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Appropriate Use of Restricted Antibiotics: Utilization, Bacterial Resistance and Impact of Clinical Interventions in Prescribing Practice – A Tertiary Care Hospital Population-Based Study.

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Abstract:
Aim of the study: The study was designed to monitor the usage of Intravenous (IV), Intramuscular (IM), Intrathecal and Nebulized preparations of restricted antibiotics and the existing resistance pattern in a tertiary care hospital. It is important to know the resistance pattern as resistance among both gram positive and gram-negative organisms become a concern in treating the disease in critically ill patients.
Materials and methods: A prospective interventional study was carried out in a 850 bedded tertiary care private corporate hospital over a period of six months (December 2017 – June 2018). All patients receiving IV, IM, Intrathecal and Nebulized restricted antibiotics in inpatient wards were included in this study. The cases were analyzed for appropriateness of the antibiotics chosen based on the dose, frequency, choice of drug for the specific site of infection.
Results: In our study, we found *Klebsiella pneumoniae* (72%) with a resistance pattern of Klebsiella Carbapenamase Producer (KCP) commonest organism isolated in the wards. Following which *Escherichia coli* (48.8%) with a resistance pattern of Extended Spectrum Beta Lactamases (ESBL). Penicillin were most commonly used empirical antibiotic and Colistimethate sodium (21.3%) was the most commonly used antibiotic following Meropenem (21.5%). Among gram positive organisms mainly *Staphylococcus aureus* with Methicillin resistance (MRSA) contribute 70% and *Enterococcus faecium* (72%) were found predominant compared to others.
Conclusion: Cefoperazone sulbactam was commonly used antibiotic prescribed to patients with suspected infections. Most patients had developed resistance to the first line antibiotic further requiring the need for antibiogram for the usage of restricted antibiotics.
Keywords: Antibiogram, Bacterial resistance, Clinical intervention, Restricted antibiotic, Utilization pattern,

I. INTRODUCTION

Antibiotics are among the most commonly used drug worldwide [1,2]. Misuse or overuse has led to the development of resistance and therapeutic failure which further increases the healthcare costs and mortality rates [3]. Data from 22 countries were reported by WHO reveals that more than 5,00,000 isolates of *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Streptococcus pneumoniae and salmonella* with alarming resistance. *Acinetobacter* isolated were resistant to carbapenems [4]. Increased morbidity and mortality are associated with inappropriate initial therapy. Specific to certain Multi Drug Resistant (MDR) gram negative organisms such as *Pseudomonas*, *Acinetobacter*, *Klebsiella pneumoniae* and *Escherichia coli* becomes difficult target if they develop resistance. Controversies do exist in targeting these organisms with either mono therapy or combination therapy, but no studies have a clear-cut evidence. So once antibiogram is available, escalation or de-escalation should be considered. Appropriate antibiotics selection has a major role in reducing both. Antibiotic resistance is shown to decline with restricting the usage and altering the empirical antibiotic of choice for a specific diagnosis [5].

For the main aim of reducing the Antimicrobial resistance, prudent use of antibiotics is essential. Antibiotic policy in a hospital is created based on the local epidemiology and evidence-based medicine. Restricted antibiotics are those which are reserved for complex infections caused by organisms that are resistant to first line antibiotic therapy. Various hospitals have developed their own list of restricted antibiotics based on their local prevalence of organisms. Certain class of antibiotics that are commonly kept as restricted, some examples are Carbapenems, Polymixins, Phosphonic acid derivatives and Glycopeptides [6].

Nebulized antibiotics help in maximizing the drug delivery at target site. Local pulmonary irritation remains the major drawback with inhaled antibiotics therapy due to the preservatives in the product. Colistin, Tobramycin and Aztreonam were certain drugs approved for use in lower airway infections [7].

