Original Article

The Study of Antibiotic Resistance on Patients of Tertiary Care Teaching Hospital of South India

Dr. Rajesh Venkataraman[1], Dr. Priyanka AS[2]*
1. Head of Department, Department of Pharmacy Practice, Sri Adichunchanagiri College of Pharmacy, B G Nagara, 571448, India.
2. Pharm D Intern, Department of Pharmacy Practice, Sri Adichunchanagiri College of Pharmacy, B G Nagara, 571448, India.
***Corresponding author's E-mail:** priyankapinky962@gmail.com

Received: 06-11-2022; **Revised:** 22-12-2022; **Accepted:** 29-12-2022; **Published on:** 15-01-2023.

ABSTRACT

Background: Antibiotic resistance is rising to dangerously high levels all parts of the world. New resistance mechanisms are emerging and spreading globally, threatening our ability to treat common infectious diseases.

Objective: To identify antibiotic resistance and bacteria which cause antibiotic resistance.

Methods: A prospective and observational study was carried out in a tertiary care teaching hospital over a period of 6 months. Data was retrieved from participant's (n = 200) case sheets, on daily basis during a period of 6 months. Obtaining permission/approval from Institutional Ethical Committee of AIMS Preparation of patient data collection form and consent form, enrolling the patients who has been prescribed with antibiotics, collection of blood and urine samples from patients, samples will be stored under controlled temperature, samples will be taken to ACU Laboratory, evaluation/analysis of collected samples for assessment of antibiotic resistance.

Results: After the informed consent process a total of 200 samples from 200 different patients were collected and cultured. There are 110 males and 90 females. 55% were males and 45% were females. Isolates of Gram-negative bacteria [GNB] were significantly more prevalent than Gram positive isolates. Among the Gram-positive isolates, the predominant isolates were Enterococcus (n=9) and Staphylococcus spp was (n=7) and micrococcus was (n=1). The Gram-negative isolates were included E. coli (n=22), Enterobacter (n=5), Klebsiella spp(n=3), NF GNB (n=4), Citrobacter(n=2), Providencia spp(n=1), Pseudomonas(n=1), Proteus s=1).

Conclusion: This study gives an overview of antibiotic resistance and bacteria's causing antibiotic resistance. And many organisms detected, and also no growth found in 144 (72%) patients. E. coli species found more 22 (11%) patients, Enterococcus in 9 (4.5%) patients, Staphylococcus in 7 (3.5%), NFGNB in 4 (2%) patients, Klebsiella pneumonia in 3 (1.5%) patients, Enterobacter Aurogenus in 3 (1.5%) patients, Enterobacter Cloacae in 2 (1%) patients, Citrobacter fruendii in 1 (0.5%), Citrobacter Kasseri in 1 (0.5%), Micrococcus in 1 (0.5%), Proteus Mirabilis in 1 (0.5%), Providencia Stuartii in 1 (0.5%), Pseudomonas Spp in 1 (0.5%).

Keywords: Antibiotic resistance, Gram negative bacteria, Gram positive bacteria, Resistance, Sensitive, Antibacterials.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2023.v78i01.011

DOI link: http://dx.doi.org/10.47583/ijpsrr.2023.v78i01.011

INTRODUCTION

An antibiotic is a type of antimicrobial substance active against bacteria. It is the most important type of antibacterial agent for fighting bacterial infections, and antibiotic medications are widely used in the treatment and prevention of such infections.[1] They may either kill or inhibit the growth of bacteria. A limited number of antibiotics also possess antiprotozoal activity. Antibiotics are not effective against viruses such as the common cold or influenza; drugs which inhibit viruses are termed antiviral drugs or antivirals rather than antibiotics.

Sometimes, the term antibiotic—literally "opposing life", from the Greek roots ἀντι anti, "against" and βίος bios, "life"—is broadly used to refer to any substance used against microbes, but in the usual medical usage, antibiotics (such as penicillin) are those produced naturally (by one microorganism fighting another), whereas nonantibiotic antibacterials (such as sulphonamides and antiseptics) are fully synthetic. However, both classes have the same goal of killing or preventing the growth of microorganisms, and both are included in antimicrobial chemotherapy. "Antibacterials" include antiseptic drugs, antibacterial soaps, and chemical disinfectants, whereas antibiotics are an important class of antibacterials used more specifically in medicine[2] and sometimes in livestock feed.

Antibiotics have been used since ancient times. Many civilizations used topical application of mouldy bread, with many references to its beneficial effects arising from ancient Egypt, Nubia, China, Serbia, Greece, and Rome. The first person to directly document the use of molds to treat infections was John Parkinson (1567–1650). Antibiotics revolutionized medicine in the 20th century. Alexander Fleming (1881–1955) discovered modern day penicillin in 1928, the widespread use of which proved significantly beneficial during wartime. However, the effectiveness and easy access to antibiotics have also led to their overuse[3] and some bacteria have evolved resistance to them. The World Health Organization has classified antimicrobial resistance as a widespread "serious threat [that] is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country".[4]

Antibiotics are used to treat or prevent bacterial infections,[5] and sometimes protozoan infections. (Metronidazole is effective against a number of parasitic diseases). When an infection is suspected of being responsible for an illness but the responsible pathogen has not been identified, an empiric therapy is adopted. This involves the administration of a broad-spectrum antibiotic based on the signs and symptoms presented and is initiated pending laboratory results that can take several days.[6]

When the responsible pathogenic microorganism is already known or has been identified, definitive therapy can be started. This will usually involve the use of a narrow-spectrum antibiotic. The choice of antibiotic given will also be based on its cost. Identification is critically important as it can reduce the cost and toxicity of the antibiotic therapy and also reduce the possibility of the emergence of antimicrobial resistance.[7] To avoid surgery, antibiotics may be given for non-complicated acute appendicitis.

