Journal of Population Therapeutics & Clinical Pharmacology

REVIEW ARTICLE
DOI: 10.53555/jptcp.v31i7.7121

COLISTIN RESISTANCE IN COMBAT AGAINST ACINETOBACTER BAUMANNII: A MULTI-ASPECT COMPREHENSIVE REVIEW EXPLORING COLISTIN RESISTANCE IN ACINETOBACTER BAUMANNII, ITS MECHANISM, CLINICAL IMPLICATIONS, EPIDEMIOLOGY, AND GLOBAL BURDEN WITH SPECIAL FOCUS ON NOSOCOMIAL INFECTIONS.

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Abstract

Nosocomial infections are the leading cause of major spread of all available antibiotic-resistant bacteria till date. Among these, Acinetobacter baumannii is the most important host of hospital-associated outbreaks due to its developed resistance to all available antibiotics which make clinicians to rely on a buried drug called colistin to put it in use which is the only option left. Acinetobacter marks the overburden of nosocomial morbidities ultimately compromising the country's economy. But now this horrible organism adopts resistance to this graved drug not only by chromosomal but also by plasmid-mediated mechanism conferring horizontal gene transfer. Colistin belongs to the class Bacillus polymyxa is a cationic peptide that targets the negative charge of LPS of all gram-negative bacteria. Major genetic factors involve the mutated genes (lpxACD) leading to complete loss of LPS and two component system (PmrAB system) that causes the overexpression of PmrC homologue eptA, modify the LPS by adding petN to lipid A moiety with some other TCS are also detected like AdeABC operon. Plasmid mediation done due to mcr1 genes and its variants which arouse from the animals due to excessive use of colistin as a metaphylactic approach disturbing the one health perspective. By examining the various factors that contribute to the resistance of last resort treatment for hospital infections, it becomes evident that significant measures must be taken to combat the highly resistant Acinetobacter bacterium and the antibiotics listed by the WHO. Many countries previously using it as a growth promoter in animals, banned its consumption due to the prevalent resistance mechanism in critically important pathogens. The fast emergence of variations is stigmatizing for society. Hence, it is crucial to thoroughly assess and monitor the resistance mechanisms in bacteria and the therapeutic window of colistin by surveillance that meets the requirements of the continuing research program. Due to the narrow therapeutic range of colistin, it is crucial to secure its targeting structures (particularly homologue eptA) and monitor its use. This is

necessary to control the prevalent resistance to colistin, which is the main cause of high mortality rates, especially in hospitals. It is important to implement appropriate antimicrobial resistance (AMR) surveillance strategies at regional, national, and international levels to effectively manage colistin as a last resort treatment for nosocomial infections. Our review focus on the resistance mechanism toward this drug in this particular nosocomial pathogen to manage its prevalence in the world which is making way to develop a new therapeutic option to consider.

Keywords: Colistin Resistance, Acinetobacter buamanii, Nosocomial infections, Antibiotic resistance

Introduction

Infections due to antibiotic-resistant bacteria in healthcare centers are increasing day by day instead of the presence of highly qualified policies and strategies that leads to the rapid development of high mortality and morbidity of nosocomial infections globally [1]. Multidrug resistant microorganisms have been the major cause of healthcare-associated infections all across the world with high frequency [2]. Multidrug-resistant strains of Acinetobacter baumannii responsible for more than one-third of nosocomial infections evoke the use of colistin in intensive care units for the cure of prevalent nosocomial infections [3]. From 2010 to 2014 MDR GNB almost 33,765 cases were tested for colistin resistance in clinical and microbiological laboratories to evaluate mortality and morbidity. Enterobacteriaceae species were 49%, pseudomonas species 29% and Acinetobacter species 22% present in combination or isolated form showing resistance to carbapenem (broad spectrum) antibiotics in isolates of Enterobacteriaceae and non-Enterobacteriaceae (pseudomonas, Acinetobacter) made colistin as last therapeutic option for these infection [4]. Recommendation of colistin by WHO as clinically important drug for these carbapenemases. Increased MIC of colistin is significantly related with high fatality. Recently from Hungary, colistin-resistant case from blood culture isolates reported as 2.6% in Acinetobacter species [5].

Classification of essential antimicrobials was done by WHO into three categories: critically important; highly important; important antibiotics. Here colistin belongs to the critically important group to be used as human medicine [6]

Recently renewed interest in colistin due to the increased prevalence of MDR gram-negative particularly Acinetobacter due to the bactericidal action of polymyxins for therapy against this pathogen and susceptibility breakpoints are recommended by CLSI [7]. There are two forms of colistin, polymyxin B which is administered as a sulfate salt in the active form on the other hand colistin is administered as a prodrug in the form of colistin methane sulfonate or CMS by masking the dab residues with methane sulfonate then active to colistin and perform its antibacterial action [8]. Polymyxin a cyclic peptide acts by disrupting outer membrane produced by bacillus polymyxa. Over time three main ways to develop resistance against colistin, reduction in the net negative charge of lipid A to which colistin bind, proteolytic cleavage of drug, and efflux pump [9].

WHO published the priority list of pathogens in three categories named critical, high, and medium in 2017 for which Acinetobacter falls under critical category which is carbapenem-resistant highlighting the need of infection prevention and antibiotic stewardship [10]. Being listed in this category as no. 1 reflects the absence of all therapeutic options for all infections by this pathogen and creates a surprising interest for newest and alternative therapies like lytic phages and monoclonal antibodies [11]. The most commonly isolated pathogen from ICU was Acinetobacter for which very few therapeutic agents are available and almost completely resistant to b-lactams including carbapenems. In ICU about 40 to 70% of infections are due to carbapenem-resistant Acinetobacter [12]. Many new drugs are required for the Acinetobacter carbapenem resistant pathogen recommended by WHO and showed that many non-human isolates (plants and animals) are reservoir of antibiotic-resistant genes that confer resistance to available antimicrobials and this one health perspective can be lined with better understanding of resistance patterns in this pathogen [13]. The diversified resistance of

carbapenem in Acinetobacter led to the use of colistin as reserve but resistance has emerged for this final resort as well due to wide usage in this particular pathogen and measure failure for treatment [14]. Three steps can be achieved with analysis of AMR profile, help in lowering infection count, developing new and effective remedies, with reduction of resistance and better understanding in Acinetobacter because of enhanced colistin tolerance due to inappropriate and overconsumption [15]. Acinetobacter baumannii is the most common nosocomial pathogen and cause number of infections including systemic and localized that the Infectious Disease Society of America has placed this pathogen among 6 antimicrobial resistant organisms causing prevalence. and 5.3% of all Acinetobacter strains are resistant to colistin according to US surveillance study [16]. Various chromosomal mutation are responsible for the acquired colistin resistance in Acinetobacter, pseudomonas and more recently klebsiella. In Acinetobacter resistance is attributable to the modified lipid A and efflux transporter regulated by Nacl. LpxMAb in Acinetobacter mutant observed to be the central part in resistance to colistin [17].

