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EMERGING MDR ENTEROBACTERIACEAE AND THE ANTIMICROBIAL RESISTANCE PATTERN IN INDIAN SCENARIO: CHALLENGE AFTER COVID-19 PANDEMIC

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ABSTRACT

Infectious disease burden and antimicrobial resistance (AMR) are of major health crisis globally, particularly in developing countries like India which has an incredibly high population rate but weak socio-economic status. *Enterobacteriaceae* has been evolving as one of the most important causative agent of nosocomial and community acquired infections endangering a greater number of individuals.

The Center for Disease Control and Prevention (CDC) has categorized Carbapenem Resistance Enterobacteriaceae (CRE) and Extended Spectrum Beta Lactamases (ESBL) producing *Enterobacteriaceae* as urgent and serious threats to human health. With the recent pandemic crisis of covid-19, there is no doubt that the present rate of multidrug resistant (MDR) will become more complex and diverse in the coming days.

This review succinct the rising MDR *Enterobacteriaceae,* AMR pattern and its epidemiological status in India with special reference to covid-19 and co-infection from varied sources.

Key word: Carbapenem Resistance Enterobacteriaceae, Extended Spectrum Beta Lactamases, COVID-19 & Bacterial Co-infection

INTRODUCTION

Antimicrobial resistance (AMR) is considered as the biggest threat affecting the entire world with respect to controlling infectious disease either in the community or in the healthcare sectors. Despite of rise in the unresolved health challenges, AMR is not only impacting the development of many countries but also the global economy. It is currently estimated that, the annual deaths of over 700,00 people across the globe is a consequence of the infections caused by resistant pathogens, which is likely to increase to 10 million by 2050, if not considered seriously **[1]**. While the global health community is trying to curb the burden of recent pandemic of covid-19, it may in no time faced with the silently emerging AMR that could be more deadly and overthrow the significant advances of modern medicine. Thus, proving it to be the 'the silent tsunami facing modern medicine' **[2]**.

Antimicrobial resistance has been increasingly reported among the Enterobacteriaceae members from sources including animals and food apart from the clinical specimens **[3]**. This could further add up to the increasing rate of AMR prevalence in developing countries like India where proper regulatory guidelines for antibiotic use in livestock and agriculture is lacking **[4]**. India as such is known as 'the AMR capital of the world' and is leading the countries of the world in total consumption of antibiotics used for humans which is a huge cause of concern **[5]**. A recent study has reported that every year 56,254 neonatal died in India due to antibiotic resistant sepsis **[6]**.

Nowadays antibiotics are used on day to day basis in various types of infections including viral either prescribed by doctors or by self-medication. The reasons behind this are lack of awareness of the particular disease, low proportion of doctor to patient ratio, easy availability over the counter drugs in country like India. Other factors like socio-economic status, over population and malnutrition further complicate the situation **[5]**. As the major population of India falls in poor category, individuals may failed to pay the necessary medical expenses or even felt in debt leading to uncountable preventable deaths **[7]**. Meanwhile there is an attempt to establish and formulate policy on the antimicrobial stewardship practices (AMSP) in India which could further provide guidance and encourage the common people on proper use of available antibiotics by training the healthcare workers and creating awareness **[8, 9]**.

Moreover, worldwide viral spread due to COVID-19 with its dissemination of various mutated form is a bigger cause of concern. The incredible amount of antibiotic use can further bring to the dead end situation of antimicrobial therapy. To think once and again, in India the AMR rate in present is almost at its peak. Additionally the increasing antibiotics administration to the in COVID-19 patients to tackle the secondary bacterial infections will not only worsen the situation but could be more deadly than expected with no further treatment option in hand.

MDR ENTERIOBACTERIACEA

Enterobacteriaceae family includes large members of Gram negative enteric bacilli which are known to cause serious infections. Common human infections such as UTIs, bacteremia, cystitis, pyelonephritis with fever, septicaemia, pneumonia, peritonitis, meningitis, and device-associated infections are mainly associated to *Enterobacteriaceae.* Their species have the propensity to infect the patient's families and at larger level the community as it can confer the multiple resistance mechanism via plasmids **[10]**.