Antibiotics may be given as a preventive measure and this is usually limited to at-risk populations such as those with a weakened immune system (particularly in HIV cases to prevent pneumonia), those taking immunosuppressive drugs, cancer patients, and those having surgery.[8] Their use in surgical procedures is to help prevent infection of incisions. They have an important role in dental antibiotic prophylaxis where their use may prevent bacteraemia and consequent infective endocarditis. Antibiotics are also used to prevent infection in cases of neutropenia particularly cancer-related.

The use of antibiotics for secondary prevention of coronary heart disease is not supported by current scientific evidence, and may actually increase cardiovascular mortality, all-cause mortality and the occurrence of stroke.[9]

There are many different routes of administration for antibiotic treatment. Antibiotics are usually taken by mouth. In more severe cases, particularly deep-seated systemic infections, antibiotics can be given intravenously or by injection. Where the site of infection is easily accessed, antibiotics may be given topically in the form of eye drops onto the conjunctiva for conjunctivitis or ear drops for ear infections and acute cases of swimmer's ear. Topical use is also one of the treatment options for some skin conditions including acne and cellulitis.[10] Advantages of topical application include achieving high and sustained concentration of antibiotic at the site of infection; reducing the potential for systemic absorption and toxicity, and total volumes of antibiotic required are reduced, thereby also reducing the risk of antibiotic misuse. Topical antibiotics applied over certain types of surgical wounds have been reported to reduce the risk of surgical site infections.[11] However, there are certain general causes for concern with topical administration of antibiotics. Some systemic absorption of the antibiotic may occur; the quantity of antibiotic applied is difficult to accurately dose, and there is also the possibility of local hypersensitivity reactions or contact dermatitis occurring. It is recommended to administer antibiotics as soon as possible, especially in life-threatening infections. Many emergency departments stock antibiotics for this purpose.[12]

Antibiotics are commonly classified based on their mechanism of action, chemical structure, or spectrum of activity. Most target bacterial functions or growth processes. Those that target the bacterial cell wall (penicillin's and cephalosporins) or the cell membrane (polymyxins), or interfere with essential bacterial enzymes (rifamycin's, lipiarmycin's, quinolones and sulphonamides) have bactericidal activities. Protein synthesis inhibitors (macrolides, lincosamides and tetracyclines) are usually bacteriostatic (with the exception of bactericidal aminoglycosides).[13] Further categorization is based on their target specificity. "Narrow-spectrum" antibiotics target specific types of bacteria, such as gram-negative or gram-positive, whereas broad spectrum antibiotics affect a wide range of bacteria. Following a 40-year break in discovering classes of antibacterial compounds, four new classes of antibiotics were introduced to clinical use in the late 2000s and early 2010s: cyclic lipopeptides (such as daptomycin), glycylcyclines (such as tigecycline), oxazolidinones (such as linezolid), and lipiarmycin's (such as fidaxomicin).[14]

Bacterial resistance is the capability of bacterial cells to prevent antibiotic bacteriostatic or bactericidal effects[15]. The excessive and unintended usage of antibiotics contributes to resistance development in bacteria. Because of the extensive uptake, the evolvement of microorganisms resistant with the time and problems have arisen with these resistant microorganisms for the treatment of certain infections. Nowadays, resistance is determining as a big issue in the path of new drug synthesis, developing antibiotic resistance is a major public health problem worldwide. [16]

MATERIALS AND METHODS

A prospective and observational study was conducted at Adichunchunagiri Hospital and Research centre, B.G. Nagara - 571448 for a period of 6 months from February 2021 to July 2021, after getting permission from Institutional Ethics Committee (Reference no:1EC/AH&RC/AC/032/2021). Patient data which was relevant to the study was obtained from the hospital, patient case sheets, medication chart, laboratory reports from participant's (n = 200) case sheets, on daily basis during a period of 6 months. Preparation of patient data collection form and consent form, enrolling the patients who has been prescribed with antibiotics, collection of blood and urine samples from patients, samples will be stored under controlled temperature, samples will be taken to ACU Laboratory, evaluation/analysis of collected samples for assessment of antibiotic resistance.

RESULTS

Table 1: Gender wise distribution of subjects.

Gender	Frequency	Percent
Female	91	45.5
Male	109	54.5
Total	200	100

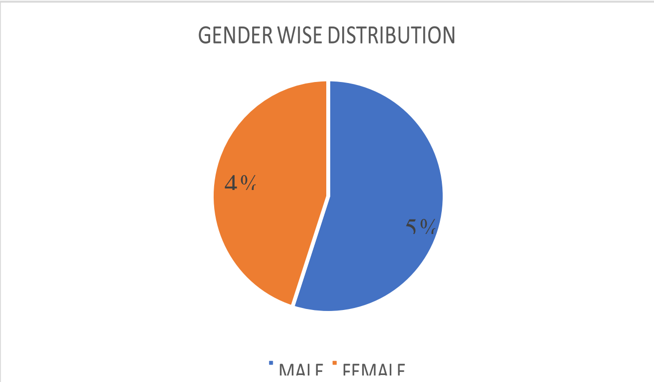

Figure 1: Gender wise distribution of subjects

In our study, males are identified more i.e., 109(54.5%) and 91(45.5%) were females.