This comprehensive review focuses on colistin resistance in Acinetobacter baumannii evaluating it in multiple perspectives like comparing its status with other available antibiotics, depicting the thorough understanding of mechanism of resistance, its significance in animal food sector, nosocomial infection and its burden in term of morbidity and mortality along with economic highlights. This review has specifically focused on nosocomial infections which may help the clinicians and researcher to devise strategies in order to combat this and improve health outcomes in these patients. It may also attract researcher to research on the resistance and develop new drugs which can be used in the cases of colistin resistance.

Colistin and its Status of Resistance:

The soil organism Bacillus polymyxa used for the production of colistin belongs to group of polymyxin that contain molecules A, B, C, D, E from which B and E are used for clinical purpose in humans and animals. In humans this is used for XDR, MDR and PDR whereas in animals for growth promotion and infection control [18]. In 1949 this polycationic peptide antidrug characterize and use as last line option for the treatment of carbapenem resistant gram negative bacteria and back to 2015 resistance observe for colistin confer by intrinsic mechanisms (phoPQ, pmrAB, and mgrB) [19]. Due to increased prevalence of infections by MDR, emerges the usage of colistin in 2000 [20]. Colistin has different components in which 2 components are most important A and B both of which are different by one carbon in fatty acyl chain and suggest that instead of monotherapy combination of it must be used to avoid risks and stopping resistance [21]. Aqua phobic acyl tails linear and tri and heptapeptide rings are contained in polymyxin group and C52H98N16013 is chemically colistin 3 main mechanism of colistin tolerance, intrinsically by arnBCADTEF operon and eptB gene, acquired but non transmissible by TCS and lastly transferable or plasmid originated by mgrb , ramA and mcr genes respectively [22]. Overexpression of efflux-pump systems and overproduction of capsule polysaccharide are seen but no enzyme realised resistance is reported or present but the strain that produce this antibiotic contains enzyme colistinase [23]. The interaction of anions of LPS and cations of antibiotics take place and it also neutralizes the inhibitory effect of LPS and transcriptional activity thus limiting the release of cytokine, facilitating cell apoptosis by degranulation of mast cells [24]. Threatening resistance in recent years, initiated the use of it despite its associated nephrotoxicity but its decreased efficacy is due to some external players such as polyamine antagonists (low molecular weight linear polyamines) consisting of various alkyl and amine groups such as spermidine and spermine [25]. There are mainly 2 pathways by which colistin resistance is conferred firstly, the addition of 4AraN and secondly, PetN to outer membrane LPS led to modification of the target and reducing the net negative charge [26]. Mobilized colistin resistance gene (*MCR-1*) the plasmid-originated gene encodes petN to the outer membrane and modifies the target of colistin and develops resistance and its spread to almost 40 countries and that comes under the 5 continents [27]. Most probably due to the combined resistance together of carbapenem and colistin posing serious concern

in treating infections [28]. In 2016 WHO placed this drug among critical antibiotics and emphasized the global discussion for its spread mcr 1 gene in both humans and animals and stopped the use of it as feed additive in animals in various countries including Brazil (2016), Thailand (2017), Japan (2018), Malaysia (2019), Argentina (2019) and China (2017), India (2019) [29].

