and is the first step in establishing recommendations for effective treatment. [7,8] A recent study of antibiotic prescribed in primary care for urinary tract infection(UTI) in Ireland identified that only 55% of antibiotic prescriptions could be interpreted as appropriately targeted when evaluated against the laboratory report on the urine sample.[9] The theme of World Health Day 2011 *"antimicrobial resistance: no action today*, *no cure tomorrow"* highlighted antimicrobial resistance as a major issue. The pathogens currently presenting the biggest problem in terms of antimicrobial resistance as the ESKAPE pathogens: *Enterococcus faecium (E. faecium)*, *Staphylococcus aureus (S. aureus)*, *Klebsiella pneumoniae (K. pneumoniae)*, *Acinetobacter baumannii (A. baumannii)*, *Pseudomonas aeruginosa (P. aeruginosa)*, and *Enterobacter species.*[10,11] Multiple drug resistance (MDR) is defined as non-susceptibility to at least one agent in three or more antimicrobial categories. Extensively drug resistant (XDR) is defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories). Pan-drug resistant (PDR) is defined as non-susceptibility to all agents in all antimicrobial categories.[12]

There has probably been a gene pool in nature for resistance to antibiotics. For most microbes that are antibiotic producers are resistant to their own antibiotic. In retrospect, it is not surprising that resistance to penicillin in some strains of staphylococci was recognized almost immediately after introduction of the drug in 1946. Likewise, very soon after their introduction in the late 1940s, resistance to streptomycin, chloramphenicol and tetracycline was noted. By 1953, during a Shigella outbreak in Japan, a strain of the dysentery bacillus (Shigella dysentery) was isolated which was multiple drug resistant, exhibiting resistances to chloramphenicol, tetracycline, streptomycin and the sulfonamides. Over the years, and continuing into the present almost every known bacterial pathogen has developed resistance to one or more antibiotics in clinical use.[13]

A study conducted in Ethiopia showed that 54.2% of eye swab cultures were positive for different bacterial pathogens.[14] *P.aeruginosa* found in urinary tract infections showed 19% multi-drug resistant strains in a German study.[15] In a study conducted in China, an opportunistic pathogen, *A. baumannii* showed more than 30% drug resistance to most of the antibiotics tested in the study.[16] In a study conducted in Karachi Pakistan, out of 312 cultured specimens, 272 (87.17%) were found to be infected with 437 microbial organisms.[17] While in a study

on blood cultures, out of 1824 blood cultures, 508 (27.9%) yielded microorganism growth.[18] In another study, the frequency of MDR *P. aeruginosa* among all the *Pseudomonas* strains isolated was found to be 22.7%.[19]

In view of emerging resistance, we conducted our study to ascertain the presence of pathogens in different human sources, and their antimicrobial sensitivity and resistance.

Patients and Methods

This study was conducted at Khan Research Laboratories Hospital, Islamabad, Pakistan, from July 2014 to December 2016. In total 3277 patients admitted in Medical, Surgical, Gynaecology & Obstetrics, ENT, Eye and Dental departments were included. Positive cultures from different sources including blood, urine, pus, central venous lines, bronchial washings and cervical swabs were taken. Age, gender, common pathogens, their sensitivity and resistance to 27 antimicrobial drugs were taken into account. The tested antimicrobials included Imipenem, Meropenem, Cefoperazone/Sulbactam, Pipercillin/Tazobactam, Trimethoprim/sulfamethoxazole (TMP/SMX), Pencillin G, Ampicillin, Amoxicillin/Clavulanic acid, Chloramphenicol, Vancomycin, Linezolid, Amikacin, Gentamicin, Nalidixic acid, Ciprofloxacin, Levofloxacin, Ofloxacin, Cefixime, Ceftriaxone, Ceftazidime, Cefoperazone, Cephradine, Tigecyclin, Doxycycline, Colistin, Nitrofurantoin and fosfomycin. The Bactec blood culture system produced by Becton Dickinson (Mountain View, CA, United States) was used. The Kirby-Bauer (KB) method was used for drug sensitivity testing on Müller-Hinton agar. The results of the drug sensitivity tests were assessed according to the standards of the US Clinical and Laboratory Standards Institute (CLSI). All urine samples were cultured on cysteine lactose electrolyte deficient (CLED) medium. The plates were incubated at 37 C for 24 hours and using gram staining, morphology and biochemical characteristics, bacteria was identified. Antimicrobial susceptibility testing was performed on all isolated bacteria by Kirby Bauer's disc diffusion method as per Clinical and Laboratory Standards Institute (CLSI) recommendations. Isolates were declared as sensitive or resistant on the basis of zone of inhibition following the Laboratory standards. Bronchial washing's samples were weighed and processed with a 4-fold volume of dithiothreitol (Sputasol, Oxoid Ltd., Hants, UK) and were cultured. Sputum samples were serially diluted and plated on chocolate agar enriched, chocolate agar with bacitracin, Haemophilus-selective agar, blood agar, and MacConkey agar. Plates were incubated for 24-48 hours at 37°C and in 5% CO2 atmosphere. Microorganisms were identified by colony morphology, Gram staining and specific culture conditions. For CSF culture, 0.15 ml of uncentrifuged CSF specimen was inoculated onto each of one 5% sheep blood plate and one chocolate agar plate (Becton Dickinson Microbiology Systems, Cockeysville, Md.), and 1.0 ml was inoculated into 5 ml of BD blood culture bottles. Agar plates were incubated at 37°C in 5% carbon dioxide and examined daily for 3 days. Broth cultures were incubated at 37°C. Cervical swab specimens were placed in Blood Agar (BA) and Sabouraud Agar (SA) for 18-24 hr in 5% CO2 atmosphere at 37°C. Statistical Package for Social Sciences (SPSS) version 20 was used for data analysis. Data of study patients were stated as number of patients and percentages.