Table 2: Blood and urine specimens of subjects.

Specimen	Frequency	Percent
Blood	46	23
Urine	154	77
Total	200	100

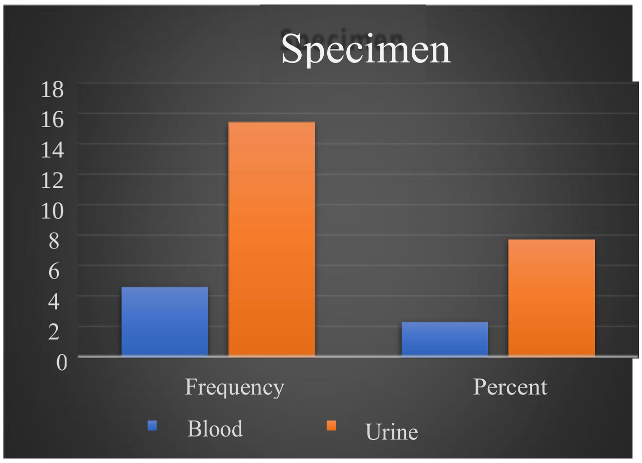

Figure 2: Specimen wise distribution of subjects.

In the study, both blood and urine samples are collected, more urine samples present and found 46(23%) were blood and 154(77%) were urine samples.

Table 3: Distribution of bacterial class in subjects.

Bacterial Class	Frequency	Percent
GNB	39	19.5
GPB	17	8.5
NG	144	72
Total	200	100

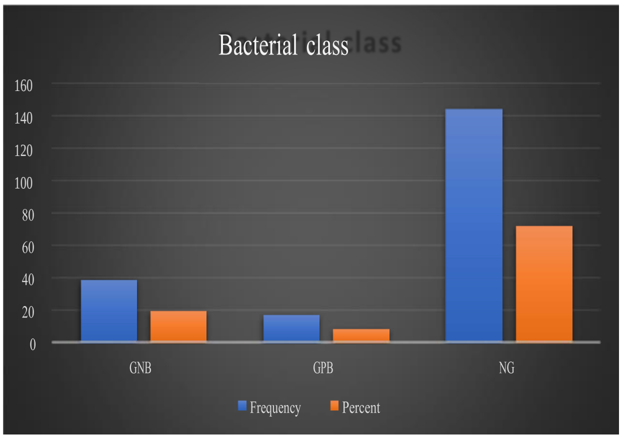

Figure 3: Bacterial class wise distribution of subjects

In the study, there are both gram positive and gram-negative bacteria's, more gram-negative bacteria's identified, out of that 39(19.5%) were gram negative bacteria's and 17(8.5%) were gram positive bacteria's.

Table 4: Organisms detected in subjects.

Organisms	Frequency	Percent
Citrobacter freundii	1	.5
Citrobacter kaseri	1	.5
E. coli	22	11.0
Enterobacter aurogenus	3	1.5
Enterobacter cloacae	2	1.0
Enterococcus	9	4.5
Klebsiella pneumonia	3	1.5
Micrococcus	1	.5
NFGNB	4	2.0
NG	144	72.0
Proteus mirabillis	1	.5
Providencia stuartii	1	.5
Pseudomonas SPP	1	.5
Staphylococcus [MR CONS]	7	3.5
Total	200	100.0

In the sample size of 200 patients, many organisms detected, and also no growth found in 144 (72%) patients. E. coli species found more 22 (11%) patients, Enterococcus in 9 (4.5%) patients, Staphylococcus in 7 (3.5%), NFGNB in 4 (2%) patients, Klebsiella pneumonia in 3 (1.5%) patients, Enterobacter Aurogenus in 3 (1.5%) patients, Enterobacter Cloacae in 2 (1%) patients, Citrobacter fruendii in 1 (0.5%), Citrobacter Kasseri in 1 (0.5%), Micrococcus in 1 (0.5%), Proteus Mirabilis in 1 0.5%), Providencia Stuartii in 1 0.5%), Pseudomonas Spp in 1 (0.5%).