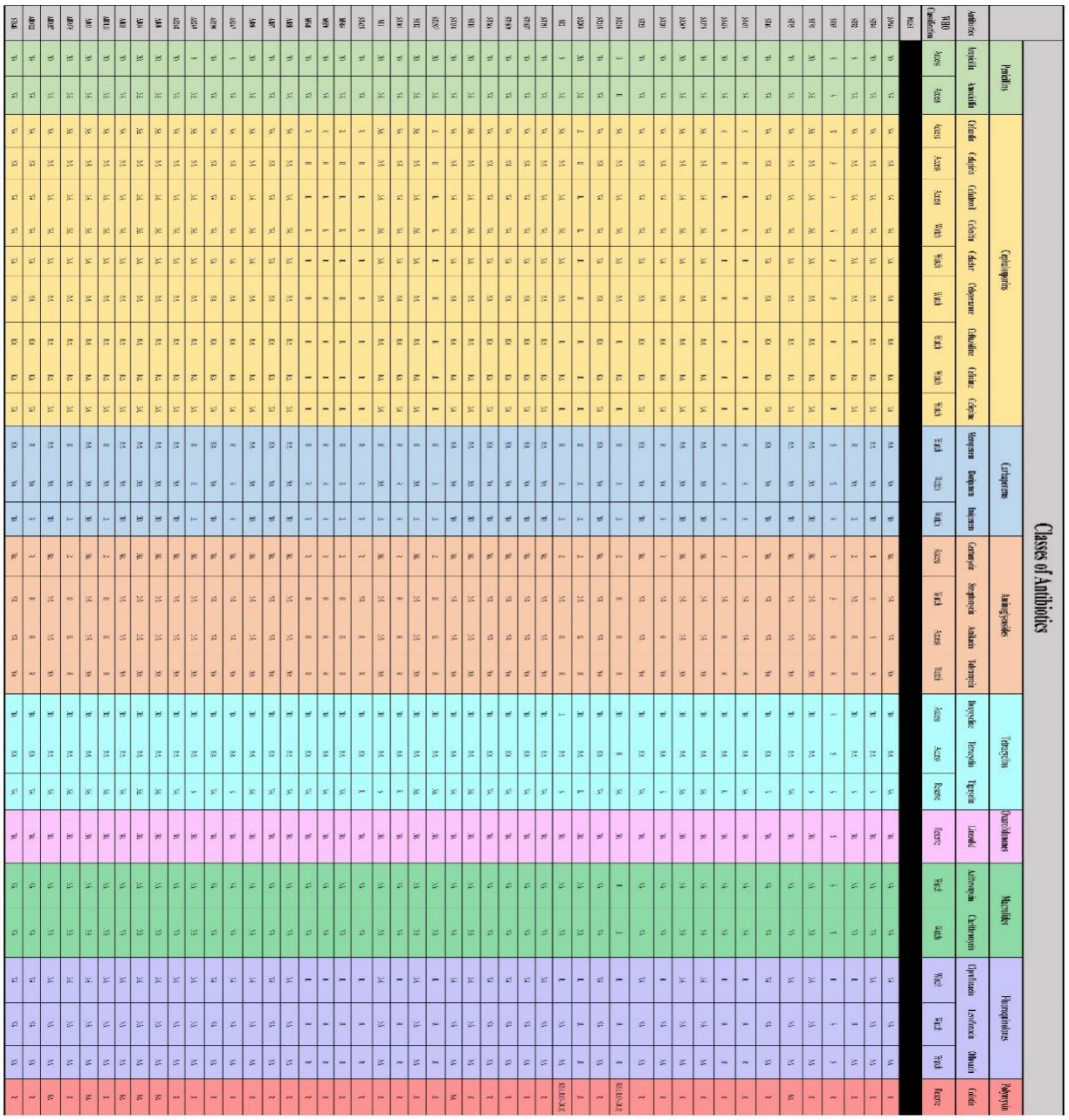

Table 1: Antimicrobial resistance to colistin in comparison to other classes of antibiotics

Understanding the Mechanism of colistin resistance in A. baumannii:

MDR Acinetobacter is characterized by two ways in developing resistance to colistin firstly, loss of LPS due to inactivation of lipid A (IpxA, IpxC, IpxD) most often genes are involved. Secondly, PmrAB two-component system mediates resistance, integrons and quorum sensing lasl gene play a central role to this drug in this pathogen [30]. Mutation in the chromosomally encoded PmrA and PmrB gene lead to overexpression of the PmrC gene which add pETN to lipid A corresponding resistance with no addition of L-Ara4N because it lack genes for this biosynthesis (Enterobacteriaceae) [31].

- PmrA-PmrB TCS: modified lipid A

Mutation in the sulfatase domain of PmrA and the histidine kinase domain of the PmrB gene causes to activate PmrA gene which in turn enhances the expression of the PmrC gene that encodes pEnT to

lipid A and modifies it [32]. In the PmrC gene the common amino acid substitutions are (I42V and L150F) with I115N associated with overexpression of PmrA, PmrB, and PmrC genes, A138T mutation of PmrB gene paves the way to colistin resistance [33]. The increased expression of PmrAB genes is associated with colistin resistance irrespective of their amino acid substitution which is partially responsible for resistance [34]. Several strains of acinetobacter showed amino acid alterations in the PmrCAB operon leading to the modifications of lipid A and the transition of colistin-dependent to colistin-resistant strains [35]. Hypothetically recent studies reveal that mutation in the PmrB locus which encodes sensor kinase causes overexpression of pmrC with whole transcript [36]. The modification of hepta asylated lipid A with phosphoethanolamine observed in all colistin-resistant strain with MIC range from 4 to 256 showing multiple factors related to this mechanism with the most prominent infection of VAP [37].

The operon activity of PmrA and PmrB genes induce resistance by a point mutation in the pmrB gene, upregulation of PmrAB, and expression of the PmrC gene and their functional role in environmental factors like pH, Fe and Mg that affect the expression of TCS [38]. Recently, patients treated with colistin developed individual resistance by mutation in the PmrB gene, Ala227Val, Pro233Ser, and frameshift from Phe26, these mutations are phospho acceptor domains of PmrB resulting in modification of lipid A [39]. Modification of lipid A with pEtN at phosphate position 4 and Galactosamine at position 1 demonstrated by tendom mass spectrometry important for resistance to colistin [40].

The point mutation of PmrAB genes with homolog of PmrC gene designed as eptA-1 and eptA-2 at another site to operon carry resistance [41]. H-NS negatively regulates the expression of PmrC homolog eptA by a mutation in this regulator through insertion sequence ISAba 125 adds PEtN showing this addition is not the sole factor but strain specific [42]. The study reported that mutation in the receiver domain of pmrA lead to the expression of PmrC and there are 5 amino acid substitution in the periplasmic and transmembrane domain of PmrB including P170L, S128R, T42P, L153F, and A28V cause elevated MIC for colistin ranging from 8 to 256 and another way to increase MIC associated with point mutation at promoter location of insertion sequence are all involve [43]. Alanine replacement at position 226 in PmrB is seen to be a contributor toward stable colistin resistance [44].

- lpxA lpxC and lpxD (complete loss of LPS):

Mutation in the above three genes results in no production of lipid A (endotoxin) among of which lpxA play a critical role where deletion of nucleotide 90 cause problem at AA 34 that encode UDP N-acetylglucosamine acyltransferase (first step) of biosynthesis leading to colistin resistance with the existence of sensitivity to other drugs [45].

It has been observed that there is no point mutation or deletion but an insertion sequence ISAba11 plays a significant role in any of these three genes highlighting the genome fluidity and resistance profile of the bacterium to colistin [46]. Mutations in ipxACD genes lead to lower fitness costs which ultimately reduce virulence of the organism [47].

The absence of LPS due to mutation in lpxC (insertion sequence) and one of the nucleotide deletions in the lpxA gene,the loss of endotoxin due to these genes has the varied effect of its inability to form a biofilm, loss of fitness, failure to grow properly in low iron availability, and increased susceptibility to disinfectant [48]. Inactivation of these genes by mutation causes enhancement of the various mechanism involved in the cell envelope and outer membrane stabilization in which lipoprotein and PNAG expression are increased to a certain level enabling bacteria to persist normally [49].

