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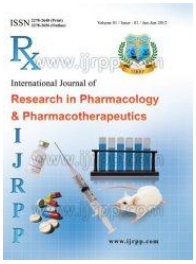

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A review on carbapenem resistance and the role of pharmacist in antibiotic stewardship programmes in India

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ABSTRACT

Carbapenems are a group of β-lactam antimicrobial agents with an exceptionally broad spectrum of activity. They are used as a last resort against many multi drug resistant, gram negative bacteria, and in cases of infections due to extended spectrum beta lactamase (ESBL) and Amp C enzyme producing Enterobacteriaceae. CRE, which stands for carbapenem-resistant Enterobacteriaceae, are a family of germs that are difficult to treat because they have high levels of resistance to antibiotics. However, widespread and irrational use of carbapenems has led to emergence of resistance to this group of drugs also, and there are at present very few available antibiotics, which are active against carbapenem-resistant (CR) organisms. Infections with CR organisms are associated with high morbidity and mortality with the attributable mortality rate as high as 40-50%. Carbapenem resistance is a global concern and the presence of CR genes in Indian subcontinent and its potential of international spread have been reported previously. Pharmacists have a responsibility to assist in the war on antibiotic resistance. They have the knowledge and resources at their fingertips to raise awareness and to act. There are multiple opportunities for pharmacists to assist in this campaign. The recognition of pharmacists as key members of antibiotic stewardship teams in health systems is a milestone in infectious-diseases pharmacy practice.

Keywords: Extended spectrum beta lactamase, Carbapenem resistant enterobacteriaceae, Carbapenem resistant genes, Antibiotic stewardship, Multi drug resistance.

INTRODUCTION

Life-threatening infections caused by multidrug-resistant (MDR) and sometimes pan-resistant Gram-negative bacteria have increased dramatically in the last decade.[1] Empiric antibiotic therapy can improve the survival among patients with infections due to such microorganisms, as inadequate initial treatment is associated with higher mortality, even if adjustment is carried out when microbiological results are available.[2] Therefore, the rationale for optimizing the antimicrobial treatment in severe infections is to give a broad-spectrum empirical therapy and then to streamline it according to the results of antibiotic-susceptibility tests.[3]Indeed, most studies suggest that inappropriate antimicrobial treatment can be reduced by the administration of an empiric combination therapy.[4,5]

Carbapenems are a group of β-lactam antimicrobial agents with an exceptionally broad spectrum of activity. They are used as a last resort against many multi drug resistant, gram negative bacteria, and in cases of infections due to extended spectrum beta lactamase (ESBL) and Amp C enzyme producing Enterobacteriaceae. The emergence and dissemination of carbapenem resistant bacteria in recent times represents a serious threat to public health. Resistance has been observed in several Enterobacteriaceae, as well as in members of the Pseudomonas and Acinetobacter genera. These organisms are associated with high mortality rates and have the potential to spread widely.

CRE, which stands for carbapenem-resistant Enterobacteriaceae, are a family of germs that are difficult to treat because they have high levels of resistance to antibiotics. Klebsiella species and Escherichia coli (E. coli) are examples of Enterobacteriaceae, a normal part of the human gut bacteria that can become carbapenem-resistant. Types of CRE are sometimes known as KPC (Klebsiella pneumoniaecarbapenemase) and NDM (New Delhi Metallo-beta-lactamase). KPC and NDM are enzymes that break down carbapenems and make them ineffective. Both of these enzymes, as well as the enzyme VIM (Verona Integron-Mediated Metallo-β-lactamase) have also been reported in Pseudomonas.

Healthy people usually do not get CRE infections – they usually happen to patients in hospitals, nursing homes, and other healthcare settings. Patients whose care requires devices like ventilators (breathing machines), urinary (bladder) catheters, or intravenous (vein) catheters, and patients who are taking long courses of certain antibiotics are most at risk for CRE infections.

