

Superbugs: An invincible threat in post antibiotic era

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ABSTRACT

Background: Superbug resistance is a very rare, invincible global problem arising as a threat in hospitals as well as in the community. *Methicillin-Resistant Staphylococcus aureus* (MRSA), *Vancomycin-Resistant Enterococci* (VRE) and *Multidrug-resistant Gram-negative bacilli* (MDR-GNB) etc are the most deadly contagious strains. This study discloses the prevalence and risk factors associated with superbugs there by aiding the adoption of preventive measures to reduce resistance patterns in hospital settings.

Aim: Identification of the superbug that predominantly shows antibiotic resistance in hospitals and analyzing the risk factors for the occurrence of antibiotic resistance.

Materials and methods: A prospective observational study was conducted for one year, from 1st September 2019 to 31st July 2020 to evaluate the prevalence and risk factors of antibiotic-resistant superbugs among the 80 patients selected from the various departments (General Medicine, General Surgery, Nephrology, Pulmonology, Orthopedics, orthopaedicsurgery, Neurology, Urology, and Neurosurgery) of a tertiary care referral hospital.

Results: *Methicillin-resistant Staphylococcus aureus* and *Pseudomonas aeruginosa* were antibiotic-resistant superbugs that predominantly showed resistance in hospital settings.

Conclusion: *Pseudomonas aeruginosa* and *Methicillin-resistant superbugs* were the predominantly found superbugs in hospital settings. Major risk factors for antibiotic-resistant superbugs were found to be Prolonged hospitalization, previous antibiotic therapy, failure to take the antibiotic as prescribed by physicians, patient co-morbid conditions, prophylactic use of antibiotics, patient diet etc.

1. Introduction

Superbug resistance, a kind of antibiotic resistance is a very rare and serious threat in hospital settings. Some causes for this include, Over prescription of antibiotics, Misuse of antibiotics or using without indication, Poor drug quality, Genetic mutation among micro-organisms, Patient not completing the entire antibiotic dosage or not strictly following the correct antibiotic regimen, Long term hospitalization, Prophylactic antibiotic therapy and Poor hygiene and sanitation.¹ Superbug is a non-specific term used to describe strains of bacteria that is resistant to at least one or more commonly used antibiotics.^{2,3} Superbug is a bacterial strain that would become resistant, only the following exposure to the antibiotic. The degree of superbugs is a term used to refer to the no of antibiotics to which it is resistant and they can increase morbidity and mortality rate and they also cause economic loss.

Major organisms that show antibiotic resistance superbugs in hospital settings are *Methicillin-resistant Staphylococcus aureus* (MRSA), *Multidrug-resistant Pseudomonas aeruginosa*, *Carbapenem-resistant Enterobacteriaceae*, *ESBL-producing Enterobacteriaceae*, *Vancomycin-resistant Enterococcus*, *E. coli* Hx30 etc.

Out of the total bacteria in a hospital, a major proportion was MDR bacteria. The repertoire of antibiotics that show susceptibility to common MDR gram-negative bacilli to higher antibiotics includes Imipenem, netilmycin, Piperacillin, Cefepiramin, and Cefepime.⁴ Many studies concluded that the extensive problem of antibiotic resistance is encountered in this hospital. Thus, it calls for the prudent and appropriate use of antibiotics is required to reduce the emergence of resistance. Each hospital should also have its antibiotic policy based on the susceptibility pattern of bacteria at a particular time, which should be reviewed as and when required. Rational antibiotic use and effective

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infection control practices can go a long way in preventing the development of antibiotic resistance.^{6,7} Endogenous acquisition, as opposed to patient-to-patient spread, was the predominant mechanism of acquisition. Residence in a long-term care facility and antibiotic exposure may be important factors promoting the spread of multidrug-resistant gram-negative bacteria among this patient population.

This study identified the superbug that commonly shows antibiotic resistance in our hospital settings. The patients who were at risk of acquiring resistance were also identified. The study also accounted for the importance of precise antibiotic usage. The use of targeted antibiotics that specifically acts on the identified organism is the key strategy to limit bacterial resistance. This study helps to disseminate information about the importance of proper antibiotic use to control the spread of antibiotic resistance particularly in medical-surgical and critical care settings and to reinforce infection control procedures.