Initially Cephalosporin classes of antibiotics were considered to be the ultimate treatment for the infections caused by Enterobacteriaceae until the rise of Carbapenem Resistant Enterobacteriaceae (CRE) worsened the scenario of MDR. The multidrug-resistant Gram-negative Enterobacteriaceae (MDR-GNE) members are usually resistant to almost all β-lactam antibiotics. The rising incidence of infections by MDR-GNE has been reported worldwide [11]. A retrospective observational study done on the Mortality Burden in India highlighted the overall mortality rate of 13.1% with a 2-3 times higher mortality rate to the infection caused by MDR gram negative pathogens mainly *Escherichia coli* and *Klebsiella pneumonia* **[12]**. Unfortunately, with the rising rate of CRE nowadays, there is a demand to search for an alternative in no time **[13, 14]**.

MDR *Enterobacteriaceae*: Resistant mechanism, gene and its classification:

Resistance to antimicrobial agents is attributed to their inherent structural/functional characteristics, genetic variations or could be acquired depending on their potential for survival **[2]**. Bacteria employ mechanisms to possess the acquired resistance to beta-lactam antibiotics such as porins and efflux pump, alteration of antibiotic target site, enzyme inactivation and antibiotic degradation by beta-lactamases enzyme production. These genes are further transferred to other organisms or to itself through plasmids, integrons and transposons making it MDR **[15]**.

The non-susceptibility by the microorganism acquired towards at least one of the agents out of three or more antimicrobial categories is referred to as Multidrug-resistant. However, such types of typical MDR in Enterobacteriaceae are mainly due to the production of beta-lactamases and less often by non-beta-lactam antibiotics creating a bigger challenge to therapy **[12]**.

The Extended-Spectrum Beta-lactamases (ESBL) is the one of the most emerging traits in resistance among the Enterobacteriaceae members. These beta lactamases show resistance to penicillins, first three cephalosporins classes of antibiotics and also aztreonam except cephamycins or carbapenems. The resistance mechanism of the beta lactamases is by the mechanism of hydrolysis that can be inhibited by clavulanic acid. The most commonly found resistant genes are TEM-1, TEM-2 and SHV-1 or its sub types. Generally beta-lactamases belong to class A of the Ambler molecular classification scheme as they contain serine at the active site. According to Bush-Jacoby- Medeiros functional classification system, ESBLs is placed under functional group 2be based on the biochemical properties of enzymes as well as the molecular structure and nucleotide sequence of the gene **[16]**.

Another clinically important cephalosporinases is the AmpC beta-lactamases which cannot be inhibited by classic beta-lactam inhibitors and confer resistance to cephamycins but fails to hydrolyze cefepime efficiently. According to Ambler classification, these beta-lactamases belong to class C whereas in Bush-Jacoby functional classification it belongs to group 1 **[17]**. AmpC can be encoded by plasmid genes or can be produced as a result of de-repression of chromosomal genes in some *Enterobacteriaceae* (typically *Enterobacter*, *Serratia*, *Citrobacter*, *Providencia*, *Morganella* and *Proteus* species). Whereas, plasmid mediated AmpC beta-lactamases are present in *E. coli*, *K. pneumoniae* and other *Enterobacteriaceae* **[18]**. AmpC enzymes are inducible and can be expressed at high levels by mutation. The commonly reported genotypes are ACC, FOX, MOX, DHA, CMY, CIT and EBC **[19]**.