Results

Present study comprised of 3277 patients. Total 1738(53.1%) were females while 1539 (46.9%) were males. Only 176 (5.4%) patients were below 20 years of age, 1081 (32.9%) patients were between 20 to 50 years, 1143 (34.9%) patients were between 50 to 70 years and 877 (26.8%) patients were above 70 years. More than half 1864 (56.9%) patients were admitted in Medical ward (Figure 1).

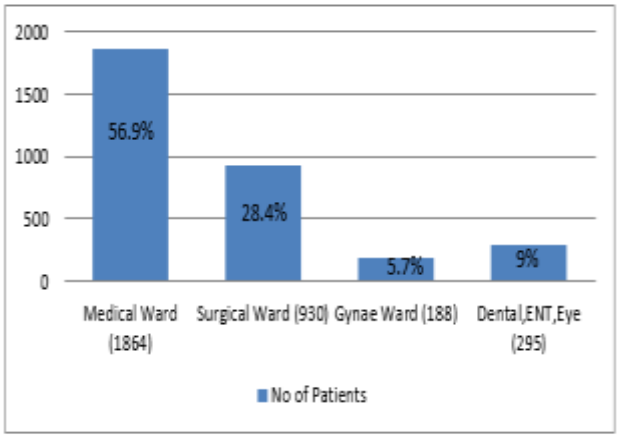

Figure 1: Distribution of patients in different wards

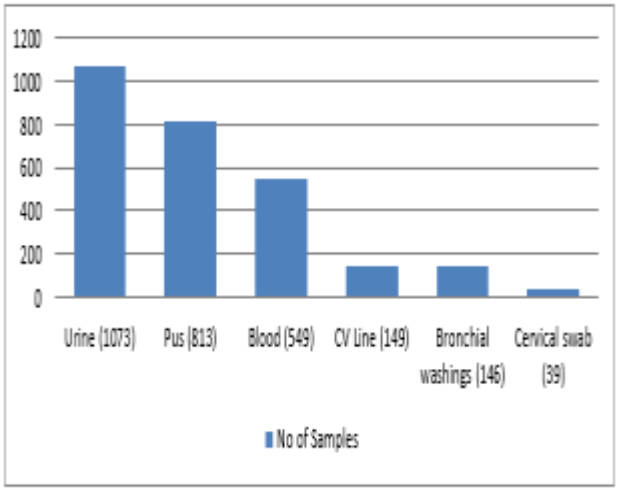

Figure 2: Source of cultures

Out of 3277 patients, culture samples of 2769 (84.5%) patients were available for analysis (Figure 2)

Table 1 illustrates frequency of microorganisms isolated. As shown in the table, Escherichia coli (E. *coli*) was the most common isolate 51.3% (n=1436), followed by S. *aureus* 19.9% (n=558) (Table 1)