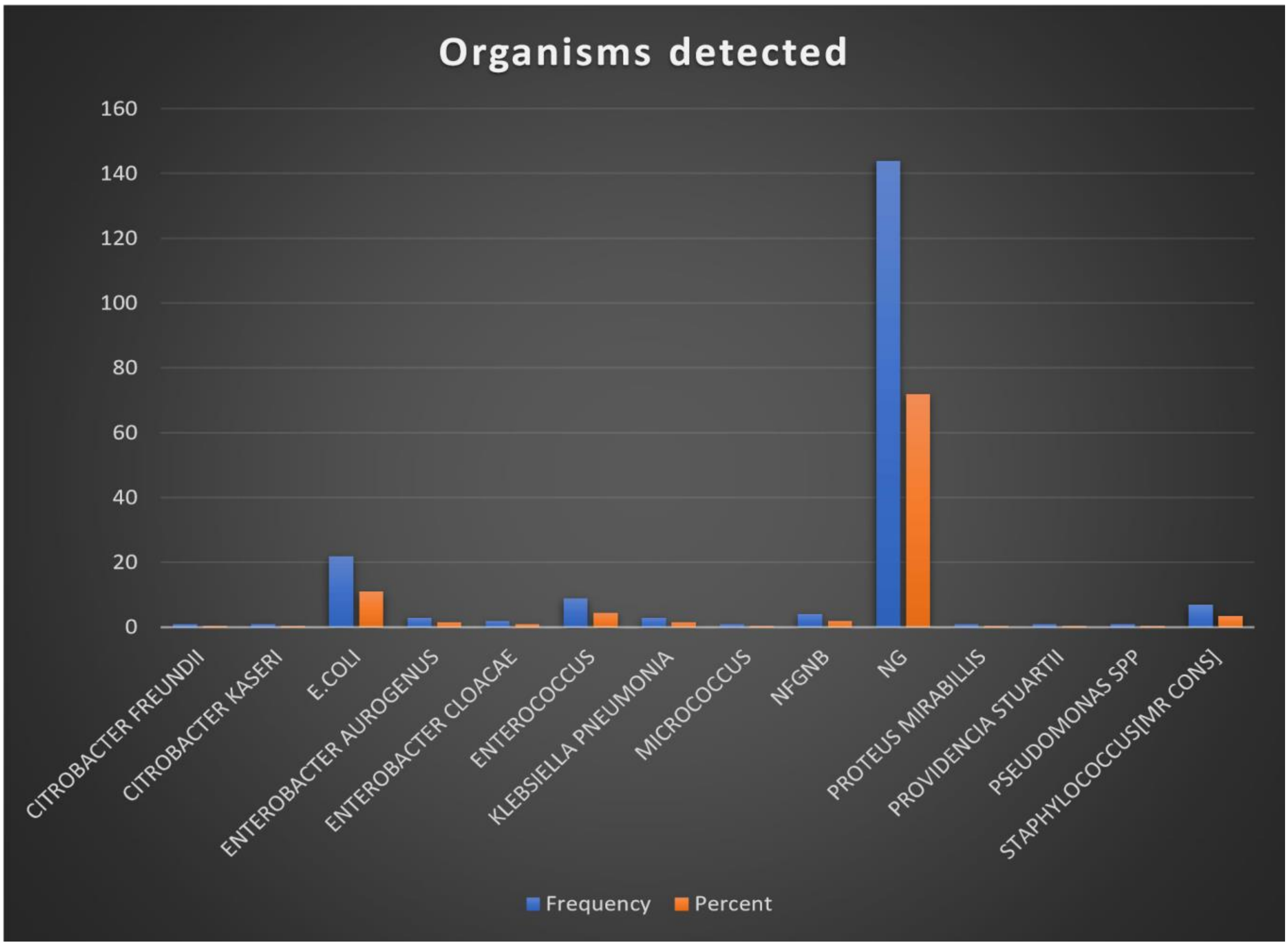

Figure 4: Organisms detected in subjects.

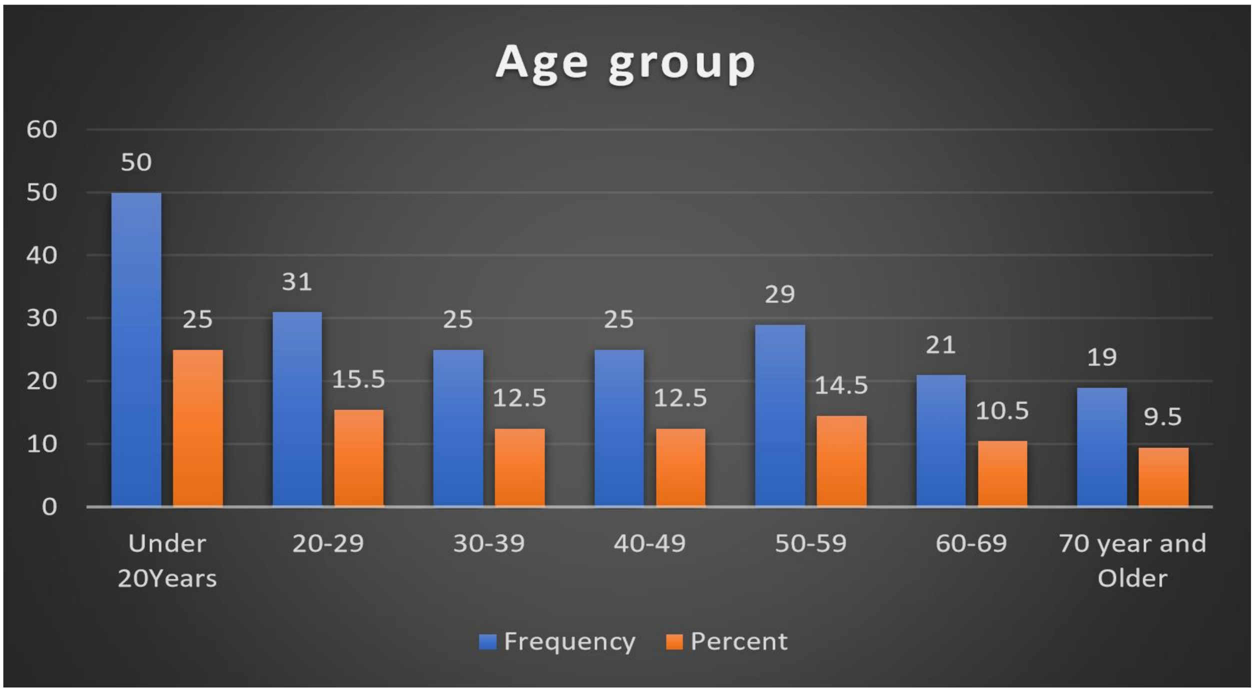

Figure 5: Age wise distribution of subjects.

