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Multidrug Resistance: Emerging Clinical Challenges Andrecent Updates

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Abstract:*Multidrug-resistant(MDR)bacteria was discovered as early as 1950s.Transmissible R factors of Enterobacteriaceae received greatest attention, the existence of plasmids were identified which confer antibiotic resistance in many genera. Plasmids also confer resistance to penicillin, chloramphenicol, erythromycin, and number of heavy metals. Multidrug-resistance Gram-negative bacteria pose a great threat to the public health due to the limited treatment options available and lack of newly developed antimicrobials medications.NewDelhimetallo-beta lactamase-1(NDM-1) are detected worldwide.Colistin-Polymyxin E remains one of the last- resort antibiotics for multi resistant bacteria.Colistin in combination with drugs are used to treat P.aeruginosabiofilim infection in lungs of cystic fibrosis patients. The plasmid-borne mcr1 gene has been found to confer resistance to colistin.This plasmid-borne-mcr-1 has been isolated in China, Europe and,UnitedStates.India reported colistin-resistance,particularly in the blood stream infection. Resistance to Polymixins is frequent in the Mediterranean,Southeast Asia(Korea and Singapore).Colistin resistant Acinetobacter baumannii strains also developed resistance to LL-37 compounds and lysozyme. Resistance to carbapenem group of drugs has been reported in many countries. A restrained policy of antibiotic usage will prevent the spread of MDR worldwide.*

Keywords:*Multi-drug reasistance,NDM-1,Multidrug-resistant Gram negative,Colistin.*

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I. Introduction

Multi-drug resistance(MDR),also known as multidrug resistance or multiresistance is antibacterial resistance shown by a species of microorganism to multiple antimicrobial drugs. The types most threatening to public health are MDR bacteria that resist multiple antibiotics, other types include MDR viruses, fungi and parasites(resistant to multiple antifungal, antiviral and antiphrastic drugs of a wide chemical variety)[1].Recognizing different degrees of MDR the terms extensively drug resistant (XDR) and pan drug-resistant(PDR) have been introduced[2].Multidrug resistant Gram-negative bacteria(MDRGN bacteria) are type of Gram negative bacteria with resistance to multiple antibiotics. They can cause bacterial infection that pose a serious and rapidly emerging threat for hospital patients, and patients in the intensive care unit(ICU).Resulting in high morbidity, mortality and prolonged hospitalization.MDRGN,pose a threat to global public health and significant burden to healthcare systems[3].New Delhi metallo-beta-lacatamase-1(NDM-1),was first detected in a *Klebsiellapnerumoniae* isolate from a Swedish patient of Indian origin.in 2008.It was later detected in bacteria in, Pakistan, UnitedKingdom, the United States, Canada, and Japan[4,-6].Colistin,orpolymixin E, remains one of the last-resort antibiotics for multi-resistant *Pseudomonas aeruginosa*,*Klebsiellapneumoniae*,and*Acinetobacter*, and NDM-1 metallo-beta-lacatamase multi-resistant Enterobacteriaceae have also shown susceptibility to colistin [7,8].The paper provides an overview and clinical challenges of MDR therapy.

II. The originof Multidrug Resistance

The emergence of multiple-drug resistant strains of *Shigella* and their rapid rise to prominence among the major causative organisms of dysentery was first observed and carefully recorded in Japan[9].From 1945,onward,outbreaks of dysentery in Japan was controlledby sulfonamide. By 1950, it was found that 80% of the *Shigella* isolates were resistant to sulfonamide, and antibiotics, streptomycin, chloramphenicol and tetracycline were used with increasing frequency. In 1956, the first multiple drug-resistant strain of *Shigella*,resistant to chloramphenicol, tetracycline, streptomycin and sulfonamide was isolated. From this time onwards, such multiple-drug resistant strains were isolated at increasing frequencies until, by 1959, approximately 50% of the *Shigella* isolates showed this pattern of multi-drug resistance[10].