II. METHODOLOGY

1. Objectives of the study:

- To evaluate the appropriateness of restricted antibiotics usage.
- To analyze the existing bacterial resistance pattern in our hospital.
- The impact of clinical pharmacist intervention for the appropriateness of therapy.

2. Materials and methods:

2.1 Study site: The study was carried out in an 850 bedded tertiary care private corporate hospital.
2.2 Study duration: Six months (December 2017 – June 2018).
2.3 Study population: 408
2.4 Study design: Prospective Interventional study.
2.5 Inclusion Criteria:
All in-patients receiving intravenous, intramuscular, intrathecal and nebulized restricted antibiotics in inpatient wards were included in this study

2.6 Exclusion criteria:

- Patients who received other antibiotics that were not included in the list of restricted antibiotics.
- Neonates and pediatric patients age less than 10 years.
- Patients who received restricted antibiotics in critical care areas.
- Patients who died after 48 hours of starting antibiotics
- Antibiotic therapy stopped within 48 hours of initiation were excluded from our study

3. Assessing the appropriateness of antimicrobial usage:

- Justification of the prescribed drug according to the microbiological and clinical condition at the time of antibiotic prescription.
- Was the appropriate antibiotic chosen and consistent with the hospital guidelines? If not whether it is justifiable?
- Was the duration of therapy adequate?
- If any combination was prescribed, was such therapy justified based on the site of infection, severity and microbiological criteria?
- Re-evaluation and adaptation of therapy after 4 to 6 days of antibiotics.

The list of restricted antibiotics analyzed were polymyxins (Polymixin E and Polymixin B), Glycylcycline (Tigecycline), Oxazolidinone (Linezolid), Glycopeptides (Vancomycin and Teicoplanin), Aminoglycosides (Streptomycin, Amikacin and Gentamicin), Carbapenems (Meropenem, Imipenem, Ertapenem and Doripenem) and Phosphonic acid derivatives (Fosfomycin). These drugs have often been the target of attempts to restrict and control their use without proper antibiogram. Considering the overuse of antibiotics and resistance problems, we developed a list of 14 restricted antibiotics that are commonly used in our hospital. Their use and course of therapy were monitored throughout the therapy.

Patient's relevant clinical and microbiological data were collected when the therapy began, as well as follow up was done until the end of the antimicrobial course. Orders were checked upon by the clinical pharmacists for appropriateness and recommended usual daily dosing of the particular drug for every patient. Any departure should be justified, if necessary, in liaison with the prescribing physician. Suggestions are provided for alternative choices and any dose adjustments to be done were informed and altered accordingly.

To analyze the appropriateness of prescribing, antimicrobial prescribing was divided into three categories. In addition, various other criteria were also considered [8].

- Prophylactic therapy – Antibiotics given in the absence of microbiological documentation with a suspected infection.
- Empirical therapy – which includes antibiotics course that were initiated empirically but were subsequently associated with microbiological documentation.
- Definitive therapy – Antibiotic course initiation with full microbiological documentation of infection and identification of pathogen.

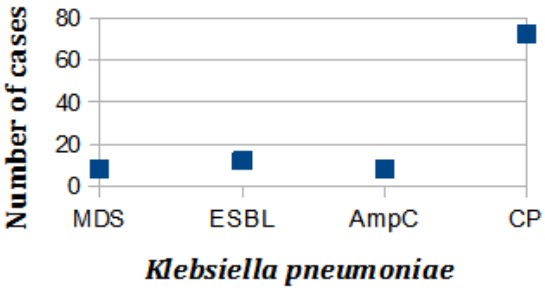
III. RESULTS

3.1. Prevalence of organism and the resistance pattern:

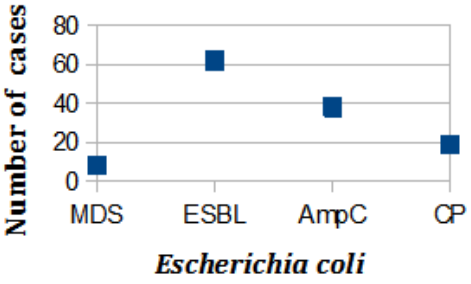
Resistance among both gram positive and gram-negative organisms have become a concern in treating

the disease in critically ill patients. In the wards greater proportion of infection is with Gram Negative organisms. Of the gram-negative organisms isolated 72% were *Klebsiella pneumoniae (KCP)* with a resistance pattern of Carbapenamase Producer (Fig 1)

