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Chapter

Post-Covid-19 Era: What is Next?

Shiela Chetri

Abstract

Antimicrobial resistance (AMR) is a natural phenomenon in bacteria which becomes a threat for health-care settings around the world. A concerted global response is needed to tackle rising rates of antibiotic resistance, without it we risk returning to the pre antibiotic era. As bacteria evolve very fast according to the environment in which they inhabit via developing different defence mechanisms to combat with the noxious agents like different classes of antibiotics including carbapenems. This results into treatment failure and clinical complications. Global emergence of antibiotic resistance due to bacterial multidrug efflux pump systems are a major and common mechanism of intrinsic antimicrobial resistance employed by bacteria which are spreading rapidly due to over use or misuse of antimicrobial agents. This review mainly focusses on the transcriptional expression of efflux pump system AcrAB-TolC, local regulatory genes (AcrR and AcrS), mediating carbapenem resistance in clinical isolates of *Escherichia coli* under antibiotic stress, a genetic interplay study between intrinsic and acquired antibiotic resistance mechanisms along with a brief summary on high risk factors and prevalence of urinary tract infections by multidrug resistant Uropathogenic *Escherichia coli*.

Keywords: *Escherichia coli*, carbapenem, AcrAB-TolC, $bla_{\text{NDM-1}}$, uropathogenic *Escherichia coli*

1. Introduction

Distribution of multi-drug resistant bacteria is a chief public health issue. Mutations have been an important factor influencing the development of the multi-drug resistant phenotypes and elucidate how they acquire antibiotic resistance [1, 2]. Several mutations are often required to acquire resistance towards a particular drug [3, 4]. However, a number of mechanisms evolved within bacteria helps them to survive against any noxious agents. Amongst the possible antibiotic resistance mechanisms, efflux pumps are membrane proteins which export noxious substances including antimicrobials out of the cell via over expressing the tripartite pump system resulting into antibiotic resistance [5]. Efflux pumps (like, AcrAB-TolC in *Escherichia coli* and MexAB-OprM in *P. aerugiosa*), are crucial for their survival and colonization/virulence, mainly during the development of infection when the pathogen is attacked by toxic substances or adhere with the host [6]. The AcrAB-TolC is constitutively expressed in *Escherichia coli*, and provides intrinsic resistance towards antimicrobials such as erythromycin and fusidic acid as well as dyes and detergents [7, 8]. In *Klebsiella pneumonia*, efflux pump mediated tigecycline resistance was reported from China in which higher expression of efflux pump systems AcrAB-TolC and OqxAB was recorded and the expression of AcrB gene was found to be connected with ramA and marA expression [9]. For

decades, as a last resort carbapenems has been used quite effectively and the idea about this antibiotic was compromised due to the rise of carbapenem hydrolysing ß-Lactamase producers strain of *Klebsiella pneumoniae* [10]. Moreover, the situation is more convoluted in Indian subcontinent after appearance of New Delhi metallo-Beta lactamases in the present decade [11]. However, from India, in a study on *P. aeruginosa* isolates obtained from hospital revealed that MexAB-OprM efflux pump can considerably contribute to meropenem resistance in the absence of an acquired resistant mechanism [12]. According to a research done by Charleric B et al. 2003, clinical isolates of *Enterobacter aerogenes* exhibited resistance towards β-lactam and other group of antibiotics. Efflux pump associated resistance against quinolone, tetracycline and chloramphenicol along with over-expression of AcrA within these imipenem resistant strains have been observed earlier [13]. As per a study done by Chetri et al., 2019 a strong association between ertapenem resistance and AcrA over-expression was observed which has not been noticed earlier. Also, the over-expression of AcrB towards imipenem stress was noticed in this study is unique of its own [14]. AcrD, a transporter protein which belongs to RND superfamily of efflux pump was found to be associated with aminoglycosides resistance [15] did not show any role in carbapenem resistance in the above study [14]. Elkins and Nikaido in 2002, reported that for an efficient efflux of amphiphilic substrate, AcrD needs an association with AcrA in intact cells [16] and this association plays an important role in carbapenem non-susceptibility. Mutations in drug target genes are still presumed to be the crucial mechanism for drug resistance. To examine the basis of the increased expression of local regulators, AcrR and AcrS in AcrAB overexpressed isolates, mRNA sequencing of the regulatory regions was executed and was confirmed that the efflux pump mediated carbapenem resistance does not have any mutational event [16]. Dzwokai Ma and co-workers in 1996, reported that the transcriptional expression of AcrAB was increased under general stress condition and further, they investigated the role of the local repressor AcrR under general stress condition [16]. Remarkably, they found that under all these stress conditions, the transcription of AcrR was insistently increased and the level of increase was even higher than that observed for AcrA however, local repressor AcrR is associated as a repressor for AcrAB. In a study by Chetri and co-workers, the isolates with increased AcrAB expression under carbapenem stress showed much higher expression of AcrR which is surprising [14]. In agreement with the earlier study [14] it can be hypothesized that stress induced transcription of AcrAB is probably under the control of global transcriptional regulators.