2. Materials and methods

This prospective observational study was carried out in KIMS Al Shifa Super Speciality Hospital, a tertiary care hospital in Perinthalmanna in Malappuram district. This study presented data on the prevalence and risk factors of antibiotic-resistant superbugs in different departments of the tertiary care hospital. Prior ethical clearance was obtained from the hospital before commencing the study. The study was carried out for a period of one year commencing from September 2019 to July 2020 among the inpatients of GeneralMedicine, GeneralSurgery, Nephrology, Pulmonology, Orthopaedics, Neurology, Urology, Neurosurgery department of a tertiary care hospital. Among the patients who were admitted to this department, Patients >18 years of age and Patients suspected of severe infection that has been screened for culture and sensitivity and receiving antibiotics were included in the study. Patients never suspected of infections, Patients receiving antibiotics as out-patients and Patients not willing to participate were excluded from the study. Patients with certain infections undergoing culture and sensitivity testing and screened for antibiotic resistance, so patients without infections were eliminated from the study.

Pre designed data collection forms were used to collect and record patient data, which describe patient demographics, past medical history, past medication history, co-morbid conditions, previous antibiotic therapy taken, procedures done, prolonged hospital admissions, OTC usage of drugs etc. The patient details are obtained from the case files and also directly from the patients/bystanders during the ward rounds. All the cases were reviewed prospectively and monitored extensively, to identify the patients at increased risk of acquiring superbug resistance. Microbiological data were also collected which included the type of specimen, name of the organism, and name of antibiotics to which the organisms show resistance or sensitivity. Resistance patterns of antibiotics were also identified. The collected data was obtained and stored in a manner that ensured its confidentiality and safety. Statistical analysis was done using collected data, which were analyzed using the SPSS 20 for the windows version. Numerical data were expressed as mean and standard deviation. For the categorical variables frequencies and percentages were computed with the Pearson Chi-square test. For quantitative variables paired T-test was used.

3. Results

From September 2019–July 2020, 80 patients were enrolled in the study. Among them, the majority of the patients 56.3 % (n = 45) were males, while the remaining 43.8 % (n = 35) were females (Fig. 1). Patients were categorized into 3 age groups (below 30, 30–60, and above 60). Among the total cases collected (n = 80), the majority of the patients were in the age group 31–60 (60 %)(n = 48), and the least number of patients were patients who were <30 years old (6.30 %)(n = 5)(Fig. 2). When the number of patients distribution among the selected

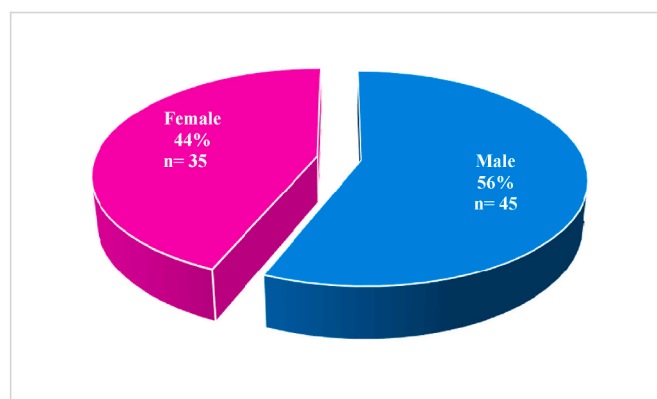


Fig. 1. Gender wise distribution

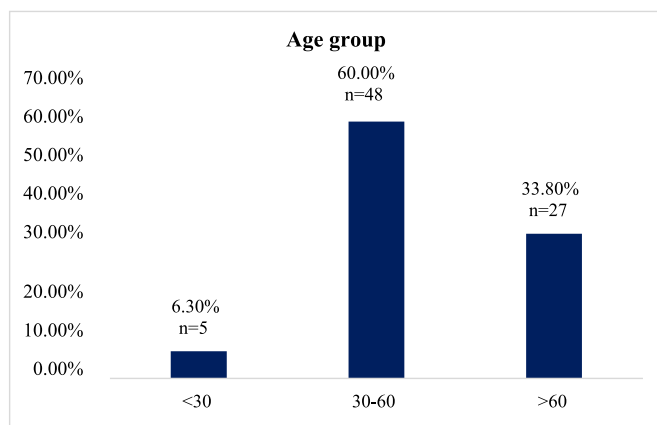


Fig. 2. Age-wise distribution.

departments was calculated, about 23.80 % (n = 19) were noticed under the orthopaedics department, followed by other departments with the least number among the orthopaedics surgery and gastroenterology departments 1.3 % in both (n = 1)(Fig. 3). While observing the co-morbidity stats, Out of the collected, 43 patients presented had both diabetes mellitus and hypertension (53.8 %), 25 patients had diabetes (31.3 %), 8 patients without any co-morbidities (10 %), 3 patients had only hypertension as co-morbidity (3.8 %) and only 1 patient had CKD (1.30 %) (Fig. 4). From the given patient data's, antibiotics are mainly prescribed in surgery cases 52.5 % (n = 42), followed by 8.8 % in CKD (n = 7), followed by 5 % in urinary tract infection (n = 4), followed by 3.8 % in respiratory tract infections (n = 3), followed by 2.5 % in sepsis conditions (n = 2) and about 1.3 % in conditions like central line (n = 1),