ıre 1: Resistance patterns of Klebsiella pneumoı



ıre 2: Resistance patterns of Escherichia c

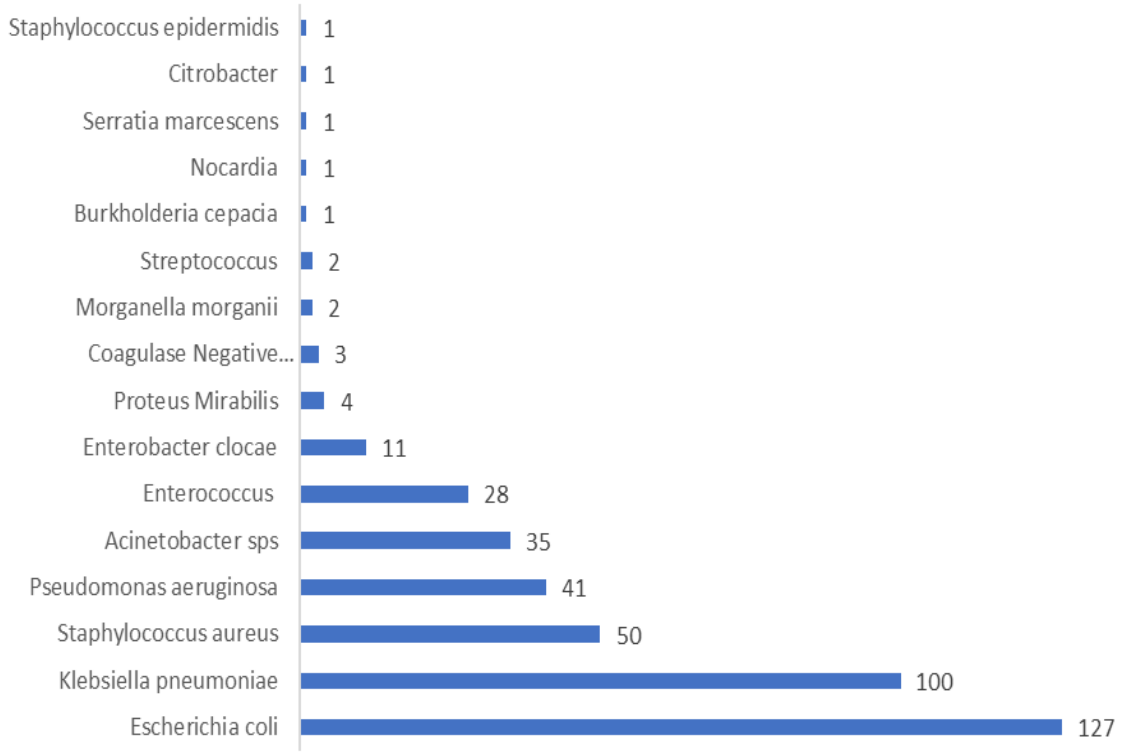


MDS – Multidrug Sensitive ESBL – Extended Spectrum Beta Lactamases
AmpC – AmpC beta lactamase producer CP - Carbapenemase Producers

and *Escherichia coli* (48.8%) with a resistance pattern of Extended Spectrum Beta-Lactamases (ESBL) causing more infection (Fig 2).