The important difference between the emergence of these strains, and the previously reported emergence of other antibiotic-resistant strains in bacterial populations was revealed when it was demonstrated that most of these multiple-drug-resistant strains could transfer the genes from conferring drug resistance by other antibiotic-sensitive strains. This transfer was known to occur between members a single genus, or between members of related genera such as *Escherichia coli* and *Shigella.*In the Japanese experience, however, there was a sudden appearance of strains which were resistant to a number of drugs and which had the capacity to transfer this resistance to other bacterial strains [10] The transfer of multiple-drug-resistance genes or R factors requires cell to cell contact and occurs via a presence of conjugation. In this process, donor cells (those possessing R factors) produce a specific appendage called a sex pilus which allows specific pair formation to occur between the donor and recipient cells. Subsequent to pair formation, a signal from the recipient causes the donor cell to transfer a copy of some of its genetic material through the conjugation tube inti the recipient cell. The gene attached to the R factor are transferred with greatest efficiency and in *vitro* experiments, would generally the transferred at frequencies of about 10^{-4} per donor cell in two- hour matting. In some cases, the genes for drug resistance and genes for conjugal transfer exist on separate replicons in the same cell and under these circumstances transfer frequencies are decreased by one or two orders of magnitude [10].

The early work in Japan, multiple-drug resistant strains, able to transfer their resistance determinants, have been discovered in most countries of the world including Australia[11,12].Although the transmissible R factors of the *Enterobacteriaceae* have received the greatest attention, the existence of plasmids able to confer antibiotic resistance has been reported in a number of genera. One of the most clearly studied groups is Staphylococcus where plasmids have been identified which confers resistance to penicillin, chloramphenicol, erythromycin,arsenate and a number of heavy metals. There has been reports of aplasmid in *Streptococcus pyogenes* which confers resistance to erythromycin,lincomycin, and staphylomycin S, an as yet unconfirmed report of plasmids in *Clostridium perfringens* conferring antibiotic resistance[13,14],There have been reports of the isolation of strains of *N.gonorhoeae* which are penicillin resistant because they produce a β –lactamase [15].The dramatic spread of R factors during the last few years and the increase in the multiplicity of resistance patterns that can be carried are very powerful arguments for a restrained and careful policy of antibiotic usage[10].

III.Multidrug- resistant organisms

Frequently isolated multidrug-resistant -organisms includes:

- Vancomycin-resistant Enterococci(VRE)
- Methicillin –resistant *Staphylococcus aureus*(MRSA)
- Extended –spectrum β-lactamase producing Gran-negative bacteria
- *Klebsiellapnumoniae*cabapenenase (KPC) producing Gram –negatives
- Multidrug-resistant gram-negative rods(MDR GRN)MDRGN bacteria such as *Enterobacter species,E.coli,Klebsiellapnerumoniae,Acinetobacterbaumannii, Pseudomonas aeruginosa, and multidrug-*resistant tuberculosios (MDRMTB) [16].

Mechanism of bacterial antibiotic resistance: Bacteria have natural ability to survive under unfavorable conditions for thousands of years, by adapting to antibacterial agents. They do so via spontaneous mutation or by DNA transfer. This processenables some bacteria to oppose the action of certain antibiotics, rendering the antibiotic ineffective [17].These bacteria employ several mechanisms in attaining-drug resistance:

1.No longer relying on a glycoprotein cell wall
2.Enzymatic deactivation of antibiotics
3.Decreased cell wall permeability to antibiotics
4.Altered target sites of antibiotic
5. Efflux mechanisms to remove antibiotics [18].
6. Increased mutation rate as a stress response [19].

Many different bacteria now exhibit multi-drug resistance, including staphylococci, enterococci, gonococci, streptococci, salmonella, as well as numerous other gram-negative bacteria and*Mycobacterium tuberculosis*. Antibiotic resistant bacteria are able to transfer copies of DNA that code for a mechanism of resistance to other bacteria even distantly related to them, which then are also able to pass on the resistance genes and so generations of antibiotics resistant bacteria are produced. This process is called horizontal gene transfer [20].

Fungal antibiotic resistance: Yeast such as Candida species can become resistant under long term treatment with azole preparations, requiring treatment with a different drug class. *Scedosporiumprolificans* infections are almost uniformly fatal because of their resistance to multiple antifungal agents [21].