Carbapenems were the only group of antibiotics active against extended spectrum beta-lactamases producing *Enterobacteriacae*.[6] However, widespread and irrational use of carbapenems has led to emergence of resistance to this group of drugs also, and there are at present very few available antibiotics, which are active against carbapenem-resistant (CR) organisms. Infections with CR organisms are associated with high morbidity and mortality with the attributable mortality rate as high as 40-50%. Carbapenem resistance is a global concern and the presence of CR genes in Indian subcontinent and its potential of international spread have been reported previously. [7] It is therefore, imperative to know the CR patterns in our health care settings and in the community and to take measures to prevent its spread.

Mechanism of Carbapenem resistance

Resistance to carbapenems can be brought about by various mechanisms, the most common being the production of carbapenemases, a class of enzymes capable of hydrolyzing carbapenems and other β-lactams. Resistance to carbapenems can also be due to the poor binding of carbapenems to penicillin-binding proteins present in the bacteria, the over-expression of multidrug efflux pumps by the bacteria or lack of porins present in the bacterial cell membrane. However, for significant resistance to emerge, it is thought that a combination of resistance mechanisms is required. Carbapenem Resistant Enterobacteriaceae (CRE) can be defined as Enterobacteriaceae that are resistant to one or all of the following carbapenems: ertapenem, meropenem, imipenem or doripenem; and resistant to all of the following third-generation cephalosporins: ceftriaxone, cefotaxime, and ceftazidime.

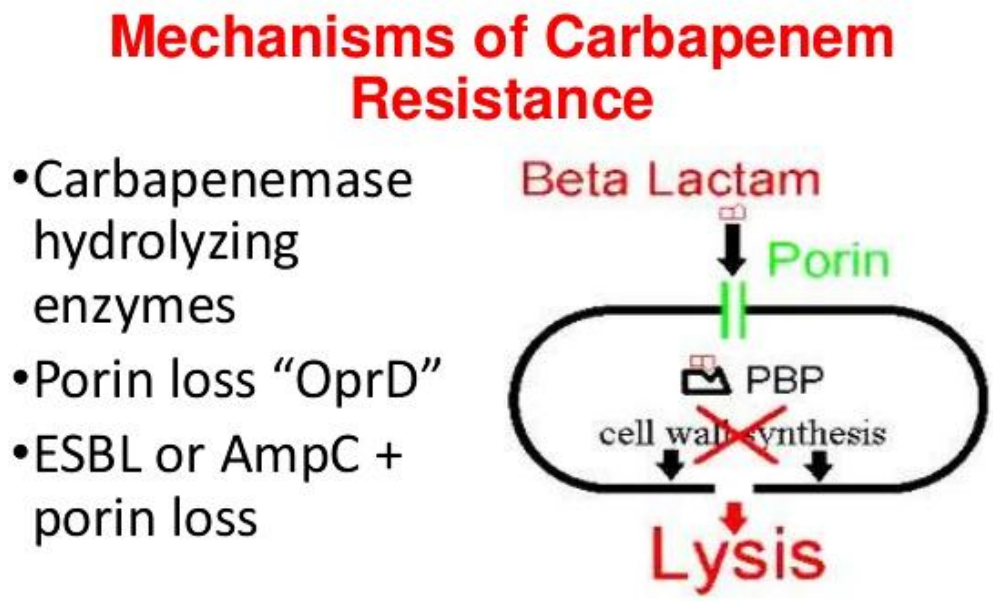

Fig: 1 Mechanism of carbapenem resistance

Status of Antibiotic use in India

Recent reports of worldwide spread of multiresistant New Delhi Metallo Beta lactamase (NDM-1) producing Enerobacteriaece have serious implications. These are highly resistant to most antibiotics except colistin and Tigecyline. Since there are hardly any new antibiotics in the pipeline we are facing a grim situation. Of note is the fact that most of the Indian isolates in the study were from community acquired infections.