Table: 1 Frequency of common isolates

Organism	Frequency (%)
Escherichia coli	1436 (51.3)
Staphylococcus aureus	558 (19.9)
Klebsiella pneumonia	405 (14.5)
Staphylococcus epidermidis	325 (11.6)
Pseudomonas aeruginosa	244 (8.7)
Acinetobacter baumannii	233 (8.3)
Salmonella typhi	228 (8.1)
Enterococcus faecalis	121 (4.3)
Salmonella paratyphi A	59 (2.1)

Antimicrobial sensitivity and resistance of the above mentioned microorganisms have been shown in table 2

Discussion

We conducted our study to determine sensitivity and resistance patterns of microorganisms in different clinical settings. Susceptibility pattern of pathogens has been changing over the years, implying the need for periodic monitoring in order to decrease the number of therapeutic failures and boost an effort to arrest the growing occurrence of antibiotic resistance. Proper collection, transportation and inoculation are other steps required for enhancing bacterial growth on culture media. Microbiologists have to work in collaboration with clinicians in installing newer and appropriate antibiotic discs according to emerging resistance patterns and local antibiogram.

In our study, E. *coli* was found to be the most predominant isolated organism (51.3%). In a study conducted in Saudi Arabia, E. *coli* was found to be the most common isolate (38.3%).[20] In another study conducted in India, E. *coli* was also the most common isolate having frequency of 59.6%.[21] This warrants the need of suspecting E. *coli* in different clinical conditions and starting appropriate empiric treatment targeting E. *coli* apart from other microorganisms. E. *coli* and K. *pneumoniae* showed greater resistance to Ampicillin, Amoxicillin and TMP/SMX, these results are comparable to another study in which E.*coli* (34.6%), coagulase-negative staphylococci (19.2%), P. *aeruginosa* (15.4%), and Klebsiella spp. (11.5%) were common bacterial isolates, where most of them were resistant against ampicillin, amoxicillin, tetracycline, TMP/SMX, and chloramphenicol.[22] Of particular interest is the resistance to Ceftriaxone of E.*coli*(77%) and K.*pneumoniae*(80%) in this study. These two gram negative organisms showed greater sensitivity to three commonly chosen antibiotics Imipenem, Amikacin and Meropenem.According to a study conducted in Quaid-i-Azam University, Islamabad, the antibiotics showing greater susceptibility towards E. *coli* and K. *pneumoniae* isolates were imipenem, piperacillin-tazobactam, ampicillin-sulbactam and amikacin. The antibiotics having the highest resistance, particularly against the Extended Spectrum Beta Lactamases (ESBLs) producers were amoxicillin/clavulanic acid, TMP/SMX, cefuroxime, cefpirome, ceftriaxone and ciprofloxacin and should be removed from the line of treatment for common urinary tract infections[23], while a study conducted in Saudi Arabia showed that E.*coli* is more than 78% resistant to Amikacin.[20] P. *aeruginosa* showed alarming resistance to the once commonly prescribed antibiotics including

Table 2: Sensitivity and resistance pattern of Various Organism					
Escherichia coli (E.*coli*) (n=1436)					
Sensitivity			**Resistance**		
Antibiotic	**n**	**%**	**Antibiotic**	**n**	**%**
Imipenem	1349	94	Ampicillin	1293	90
Amikacin	1335	93	Cefixime	1136	79
Meropenem	1250	87	Amoxicillin/Clavulanate	1111	77
Cefoperazone/Sulbactam	1045	73	Ceftriaxone	1105	77
Pipercillin/Tazobactam	979	68	TMP/SMX	1082	75
Staphylococcus aureus (n=558)					
Linezolid	548	98	Penicillin G	535	96
Chloramphenicol	470	84	Ampicillin	532	95
Amikacin	457	82	Ciprofloxacin	304	54
Doxycycline	447	80	Levofloxacin	299	54
Vancomycin	548	98	Ofloxacin	245	44
Klebsiella pneumoniae (n=405)					
Imipenem	304	75	Ampicillin	395	98
Meropenem	297	73	Amoxillin/clavulanic acid	384	95
Amikacin	270	67	Cefixime	336	83
Cefoperazone/Sulbactam	210	52	Ceftriaxone	326	80
Pipercillin/Tazobactam	181	45	TMP/SMX	300	74
Staphylococcus epidemidis (n=325)					
Linezolid	323	99	Ampicillin	316	97
Amikacin	294	90	Penicillin G	314	97
Vancomycin	277	85	Ciprofloxacin	208	64
Chloramphenicol	270	83	Levofloxacin	207	64
Gentamicin	215	66	Ofloxacin	177	54
Pseudomonas aeruginosa (n=244)					
Piperacillin/tazobactam	186	76	Levofloxacin	95	39
Amikacin	183	75	Ciprofloxacin	90	37
Cefoperazone/sulbactam	182	75	Ceftazidime	80	33
Imipenem	179	73	Cefoperazone	80	33
Gentamicin	164	67	Gentamicin	74	30
Acinetobacter baumannii (n=233)					
Colisitin	213	91	Amoxillin/clavulanic acid	231	99
Tigecycline	187	80	Ceftriaxone	227	97
Gentamicin	91	39	Ampicillin	226	97
Amikacin	70	30	Cefixime	225	97
Cefoperazone/sulbactam	60	26	Ciprofloxacin	224	96