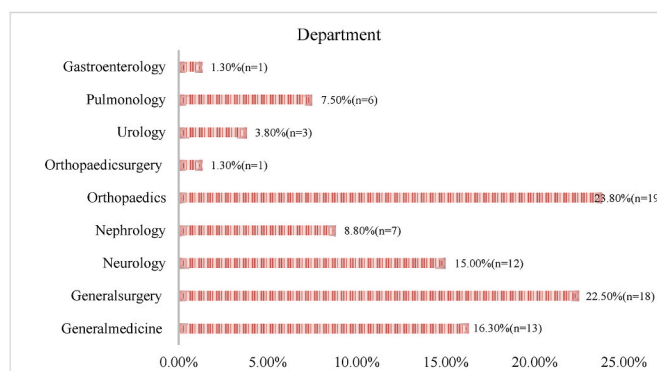


Fig. 3. Department-wise distribution.

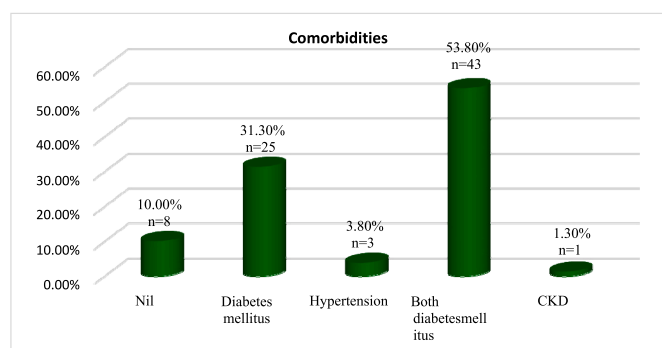


Fig. 4. Co morbid conditions of the patient.

asthma(n = 1), COPD(n = 1), AKD(n = 1). For about 18 patient conditions that led to the use of antibiotics was not specified (Fig. 5). In hospital settings, about 57 % resistance was shown by *Pseudomonas aeruginosa* (n = 46), followed by about 43 % in MRSA (n = 34). *Pseudomonas aeruginosa* was the predominant superbug that shows antibiotic resistance (Figure-6) and The resistant organism were collected from different specimens, out of this, around 43.8 % resistant organisms were collected from the pus swab (n = 35), followed by 25 % from urine (n = 20), followed by 13.8 % from blood (n = 11) and sputum (n = 11), followed by 2.5 % from mucus (n = 2) and 1.3 % from suction tube (n = 1) (Fig. 7). Among the patients, about 67 have undergone certain procedures of which, about 60 % of patients undergone surgical procedures (n = 48), 13.8 % catheterization (n = 11), 5 % of patients other procedures (name of the procedures were not specified) (n = 4), 3.8 % patients with a central line (n = 3) and 1.3 % in that patient with nasogastric tube use (n = 1) (Fig. 8). Patients not completing the antibiotic dosage as prescribed by the physician was the major risk factor for the emergence of resistance. From the collected data, about 85 % of patients never completed the course of antibiotics (n = 68 %) (Fig. 9). Another major risk factor for antibiotic resistance is prolonged hospitalization. From the 80 cases collected, 71.3 % of patients underwent prolonged hospital admissions (n = 57) (Fig. 10). Among other factors for resistance, About 93.80 % of patients were using over-the-counter medications (n = 75) (Fig. 11) and about 56.30 % has undergone prophylactic use of antibiotics (n = 45) (Fig. 12), considering the diet as a risk factor, out of 80 patients, about 90 % patients were non-vegetarians (n = 72) and about 10 % patients were vegetarians (n = 8) (Fig. 13). In the hospital scenario, the predominant organism (57 %) that shows antibiotic resistance is *Methicillin-resistant Staphylococcus aureus* (MRSA). In the case of MRSA, the antibiotics such as Amoxicillin clavulanic acid (51.20 %), Ampicillin (51.20 %), Cefotaxime (51.20 %), Ceftriaxone (51.20 %), Ceftriaxime (51.20 %), Benzylpenicillin (51.20 %), Oxacillin (51.20 %), Ciprofloxacin (51.20 %), Levofloxacin (51.20 %), Erythromycin (51.20 %), clindamycin (51.20 %) are resistant hence shows the least sensitivity

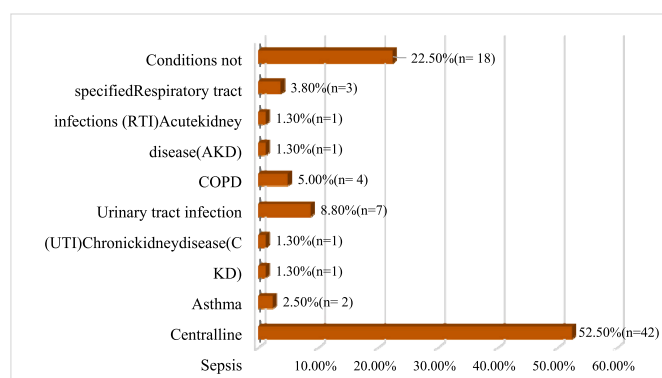


Fig. 5. Conditions leading to the prescription of antibiotics.