We had 41 cases (10%) of *Pseudomonas aeruginosa*, *Acinetobacter Sps* though found it contributed only to 8.57%. Certain other organisms like *Burkholderia*, *Serratia*, *Staphylococcus epidermidis* and *Nocardia* species appear to be the least common organism, we had only one case of each. Details of the organisms isolated is given in figure 3. For serine carbapenemase producing organisms Ceftazidime avibactam and Polymixins remain the therapeutic choices and for ESBL producers the choices are Carbapenems and Ceftazidime-avibactam.

Figure 3: Prevalence of micro-organisms from the documented microbiological data during the study period



Beta Lactamases are divided into four classes based on their substrate profile, each of which can confer resistance [9,10].

(1) Class A beta-lactamases include Extended Spectrum Beta Lactamases (ESBL) conferring resistance to Cephalosporins including third generation (Ceftriaxone and Ceftazidime), Penicillin beta-lactamase inhibitor combinations (Ampicillin sulbactam, Piperacillin tazobactam), Aztreonam and serine carbapenamases as Klebsiella pneumoniae Carbapenemase (KPC) resistant to all betalactams.

(2) Class B metallo beta-lactamases hydrolyze all Penicillins, Cephalosporins and Carbapenems but not Aztreonam.

(3) Class C includes AmpC beta lactamases that confer resistance specifically to third generation Cephalosporins.

(4) Class D Oxacillinases extended resistance variably to Penicillins, Cephalosporins and Carbapenems, eg., OXA-48 that hydrolyses penicillin efficiently, carbapenemase slowly and Cephalosporins poorly [5].

Among Gram positive organisms *Staphylococcus* and *Enterococcus* were found predominant in the wards compared to others. We encountered eleven cases of *Enterobacter* and 28 cases of *Enterococcus. Staphylococcus aureus* that is resistant to Naficillin and other semisynthetic Anti-Staphylococcal Penicillins present as Methicillin Resistant *Staphylococcus Aureus* (MRSA) account for 70% of the infection (Fig 4). Most of the MRSA cases are treated with Glycopeptides (Vancomycin, Teicoplanin) and if clinical and microbiological response to vancomycin therapy is unsatisfactory alternative therapy with Linezolid were considered regardless of MIC values.

Figure 4:
Prevalence of Staphylococcus aure infection.

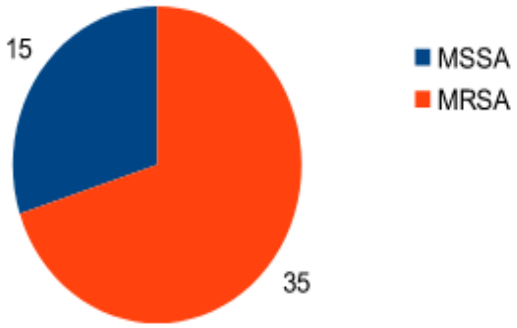
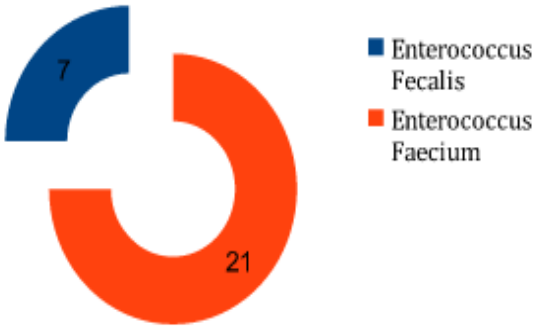


Figure 5:
Prevalence of Enterococcus infection



Enterococcus, a gram positive cocci commonly present as *Enterococcus faecium* which is often resistant to Penicillin, Aminoglycosides and Vancomycin and *Enterococcus faecalis* resistant to Vancomycin and rare penicillin resistance [10]. These organisms treated based on susceptibility to penicillin, those which are resistant to Penicillin are treated with Vancomycin or intravenous Daptomycin or Linezolid. In our study we found *Enterococcus faecium* (72%) being most common and treated based on sensitivity pattern (Fig 5).