Table 5: Age wise distribution of subjects.

Age group	Frequency	Percent
Under 20Years	50	25.0
20-29	31	15.5
30-39	25	12.5
40-49	25	12.5
50-59	29	14.5
60-69	21	10.5
70 year and Older	19	9.5
Total	200	100.0

In the study, the most prominent age group was found to be of age group under 20 years (25%), they are found to be more susceptible to antibiotic resistance. The least age group was found to be above 70 years (9.5%).

In gram positive bacteria's, it is more resistant to ciprofloxacin and more sensitive to tigecycline, and it is less resistant to imipenem, piptaz, tobramycin, tigecycline, colistin and less sensitive to cefepime, imipenem, piptaz, tobramycin antibiotics and having P value < .001.

In gram negative bacteria's, it is more resistant to ampicillin and more sensitive to tigecycline and it is less resistance to chloramphenicol, clindamycin, erythromycin, tetracycline and less

Resistance to chloramphenicol, clindamycin, erythromycin, tetracycline and less sensitive to azithromycin, chloramphenicol, clindamycin, erythromycin, linezolid, penicillin, teicoplanin, tetracycline, vancomycin antibiotics and having P value <.001.

Table 6: Antibiotic susceptibility testing

Antibiotics	AST	Gram positive	Gram negative	P value
Amikacin	Sensitive	9	29	< .001
	Resistance	3	9	
Amoxiclav	Sensitive	7	18	< .001
	Resistance	9	20	
Ampicillin	Sensitive	3	1	< .001
	Resistance	4	37	
Cefepime	Sensitive	0	11	< .001
	Resistance	2	26	
Ceftazidime	Sensitive	1	6	< .001
	Resistance	3	31	
Cefotaxime	Sensitive	5	8	< .001
	Resistance	8	30	
Gentamicin	Sensitive	6	24	< .001
	Resistance	2	10	
Imipenem	Sensitive	0	26	< .001
	Resistance	0	13	
Meropenem	Sensitive	1	30	< .001
	Resistance	1	7	
Levofloxacin	Sensitive	3	13	< .001
	Resistance	12	24	
Ofloxacin	Sensitive	3	11	< .001
	Resistance	9	19	
Piptaz	Sensitive	0	22	< .001
	Resistance	0	16	
Tobramycin	Sensitive	0	23	< .001
	Resistance	0	12	
Tigecycline	Sensitive	17	31	< .001
	Resistance	0	8	
Colistin	Sensitive	1	8	< .001
	Resistance	0	1	
Nalidixic acid	Sensitive	2	4	< .001

	Resistance	10	33	
Norfloxacin	Sensitive	3	13	< .001
	Resistance	9	26	
Co trimoxazole	Sensitive	2	14	< .001
	Resistance	9	23	
Ceftriaxone	Sensitive	1	5	< .001
	Resistance	1	33	
Nitrofurantoin	Sensitive	9	28	< .001
	Resistance	3	11	
Ciprofloxacin	Sensitive	3	11	< .001
	Resistance	13	25	
Azithromycin	Sensitive	3	0	< .001
	Resistance	5	1	
Chloramphenicol	Sensitive	2	0	< .001
	Resistance	4	0	
Clindamycin	Sensitive	4	0	< .001
	Resistance	4	0	
Erythromycin	Sensitive	1	0	< .001
	Resistance	7	0	
Linezolid	Sensitive	16	0	< .001
	Resistance	0	0	
Penicillin	Sensitive	3	0	< .001
	Resistance	12	1	
Teicoplanin	Sensitive	8	0	< .001
	Resistance	0	0	
Tetracycline	Sensitive	9	0	< .001
	Resistance	6	0	
Vancomycin	Sensitive	14	0	< .001
	Resistance	0	0	

Table 7: Distribution of isolates in blood cultures and urine cultures.