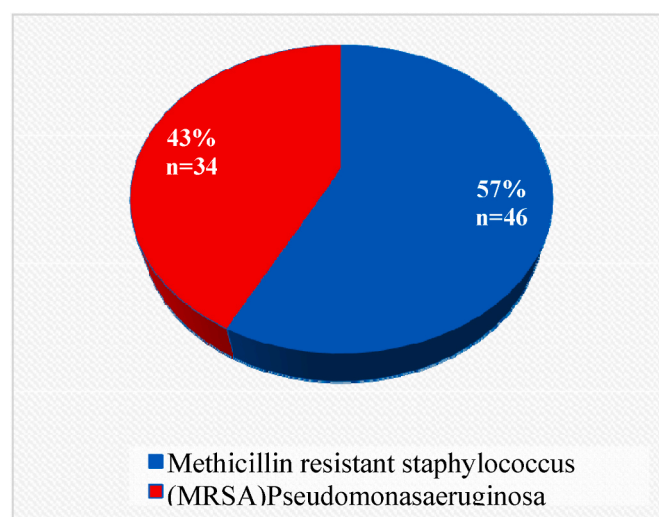


Fig. 6. Microbiological data's Organism.

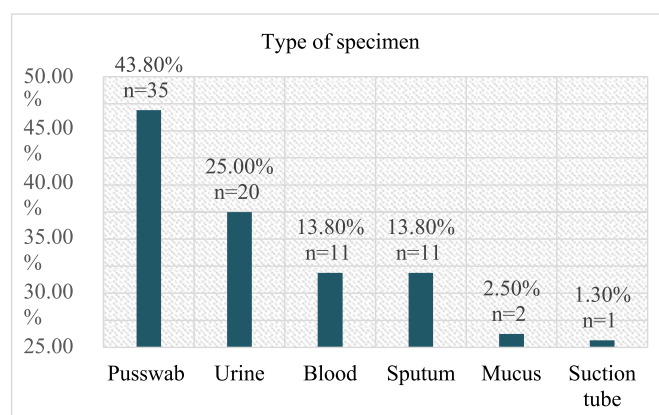


Fig. 7. Type of specimen.

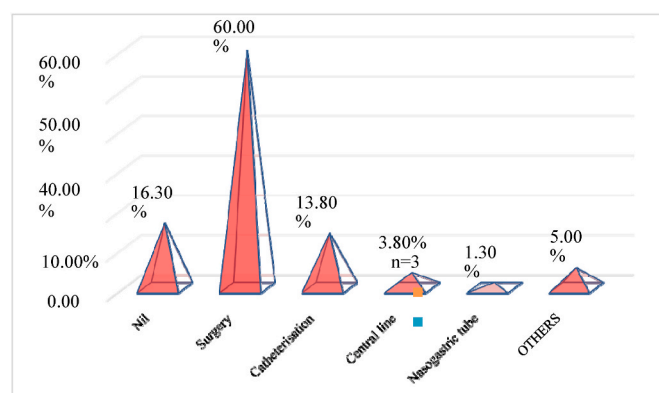


Fig. 8. Procedures are done for the patient.

to MRSA. Antibiotics such as Gentamycin, Linezolid, Teicoplanin, Tetracycline, Trimethoprim-sulfamethoxazole, and Doxycycline are highly sensitive to MRSA (Fig. 14). In the case of *Pseudomonas aeruginosa*, the antibiotics such as Ticarcillin-clavulanic acid, Piperacillin/Tazobactam, Ceftazidime, cefoperazone/Sulbactam, Cefepime, Imipenem, Meropenem, Amikacin, Gentamycin, Ciprofloxacin, Levofloxacin and Tigecycline shows most resistance. Only the antibiotic Colistin (48.80) shows sensitivity to *Pseudomonas aeruginosa* (Fig. 15).