In a recent article in JAPI by Deshpande et al from Hinduja Hospital 22 out of 24 carbapenem resistant enterobacteriaece were NDM-1 produces rendering carbapenems useless as choice of antibiotic of enterobacteria. Carbepenem resistance in pseudomonas and acinetobacter is well known. Already there is widespread β lactam resistance reported since 2004 amongst enterobacteriaece. ESBL prevalence rate of 70-90% is reported from most tertiary hospitals. Prior use of cephalosporins is an important contributor to this. Methycillin resistant staphylococcus aureus, pathogenic coagulase negative staphylococcus aureus and vancomycin resistant enterococci have been increasingly reported from various hospitals in India.

Recent research of Seema. B et al studied the carbapenum resistance activity in Enterobacteriaceae from New Delhi. In this research CRE positive cases were founded to be increasing studied. Out of 80 cases 57 (71.25%) cases showed carbapenem resistance, showing a rise in proportion from 65% to 85 %. ICU patient's positivity was founded about 66%. The proportion of KPC positive patients transferred from a long-term care facility or long-term acute care hospital have risen during both the consecutive months. Urine (37%), sputum (32%), blood (19.3%) and endotracheal secretions (3.5%) were the most common sites of CRE infection or colonization. From the CRE positive cases 86% were *Klebsiella pneumoniae (KPC- Klebsiella pneumoniae Carbapenem),* 8.80% were *E.coli* isolates & 5.3% of *Enterobacter cloacae.* All these isolates were ESBL producing organisms and were found resistant to almost all drugs of cephalosporin subclass4 (Ceftriaxone, Ceftizozime, Ceftazidime, Cefotaxime, Cefoperazone), Cefepime, Cefoperazone-Sulbactam, Collistin, Aztreonam, Co-Trimoxazole and very few to Chloramphenicol, Tetracycline, Gentamicin and most were sensitive to Amikacin.

With continued antibiotic overuse, clostridium difficile may become a menace as seen in the West. Raghunath D has reviewed available data on antibiotic susceptibility of common organisms from the community. In typhoid fever, quinolones which were initially favoured drugs in 80's are no longer effective. In lower respiratory tract infections, streptococcus pneumonia has retained sensitivity to penicillins, macrolides and fluoroquinolones but not to cotrimoxazole. Vibrio cholerae and shigella have

acquired resistance to the usual antibiotics. Hence at both at community and hospital level there is urgent need for reforms. The editorial in March 2010 issue of JAPI by Dr. Abdul Ghafur states that it is already too late however it is important to at least take responsibility and change our practices for the better.

Steps needed to control antibiotic resistance

This is the time for all the health care providers to unite and execute certain steps to control the use of antibiotics and to minimise these serious problems in the treatment of infectious diseases.

The following are the needs of the hour

At community level

1. Public and professional education towards rational use of antibiotics
2. Regulatory measures to control over the counter availability of antibiotics.
3. Guidelines at National / regional / local levels for use of antibiotics.
4. Improvement in standards of hygiene.

At hospital level

1. Strict enforcement of hand hygiene.
2. Infection control committee, antibiotic managers to keep a check of usage.
3. Regular surveillance of data and antibiograms to guide empiric antibiotics selection.
4. Antibiotic Stewardship Programme
   This involves selecting an appropriate drug, optimizing its dose and duration to cure an infection while minimizing toxicity and conditions for selection of resistant bacterial strains.
5. Ensuring that cultures are sent prior to starting antibiotics to a good microbiology laboratory.
6. Measuring outcomes to evaluate effectiveness of policies.

Role of pharmacists in antibiotic stewardship programmes

The pharmacist's role in combating and preventing infectious diseases is essential as antibiotic and vaccine regimens become more complex due to the continuously evolving epidemiology of infections. The decrease in drug development makes the preservation of currently available antibiotics paramount, highlighting the roles that pharmacists play in maximizing the utility of available drugs. While further training in infectious diseases may be necessary for some pharmacist roles in preventing antibiotic resistance, many others exist that all pharmacists can embrace.