Antiviral drug resistance: The best example of antiretroviral resistance in human immunodeficiency virus (HIV) infection.Virologic failure that results from resistance to antiretroviral agents is a major cause of treatment failure [22].The clinical significance of antiretroviral drug resistance was demonstrated not long after the introduction of the nucleotide analogues[23].Subsequent studies show an increased risk of virologic failure when patients are treated with drugs to which the virus shows genotypic or phenotypic resistance[24].Resistance to anti-viral drugs also been reported in Cytomegalovirus infection and Herpes simples virus infection.

Parasitic antibiotic resistance: The prime example for MDR against parasitic drugs is malaria.*Plasmodium vivae* has come chloroquine and sulfadoxine-primemethamine resistant few decade ago,and as of 2012 artemisinin-resistant *Plasmodium falciparum* has emerged in wetren Cambodia and western Thailand.*Tosoplamsmagondii* can also become resistant artemisnin,as well as atovaquone and sulfadiazine,but is not usually MDR[25].Antihelmintic resistance is mainly reported in the veterinary literature, for example in connection with the practice of livestock drenching, and has been recent focus of FDA regulation [26].

New Delhi metallo-beta lacartamase- 1(NDM-1)[27], is an enzyme that makes bacteria resistant to a broad range of beta-lactam antibiotics. These include the antibiotics of the carbapenem family, which are mainstay for the treatment of antibiotic resistant bacterial infections. The bacteria that produce carbapenemases are often referred to in the news media as "superbugs" because infections caused by them are difficult to treat. Such bacteria are usually susceptible only to polymxins and tigecycline[28].The most common bacteria that make this enzyme are gram- negative such as *Escherichia coli* and *Klebsiellapneumoniae*,but the gene for NDM-1 can spread from one strain of bacteria to another by horizontal gene transfer[29].

NDM-1 enzyme development: Thecarbapenems were developed to overcome antibiotic resistance mediated by bacterial beta-lactamase enzymes. However, the**bla_{NDM-1}** gene produces NDM-1 which is carbapenemase beta-lactamase-an enzyme that hydrolyzes and inactivates these carbapenemantibiotics.Carbapenemases are particularly dangerous resistance mechanisms since they can inactivate a wide range of different antibiotics[30].The NDM-1 enzyme is one of the class B metallo-beta-lacatamase;ther types of carbapenemase are class A or class D[31].The class A *Klebsiella pneumoniae*cabapenemase(KPC) is currently the most common carbapenemase,which was first detected in North Carolina,UnitedStates,in 1996 and has spread worldwide [32].A later publication indicated that Enterobacteriaceae that produce KPC were becoming common in the United States[33].

Discovery and worldwide spread of NMD-1: The NDM-1 enzyme was named after New Delhi,the capital city of India,as it was first described by Yong et al in 2009 in a Swedish national who fell ill with an antibiotic-resistant bacterial infection that acquired in India[34].The infection was identified as a carbapenem-resistant *Klebsiella pneumoniae* strain the novel gene bla_{NMD-1}.The authors concluded that the new resistance mechanism "clearly arose from India, but there are few data arising from India to suggest how widespread it is"[34].In 2010,a study in hospital in Mumbai found that most carbapenem-resistant bacteria isolated from patients carried the bla_{NDM-1}gene[35].Later the Journal(The Lancet) authority apologized for using the of New Delhi, India to describe a pathogen[36].

NDM-1 β-lacatamase was also found in an *K.pneumoniae* isolate fromCroatia,and the patient arrived from Bosnia Herzegovina.The second geographical origin is considered to be eastern Balkan[37].In 2010, a case of infection with E.coli expressing NDM-1 was reported in Commentary in the United Kingdom. The patient of Indian origin, with history of visit to india,18 months previously, and he had undergone renal dialysis in India[38].The authors warned that international travel, and patients' use of multiple countries' healthcare system could lead to the "rapid spread of NDM-1 with potentially serious consequences: [38].In2010,there were three reported cases of Enterobacteriaceae isolates bearing this new described resistance mechanism in the US,CDC stated that :All three US isolates were from patients having received recent medical care in India[39].In 2010,a team in New Delhi reported a cluster of three cases of Acinetobacter baumannii bearing bla_{NDM-1} that were found in the intensive care unit in Channai, India, in April 2010.The isolates were fully resistant to all the aminogkycoside beta-lacatam and quinolone antibiotics, but were susceptible tigecycline and colistin.This particularly broad spectrum of antibiotic reissuance was heightened by the strain's expressing several different resistance genes in addition to bla_{NDM-1}[40].