The utilization of advance sequencing technologies like TraDIS, WGS, RNAseq has uncovered the presence of genotypic alterations that confer colistin resistance in Acinetobacter baumannii , it's also

been observed that survival of this bacteria is dependent on presence of genes responsible for membrance synthesis such as LOS and phospholipids. Genes in the Mla pathway are essential for outer membrane stability, adeIJK efflux by TetR transcription leads to resist inhibitory concentration, MlaA is OM lipoprotein disrupted by ISAba1, nonsense mutation in zinc peptidases, SNPs in pmrB lead to increase expression of efflux pumps such as MacAB and adeIJK, all these changes analyzed for mechanisms of colistin resistance [50].

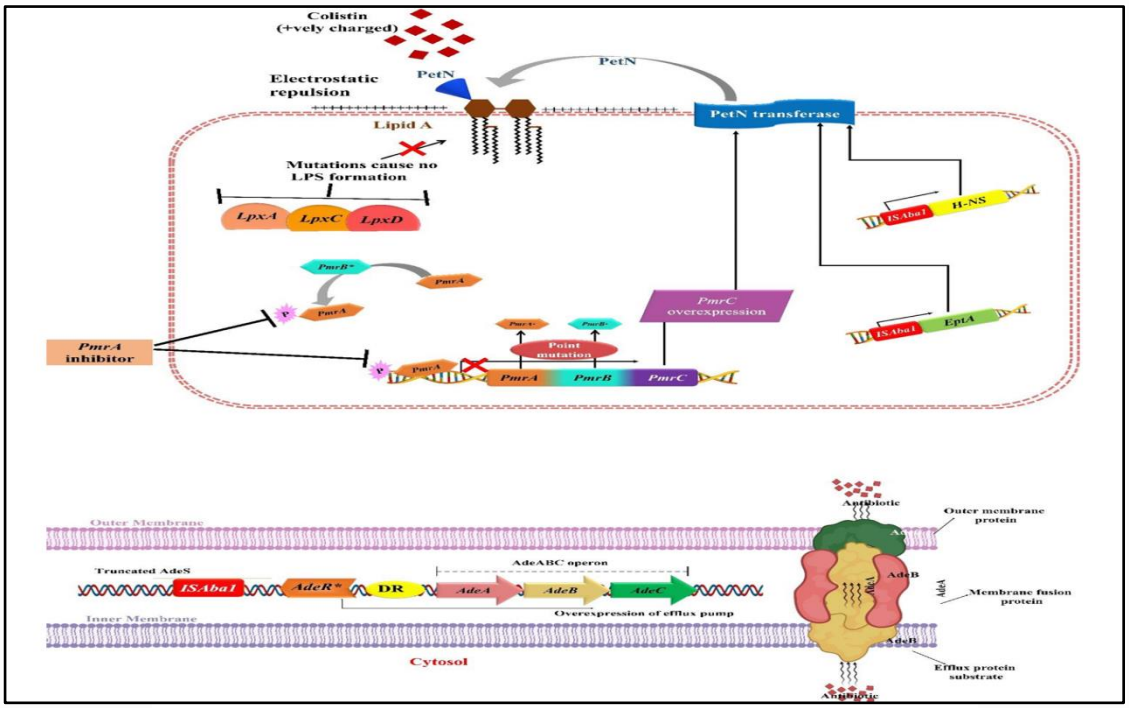

Figure 1. Two-component system and mutual genes mechanism

- Other TCS and genes

There are various TCS that play their role in the virulence of pathogen among which are AdeRS which regulate efflux pump, BaeSR that regulates efflux pumps, GacSA that regulate phenyl acetic acid pathway BfmRS which regulate OM structures like capsule and biofilm and at last PmrAB involved in colistin resistance, StkSR TCS contain StkR gene that act to repress the genes of PmrAB system and there is 2 fold increase of colistin resistance by inactivation of this gene showing its influence on the PmrAB system [51]. There exist a somewhat relationship between AB virulence genes and colistin resistance showing that the recA gene resists stress in the host and the lpsB gene plays role in LPS biosynthesis,blsA gene inhibits biofilm formation hence increasing the susceptibility so suggesting reduced expression of recA and enhanced expression of all other genes in vivo play crucial relation with colistin resistance and also demonstrate the impact of reduced d]virulence and fitness of formidable pathogen [52]. BfmS TCS regulates the production of OmpA in outer membrane vesicles and is responsible for the cytotoxic effects of epithelial cells link to aztreonam and colistin resistance due to the overproduction of OmpA due to sensor kinase mutation of this system [53]. Another NaxD gene expression regulated by PmrAB operon is associated with minor colistin resistance by encoding galactosamine to lipid A [54]. Recently a novel gene mcr 4.3 (animal origin) on the mobile element of tn3 family transposon was found to be related to colistin resistance in the A. baumannii 597A strain [55].

- A novel RND efflux system

Rnd stands for resistance nodulation division that constitute various categories of efflux system among which the AdeABC system known for A. baumannii though the expression of it controlled by adeRS operon to which genomic insertion of ISAba1 at adeS gene induce over appearance of

AdeABC operon lead to enhance MICs for colistin [56]. Other pumps of the rnd system are AdeIJK and AdeFGH, showing working simultaneously and inactivation of AdeIJK causes strong antidrug activity and inactivation of AdeFGH induces overexpression of AdeABC [57]. The insertion sequence ISAba1 at upstream of the AdeAB operon and mutation in the regulatory system affects DNA binding to the upstream operon [58]. AdeA codes MFP, AdeB channel transporter and AdeC code OMP, and two regulatory genes at upstream of an operon in opposite directions [59]. Mutation in the signal receiver domain of response regulator AdeR modifies the interaction of AdeS and AdeR and provokes the overexpression of operon [60]. The efflux pump gene EmrB plays a crucial role in not only the development of colistin tolerance but also adaptation to osmotic stress [61]. The efflux system positively plays a role in the development of colistin hetero resistance in A. baumannii but the use of CCCP inhibitor can make it susceptible and lower the MIC [62]. Hospital wastewater isolates investigated for colistin resistance showing that increase level of ept A gene contribute essential role due to other cationic surfactants that may cross react with colistin [63].