Ceftazidime (33%), Ciprofloxacin (37%) and Gentamicin (30%). Similar pattern of resistance was observed in another study with resistance to ceftazidime (41%), gentamicin (27%) and ciprofloxacin (26%).[24] In our study S. *aureus* was sensitive to Vancomycin & Linezolid (98%). S. *epidermidis* showed 99% sensitivity to

Table 2a: Sensitivity and Resistance Pattern of Various Organism (n=228)					
Sensitivity			**Resistance**		
Antibiotic	**n**	**%**	**Antibiotic**	**n**	**%**
Salmonella Typhi (n=228)					
Ceftriaxone	227	99	Ciprofloxacin	214	94
Cefixime	222	97	Levofloxacin	212	93
Ampicillin	99	43	Naladixic acid	200	88
TMP/SMX	95	42	Ofloxacin	179	79
Chloramphenicol	77	33	TMP/SMX	133	58
Enterococcus Faecalis (n=121)					
Linezolid	121	100	Ceftriaxone	108	89
Vancomycin	109	90	Ciprofloxacin	108	89
Amoxillin/clavulanic acid	74	61	Levofloxacin	108	89
Ampicillin	70	58	Cefixime	107	88
Nitrofurantoin	55	45	Cephradine	94	78
Salmonella Paratyphi A (n=59)					
Cefixime	59	100	Ciprofloxacin	57	97
Ceftriaxone	59	100	Levofloxacin	57	97
Ampicillin	54	92	Naladixic acid	57	97
TMP/SMX	53	90	Ofloxacin	56	95
Chloramphenicol	50	85	Ampicillin	5	8

Linezolid and 85% to Vancomycin. However, in a study conducted in Saudi Arabia it was found that resistant and susceptibility profile of S. *aureus* showed high resistance to both ampicillin and linezolid (94.1%) and high sensitivity to more than one antibiotic such as daptomycin, penicillin, Synercid, teicoplanin, vancomycin, and TMP/SMX, which have sensitivity rate more than 88%.[21] E. *faecalis* which frequently cause urinary tract infection, endocarditis and bacteremia, showed resistance to generally prescribed empiric antibiotics regimen like Ceftriaxone, Levofloxacin and Ciprofloxacin (89%). E. *faecalis* was sensitive to Linezolid (100%), Vancomycin (90%) and Amoxicillin/Clavulanic acid (61%). Linezolid, vancomycin and teicoplanin are currently widely used drugs for the effective treatment of enterococcal infections.[25-27]

A *baumannii* showed sensitivity to Colistin (91%) and Tigecyclin (80%), while is resistant to Amoxicillin/Clavulanic acid (99%), Ceftriaxone, Ampicillin and Cefixime (97%). Therefore, it is sensitive to antibiotics prescribed for ventilator associated pneumonia(VAP) (A. *baumannii* is a common cause of VAP). Colistin and tigecycline are in many cases the unique options for the treatment of many episodes of VAP caused by multiple drug resistant- gram negative bacteria (MDR-GNB).[28] S. *typhi* and S. *paratyphi A* showed high degree of resistance to Quinolones. Ciprofloxacin (94%), Levofloxacin (93%) for S.*typhi*; Ciprofloxacin and Levofloxacin (97%) for S.*paratyphi A*. Both these organisms showed almost no resistance to Ceftiaxone and Cefixime. According to a study conducted in Islamabad the prevalence of MDR and fluoroquinolone resistance was very high among salmonella serovars. No resistance was found to third-generation cephalosporins.[29]

Conclusion

Antibiotic resistance is an emerging problem. Rationale use of antibiotics is required to curtail the surge of antibiotic resistance. There is also a need to modify treatment guidelines in different clinical situations based on local sensitivity and resistance patterns. Emphasis

stays on reducing hospital stay, morbidity and mortality.

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