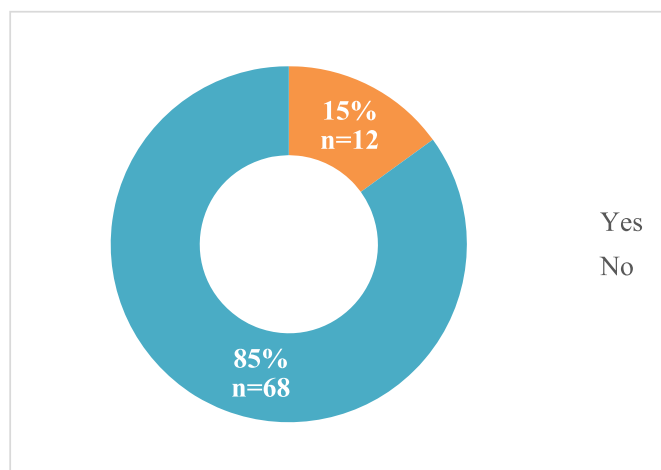


Fig. 9. Whether the course of antibiotics was completed or not.

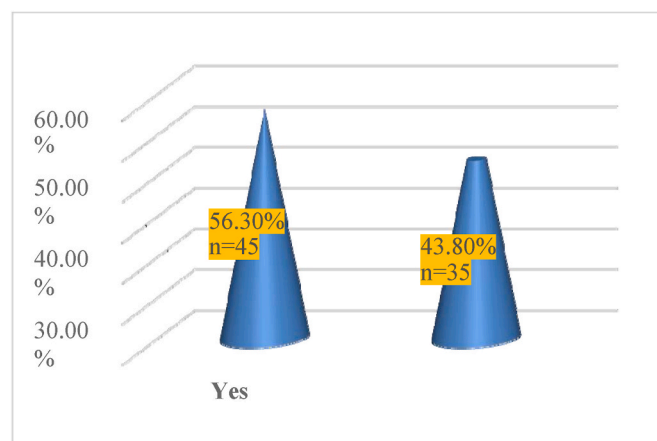


Fig. 12. Prophylactic use of antibiotics.

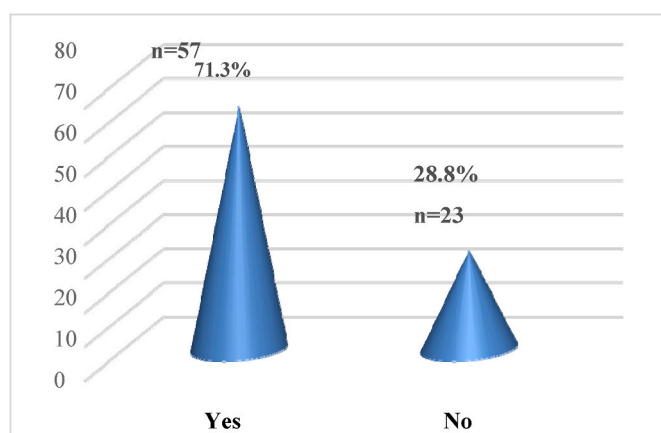


Fig. 10. Prolonged hospitalization.

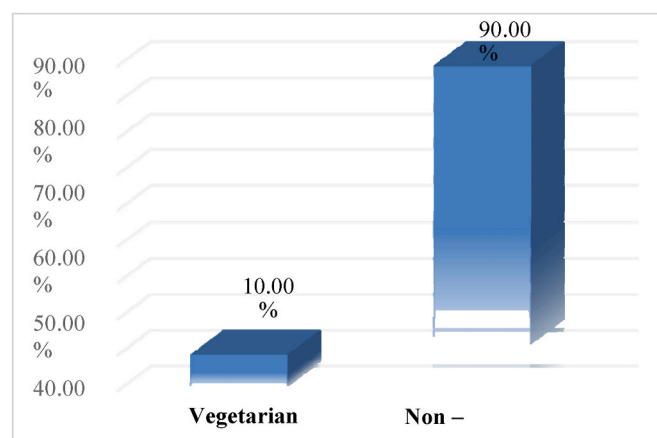


Fig. 13. Patient diet.

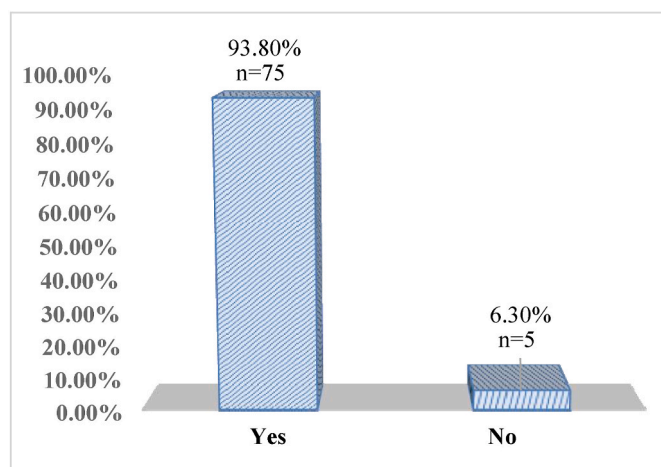


Fig. 11. OTC/off-label antibiotic usage.