- MCR 4.3 gene with ept A gene:

New gene with 1626bp in the strain 597 acinetobacters was found to be present in the plasmid called pAB mcr 4.3 embedded in Tn3 family transposons with pmrC related gene ept A having 50.5% nucleotide similarity with this gene encoding phosphoethanolamine transferase mediate resistance [64]. The RepB plasmid-mediated mcr 4.3 gene caused A. nosocomialis to be resistant to colistin but not in E. coli showing difference in genomic environment [65].

Usage of colistin in the clinical and animal food sector:

Colistin is used in humans as medicine and in animals as a growth promoter as as treatment regimen and also as a metaphylactic approach for disease control due to its use in low doses in food producing animals develops resistance and according to one health aspect, the use of it as metaphylactic should be prohibited [66]. The ranking of polymyxin by WHO among high priority ones for limiting in animals as it is critically essential need of humans. Since 2012 this drug get importance for use as last line in humans as critical WHO reclassify it [67]. In seventies about its toxicity concerns its prohibited in human and also due to livestock practices and especially in Italy its use for decades still widely used and in Europe its usage is decreased which in animals recommend for GIT therapy caused by E. coli [68]. That's why due to enteric infections caused by e.coli implicate the widespread mobilized colistin resistance prevalence [69]. Due to its increased use in animal husbandry, resistance move to higher speed so its usage re-checked. The European medicine agency in 2016 made an update on its use within EU in animals then the Ministry of Agriculture of China stopped the use of colistin as growth promoter in animals in 2016 Nov , after that in 2017 department of livestock development in Thailand also banned it as feed and some other countries including India, Argentine, Malaysia and Brazil invalidate it as growth promoter, despite all these efforts its consumed for treating diseases in animals leading to selection pressure for animals bacteria like mcr 1 originating from animals and spread to humans bacteria [70]. In order to avoid the mobilized mcr 1 gene spread then surveillance of pets must be priority as these pets' encouraging contribution of mcr containing bacteria and from Asia, the US, and China this gene (enterobacteriaceae) has been reported mainly in cats and dogs [71]. In China in 2015 mcr 1 was isolated in enterobacterales from pigs meat in patients which facilitate the transmission between human and animals easily [72]. The strains of E. coli indirectly from meat and directly from animals accounted 15 and 21% between 2012 and 2014 [73]. Monitoring the use of colistin in europe is regulated for veterinary use while no regulation exist in Asia and from China correlation was found between the agricultural and spread of resistance, a study documented from China observed a lower level from 37% to 1% for the prevalence of mcr gene among hospitalized patients when its farming use is banned [74]. In South Asian regions (Nepal, Pakistan, India and Bangladesh) the prevalence of E. coli was 73% after the meta-analysis of 9 studies and in poultry was 28% [75]. In aspect of humans colistin is available in 2 forms 1 is for parenteral use named colistin methansulfonate sodium and 1 is for oral and topical use named colistin sulfate but

due to wide consumption of it in agriculture estimated at about 11942 tons per year specifically in Asia, Europe and America raise a concern about horizontal transfer of resistance [76]. From 2016 to 2019 due to restriction policies all across the world banned the farm use of colistin and decrease the production from 13,746 tons to 4292 tons and from 2017 in China, surprisingly reduce the production (27,170 tons in 2015 vs 2497 tons in 2018) and sales (US$71.5 million in 2015 vs US$8.0 million in 2018 [77]. During 2013–2015 European Surveillance of Veterinary Antimicrobial Consumption network presented most highly used antimicrobials were polymyxins which were the 5th most whereas in countries like Canada and US colistin never used in animals on the other hand resistance greatly isolated from animals than humans whereas no polymyxin was sold in Finland, Iceland, and Norway. In several developed countries, such as Canada and the United States, colistin has never been approved for use in animals. the occurrence of colistin resistance among isolates from food animals (0.9–76.9%) is more frequent than isolates from humans (0.1–8.8%) [78]. The concept of one health acknowledges the interconnection between human, animal and environmental health which also applied to antimicrobial resistant genes, specifically mcr gene through food chain contribute to environmental pollution and pose significant threat to human health [79].

CR-AB and nosocomial infections:

Hospital-acquired infections are the major drivers of antimicrobial-resistant genes globally. Genetic relatedness and evolution of species in hospitals led to outbreaks of bacterial infections on the basis of WGS surveillance and also showed AMR is abundant among bacteria [80]. HAI is also equipped with a ventilation system, type of furniture (free of any moisture) used and patient surroundings like medical equipment, staff, contact that account for 45.3% of outbreaks, and waste disposal system [81]. The most common NI is the UTI which accounts for about 40% of NI whether it is related to the catheter or not mostly due to comorbidities and length of stay, CDC shows that 25% of UTIs are non-catheters [82]. NI are prevalent in internal ICU (RTI 46.9%, UTI 37.5%) and surgical ICU (RTI 38.3%, SSI 22.0%) due to long-term disability, mechanical ventilation, nasogastric tubes, and intravenous and urinary catheters. National nosocomial infection surveillance classifies NI in pulmonary, urinary, surgical, and bloodstream [83]. The most common HAI includes SSI 21.8%, UTI 1.9%, BSI 9.9% other localize infections 5.6%, RTI 4%, CNS 0.8%, and reproductive tract infection 0.6% respectively. Two-thirds of healthcare workers showed poor practice toward HAI prevention due to the lack of PPE and hygiene practices [84]. Interprofessional learning refers to the event at which collaboration occurs to improve the quality of care and the main purpose of this learning is to promote collaboration and provide high-standard management of the patient to control HAI [85]. HAI are a major public health concern that contribute to mortality, morbidity-compromised patients, AMR, and financial problems to the patients for treating appropriately. HAI including UTI, SSI, and HAP were 15.3%,16%, and 50.3% broadly due to inappropriate AMT among of which HAP is highly considered and can be decreased by culture and susceptibility approaches [86].

Nosocomial infections increase due to length of stay of more than 25 days which also increases the cost and can be decreased by lesser use of resources and incidence of such infection is considered to be 2 to 20% in developing countries, and annually cost 4.5 billion dollars on hospital according to CDC [87]. The pathogenic bacteria involving HAI are P. aeruginosa, A. baumanni, S. aureus, E. coli, K. pneumonia respectively with drug resistance for pseudomonas account for almost 30% and for acinetobacter beyond 50% [88].