Bacterial Isolates	Isolates	% of total isolates	% of BSI Pathogens (N=6)	% of urine isolated pathogens (N=50)
Klebsiella spp	3	5.35%	33.33%	6.00%
E. coli	22	39.28%	16.66%	40.00%
Enterococcus	9	16.07%		16.00%
Staphylococcus [MR CONS]	7	12.50%	50.00%	8.00%
NFGNB	4	7.14%	0%	8.00%
Micrococcus	1	1.78%	0%	2.00%
Providencia stuartii	1	1.78%	0%	2.00%
Proteus mirabilis	1	1.78%	0%	2.00%
Pseudomonas spp	1	1.78%	0%	2.00%
Citrobacter freundii	2	3.57%	0%	4.00%
Enterobacter	5	8.92%	0%	10.00%
Total	56	100%	100%	100%

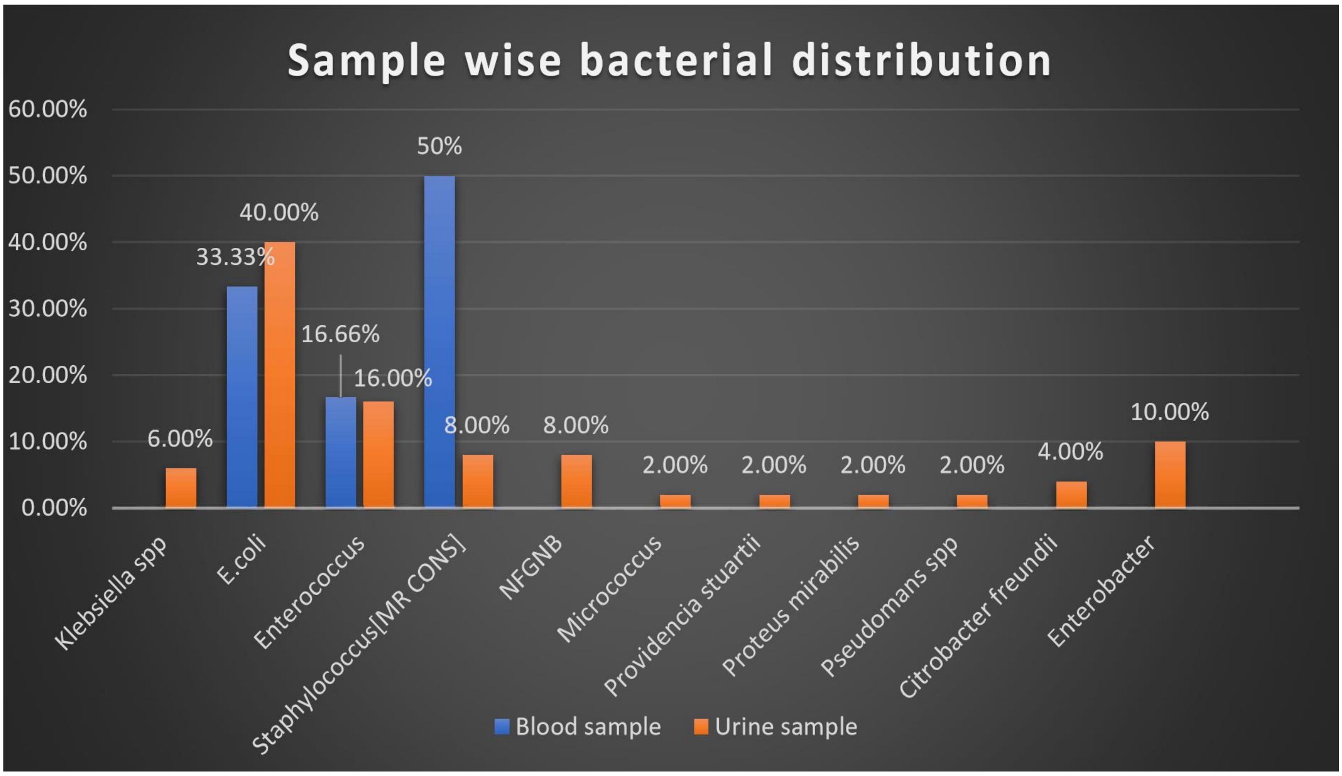

Figure 7: Distribution of isolates in blood cultures and urine cultures.

Isolates of Gram-negative bacteria [GNB] were significantly more prevalent than Gram positive isolates. Among the Gram-positive isolates, the predominant isolates were Enterococcus (n=9) and Staphylococcus spp was (n=7) and micrococcus was (n=1). The Gram-negative isolates were included E. coli (n=22), Enterobacter (n=5), Klebsiella spp (n=3), NF GNB (n=4), Citrobacter (n=2), Providencia spp (n=1), Pseudomonas (n=1), Proteus spp (n=1).

In case of the Enterococcus GPB, Cefotaxime, Levofloxacin, Ofloxacin, Nalidixic acid were highest resistance (100%). Very less commonly occurring resistance are Ampicillin and Tetracycline (50%) whereas Linezolid, Vancomycin more susceptible to Enterococcus bacteria. Seven isolates of the Staphylococcus were found, among them more often resistance found in the case of Penicillin (100%) and followed by more sensitive to the Gentamicin, Linezolid, Teicoplanin (100%). Chloramphenicol is the low resistance (50%) which was seen in the Staphylococcus bacteria. Again, Clindamycin was very less sensitive (25%) to Staphylococcus. Only one isolate of the Micrococcus was found, among them more resistance was Levofloxacin, Ofloxacin, Nalidixic acid (100%) and followed by more sensitive to the Amikacin, Gentamicin, Nitrofurantoin (100%) to Micrococcus.