Linezolid being a bacteriostatic drug, its long-term use may put patients in risk with various side effects as neuropathy and bone marrow toxicity is kept as a second line keeping Vancomycin as the drug of choice for *Enterococcus* infection [12]. Further *Enterococcus feacalis* are resistant to Quinupristin and Dalfopristin, whereas in Vancomycin Resistant Enterococcus faecium (VRE) it can be used as an alternate regimen.

3.2 Antibiotic audits and utilization:

A very high resistance to Piperacillin Tazobactam for Gram Negative organism were found, which is the second most commonly used antibiotic as empirical therapy. Cefoperazone sulbactam, a third generation Cephalosporin being the highest preferred antibiotics in the wards following which Piperacillin Tazobactam and Amoxicillin Clavulanate is mostly used. We also had observed that patients who had already received antibiotics in ICU or before admission in our hospital, showed higher proportion of infection and resistance compared to those with no prior antibiotic use. Colistimethate sodium (21.3%) was the most commonly used antibiotic following Meropenem (21.5%).

Figure 6 explains the usage of listed restricted antibiotics in our hospital. Antibiotics were chosen according to the resistance pattern of various organisms, and for certain organisms like *Pseudomonas aeruginosa* and *Acinetobacter species* restricted antibiotics are chosen directly as first line.

Polymixin B (1.47%) and Imipenem-Cilastatin (1.71%) being least commonly used restricted antibiotic in the inpatient wards. Usage of Fosfomycin a low molecular weight Phosphonic acid derivative has increased recently as they have excellent in-vitro activity against gram positive and gram-negative bacteria [13]. In-vitro activity include its use for ESBL and carbapenemase producing *Enterobacteriaceae* [10,13].

3.3 Impact of clinical interventions in prescribing practice:

Interventions were done during the study period, where appropriateness and recommended usual daily dosing of the particular drug for every patient is justified based on antibiogram. Correct dose, dosing intervals and dose adjustments for hepatic and renal impairment were also done during the intervention. Improper drug of choice for therapy is also intervened and changed accordingly where pharmacokinetics of each drug plays an important role in selecting them. Penetration and distribution of drugs to the target site is important for the desired effect, the agents of same class exhibit different distribution and penetration to the target site. Time course of antibacterial therapy is also followed up until the cessation of therapy [14].

Loading doses for majority of drugs given were missed out and the importance of it is educated and high-lightened during our intervention period. Various concentration dependent antibiotics need loading dose to reach the therapeutic level and exhibit the antibacterial effect which is further kept in therapeutic range by administering maintenance doses at regular intervals. A drug below the therapeutic level may take more time to reach steady state than ones with loading dose.

Certain transcribing and administration errors were also identified and altered accordingly. Examples of this problem includes prescribing Ceftriaxone 6 g/day where the maximum daily dose is only 4 g/day. Administration errors like diluting Amphotericin B in Normal Saline (NS) or any sodium containing solutions instead of dextrose solutions. When diluted in sodium containing solutions Amphotericin loses its potency due to its incompatibility, administration techniques and possible adverse effects like hypokalemia and hypomagnesemia were also analyzed and followed up [15]. Teaching other healthcare professionals during prescribing and administration helps minimizing the errors and aids in appropriate prescription of an antibiotic.

IV. DISCUSSION

Auditing antibiotics usage and updating practice guidelines through direct counseling appears to be warranted (15). This multifaceted approach should involve pharmacists, microbiologists, primary consultants and infectious disease specialist [1]. Nosocomial infections resulting from drug resistant pathogen further complicate the existing problems [16]. Inappropriate use of antibiotics has led to the development of resistance for most existing antibiotics, which further increase the health care cost and increases the mortality rate [2]. Antibiotic prescription is largely empirical and evidence based, hence in patients who receive inappropriate antibiotics, interventions should be done accordingly and de-escalated where-ever necessary [9].