New Delhi metallo beta-lactamase (NDM) is the predominant carbapenem resistance determinant in India which is harboured within members of enterobacteriaceae family and non-fermenters [17], and different variants have been reported from this country. Carbapenem resistance is a complex phenomenon which involves interplay between multiple acquired and intrinsic resistance mechanisms which includes loss or downregulation of porins, overexpression of different efflux pump systems and plasmid mediated acquirement of carbapenemase genes [18]. A previous study has noticed that efflux pump system plays an important role in carbapenem resistance compared to blaNDM-1 in *Pseudomonas aeruginosa* [18]. In another study, simultaneous expression of single component and multi component efflux pump was attempted in *E. coli* and *Pseudomonas aeruginosa* but it did not increase antibiotic resistance [19]. In similar work interplay between overexpression of AcrAB-TolC and mutation in gyrA and parC in quinolone resistance in *E. coli* was observed [20]. Also, a previous study has highlighted greater role of acrB in beta-lactam and quinolone resistance [21]. However, a study showed same pattern of transcriptional expression for both acrA and AcrB, which is probably due to the presence of both the genes in same transcript [22]. In a study done by Chetri

et al., 2019 showed that in an *E. coli* isolate over-expressing both AcrAB-TolC and blaNDM-1, showed higher level of mRNA for both the genes when compared with other groups (II, III and IV) [22] and was observed that even a smaller amount of imipenem and meropenem was able to trigger the expression of NDM although; the role of ertapenem in induction was still unclear. Unlike *Pseudomonas aeruginosa*, where expression of efflux pump system MexAB-OprM was significant than that of blaNDM-1 [18], a study found contrasting pattern in *E. coli* [14]. In Indian subcontinent resistance against carbapenem is an evolving problem. However, acquirement of New Delhi metallo beta-lactamase is considered as the major reason for treatment failure and along with that efflux pump mediated resistance too remains a matter of concern as together both the mechanisms pose a grander risk. Study done by Chetri et al., 2019 was able to highlight a higher mRNA transcript of both the resistance genes when coexist within an isolate [22] and require further investigation to identify the concentration of antibiotics, duration of exposure and other factors responsible induction of these intrinsic and acquired mechanisms that exert an isolate a multidrug resistant phenotype.

Further, the active participation of *Escherichia coli* in causing Urinary tract infections, which is mainly caused by Uropathogenic *Escherichia coli* (UPEC) are the common bacterial infections [23]. In females, the high risk of UTIs is due to the intrinsic virulence of *E. coli* for colonization in urinary tract such as its capabilities to adhere to the tract and its association with other microorganisms moving from the perineum regions to the warmth moist environment of the female genitalia contaminated with fecal microbes [24, 25]. The worldwide rise of multi-drug resistant uropathogens, underscores the need for substitute non-antibiotic therapeutic and preventive approaches against Urinary tract infections.

However, a study done by Linsenmeyer et al. demonstrated a high level of indefinite empiric treatment for urinary tract infections caused by MDR gram-negative bacteria and patients suffering from MDR UTI is treated with an inactive antimicrobial agent as their preliminary therapy [26]. As in the previous study, estimation of non-fluoroquinolone antibiotics demonstrated the enhancement in accuracy of empiric therapy, considered as key concepts for stewardship programs [26]. Though, based upon the severity of illness, other patient factors and favoured means of drug administration, the therapeutic options can be selected. However, the high usage of fluoroquinolone is disturbing with the emergence of high resistance rates [27–29].

Other than *E. coli, Staphlylococcus aureus* which is a common cause of infections in health-care facilities and also in the community are part of our skin flora. A new AMR indicator was introduced in 2019 in the SDG monitoring framework which observes the frequency of bloodstream infections caused by two particular drug resistant microbes: *Escherichia coli* resistant to third generation cephalosporins and methicillin-resistant *Staphylococcus aureus (MRSA)*. Extensive resistance in extremely variable strains of *N. gonorrhoeae* has rapidly emerged and developed resistance towards macrolides, sulphonamides, fluoroquinolones, tetracyclines and early generation cephalosporins. The utilization of extended-spectrum cephalosporin ceftriaxone in injectable form are the only available therapeutic option for gonorrhoea in most countries currently. The threat of carbapenem resistant enterobacteriaceae (CRE) is emmerging and numerous mechanisms are associated in their non-susceptibility against carbapenem. This situation complicates the therapeutic scenario in critical care conditions in hospital setting as carbapenem resistant pathogens are most commonly found to be multidrug resistant. The epidemiology and occurrence rate of CRE differs in different geographical regions [30].

Antimicrobial resistance is an intricate issue which requires a combined multisectoral approach. One health approach brings together various divisions and

stakeholders involved in human, aquatic and terrestrial animals and plants health, feed and food production and the environment to interact and work together for designing and execution of programmes and research to accomplish improved public health outcomes. The research and development of novel antimicrobials, vaccines and rapid diagnostic tools especially for targeting dangerous gram-negative bacteria like carbapenem resistant Enterobacteriaceae requires greater innovations and investments [30].

2. Conclusion

Multidrug efflux pumps are primeval elements encoded in the microorganism's chromosomes which confer resistance to antibiotics at different levels: intrinsic resistance, acquired resistance, and transient induced phenotypic resistance. Additionally, multidrug efflux pumps exhibit various functions with relevance to bacterial adaptation to altered habitats. Some of these functions, like resistance to heavy metals, resemble antibiotic resistance, biocides, or solvents, as they are adaptive responses to diverse types of external injuries, whereas, others are associated to internal detoxification of intermediate toxic bacterial metabolites. AcrAB pump is an important antibiotic resistance determinant in bacterial pathogen, having a dynamic role in developing resistance towards carbapenem group of antibiotics and the role of regulatory genes in inducing the expression of these pumps highlights the fact that the regulators directly or indirectly involved in increasing the expression of efflux pump system leading towards the development of carbapenem resistant MDR *Escherichia coli* isolates in clinical settings.

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Conflict of interest

None.

Abbreviations

MDR	Multidrug Resistant
AMR	Antimicrobial resistance
CRE	carbapenem resistant Enterobacteriaceae
UTIs	Urinary tract infections
MRSA	methicillin-resistant *Staphylococcus aureus*
UPEC	Uropathogenic *Escherichia coli*
NDM	New Delhi metallo beta-lactamase

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