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Review article

The burden of hospital acquired infections and antimicrobial resistance

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ABSTRACT

The burden of Hospital care-associated infections (HCAIs) is becoming a global concern. This is compounded by the emergence of virulent and high-risk bacterial strains such as "ESKAPE" pathogens – (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species), especially within Intensive care units (ICUs) that house high-risk and immunocompromised patients. In this review, we discuss the contributions of AMR pathogens to the increasing burden of HCAIs and provide insights into AMR mechanisms, with a particular focus on last-resort antibiotics like polymyxins. We extensively discuss how structural modifications of surface-membrane lipopolysaccharides and cationic interactions influence and inform AMR, and subsequent severity of HCAIs. We highlight some bacterial phenotypic survival mechanisms against polymyxins. Lastly, we discuss the emergence of plasmid-mediated resistance as a phenomenon making mitigation of AMR difficult, especially within the ICUs. This review provides a balanced perspective on the burden of HCAIs, associated pathogens, implication of AMR and factors influencing emerging AMR mechanisms.

1. Introduction

Hospital care-associated infections (HCAI) are major health safety issues worldwide and are defined as infections acquired while receiving treatment for medical or surgical conditions, which were not present during time of admission [1]. HCAIs include hospital-acquired (nosocomial), long-term care-associated, outpatient care-associated and home care-associated infections [2]. Information on the burden of HCAIs outside of the hospital setting is limited due to the onerous process in gathering reliable data on infection, prevention and control practices [3]. However, data on hospital settings points to hospital-acquired infections (HAIs) as the most frequent health challenge within the hospital setting [4]. Hospital-acquired infections (HAIs) occur globally in developed and developing countries with high morbidity and mortality [5]. For example, in the USA and Europe, HAIs are among the leading cause of death [6]. Additionally, HAIs result in prolonged hospital stay, increased microbial resistance to antimicrobials and elevated financial burden on the patient, family and the economy. HAIs from high-income countries show incidence rates ranging from 3.5% to 12% (Fig. 1) and are especially prevalent within intensive care units (ICU) with patient rate of infection about 40% [7,8]. These incidences

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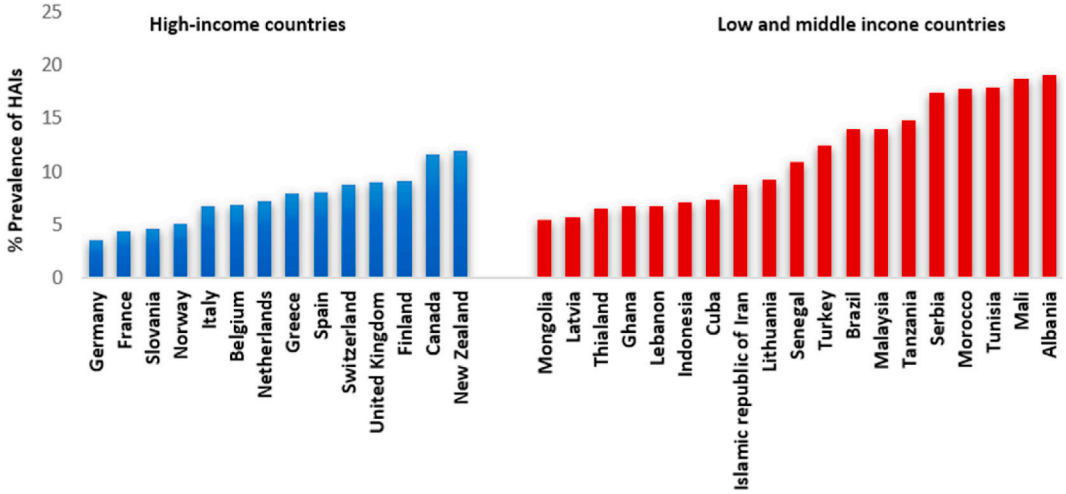

Fig. 1. Prevalence of health care-associated infection in high and low/middle income countries by prevalence of HAIs, 1995–2020. 123.

varied from body sites and determined by the underlying condition of the patient following exposure to medical interventions and hospital environment [7]. High-risk population individuals include patients admitted to ICUs, burn wound and transplant patients, and neonates. The most frequent types of HAIs reported include central line-associated blood stream infections, surgical site infections (SSIs), and ventilator-associated pneumonia, as well as catheter-associated urinary tract infections as the most predominant pathologies [5]. There is an urgency to understand the evolving dimensions of AMR globally, especially in Africa with the recent emergence of 'Global Priority Pathogens' in association with HAIs. Therefore, this mini review highlights relevant pathogens majorly implicated in HAIs, prevalence in developed and developing countries. It also provided insights into possible AMR mechanisms employed by Gram-negative ESKAPE pathogens and re-emerging HAI pathogens such as *Citrobacter* spp. and *Proteus* spp., majorly to last resort antibiotic polymyxins. Additionally, some of the strategies to mitigate AMR and HAIs in ICUs and the general hospital environment are highlighted.