Lowe et al., (2012) analyzed the prevalence of resistance over 4 years and concluded that both *Klebsiella Pneumoniae* and *Escherichia coli* producing ESBL has increased from 0.1 to 1.1% and 0.3 to 14 % respectively. Most organisms isolated were resistant to beta lactam antibiotics (18). Powell et al., studied the utilization pattern of antibiotics with Cornwall Antimicrobial Resistance Group (CARG) and reported that antibiotic consumption fell by 12.8 % in total from 2012 – 2013 to 2015 – 2016. Main drop was with broad spectrum antibiotics as Cephalosporins, Quinolones and Co amoxiclav (3.9%) after introduction of NHS England antibiotic stewardship programs that educated the health care professionals which successfully reduced the utilization over the past 10 years [19].

As per the fifth annual report by English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR), the organism that cause Blood Stream Infections (BSI) are resistant to key antibiotics and they are stable during the period of analysis. The burden of resistance of antibiotics increased by 35% . In accordance with our study they also had *Klebsiella Pneumoniae* and *Escherichia coli* producing ESBL to be more predominant and are sensitive to carbapenems. They also had surveillence program for antibiotic utilization and concluded that penicillins were most commonly used drug accounting for about 44.6%[20].

Pseudomonas aeruginosa an aerobic gram-negative bacillus, glucose non-fermenter which has acquired a wide variety of antibacterial resistance mechanisms as production of Extended Spectrum Beta Lactamases, Carbapenemases and presence of Multidrug efflux pumps, drugs were chosen according to the resistance patterns they show [10]. *Acinetobacter* species being a strict aerobic non-fermentive cocco-bacillary gram-negative bacillus remains the frequent cause of Ventilator Associated Pneumonia (VAP) and almost demonstrate Multi Drug Resistance (MDR) [21]. Its resistance mechanism included ESBL, production of AmpC, Cephalosporinases, serine carbapenamases, aminoglycosides modifying enzymes and changes in target binding sites [15]. Inhalational antibiotics are used for certain MDR gram negative bacilli, *Pseudomonas aeruginosa*,

Acinetobacter baumanii or *Klebsiella pneumonia* susceptible only to Polymixins. Airway irritation that may lead to broncho-spasm remains the most common side effect with Inhalational therapy, which is managed by administering nebulised broncho-dilators [7].

Probably over usage of antibiotics have led to the development of resistance with primary antibiotics. Although Indian Council of Medical Research (ICMR) guidelines recommend Beta-Lactam and Beta-Lactam Inhibitors (BL-BLI) as the empirical choice of therapy for most organisms, we found most isolates resistant to them [22]. Auditing antibiotic usage and reinforcing practice guidelines appears to improve the usage of proper antibiotics based on the antibiogram [1,5].

There are certain shortcomings in our study, limited analysis only was carried out due to small number of patients in the wards with restricted antibiotic usage compared to Intensive Care Units. Although conclusions from our findings are reliable, we were not able to distinguish the outcomes with mono therapy and combination therapy. Many critically ill patients have already received antibiotics during their ICU stay and that lead to insignificant results with the number of antibiotics used in prior. Our study contributed a better understanding of antibiotic use and microbial pattern and development of hospital acquired resistance in in-patients. Antibiotic selection was also based on previous infection, age and days of hospitalization. Understanding the local microbiological pattern have a greater impact on choosing empirical antibiotics.

V. CONCLUSION

Prudent use of antibiotic is mandatory to reduce the burden on resistance. Antibiotic usage should be monitored and duration of restricted antibiotic usage should be monitored. Cessation of usage or de-escalating according to the microbiological data is essential. Improve awareness and understanding of antimicrobial resistance through effective education and training. Incidence of infection can be reduced by effective infection control practices and prevention measures. Evidence based prescribing and local microbiological data are needed to optimize antimicrobial usage. Stronger compliance to antibiotic treatment regimens and restriction of non-therapeutic use of antibiotics is also necessary.

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