A. baumannii with the ability to survive in varying environmental conditions and defense mechanisms like efflux pumps, enhance metabolism, conjugation, and biofilm formation attack hospitalized patients and lead to need of alternative therapies like ZnO due to diverse resistance [89]. Capsule of the nosocomially acquired A.baumannii is the key component of its virulence and evasion from the innate immunity and its ability to persist in surfaces in hospitals leading to infections in patients with associated medical equipment also contributes to its virulence [90]. There is more than 50% mortality of BSI and pulmonary infections by XDR A. baumannii and monoclonal Ab found to be protective

against these infections within 1 hour of administration [91]. Recent finding shows that chaperon-usher pili are involved in the adhesion of this bacterium to host cells and medical persistence in critical care resulting in biofilm contributing to BSI and RSI [92]. This critical pathogen is regularly implicated to show pneumonia and catheter-associated bacteremia along with wound, endocarditis, meningitis, urinary tract, arthritis, peritonitis, liver, and eye infections. On species level further 2 are investigated A. schindleri harbor nonsterile body sites and A. ursingii in critically ill patients that are either catherized or immunosuppressed [93]. Acinetobacter act as a pathogen and colonizer making it a serious concern for physicians, almost 25% of nomadic harbor this organism on the skin, its presence as nosocomial is about 10.7%, and OPD about 2.2%, VAP with fever leukocytosis and lung infiltrate also being reported due to its RAPID colonization in RT [94]. Most significantly this accounted for 20% of NI in ICU and the rest of 1.6 to 6% of other infections [95]. Polymicrobial AB is primarily responsible for BSI that causes septic shock majorly due to skin and soft tissue infections and burns injury and relevant signs are fever, tachycardia, hypothermia, leukocytosis and leukopenia with an overall percentage of 9 to 35% [96]. In ICU most cases are also found for lower respiratory tract infections with accountability of 26.2% showing its clinical prevalence worldwide especially nosocomial [97]. Waste water and sludge are the secondary habitats providing an anaerobic environment niche for this harmful clinical pathogen outside the hospital leading to hospital outbreaks [98]. The CRAB assisted with BSI mainly use of nasogastric tubes, foley catheters, endotracheal intubations and tracheotomy [99]. The biofilm formation ability of the Acinetobacter strain in ICU patients infecting burns wounds shows its etiological importance as opportunistic pathogen [100].

Colistin in critically ill patients:

In ICU long stay increase the risk and treatment duration in patient which ultimately cause reliance on colistin as an option, leads to resistance emergence [101]. The study reported that ICU patients with Acinetobacter-related bacteremia having colistin tolerance in 3 out of 4 patients with fulminant "Acinetobacter" - Please note that the first letter of the word is "A" and not "a".nt SS and mortality [102]. In patients of ICU are critically ill and infected with Acinetobacter showed colistin resistance with clinical infections of mechanical ventilation, CVC, morbid obesity, and sleeve gastrectomy [103]. Long ICU stays, age, ventilation, surgery, and use of monobactams, colistin, and cephalosporins are major risk pillars for colistin resistance [104]. Another study reported that a high APACHE II score and prior teicoplanin usage were the risk factors for colistin tolerance [105]. The prevalence of colistin tolerance in Acinetobacter is 2.8% and that of pseudomonas 1.4% and transmission between patients plays a role for these pathogens. Due to the narrow therapeutic window following current guidelines does not help to maintain colistin level and use of it without therapeutic drug monitoring remains unsafe and not get the target hit in critically ill patients [106].

Colistin mortality and case fatality in hospitals:

Hospital-acquired ailments are closely linked to higher rates of sickness, fatality, and financial strain on healthcare systems. The two most significant sepsis infections are triggered by Pseudomonas aeruginosa and Acinetobacter baumannii, the two non-fermentative gram-negative bacteria. The crucial medicationS for infestations brought on by carbapenem-resistant K. pneumoniae, A. baumannii, and P. aeruginosa, is polymyxins which encompasses colistin. Unfortunately, as indications of resistance have grown in past few years, so has the usage of colistin. It is a dilemma that only a few of antimicrobial drugs are readily available to cure such illnesses [107]. A study conducted in USA indicated the association of colistin resistance with higher mortality in which it has been revealed that 13% of the total individuals (246) died due to carbapenem-resistant K. pneumonia isolates [108]. Furthermore, in another study performed at Sultan Qaboos University Hospital Oman from 2007-2016, it has been demonstrated that 29.8% of bacteraemia caused by these pathogens were due to poor healthcare standards and had carbapenem resistance.A. baumannii, and P. aeruginosa were each responsible for 30%, and 18% of this resistance respectively. When

compared to 2007, in 2016 the rates of carbapenem resistance in P. aeruginosa and A. baumannii bacteraemia were higher i.e., 25% (earlier 20%) and 86% (increased from 67%), respectively. 7.9 % of the patients of carbapenem-resistant bacteraemia also exhibited colistin resistance. They further described that individual with carbapenem-resistant bacteraemia had an all-cause death rate of 62% after 30 days, compared to 22% in individuals with carbapenem-sensitive bacteremia [109]. Similar studies have demonstrated that A. baumannii primarily affects older individuals; for instance, [110] found that approximately 84% of patients with multi-drug resistance A. baumannii were older than 60, indicating that senescence is a significant peril for A. baumannii infection. Likewise, a study has revealed that 58% of patients infected with A. baumannii were over the age of 60. All of them draw attention to the fact that patients with A. baumannii infections tend to die more frequently as they get old, which is quite relatable to the latest findings showed by [111]. They collected the data from 169 patients admitted at the ICU ward of Firoozgar Hospital infected with these pathogens. P. aeruginosa was found nearly 8-fold less prevalent than A. baumannii. Only 2.4% were tested positive for colistin resistance. It has also been observed that A. baumannii sufferers had much older median ages than P. aeruginosa patients did. Also, there were no discernible changes in the mean length of the hospitalization term across the various groups. The preponderance of recovered P. aeruginosa and A. baumannii were found to be colistin-sensitive. Consequently, to reduce the incidence of A. baumannii infection in older individuals, preventive measures are obligatory [112].