In our study we found 22 isolates of E. coli, where in high resistance was observed in Ampicillin, Chloramphenicol, Penicillin (100%), then less resistance was found in the Nitrofurantoin [15.78%], Gentamicin [16.66%]. Likewise, we found the more sensitive to Tigecycline, Colistin (100%) and less sensitive to Ceftriaxone (15.78%). In case of Enterobacter spp were found more resistance to Ampicillin, Cefepime, Cefotaxime (100%), and less resistance to Amikacin (20%), Gentamicin (25%) and more sensitive to Cotrimoxazole, Colistin (100%), and less sensitive to amoxiclav, Nalidixic acid (25%). In case of Klebsiella spp were found more resistance to Ampicillin, Nitrofurantoin (100%) and more sensitive to Amoxiclav, Imipenem (100%). In case of NFGNB more sensitive to Cefotaxime, Ceftriaxone, Ceftazidime (100%) and more sensitive to Amikacin, Nitrofurantoin (100%). In case of Citrobacter spp were found more resistance to Ampicillin (100%) and more sensitive to Cefepime, Nitrofurantoin, Norfloxacin, Imipenem (100%). In case of Providencia spp were found more resistance to Amoxiclav, Ampicillin (100%) and more sensitive to Amikacin, Nitrofurantoin (100%). In case of Proteus spp were found more resistance to Amikacin, Ampicillin (100%) and more sensitive to Amoxiclav, Piperacillin (100%). In case of Pseudomonas spp were found more sensitive to Amoxiclav, Ampicillin (100%) and more sensitive to Amikacin, Nitrofurantoin (100%) to Pseudomonas spp.

DISCUSSION

The aim of the study was to detect the antibiotic resistance and also identify the bacterias causing antibiotic resistance in departments of AH&RC. Considering the inclusion and exclusion criteria, patients will be enrolled. The suitably designed data collection form was used to record all the necessary information. The data was entered to Microsoft Excel spread sheets and cross checked for its accuracy. The statistical analysis was performed using IBM SPSS Statistic software for windows.

Descriptive statistical methods were used including frequency, standard deviation. Variables included in the analysis was age, sex, bacterias and commonly prescribed antibiotics. The study defines antibiotic resistance in Tertiary care teaching hospital of South India. Majority of enrolled among 200 samples from prospective study were males and prominent age group below 20 years. The most commonly identified is gram negative type of bacteria.

Irenge LM, Kabego L, Kinunu FB, Itongwa M, Mitangala PN, Gala JL, Chirimwami RB. Antimicrobial resistance of bacteria isolated from patients with bloodstream infections at a tertiary care hospital in the Democratic Republic of the Congo. S Afr Med J. 2015 Sep 14;105(9):752-5. DOI: 10.7196/SAMJnew.7937. PMID: 26428974. We cultured 112 clinically relevant isolates from 320 blood cultures. Of these isolates, 104 (92.9%) were Gram-negative bacteria (GNB), with 103 bacilli (92.0%) and one coccus (0.9%). Among GNB, Escherichia coli (51.9%), Klebsiella spp. (20.2%), Enterobacter spp. (6.7%), Shigella spp. (5.8%) and Salmonella spp. (4.8%) were the most frequent agents causing BSIs. Other GNB isolates included Proteus spp., Citrobacter spp. and Pseudomonas aeruginosa (both 2.9%), and Acinetobacter spp. and Neisseria spp. (both 0.9%). High rates of resistance to cotrimoxazole (100%), erythromycin (100%) and ampicillin (66.7-100%) and moderate to high resistance to ciprofloxacin, ceftazidime, ceftriaxone, cefuroxime and cefepime were observed among GNB. Furthermore, there were high rates of multidrug resistance and of extended-spectrum β-lactamase (ESBL) production phenotype among Enterobacteriaceae. Gram-positive bacteria included three Staphylococcus aureus isolates (2.7%), four oxacillin-resistant coagulase-negative staphylococci (CoNS) isolates (3.6%) and one Streptococcus pneumoniae (0.9%). No oxacillin resistant S. aureus was isolated. Among clinically relevant staphylococci, susceptibility to co-trimoxazole and ampicillin was low (0-25%). In addition, 58 contaminant CoNS were isolated from blood cultures, and the calculated ratio of contaminants to pathogens in blood cultures was 1:2.

Mamishi S, Mohammadian M, Pourakbari B, Hosseinpour Sadeghi R, Haghi Ashtiani MT, Abdosalehi MR, Rahmani M, Mahmoudi S. Antibiotic Resistance and Genotyping of Gram-Positive Bacteria Causing Hospital-Acquired Infection in Patients Referring to Children's Medical Centre. Infect Drug Resist. 2019 Nov 27; 12:3719-3726. DOI: 10.2147/IDR.S220522. PMID: 31819554; PMCID: PMC6885556. In this cross-sectional study, 6524 cultures were performed and 138 Gram-positive bacteria were isolated (2%). Staphylococcus aureus strains showed the highest antibiotic penicillin resistance (96.3%). Twenty-six per cent of the strains were methicillin-resistant S. aureus (MRSA) and no resistance was found against vancomycin. All isolates of Enterococcus faecium were resistant to ciprofloxacin (100%). The resistance to vancomycin was very high (67%) and no resistance was observed to linezolid. The results of genotyping analysis of S. epidermidis strains showed the presence of two clones with a genetic relationship of over 80%. All of the S. aureus strains were in one cluster and half of the E. faecium strains were in a cluster with a genetic predilection of 80%.