2. Methods

2.1. Literature search strategy and extraction

Search terms "Antimicrobial Resistance", "Antimicrobial Resistance Mechanisms", "Global Burden of Hospital Acquired or Nosocomial Infections", "ESKAPE and Pathogens Implicated in HAIs", "Polymyxins Antimicrobial Resistance Mechanisms" "Plasmid-mediated Mobile Colistin Resistance" "Infection Prevention and Control of AMR" were used by at least two independent reviewers to conduct literature search. The search was conducted broadly on the global relevance of the highlighted keywords with special focus on their implications in Africa. Pubmed (National Library Medicine), Google Scholar, Scopus, Medline and Web of Science databases were used for literature search. Literature mapping and ranking performed with visual tools like Connected Papers (https://www.connectedpapers.com/), Open Knowledge Maps (https://openknowledgemaps.org/) and LitMap (https://www.litmaps.com/). Referenced database was built with Mendeley (Version 1.19.8) and information generated where processed and represented as figures, graphs and tables; other relevant data processed into paragraphs with headings and subheadings.

2.2. Pathogens Implicated in HAIs

Gram-negative bacteria are commonly implicated in HAIs, contributing as much as 87% of reported cases [9]; however, *Staphylococcus aureus* is the predominant Gram-positive strain [7]. *Pseudomonas aeruginosa, Acinetobacter baumannii* and *Enterobacteriaceae* are the most predominant Gram-negative strains within Europe and Asia [7,10,11]. *A. baumannii* is the most prevalent pathogen causing ventilator-associated pneumonia (VAP) and catheter-associated bloodstream infections (CAB) among high-risk populations, especially the immunocompromised in the ICUs [12]. In Africa, *Klebsiella* spp., *S. aureus*, *Acinetobacter* spp., and *E.coli* are the predominant pathogens [13] causing HAIs. High levels of HAI-related methicillin-resistant *S. aureus* (MRSA) are reported globally [12]. Carbapenem-resistant and Extended spectrum β-lactamases *Enterobacteriaceae* have been associated with paediatric HAIs [14].

2.3. Burden of antibiotic resistant bacteria and HAIs

Antibiotic resistant bacteria have contributed to the burden of HAIs globally with increasing health-risks especially in developing countries. Their consistent emergence and evolution have made many conventional antibiotics ineffective [15], where there is often only a limited set of last-resort antibiotics as the main treatment option for multidrug resistant (MDR) HAIs [16]. In 2017, the WHO

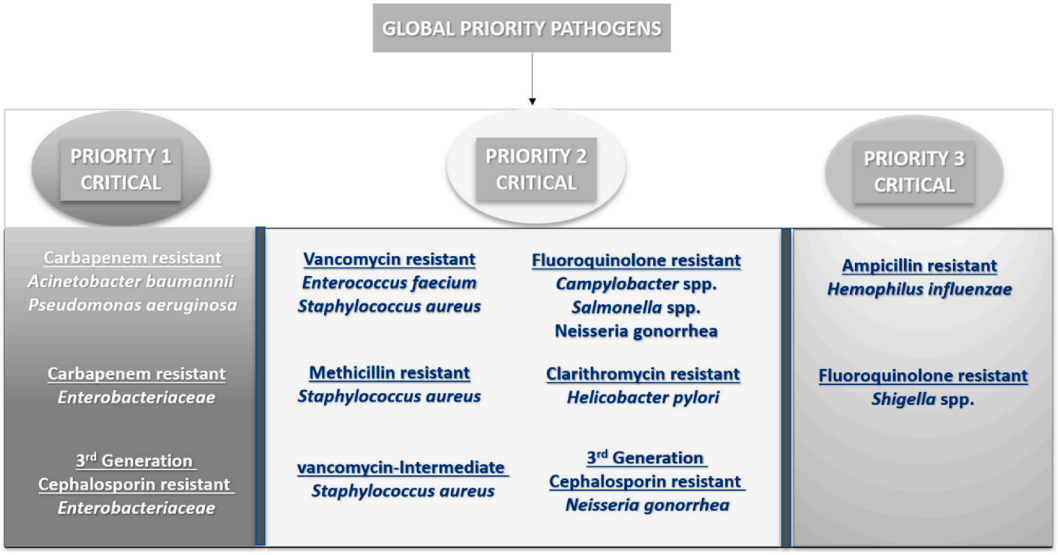

Fig. 2. WHO Pathogen Priority list of antibiotic resistant bacteria; figure designed by the authors as adapted from WHO [22].