A study by a multi-national team was published in the August 2010 issue of the Journal, The Lancet Infectious Diseases. This examined the emergence and spread of bacteria carrying the **bla_{NDM-1}**genes. This reported on 37 cases in the United Kingdom,44 isolate with NDM-1 in Chennai,26 in Haryana, and 73 in various other sites in Pakistan and India[27].An environmental study conducted in 2010 found bacteria with NDM-1 gene in drinking water and seepage samples in New Delhi[41].

In August 2010,the first reported death due to bacteria expressing NDM-1 enzyme was recorded after a Belgian man, who was involved in a car accident during a trip Pakistan[42].In 2016,a 70 year-old woman in Reno, Nevada,with travel record to India, died of septic shock following infection with NDM-1,producing *Klebsiella pneumoniae* [43].

Diagnostic test for detection of NDM-1: Detection of NDM-1 gene depends upon the phenotypic determination of the enzyme activity. These enzymes are zinc dependent and therefore termed as-metallo-beta-lacatamse.Indian studies have been done which demonstrate their dependency on zinc and the ability of zinc chelating like EDTA to decrease their activity. The Modified Hodge Test and a newly developed Re-Modified Hodge Test were developed foe detection on a routine basis in resource limited laboratories other tests for phenotypic detection are:a) Double disk synergy testing(DDST),b) Vitek detection(automated system),c)E.test(E.strip)[44].

Multidrug-resistance in Gram –negative organism:MDRGN bacteria pose a great threat to the public health due to the limited treatment options available as well as lack of newly developed antimicrobial medications.MDR strains of *Enterobacteriaceae,Pseudomonasaeruginosa,*and*Acinetobacter baumannii* have become the most concern because they have been reported by hospitals all around the United States. There are many factors which could be contributed to the existence and spread of MDR gram-negative bacteria such as the overuse of existing antimicrobial agents, which has led to the development of adaptive resistance mechanisms by bacteria, a of responsible antimicrobial stewardship such that use of multiple broad-spectrum agents has helped perpetuate the cycle of increasing resistance, and a lack of good infection control practices [3]..

Choice of antibiotics in MDRGN therapy: Currently there is a shortage of new drugs in the antimicrobial realm, there are a few antibiotics currently being studied for the treatment of serious Gram-negative bacterial infections. These include cephalosporins,ceftabiprole, ceftarolin,and FR-264205[45].The lack of newly emerging antimicrobial drugs have resulted in the revisit of old antibiotic drugs such as colistin and fosfomycin (Polymixins), which are traditionally considered to be toxic but have gained a principal role in the treatment of the most problematic MDR Gram-negative pathogens including *Pseudomonas aeruginosa,Acinetobacter baumannii,Klebsiella pneumoniae,*and*Stenotrophomonasmaltophila*. Also, there has been interest in the drug Tigecyclinewhich is grom the same class of antibiotics called glycyclcilines, for treating MDRGN infections[45].This drug shows promise in infections from multi-drug resistant K.pneumoniae(K*pneumoniae*carbapenemase[KPC]-and ESBL-producing strains and Enterobacteriaceae with various mechanisms of resistance[46].A study of MDRGN in long- term care facilities, reported in 2010,concluded that patients with severe dementia who require assistance with the activities of daily life are at high risk of MDRGN co-colonization and may be the "super spreaders: of MDRGN in these facilities[47].

IV. Therapy challenges

Colistin or polymyxin E is a decades –old drug that fell out of favor in human medicine due to its kidney toxicity. It remains one of the last- resort antibiotics for multidrug-resistant *Pseudomonasaeruginosa,Klebsiellapneumoniae*,andAcinetobacter, NDM-1metallo-beta-lacatamase multidrug resistant Enterobacteriaceaer have also shown susceptibility to colistin [48,27].Colistin was first discovered in 1949 from a flask of fermenting Bacillus polymyxavarcolistinus by the Japanese scientist Koyama and became available for clinical use in 1959[49,50].Cloistimethatesodium,a less toxic drug, became available for injection in 1959.In 1980s,polymyxin use was widely discontinued because of nephron-and neurotoxicity. A multi-drug resistant bacteria became more prevalent in the 1990s,colistin started to get a second look as an emergency solution, in spite of toxic effects [51].

