

Review on Colistin resistance among gram-negative bacteria

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ABSTRACT

Colistin drug is used as last line of drug for the treatment of gram-negative bacterial infection which is the main cause of morbidity and mortality. These life-threatening bacteria are on the peak priority list of World Health Organization, carbapenem resistant bacteria. *E. coli*, *pseudomonas* and *Acinetobacter baumannii*. Colistin is used to treatment of multi-drug resistant gram-negative bacteria but the colistin resistance has been occurred. This review contains information of recent research papers in last five years. Genes involved in the mechanism of colistin resistance are *pmrA/pmrB*, *phoP/phoQ*, *arnBCDTEF*, *mcr1-mcr5*, *mcr7*, *mcr8* and many other genes. There are various methods used to know the mechanism of resistance like antibiotic susceptibility test, agar dilution method, Quantitative RT-PCR, Transposon mutant technique and MALDI-TOF MX. So, the combinational therapy, triple vaccination, bacteriophages and monoclonal therapies could be useful for treatment.

INTRODUCTION

Antibiotic resistance among gram negative bacteria was begin in 1917 and now a days it is a major health and public concern. The urgency to treat the multi- drug resistance the novel sources against these pathogens requires the revival of Colistin and previous useful antibiotics as a optimum treatment option. Currently there has been a huge growth in the rate of condemnatory infections due to multi drug resistance gram-negative bacteria, in specific Cephalosporin & Carbapenem resistant *Enterobacteriaceae*. Colistin was used for the treatment of infections caused by multi drug resistance bacteria. But due to its toxic effects it was prohibited for further use. Due to the sudden rise of multi drug resistance infections it was again used and named as last resort antibiotic. Carbapenem resistant bacteria- currently has been a huge growth in the rate of condemnatory infection due to the multi drug resistance gram negative bacteria in specific cephalosporin and carbapenem resistant *Enterobacteriaceae*. As per WHO report the carbapenem resistant bacteria are included in critical priority list are *Acinitobacter baumannii* , *Pseudomonas aeruginosa* and *Enterobacteriaceae*

INTRODUCTION OF COLISTIN

Colistin is narrow spectrum bactericidal agent which was discovered in 1947 and was used clinically. It's a mixture of two group of molecules that is polymixin E & B. It acts as a last line drug for treatment of multidrug

resistant gram-negative bacteria. Due to toxicity of colistin its clinical use was withdrawn but in 1990 due to the increase of multi drug resistance gram negative infection it had been re-introduced in the treatment line.

COLISTIN RESISTANCE

Recent studies showed that colistin is being used as last resort drug for the treatment of multi drug resistance gram negative bacteria, shows colistin resistance among these bacteria. It kills the gram-negative bacteria by binding the outer membrane which consists of lipopolysaccharides and phospholipids but the use of colistin shows many side effects such as renal and neurological problems. First colistin resistance gene was found in China in 2011 and in 2016 US identified the colistin resistant *E. coli*.

MECHANISM OF COLISTIN RESISTANCE

Although the colistin resistance mechanism is not well understood. But according to various research there are various mechanisms which has been enlisted in the literature. Most common mechanisms which is involved in colistin resistance is lipopolysaccharide modifications with different routes. The first report from India showed that *K. pneumonia* which causes bacterial infections are resistant to colistin and the resistance caused by the modification of lipopolysaccharides by chromosomal genes. Second mechanism includes the over expression of efflux pump system. Other mechanism of actions include intrinsic resistance mechanism and over production of capsule polysaccharides and there are various genes which are responsible for the colistin resistance i.e *pmrA/pmrB*, *phoP/phoQ*, *arnBCDTEF*, *mcr1-mcr5*, *mcr7*, *mcr8* and many other genes.

TREATMENT OF COLISTIN RESISTANCE

Colistin resistance has been increasing rapidly so, the treatment of this is crucial these days. The literature showed that colistin resistant *E. coli*, *K. pneumoniae* and *Enterobacter* were killed by the combinational therapy of colistin drug with PFK-158 (anti-tumor drug). Triple vaccination is also considered as the method to treat colistin resistant bacteria. One of the studies revealed that combination of colistin with Rifampicin and Linezolid gives the best results to treat the colistin resistant *E. coli*, *Pseudomonas* and *Acinetobacter baumannii*. Along with this bacteriophages and monoclonal therapies are equally important to retard the colistin resistance in gram negative bacteria but sometimes this therapy shows failure as colistin resistant bacteria are resistant to multi drug, due to long process. Substitute provided against this therapy is repurposing drug.

METHODS USED FOR IDENTIFICATION

Table 2: Various methods used for the identification of mechanism of resistance:

Antibiotic susceptibility test	Used for testing whether drug is resistant or not
Agar dilution method	For identification of minimum inhibitory
Quantitative RT-PCR	For detection of <i>mcr</i> gene

Transposon mutant technique	Not a good choice method
MALDI-TOF MX	Lipid A modification

METHODS USED FOR DETECTION:

In various studies antibiotic susceptibility test by disc diffusion method used for the detection of resistance by checking the minimum inhibitory concentration of colistin. Various genes which are responsible for colistin resistance are identified by using quantitative RT-PCR. Other techniques are also used like transposon mutant technique and MALDI-TOF MX but transposon mutant technique is rarely used for research purpose.

CONCLUSION

Several reports pointing out that the spreading of Colistin resistance has raised on a fast pace among *Enterobacteriaceae*. Hence, further investigations need to be done to sort out this global problem. As multi drug resistance bacteria is increasing and effecting the health of human and it's really getting difficult to treat the infections caused by these bacteria. As colistin is one of the best option to treat drug resistance gram negative bacteria, some of the studies revealed that nowadays the multi drug resistance bacteria is also getting resistant to colistin. The review focused on the occurrence of colistin resistance gram negative bacteria, there mechanism, and the various methods to identify how the mechanism of colistin resistance is emerging in clinical settings. As per reviewed paper the MDR gram negative bacteria is showing colistin resistance by various mechanism and some of the paper show the new genes which are leading to colistin resistance. At least to reduce the burden of colistin resistance among gram negative bacteria it's compulsory to identify the genes which lead to resistance. Along with this new antibiotic should be discovered to treat this problem.

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