Among all the beta-lactamases the most concerning is the Carbapenem hydrolysing beta-lactamases. Carbapenem were often considered to be the last line of therapy for ESBLs and AmpC producing *Enterobacteriaceae* infections until the emergence of carbapenem resistance *Enterobacteriaceae* (CRE) in 1993 and is reportedly increasing worldwide till today. These beta-lactamases hydrolyse almost all beta-lactam drugs including the carbapenems. According to the Ambler classification scheme, the clinically significant carbapenemases in Enterobacteriaceae belongs to three classes. KPC type belongs to class A, NDM, IMP, VIM types which possess the highest carbapenemase activity belongs to class B and Ambler class D enzymes with carbapenemases activity in

Enterobacteriaceae are mostly OXA-48 and OXA-181 **[20]**.

Epidemiological distribution

Antimicrobial resistance has been depicted with a notable increase among the members of *Enterobacteriaceae* in the past decades in various parts of India. Yet, another matter of concern is that lesser research is carried out in this aspect in India **[21]**.

For instance, Indian Council of Medical Research (ICMR), New Delhi initiated the Antimicrobial Resistance Surveillance & Research Network (AMRSN) in 2013 to assemble nationwide data. The nationwide surveillance in India (2016-2018) highlighted that majority of the Gram-negative isolates were MDR, where *K. pneumoniae* and *E. coli* being the increasingly reported isolates with a high percentage of resistance to cephalosporins and aminoglycosides class of antibiotics. These data is being supported by several world data like U.S. National Healthcare Safety Network and the European Antimicrobial Resistance Surveillance Network **[2]**. Similar pattern was echoed in a multispecialty hospital study in Chennai, Southern India **[22]**.

Quite a few Indian studies on AMR have been reported recently. An analysis from the Global Antimicrobial Resistance Surveillance System (GLASS) highlighted an extreme resistance to carbapenem in *E.coli* (43%-100%) and *Klebsiella pneumoniae* (44-72%), the priority pathogens from India in the last few years **[23]**. A multi-centric study from tertiary care hospitals in India reported cephalosporins resistance of 13-91% in *E.coli* and 29-88% in *Klebsiella pneumoniae* isolates. Among carbapenem resistant isolates, imipenem (49-88%) showed higher resistance than meropenem (20-69%) for both the organisms **[24]**.

A 6 year retrospective study done on blood stream isolates in Eastern part of India also showed a notable resistance to cephalosporins (61%-85%) but reported a lower resistance to carbapenem (5%-10%) **[25]**. The retrospective surveillance study done to understand the common pathogens causing infections in Indian children, highlighted a resistance rate as high as 72% in *E. coli* and 63% in *Klebsiella* spp. to 3rd generation cephalosporins and up to 46% resistance to carbapenem **[26]**.

In another recent study done in a tertiary care hospital in Sikkim, North-East India highlighted as high as 76% MDR wherein *E. coli* and *K. pneumoniae* being the major MDR pathogen. It also showed 58% ESBL, 13.1% AmpC and 14.8% MBL production by the isolates **[27]**.

According to the antimicrobial surveillance done by ICMR (2013-2018), the percentage of extended-spectrum β-lactamases (ESBL) producing *E. coli* and *K.*

pneumoniae were predominantly high with TEM (54%), OXA-1 (22%) and SHV (16%) being the most predominant. Among carbapenemases, NDM was the most prevalent (27%) carbapenemases followed by VIM (19%), IMP (15%) and KPC (15%) but prevalence of AmpC production was less than 10% **[28]**.

Another hospital-based study too detected NDM and OXA-48 as the most common beta lactamases genes among *E. coli* and *Klebsiella* species. Further, 16 isolates were found to have more than one carbapenemases genes **[29]**. A point prevalence study done on uropathogens in Eastern India highlighted 13.4% of ESBL production conferred by the presence of CTX-M, OXA, TEM-1 and SHV; 12.9% of carbapenemases with NDM, OXA, IMP and VIM and only 1.9% of AmpC beta-lactamases with CIT and DHA **[30]**.