REFERENCES

1. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, Vlieghe E, Hara GL, Gould IM, Goossens H, Greko C, So AD, Bigdeli M, Tomson G, Woodhouse W, Ombaka E, Peralta AQ, Qamar FN, Mir F, Kariuki S, Bhutta ZA, Coates A, Bergstrom R, Wright GD, Brown ED, Cars O. Antibiotic resistance-the need for global solutions. Lancet Infect Dis. 2013 Dec;13(12):1057-98. Doi: 10.1016/S1473-3099(13)70318-9. Epub 2013 Nov 17. Erratum in: Lancet Infect Dis. 2014 Jan;14(1):11. Erratum in: Lancet Infect Dis. 2014 Mar;14(3):182. PMID: 24252483.

2. Gould K. Antibiotics: from prehistory to the present day. J Antimicrobe Chemotherapy. 2016 Mar;71(3):572-5. Doi: 10.1093/Jac/dkv484. PMID: 26851273.

3. Abushaheen MA, Muzaheed, Fatani AJ, Alosaimi M, Mansy W, George M, Acharya S, Rathod S, Divakar DD, Jhugroo C, Vellappally S, Khan AA, Shaik J, Jhugroo P. Antimicrobial resistance, mechanisms and its clinical significance. Dis Mon. 2020 Jun;66(6):100971. Doi: 10.1016/j.disamonth.2020.100971. Epub 2020 Mar 20. PMID: 32201008.

4. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022 Feb 12;399(10325):629-655. Doi: 10.1016/S0140-6736(21)02724-0. Epub 2022 Jan 19. Erratum in: Lancet. 2022 Oct 1;400(10358):1102. PMID: 35065702; PMCID: PMC8841637.

5. Maynard C, Weinkove D. The Gut Microbiota and Ageing. Subcell Biochem. 2018; 90:351-371. Doi: 10.1007/978-981-13-2835-0_12. PMID: 30779015.

6. Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. Mayo Clin Proc. 2011 Feb;86(2):156-67. Doi: 10.4065/mcp.2010.0639. PMID: 21282489; PMCID: PMC3031442.

7. Rollins KE, Varadhan KK, Neal KR, Lobo DN. Antibiotics Versus Appendicectomy for the Treatment of Uncomplicated Acute Appendicitis: An Updated Meta-Analysis of Randomised Controlled Trials. World J Surg. 2016 Oct;40(10):2305-18. Doi: 10.1007/s00268-016-3561-7. PMID: 27199000.

8. Flowers CR, Seidenfeld J, Bow EJ, Karten C, Gleason C, Hawley DK, et al. (February 2013). "Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline". Journal of Clinical Oncology.31(6):794–810. Doi:10.1200/JCO.2012.45.8661. PMID 23319691.

9. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR; Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in

neutropenic patients with cancer: 2010 update by the infectious disease's society of America. Clin Infect Dis. 2011 Feb 15;52(4): e56-93. Doi: 10.1093/Cid/cir073. PMID: 21258094.

10. Sethi NJ, Safi S, Korang SK, Hróbjartsson A, Skoog M, Gluud C, Jakobsen JC. Antibiotics for secondary prevention of coronary heart disease. Cochrane Database Syst Rev. 2021 Feb 23;2(2):CD003610. Doi: 10.1002/14651858.CD003610.pub4. PMID: 33704780; PMCID: PMC8094925.

11. Pangilinan R, Tice A, Tillotson G. Topical antibiotic treatment for uncomplicated skin and skin structure infections: review of the literature. Expert Rev Anti Infect Ther. 2009 Oct;7(8):957-65. Doi: 10.1586/eri.09.74. PMID: 19803705.

12. Lipsky BA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. Clin Infect Dis. 2009 Nov 15;49(10):1541-9. Doi: 10.1086/644732. PMID: 19842981.

13. Heal CF, Banks JL, Lepper PD, Kontopantelis E, van Driel ML. Topical antibiotics for preventing surgical site infection in wounds healing by primary intention. Cochrane Database Syst Rev. 2016 Nov 7; 11(11): CD011426. Doi: 10. 1002/14651858.CD011426. pub2. PMID: 27819748; PMCID: PMC6465080.

14. Hung KK, Lam RP, Lo RS, Tenney JW, Yang ML, Tai MC, Graham CA. Cross-sectional study on emergency department management of sepsis. Hong Kong Med J. 2018 Dec;24(6):571-578. Doi: 10.12809/hkmj177149. Epub 2018 Nov 14. PMID: 30429360.

15. Slama TG, Amin A, Brunton SA, File TM Jr, Milkovich G, Rodvold KA, Sahm DF, Varon J, Weiland D Jr; Council for Appropriate and Rational Antibiotic Therapy (CARAT). A clinician's guide to the appropriate and accurate use of antibiotics: the Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria. Am J Med. 2005 Jul;118 Suppl 7A:1S-6S. Doi: 10.1016/j.amjmed.2005.05.007. PMID: 15993671.

16. Slama TG, Amin A, Brunton SA, File TM Jr, Milkovich G, Rodvold KA, Sahm DF, Varon J, Weiland D Jr; Council for Appropriate and Rational Antibiotic Therapy (CARAT). A clinician's guide to the appropriate and accurate use of antibiotics: the Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria. Am J Med. 2005 Jul;118 Suppl 7A:1S-6S. Doi: 10.1016/j.amjmed.2005.05.007. PMID: 15993671.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.