Pharmacist-directed antibiotic stewardship programs (ASPs) have proliferated considerably in the past decade. After evidence emerged that these programs improve patient care, the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America published a guideline for the development of ASPs specifying that an infectious diseases–trained clinical pharmacist was an essential core member.[8,9] As resistance has increased and antibiotic development has lagged, ASPs have become important to improve clinical outcomes, prevent resistance, and decrease adverse events such as *Clostridium difficile* infections.[10] ASPs take many forms, but all utilize a team approach to improve the utilization of antibiotics through means such as interventions on individual patients, guideline development, and system-wide improvement. These methods are only implemented in America and the same system has to come in India for avoiding these serious problems.

Table 1. Examples of Antibiotic Stewardship Initiatives

Direct Interventions
Re-evaluating continued need for antibiotics after 48–72 hours
Stopping antibiotics if cultures are negative and infection is unlikely
Stopping antibiotics when the infection is resolved
Screening for drug–drug interactions or duplicate therapy
Maximizing PK/PD parameters for dose optimization of antibiotics
Switching therapy to the most appropriate antibiotic based on results

Education

Providing guidelines or pathways for appropriate empiric use of antibiotics

Working in conjunction with the microbiology laboratory to aid in the selection of diagnostic tools or tailoring susceptibility reports based on available formulary antibiotics and susceptibility patterns

Assisting in the interpretation of results from diagnostic tests or cultures (colonization vs. contamination vs. Infection)

Avoiding chronic or long-term antibiotic prophylaxis

Minimizing the use of broad-spectrum antibiotics

Policies/Procedures

Antibiotic order forms

Prior authorization

Various methods may be employed for ASPs, and pharmacists are generally the key personnel members following the patients and intervening when necessary. While some of these interventions require an in-depth knowledge of infectious diseases, others are within the scope of general pharmacy practice. For example, it has been reported that dosing of vancomycin may be inadequate in obese patients.[11] Since it has been suggested that inadequate vancomycin dosing may be associated with the promotion of resistance in *Staphylococcus aureus*, this represents an opportunity for nonspecialist pharmacists to intervene.[12] More complex antibiotic selection or dose optimization methods may be utilized by those pharmacists with a comprehensive understanding of diagnostic tests or antibiotic pharmacokinetics and pharmacodynamics.

Each intervention is an opportunity to provide feedback and education to the prescriber, which is vital to the maintenance of a stewardship program and further promotes the improvement of antibiotic utilization. Further, pharmacists frequently collect and report data about interventions and antibiotic-use patterns at hospital committees in order to assess the effectiveness of the program, identify areas for improvement, and garner continued support for stewardship.

Pharmacists have a responsibility to assist in the war on antibiotic resistance. They have the knowledge and resources at their fingertips to raise awareness and to act. There are multiple opportunities for pharmacists to assist in this campaign. The recognition of pharmacists as key members of antibiotic stewardship teams in health systems is a milestone in infectious-diseases pharmacy practice. Community pharmacists have a critical role to play in combating antibiotic resistance as front-line practitioners who can educate and vaccinate patients.

The concept of clinical pharmacist in India is very weak and should be needed to improve the situation that is present in the country in order to minimize these serious health problems due to antibiotic resistance.

CONCLUSION

Carbapenems resistance is a major clinical issue in the treatment of infectious diseases because of the lack of alternatives for this highly effective class of antibiotic. One of the major reasons for this is irrational use of these classes of antibiotics. Without significant intervention, we are coming to the end of the days where 10 different antibiotics can be utilized to treat a serious *E coli* infection. If we do not make it our problem now, it will certainly be our problem later when we are asked what antibiotic to use for a pan-resistant *E coli* infection and the answer is: nothing.

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