An alarm study was found on a *K. pneumoniae* in Tamil Nadu, South India having high MDR rate of 75% including 58% carbapenem and 97% ESBL producers with a prevalence of CTX-M, SHV, TEM, NDM, GES and IMP genes **[31]**. Another multi centric study done in South India reported a high prevalence of MDR among nosocomial infections (64%), hospital-acquired infection (21%) and community acquired infections (15%). Co-occurrence were seen among TEM, CTX-M, AmpC, NDM-1, SHV beta lactamases gene and reported as high as 9.2% mortality in patients with co-carriage isolates **[32]**.

Apart from the various studies on antimicrobial resistance of *Enterobacteriaceae*, the gut colonization with these strains is an important aspect to analyse the source of endogenous infection and horizontal transfer of these genes. In a study done to access the faecal colonization among intensive care unit patients in India, colonization with carbapenem resistance *Enterobacteriaceae* (CRE) was observed in 6.6% with OXA- 48, KPC and NDM-1 being the predominant carbapenemases. The risk factors associated with CPE carriage were duration of ICU stay, use of ventilator and aminoglycosides **[33]**.

The community-based study done in the faecal samples for the presence of AMR *Enterobacteriaceae* in North India had highlighted the overall AMR of 70.5% in which maximum resistance was seen in cephalosporins (60.4%) and fluoroquinolones (41.5%). *E. coli* being the most common isolated organism. TEM, SHV, OXA-1, CTXM-1, CTXM-2, CTXM-9 and CTXM-8/25 were the most common β-lactamases detected **[34]**.

Resistance to antimicrobials is emerging rapidly in the last few years among members of *Enterobacteriaceae* not only in humans but also in the environment. As such many recent studies have focused on the prevalence of the emerging

Enterobacteriaceae isolates and also analysed the antibiotic profile for such MDR isolates. For instance, Shivakumarswamy *et al* had conducted a study to determine the antibiotic susceptibility pattern in gram-negative bacteria from environmental samples by phenotypic and genotypic methods. Out of which one-third showed MDR, 39.4% of the isolates being *Enterobacteriaceae* family **[35]**.

The study done by Ragupati *et al* had revealed the presence of single or multiple plasmids related to AMR among the Gram-negative isolates **[36]**. Amladi *et al* have evaluated the utility of fosfomycin, nitrofurantoin and colistin in treating UTI caused by CRE and they found that fosfomycin and colistin may be most effective for treating *E. coli* and *Klebsiella* species in UTI's **[37]**. The presence of *qnr A*, *qnr B* and *qnr S* resistance genes among the fluroquinolone resistant extra-intestinal *E. coli* isolated from hospitalized patients was studied by Shetty *et al* **[38]**. The study conducted on clinical isolates of *Shigella* species had revealed the beta-lactamases genes (*bla*OXA, *bla*TEM-1B and *bla*EC) and also cotrimoxazole resistance gene among *S. flexneri* which was the most isolated species in all serogroups **[38]**.

There are investigations on antibiotic hybrids as the next generation strategy for tackling MDR bacteria. One of the antibiotic hydrids for treating superficial bacterial infections and bacteremia which is under clinical trials is CBR-2092 (a combination of rifamycin + quinolone). It also showed the antimicrobial hybrid against carbapenemases namely Cefiderocol and ceftazidime, which are under phase 2 or 3 trials **[39]**.

COVID-19 AND CO-INFECTION CRISIS

The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is the most known causative agent for the rapidly spreading corona virus pandemic in recent days. The latest spread of COVID-19 is the major public health threat globally, mainly affecting the adult and older population, at present. Microbial co-infection in such situation not only causes difficulties in diagnosis, treatment and prognosis of COVID-19 but further increases the disease symptoms leading to high mortality rate **[40]**.

Ever since the widespread of pneumonia like COVID-19, unexpected death of people have occurred worldwide **[41]**. Focusing on both the current pandemic of COVID-19 and antibiotic uses, it is not inadvertent to say that not only in India; indeed there is a threat of antimicrobial resistant bacteria. In the endeavours to tackle the emerging AMR and the superbugs, the global health fraternity is now facing the recent pandemic. Several deaths have also been reported due to

COVID-19 in India thereby making the world wide death cases more worrisome **[42, 43]**.