4. Discussion

A prospective observational study was carried out from September 2019 to July 2020 among the in patients of a tertiary care hospital to evaluate the prevalence and risk factors of antibiotic-resistant superbugs in various departments such as general medicine, General surgery,

Neurology, Nephrology, Urology, Orthopedics, orthopaedics surgery. Drug-resistant microbes, i.e. superbugs, are one of the most dangerous threats in our health care facility. The study was conducted with primary objectives to find out the prevalence of antibiotic-resistant superbugs in tertiary care hospitals and to find out risk factors for superbug infection. The study also helps to find out Patients who are at risk of developing superbug infection. The data were collected from 80 subjects prospectively as per inclusion and exclusion criteria. The majority of the patients (56.3 %) were males. A study done by Jon p. Furuno et al. strengthens our study because out of 147 patients enrolled for the study majority of the population was males (61 %).¹⁰ The study done by Reshma Rajendran shows that out of 401 patients who participated, 200 were males and 201 were females.¹ Here female population is more with superbug infection than males, but the difference is marginal. When the age was categorized, among the total cases (80) collected, the majority of the patients were in the age group 31–60 (n = 48). The result is in agreement with the studies conducted by Alkali Bashir et al., which show that the majority of antibiotic-resistant superbug infections belong to the age group of 49–58 years while the 18–28 years of age group constituted the least age group and most of the patients with superbug infection were females compare to males.⁴ In a study conducted by Tamara Milovanovic et al., they found that being >65 years is one of the risk factors for MDR infections.¹¹ Both of the studies show that highly aged patients are more at risk of having antibiotic resistance. The study observed that most of the patients with superbug infection presented with much co-morbidity. Co-morbidities were identified which included hypertension, diabetes mellitus, those having both diabetes mellitus and hypertension, CKD and others. 43 patients among the study population

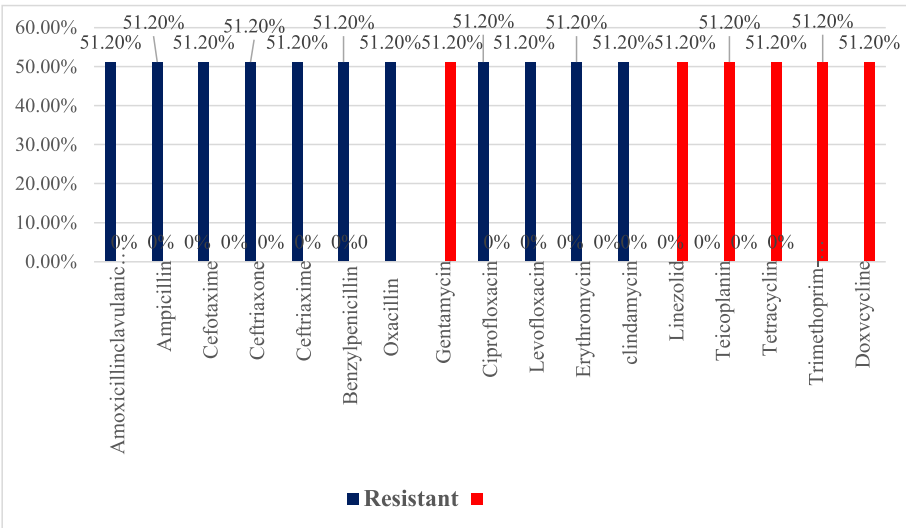


Fig. 14. MRSA.