listed twelve antibiotic resistant priority pathogens (Fig. 2.) requiring urgent attention for the development of new antibiotics [17]. The critical group included several high-risk pathogens, namely MDR *A. baumannii,* carbapenem-resistant *Pseudomonas aeruginosa* and *Enterobacteriaceae*. These pathogens exhibit both multidrug resistance and high levels of virulence, especially the notorious 'ESKAPE' (***E****nterococcus faecium*, ***S****taphylococcus aureus*, ***K****lebsiella pneumoniae*, ***A****cinetobacter baumannii*, ***P****seudomonas aeruginosa* and ***E****nterobacter* species) pathogens [18,19]. These pathogens have been implicated in HAIs in both developed and developing countries, with a tendency to *'escape'* lethal doses of antibiotics [20,21].

ESKAPE pathogens represent a group of Gram-positive and -negative bacterial pathogens with high-risk public health implications [20]. Methicillin and vancomycin–resistant *S. aureus* (MRSA-VRSA) as well as vancomycin-resistant *E. faecium* (VRE) (the Gram-positive bacteria of the ESKAPE group) have drawn global attention; however, infections caused by Gram-negative ("KAPE") pathogens are likewise extremely critical causing high morbidity and mortality [23,24]. These pathogens are ubiquitous as they are not restricted to clinical inpatients only, but thrive in diverse environments including water, soil, poultry and air. This environmental diversity promotes unrestricted shedding, sharing and spread of antibiotic resistance genes (ARGs) aided by mobile genetic elements such as plasmids and integrons [25].

2.3.1. Acinetobacter baumannii

Acinetobacter spp., are widely distributed within hospital environments [26]. *Acinetobacter* spp are non-fermentative, non-motile Gram-negative coccobacilli which represent some notable nosocomial pathogens that rapidly develop resistance to multiple antibiotics [27]. An important member of the genus is *A. baumannii*, which colonises the skin, infects the bloodstream, urinary tracts and other soft tissues, especially in the immunocompromised individuals, accounting for 20% of ICU-associated infections globally [7]. *A. baumannii* is becoming MDR globally (to chloramphenicol, first and second-generation cephalosporins and aminopenicillins) with some hospitals reporting pan drug-resistant strains [28]. Also, it exhibits diverse resistance mechanisms such as production of β-lactamases, modifying aminoglycoside target sites, multidrug efflux pumps and antibiotic impermeability [29]. Combination therapy of minocycline/tigecycline and polymyxin is the treatment option since the emergence of *A. baumannii* strains resistant against carbapenems (meropenem, doripenem, imipenem) [27,30].

2.3.2. Pseudomonas aeruginosa

Pseudomonas aeruginosa is ubiquitously present within the normal intestinal flora of humans and widely distributed in the environment, including commonly hospital ICUs [31]. Its broad environmental distribution is based on its metabolic versatility as a pathogen that adapts and survives diverse environmental conditions (broad temperature ranges, salinity, actinomycin, etc) [32]. *P. aeruginosa* is an opportunistic pathogen that rarely causes infections in healthy individuals; however, it readily causes community and hospital-acquired infections in patients with weakened immune systems. *P. aeruginosa* has been implicated in surgical site infections, burn and eye injuries, skin/soft tissue, non-healing diabetic wounds, UTIs, bloodstream infections (BSIs) and pneumonia [31]. It is the fourth most isolated nosocomial pathogen, second major cause of VAP, the third most common Gram-negative pathogen implicated in BSIs and a major concern in patients with cystic fibrosis [33,34]. Inherently resistant to a number of antibiotics and antiseptics; *P. aeruginosa* exhibits diverse AMR mechanisms to many classes of antibiotics [35], including β-lactams, fluoroquinolones, aminoglycosides and third-generation cephalosporins. Historically, carbapenems were the antibiotics of choice for MDR *P.* aeruginosa; however, with emerging resistance, a combination of polymyxin and anti-pseudomonal agents (piperacillin/tazobactam, imipenem, aztreonam, ceftazidime, cefepime) are currently most effective in treating MDR *P. aeruginosa* infections [36].