Mortality of AMR vs Colistin Resistence:

Antibiotic resistance is a global threat in most of the pathogens placed at top 10 global health problem by world health organization in 2019. Rapid emergence of antimicrobial resistance lead to almost 10 million deaths per year by 2050 universally among of these 75% of AMR infections were of gram-negative bacteria [113]. Non fermenter gram-negative bacteria including acinetobacter known to cause nosocomial infections with emerging AMR. Acinetobacter was resistant to all antibiotics except colistin with 93.3% MBL production. Providing that MBL NFGNB is associated with high mortality and morbidity. The use of various antibiotics as therapy lead to MDR AND XDR NFGNB among hospitalized patients [114]. Nonfermenter gram-negative bacilli are among the critical pathogens for which the discovery of development of new antimicrobials is of great concern due to limited therapies and listed as top priority pathogens by WHO because of their carbapenem resistance. Gene blaOXA 23 is attributable to Acinetobacter carbapenemase resistance for which colistin is last resort with emerging heteroresistance to this particular drug in this particular pathogen [115]. Recently mortality rate has been between 30% and 76% by the pathogens for which colistin is prompt as last therapeutic option due to its rapid killing effect, narrow spectrum, and slow resistance development. Acinetobacter with colistin heteroresistance is a distinct concern [116]. More than 30% AMR isolates were colistin resistant in a report [117]. A comparison of ICU and surgical wards was carried out for evaluating AMR showing that CRE-GNB were higher in ICU than surgical wards whereas NF-GNB were resistant to all antibiotics like 98.35% fosfomycin, 94.40% cefepime,90% meropenem, 76.50% ertapenem, 62.50% ciprofloxacin,59.10% imipenem, 69.60% for piperacillin and tazobactam, etc. while low resistance for tobramycin, tigecycline and colistin (33.30%,31.25%,15.50%) [118].

CRE GNB was showed to be the emerging MDR threat by CDC. Recently whole genome sequence technique use to classify emerging resistant strains by analyzing resistant genes that were of chromosomal origin and plasmid-associated. WGS revealed resistance to carbapenems, fluoroquinolones, aminoglycosides and colistin in about 60 to 100% isolates from which 30 to 40% resistance for tetracycline limited its use in PAKISAN [119]. WHO has listed colistin as the highest priority critical antimicrobial for human medicine due to its use for multidrug and extensive drug pathogens and mcr 9 (type of plasmid gene) found to be critically associated with plasmid-mediated colistin resistance in Enterobacteriaceae and should be considered [120]. It has been seen that when combining colistin with any of the peptide (OTD-244, MSI-78) reduce the MIC of colistin and makes

it sensitive to the tested isolates instead of using it alone making it resistant. The bacterial strains having mcr 1 and mcr 2 plasmid-associated genes had higher MIC value from 1.25 to 5 μg/ than those lacking these resistant genes [121]. Induction of the cross-resistance to host antimicrobials (LL-37 and lysozyme) due to the increased use of colistin as a last resort that lead to its emerging resistance so therefore cross-resistance should be considered during the development of new antimicrobials [122]. In 2013 and 2015, 935 patients with nosocomial infections were enrolled and antibiotic resistance was increased for almost all antibiotics including ampicillin/sulbactam, piperacillin/tazobactam, ceftriaxone, ceftazidime, cefepime, meropenem, gentamicin, amikacin, ciprofloxacin, levofloxacine, nitrofurantoin, and ampicillin. but the rate of resistance was lesser for colistin and in 2013 age was not linked with any antibiotic resistance, in 2014 clindamycin resistance was observed, and in 2015 clindamycin and gentamycin resistance was observed [123]. Between 2009 and 2011, 56 patients with acinetobacter were analysed according to CDC criteria and the most effective antibiotic was found to be colistin, tigecycline, meropenem, and imipenem. Due to increased carbapenem resistance, colistin resistance is also reported in some cases but by combining colistin with sulbactam make it effective in patients. CLSI resistance rates were 95.5% against cefepime 76.5% against gentamicin 86.3% against amikacin 89.2% against piperacillin-tazobactam and the mortality rate was found to be 39.2% in these diagnosed patients [124].

There are 4 risk factors correlated with the acquisition of antibiotic-resistant bacteria age of more than 70, hospital stay more then 16 days, use of carbapenem drugs and HIV infections but antibiotic drug exposure has a strong relation with infection due ARB [125].

32 isolates of MDR Acinetobacter were examined for the resistant genes responsible for resistance to various antibiotics in which S83L mutation in GyrA responsible for quinolones resistance, blaOXA23 and ampC with resistance to carbapenem and cephalosporins and strB gene cause aminoglycoside resistance, folA cause trimethoprim resistance, blaTEM1 associated with beta lactam resistance in these isolates [126]. Acinetobacter and pseudomonas species causing nosocomial infection having genes IMP, VIM, OXA-23, OXA-40 and OXA-58 and all the classes of beta-lactamase producing CRE has susceptibility to cefiderocol, a novel antibiotic [127]. Colistin a defensive drug was used for MDR and CRE GNB, but is unreliable use led to the worldwide emergence of colistin resistance responsible for public health threat and require immediate action [128].

Beta-lactam drugs like tigecycline and aminoglycosides can be used as therapy in patients of BSI caused by colistin-resistant GNB especially for Acinetobacter baumannii because tigecycline has low concentration in serum and the prevalence of these colistin-resistant GNB was 1.6% to 17.3% [129]. Colistin and carbapenem-resistant GNB are the main serious concern of AMR that pose health care challenges and critical clinical threats [130]. As colistin has a narrow therapeutic window so to control its prevalent resistance, drug therapeutic monitoring is essentially required and appropriate AMR surveillance strategy in particular to this last resort should considered in nosocomial infections.