Although co-infection seems to occur among COVID-19 patients, it is still an under studied phenomenon **[44]**. The bacterial and fungal co-infections are common in prolong viral pneumonia like diseases but in case of COVID-19 where there is no particular clinical manifestations/symptoms for assessing the severity of infected patients, antibiotics are assumed to be the only option in treating bacterial co-infection. Despite of such pandemic outbreak, there is incredible rise of antibiotic prescription to patients even after the WHO recommendation against unnecessary use of the antibiotics in COVID-19 patients **[45]**. In one such report on COVID-19 cases, more than 70% of patients in Asia received antimicrobial treatment while only less than 10% were found to have bacterial or fungal co-infections which also highlights the use of common broad spectrum antibiotics **[46]**. Similar reports have also been given by various other studies **[41, 47, 48]**.

There are a fewer study suggesting the nosocomial infections associated with the morbidity and mortality of COVID-19 patients. Uses of broad-spectrum antibiotics have been reported in COVID-19 patients with no evidence of bacterial co-infection **[28]**. It is not less known that India is listed as the top most antibiotic consuming country among the world. Although in India, ICMR suggested treatment guidelines for nosocomial infection, it is less considered as many people received antimicrobial therapy, with no proper prescriptions provided. It seems to be frightening, but is not surprising to say that the AMR may be on a peak in India with the recent pandemic of COVID-19.

In a study conducted at AIIMS, Delhi it was reported that the high rate of secondary infections was caused by drug resistant Gram negative bacteria, in which the *K. pneumoniae* (33%) being the main cause of high in-hospital mortality among COVID-19 patients **[49]**. A recent surveillance study by ICMR has revealed as high as 56.7% of bacterial or fungal co-infection, out of which *K. pneumoniae* (29%) was the predominant pathogen with 72.8% resistance to Carbapenem **[50]**.

It is a much bigger challenge for the developing country like India to tackle the enormous crisis hand in hand due to the low socio-economic status, the increasing population, limited/no readily available health care facilities and cost effective markers for quick and easy detection of bacterial/viral infections **[51]**.

Keeping these into account, it is necessary to reconsider the bacterial co-infection and secondary infection not only during the COVID-19 pandemic but in the coming future. Maintaining proper personal hygiene, application of disinfectants on surfaces, frequent washing of hands or using sanitizers and social distancing are the golden rules which should be followed to stay protected from COVID-19 infection. Moreover, it is the need of the hour to reform strict antimicrobial stewardship programs, infection prevention and control measures in community and health care settings along with the resistance surveillance. The failure in strict compliance of antibiotic usage leads to the unexpected raise of MDR pathogens paving a way for the pandemic of AMR, particularly in developing country like India.

CONCLUSION

The emerging Carbapenem Resistant *Enterobacteriaceae* is the most important issue at present with regard to antimicrobial therapy. Perceptive analysis of antimicrobial resistance in specific geographical regions is important for effective therapeutic practices. As very limited surveillance studies are conducted in India, congregating and analysing the various point studies had become essential to have a thorough knowledge of the prevalence of such emerging MDR Enterobacteriaceae and their antibiotic profile both in hospital and in community settings.

In fact, as just the recent COVID-19 crisis with no known borders, AMR is spreading like a wild fire, if it is not taken seriously which may even take over the recent pandemic in the near future. Hence, researchers must give equal weight to the increasing threat of AMR along with the COVID-19 and its co-infection.

The COVID-19 pandemic has inclined towards the use of antibiotics including carbapenem which is considered to be the last drug of choice for treating severe MDR cases. With this, the time has come to give equal importance to all MDR organisms in addition to tuberculosis and HIV. This is not too far where the healthcare professionals will be left with no choice other than just seeing people dying helplessly. Here about, in search of the last straw, the least focused pathogen may lead to unrelenting deaths causing another bigger pandemic ever.

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