Clinical dosage,antibacterial activity and resistance:Colomycin 1,000,000 units is 80 mg colistimethate[52],Coly-mysin M150 mg"Colistin base" id 360 mg colistimethate or4,500,000 units[53].Colistin has been effective in treating infections caused by *Pseudomonas aeruginosa,Escherichiacoli*,and*Klebsiella*species.MIC(minimal inhibitory concentration for medically significant pathogens include:

Escherichia coli:012-128 ug/ml,Klebsiella pneumoniae: 0.25-128 ug/ml and Pseudomonas aeruginosa:<0.06-16 ug/ml.[54].Colistin in combination with other drugs are used to attack P.aeruginosa biofilm infection in lungs of CF(cystic fibrosis) patients[55].Biofilms have a low oxygen environment below the surface where bacteria are metabolically inactive and colistin is highly effective in this environment. However aeruginosa reside in the top layers of the biofilm,where they remain metabolically active [56].This because surviving tolerant cells migrate to the top *of biofilm* via pili motility and form new aggregates via quorum sensing[57].

The plasmid-borne mcr-1 gene has been found to confer resistance to colistin[58].The first colistin resistance gene in a plasmid which can be transferred between bacterial strains was found in 2011 and became publically known on November 2015[58].This plasmid-borne- mcr-1 gene has since been isolated in China[58],Europe[59,],and the United States[60].India reported the first detailed colistin-resistance study which mapped 13 colistin resistant cases recorded over 18 months. It concluded that pan-drug resistant infections, particularly those in the blood stream, have a higher mortality. Multiple other cases were reported from other Indian hospitals[61].Although resistance to polymixins is generally less than 10%,it is more frequent in the Mediterranean and Southeast Asia(Korea and Singapore),where colistin resistance rates are continually

increasing[62].Colistin resistant E.coli was identified in the United States in May 2016[63].The use of colistin to treat *Acinetobacter baumannii* infections has led to the development of resistant bacterial strains, which have also developed resistance to antimicrobial compounds LL-37 and lysozyme, produced by the human immune system[64].Inherent resistant also has been reported in many other bacterial strains including *Stenotropohomonasmaltophilia*[65].Hussain T teleported wide spread resistance to carbapenem group of drugs in the clinical and non-clinical environments in Pakistan[20,,27,66].Tarquinio and associated advocate use of Tobramycin and Poymixin E against *Pseudomonas aeruginosa*Biofilim coated Medical grade Endotracheal tubes, when*Pseudomonas aeruginosa* is a potential pathogen[67].

V. Prevention of Antibiotic Resistance

Suggestive prevention of antimicrobial resistance includes:

1. The action plan, first annual report, and many issues related to antibiotic resistance are available at www.cdc.gov/drugresistance.[68].
2. More prudent use of antibiotics in humans and animals is critical [69].Appropriate pharmaceutical advertising and promotion is essential[70].
3. Improved surveillance (in the hospital and health care facilities).[68]
4. Increase in funding for basic research [68].
5. New antibacterial agents. Research and development must be expedited, with 'fast track" for new antibiotics for MDR bacteria [68].
6. Prevention of transmission with infection control practices[68]
7. Hospital administration(hospital antibiotic policy).Each hospital should establish its own strategies to optimize the prophylactic, empiric, and therapeutic use of antimicrobials in the hospital [71]
8. To deal with increasing problem of MDR bacteria the answer lies in efforts from all of us,physician,patient,microbiologist,and manufacturer, public health, and Government policy officials. No one can sit back and expect someone else will solve the problem. In the past, we have relied on the pharmaceutical companies to develop new drugs to deal with the resistance and, they have largely succeeded. But the ability to stay one step ahead of the bacteria has led to complacency about the resistance problem. We can no longer maintain this attitude [72].

VI. Conclusions

A careful policy of antibioticusage.Concerted efforts by all concerned to prevent multidrug-resistance and develop new antimicrobials by 'fast track' for multidrug resistant organisms.

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