Economic burden of AMR vs Colistin Resistance:

Globally, it has been noticed that inability to overcome raising AMR by 2050 can lead to 10 million deaths and an annual cost almost 100$ trillion with the switching of resistant infections from susceptible ones ensuring 42% cost of treatment per patient [131]. The attribution can relate to the fact that the economic burden of AMR can be due to long hospital stays, high and potent doses of medication and the importance of alternate to antimicrobials which is expensive, all adding trillion of dollars cost to all nations [132]. A global action plan was passed by WHO in May 2015 to address the AMR in the 68th World Health Assembly and in each state to call the national action plan [133]. According World Bank by the year 2050 the impact of AMR magnitude will be in the same order as that of the global financial crisis in 2008 and after 2030 1$ trillion loss and move to 2$ trillion in 2050, if not controlled the economic loss output will be 0.14% GDP per year globally and at local

state to make cost effectiveness AMR economy should be done in view of local epidemiological services and norms [134]. According to the CDC in US about the 55$ billion cost for AMR, 20$ billion for health care and loss of productivity is almost 35$ billion dollar, world bank also showed that due to resistance the level of poverty would raise which ultimately impact low-income countries and global annual GDP will low by 1% and there would be 5-7% loss in 2050 for developing countries. In contrast to all this TB alone can cost 16.7$ trillion in 2050 to whole world [135]. In outpatients of the US approximately 400 million to 18.6$ million is estimated as economic burden of AMR and according to WHO, AMR cost in Europe is recorded to be about 9$ billion per year [136]. According to the EU estimates it was noted that AR contributed to €1.1–1.5 billion in economic loss and 33,000 deaths each year. In the United States (US), about 55$ billion relate to societal and health care costs with 35,000 deaths each year. Infections that are MDR caused by *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* experienced higher individual patient cost $3391, longer hospital stay 5.48 days, and higher in-hospital mortality rates 1.50% [137]. Great sagacity needs to equipped with carbapenems which make in last resort in line called colistin as new and serious concern for therapeutic purpose. Additional 5.8$ million and 5.5$AUD million per year for treating resistant E. coli BSI and MRSA patients [138]. A study documented from Ireland provide that due to increase length of stay at hospital burden 12$ million cost for resistant infections based upon European Antimicrobial Resistance Surveillance Network data [139]. In 2019, 4.95 million deaths attributed to resistance round the globe which exceed due to HIV/AIDS and malaria in Sub-Saharan Africa and south Africa [140]. In 2015 WHO launched the GLASS and Pakistan enrolled in the system by 2017 for AMR surveillance Pakistan, back in 2011 global study reported that 9% of antibiotics are without prescription and in 2019 WHO ranked Pakistan in top 5 countries due to resistant bacterial-associated deaths in neonates [141]. As low middle-income country Pakistan is the sixth most popular country and by 2050 it will become 4th most one, recommends 86 USD benchmark and in 2017 Pakistan spent about 36 USD with 0.46% of GDP recorded for health care and total consumption of any form of antibiotic was 26.69 billion PKR [142]. The manual named antimicrobial consumption by WHO focus on data aggregation like import and wholesale data of antibiotic at the national level [143].

Future Directions:

The current increase in antimicrobial resistance is going to cause an immense burden on healthcare sector. In this review we have dived deep into diverse aspects of resistance to colistin in Acinetobacter baumannii which is a challenge to public health and making it inevitable to be addressed in order to develop novel approaches and strategies for prevention, detection, and treatment.

This study alongside highlighting the importance of colistin resistance in Acinetobacter baumannii, urges and encourages the healthcare researches to carry deep investigations of development of this resistance and direct the focus of their researches towards this critical issue considering several key areas. First of these is to carry out mechanistic studies to understand the molecular mechanism involved in colistin resistance in A. baumannii. It is highly necessary to understand the genetic and biochemical pathways in detail. For this purpose, advance proteomic and genomic technologies can be used. Secondly, Rapid, sensitive, and specific diagnostic tools should be developed. This is critical in clinical management and infection control. Prioritizing this, will help increase patient health outcomes in CR-resistant infections of A. baumannii. Thirdly, novel therapeutic approaches should be discovered and developed via exploration of new antimicrobial agents including those with novel mechanisms. In-depth knowledge and exploration of newly trending approaches like immune modulation and nanoparticles could provide potential these resistant infections. Fourthly, developing preventive measures and infection control strategies. Researchers should evaluate the effectiveness of various infection control strategies in different healthcare settings including environmental hygiene and AMR stewardship programs. Additionally, research on development of effective vaccines could

help prevent A. baumannii infection. Fifthly, enhancing surveillance and epidemiological studies to monitor global development and spread of colistin resistant A. baumannii infections. It is necessary for large-scale interventions and infection control. Sixthly, addressing the role of horizontal gene transfer in colistin resistance among A. baumannii and other bacterial species is crucial to combat these resistant-infections in environmental and clinical settings. Finally, devising policies and regulatory frameworks to augment the development and implementation of effective strategies and measures to overcome colistin resistance.

By focusing on these future recommendations and directions, the healthcare community can develop significant strides in mitigating the impending threat posed by colistin resistant A. baumannii, improving health outcomes and preservation of efficacy of this critical antibiotic.

Conclusion

The available current situation of countries all over the world realize the significance of colistin resistance especially when it is used as the only option to treat deadly infections. These epidemiological data represent how different genes mutated themselves to promote bacterial existence. Uncontrolled usage of all available drugs has led to rely on colistin and because of unfair consumption of it in livestock disturbs the one health by its accumulation in the waste water impacting the environment and increasing the hospital out breaks. Persistence of Acinetobacter baumannii in the intensive care unit make the situation even worsen by developed mechanism of intrinsic and plasmid mediated mode of resistance. Additionally, the risk is increased by distinct feature of hetero-resistance suboptimal concentration of colistin dosage. Many developed countries inhibited its usage in animals so that not to transfer plasmid variants in environment and humans. GDP is becoming very low due to high economic credentials required by the burden of AMR and for development of novel therapeutics. Resource limited countries have not enough budget to make the expense of different treatment options.

The rapidly emerging variants of resistance is stigma for the society. Therefore, resistance mechanism in bacteria and therapeutic window of colistin should be evaluated and monitored properly by surveillance fulfilling the credentials of ongoing research agenda. As colistin has narrow therapeutic window, so to control its prevalent resistance which is the ultimate cause of significant mortality rates particularly in hospitals, its targeting structures should be secured. Monitoring is an essential aspect while appropriate AMR surveillance strategies should consider at each regional, national, and international level to this last resort colistin in nosocomial infections.

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