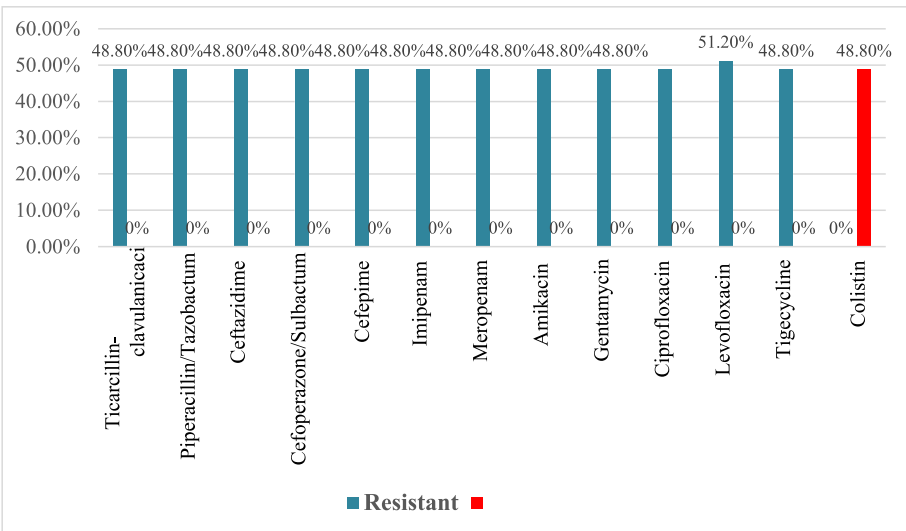


Fig. 15. Pseudomonas aeruginosa

had both diabetes mellitus and hypertension (53.8 %) followed by other co-morbidities. A study conducted by Urvish Trivedi et al. shows that co-morbidities like DM, peripheral vascular disease(PVD), CKD, CHF, CAD, and COPD were found significant risk factors for superbug infection.¹² In a study conducted by Jon p. Furuno et al. shows that diabetes mellitus, heart failure, and renal disease were the most prevalent co-morbid conditions.¹⁰ From the above studies, it is clear that diabetes patients are in an important risk category for those having antibiotic-resistant infections. A study conducted by Valerie aloush et al. concluded that critically ill patient with multiple co-morbidities and treatment with multiple antibiotic agents is more likely to have antibiotic resistance.⁹ When the number of patient distribution among the selected departments was calculated, most of the patients with superbug infection among the total of 80 patients were involved in the study, about 23.80 % (n = 19) were coming under the orthopaedics department, followed by other departments. From the given patient data, antibiotics are mainly prescribed in surgery cases 52.5 % (n = 42), followed by other conditions. For about 18 patients conditions that led to the use of antibiotics were not specified. In hospital settings, about 57 % resistance was shown by *Pseudomonas aeruginosa* (n = 46), followed by about 43 % in MRSA (n = 34). *Pseudomonas aeruginosa* was the

predominant superbug that shows antibiotic resistance. In a study conducted by Jon P. Furuno et al. prevalence of MRSA at any site was high when compared to other organisms like *Acetobactor baumannii*.¹⁰ In a study done by Urvish Trivedi et al., among 63 MDR bacterial strains isolated from the wounds, MRSA was the most prevalent in MDRO, followed by enterococcus and pseudomonas species.¹² The above studies reveal that MRSA is the most prevalent organism obtained, which shows is not in agreement with our results. The resistant organism was collected from different specimens, out of this, around half of the resistant organisms were collected from the pus swab(n = 35), followed by other samples like urine, blood, sputum, mucus and suction tube. From the collected data, about 67 patients have undergone certain procedures with surgical procedures (n = 48) being the major one. Other procedures include catheterization, central line, and nasogastric tube use. In 5 % of them, a procedure was done, but it was not specified. 16.3 % of patients didn't undergo any procedures. The study done by Min-Sook kang et al., observed that inpatients and patients who used in dwelling catheters showed a high risk of MDR organism isolation.¹³ A study conducted by pinyo rattanauwpawan shows that previous antibiotic use and certain procedures like previous nasogastric tube use were common risk factors for the various species of MDR pathogens.⁵ From the 80 cases

collected, 71.3 % of patients have undergone prolonged hospital admissions ($n = 57$), therefore prolonged hospitalization is one of the major risk factors for superbug infections. A study done by Pinyo Rattanapawan et al. strengthens this study; it shows that there was a slightly increasing trend of MDR bacteria colonization by all important pathogens after hospitalization.⁵ In a study conducted by Ching Jou Lim et al. shows that long-term hospital stay is an important reservoir of MDR organisms, with person-to-person transmissions being a potential issue.¹⁴ A study done by Kivanc Serefhanoglu et al. showed similar results like duration of hospitalization before bacteraemia was only an independent risk factor for MDR infections.¹⁵ Similar results are shown from a study conducted by Aurora Pop-Vicas et al., who concluded that residence in long-term care facility and antibiotic exposure may be the important factors promoting the spread of MDR bacteria among the patient population.⁸ The results of the above studies strengthen this study. To add to that, over-the-counter (OTC) drug is another major risk factor as about 93.80 % of the total patients were using over-the-counter medications. A study done by Anthony Ayodeji et al. strengthens this study, it shows that over-the-counter (OTC) drug use or self-medication prior to hospital visits is one of the reasons for the emergence of antimicrobial resistance, especially in developing countries.¹⁶ Previous antibiotic therapies are also an important risk factor, certain physicians prescribe antibiotics without any indication. From the patient's data, about 91 % of the patients are taken previous antibiotic therapy ($n = 73$). A study conducted by Pinyo Rattanapawan shows that previous antibiotic use and certain procedures like previous nasogastric tube use were common risk factors for the various species of MDR pathogens, these studies also strengthen our results.⁵ Patients not completing the antibiotic dosage as prescribed by the physician are one of the major risk factors for the emergence of resistance. From the collected data, about 85 % of patients never complete the course of antibiotics. Along with that, patient diet could also be a risk factor for the acquisition of resistance. Out of 80 patients, about 90 % of patients were non-vegetarians ($n = 72$) and about 10 % of patients were vegetarians ($n = 8$). A study done by Reshma Rajendran in this area strongly supports our results, the animals (chicken, meat, pig etc.) are given regular dosages of antibiotics for more weight gain, growth etc which will develop resistant bacteria in their guts.¹ So non-vegetarians are more prone to antibiotic resistance. In the hospital scenario, the predominant organism that shows antibiotic resistance is *Methicillin-resistant Staphylococcus aureus* (MRSA), which is about 57 %. In the case of MRSA, the antibiotics such as Amoxicillin clavulanic acid (51.20 %), Ampicillin (51.20 %), Cefotaxime (51.20 %), ceftriaxone (51.20 %), Ceftriaxime (51.20 %), Benzylpenicillin (51.20 %), Oxacillin (51.20 %), Ciprofloxacin (51.20 %), Levofloxacin (51.20 %), Erythromycin (51.20 %), clindamycin (51.20 %) are resistant hence shows the least sensitivity to MRSA. Antibiotics such as Gentamycin, Linezolid, Teicoplanin, Tetracycline, Trimethoprim-sulfamethoxazole, and Doxycycline are highly sensitive to MRSA. In a study done by Sujata Baveja et al., they show that out of 2987 bacteria grown about 60 % of *Staphylococcus aureus* was MRSA. Out of 233 MRSA isolated, all were sensitive to vancomycin, netilmicin, and linezolid and all the MRSA were resistant to 1st line antibiotics.⁶ In our hospital settings MRSA is resistant to all 1st line antibiotics used for treatment, so the above study strengthens our results. In the case of *Pseudomonas aeruginosa*, the antibiotics such as Ticarcillin-clavulanic acid, Piperacillin/Tazobactam, Ceftazidime, cefoperazone/Sulbactam, Cefepime, Imipenem, Meropenem, Amikacin, Gentamycin, Ciprofloxacin, Levofloxacin and Tigecycline shows most resistance. Only the antibiotic Colistin (48.80) shows sensitivity to *Pseudomonas aeruginosa*. The strength of the study is to identify the superbug that predominantly occurs in hospital settings and to identify patients who are at risk for developing antibiotic resistance, there by providing updated knowledge regarding the appropriate and effective use of antibiotics to all health care professionals to control the spread of antibiotic resistance. The study has some of the limitations such as it is a single centre study, extending the study to different settings reveals prescribing practices of

that population, it was conducted in short duration and in small sample size, it was performed only in inpatient data bases, which can be extended to outpatient, Irrational prescribing of antibiotics is the major factor responsible for the emergence of antibiotic resistance but this factor is not included and this study only addresses information of selected departments. Future directions of the study are to provide awareness regarding the safe use of antibiotics especially in those patients who have poly pharmacy and co-morbidities.

5. Conclusion

Now a day's antibiotic resistance superbug is one of the most dangerous threats in our hospital and community setting. In a tertiary care setting most found superbugs were *Pseudomonas aeruginosa* and methicillin-resistant superbugs. Prolonged hospitalization, previous antibiotic therapy, failure to take the antibiotic as prescribed by physicians, patient comorbid conditions, prophylactic use of antibiotics, patient diet etc. are the major risk factors for antibiotic-resistant superbugs. Patients with comorbid conditions like diabetes mellitus and hypertension and those who undergo surgeries are more at risk of developing resistance.

Ethics approval

The study has been approved by ethical committee with ref no-KAS/IEC/Mpharm/2019-09.

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Authors contribution statement

Concept of study- Dilip C, Jafer, Christy Mary.
Acquisition of data- Christy Mary.
Analysis and interpretation- Christy Mary and Sharath Murali.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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Abbreviations

MRSA	Methicillin-resistant staphylococcus aureus
VRE	Vancomycin-Resistant Enterococci
MDR - GNB	Multidrug-resistant Gram-negative bacilli
MDR	Multidrug resistant
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
AKD	Acute Kidney Disease
OTC Drugs	Over The Counter Drugs
DM	Diabetes Mellitus
PVD	Peripheral Vascular Disease
CHF	Congestive Heart Failure
CAD	Coronary Artery Disease

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