2.3.3. Enterobacteriaceae

Enterobacteriaceae contain both opportunistic and "professional" pathogens which cause diverse infections, including UTIs, BSI, enteric infections, and hospital-acquired pneumonia. The notable pathogens include species of *Klebsiella*, *Enterobacter*, *Escherichia coli*, and *Citrobacter* [37]. The global challenge associated with *Enterobacteriaceae* is the production of ESBL for AMR [37]. ESBL hydrolyse most beta lactam antibiotics, including cephalosporins. These genes are present on plasmids that also harbour resistance to aminoglycosides, sulphonamides and cross-resistance to fluoroquinolones, typically making carbapenem the drug of choice for treatment of ESBL-producing pathogens [38]. However, the increased use of carbapenem has resulted in the development of Carbapenem-resistant Enterobacteriaceae (CRE) [39]. Currently, the treatment of infections from MDR *Enterobacteriaceae* is challenging due to limited treatment options that include some aminoglycosides, tigecycline and polymyxins [40].

2.3.4. Escherichia coli

Escherichia coli is the most common Gram-negative bacterium presenting both a clinical and epidemiological challenge [41]. It is naturally a commensal of the intestinal tract; however, several strains are specialized pathogens of humans and animals [42]. The commensal form inhabits the gastrointestinal tract of humans aiding in digestion [43], whiles the pathogenic forms cause infections resulting in two million deaths annually [44]. Pathogenic *E. coli* strains are subdivided into several pathotypes causing infections with three main clinical syndromes; UTIs, meningitis/sepsis and enteric diseases [45]. *E. coli* infections are commonly treated with ciprofloxacin, levofloxacin, fosfomycin and fluoroquinolones; however, resistance to multiple antibiotics have been reported [46]. Resistance to fluoroquinolones and the emergence of ESBLs are of major concerns in treatment [47]. Carbapenems are considered the drug of choice for MDR *E. coli* infections; however, resistance to carbapenems is also emerging [48].

2.3.5. Klebsiella pneumoniae

Klebsiella is second to *E. coli* as the most common member of the *Enterobacteriaceae*. It is responsible for community and hospital-acquired infections (respiratory tract infections, cardiovascular, bacteraemia and UTI [49]. *K. pneumoniae* causes HAIs, and is frequently isolated in immunocompromised patients with pneumonia, as well as neonatal infections [50]. *K. pneumoniae* is second to *E. coli* as the most frequent cause of hospital-acquired BSI globally [51]. It is mainly an opportunistic pathogen; however, hypervirulence (typically associated with hypercapsulation) [52] and resistance to antibiotics has emerged [53,54]. Carbapenem-resistant *K. pneumoniae* are emerging globally, causing high mortality rates [55], mostly due to acquisition of the namesake *Klebsiella* ***p****neumoniae* **c**arbapenemases (KPC). MDR *K. pneumoniae* can thus be resistant to all beta-lactams, aminoglycosides, fluoroquinolones. Typically, polymyxin B and colistin E in combination with fosfomycin/tigecycline and some aminoglycosides are used as last resort treatment options [56].

2.4. Enterobacter species

Enterobacter spp. are facultative anaerobic bacteria that are natural commensals of the human gut microbiota [56], but also opportunistic pathogens, typically in the immunocompromised. Twenty-two species of *Enterobacter* have been identified with *E. aerogenes* and *E. cloacae* as the most frequently reported human pathogens. *E. cloacae* has been implicated in hospital-acquired sepsis, pneumonias, UTIs and postsurgical wound infections [57]. Most isolates of *Enterobacter* are susceptible to fluoroquinolones, trimethoprim, aminoglycosides and some β-lactams, however intrinsic resistance has emerged to ampicillin, cephalothin and first-generation cephalosporins [58,59] due to the possession of an AmpC type beta lactamase, often in conjunction with porin mutations [60]. The use of extensive broad-spectrum antibiotics has facilitated the development of resistant *Enterobacter* strains, particularly ESBL-producers in conjunction with multiple other resistance genes circulating globally [58]. Fourth-generation cephalosporins and carbapenems remain effective for treating infections, although there are reports of resistance to these antibiotics [58,61]. In addition, species of *Enterobacter* easily acquire antibiotic resistance mechanisms hence often restricting treatment options to tigecycline and colistin [57].

2.4.1. Citrobacter spp.

Citrobacter species are motile, non-spore forming bacilli diversely distributed in the soil, water, intestinal tracts of humans and animals as commensals [62,63]. There are 13 species of *Citrobacter* with *Citrobacter freundii* as the most commonly isolated [63]. As opportunistic pathogens, they are associated with UTIs, meningitis, septicemia, intestinal infections in neonates and immunocompromised individuals [64]. The different species of *Citrobacter* show different antimicrobial susceptibility profiles, with *C. freundii* displaying inherent resistance to ampicillin, carbenicillin and some quinolones [65,66]. Clinical species of *Citrobacter* are often reported to harbor ESBLs [67] and plasmid-mediated quinolone resistant markers [68]. *C. freundii* often displays resistance to piperacillin [69], third-generation cephalosporins [70], monobactams and some carbapenems [71]. MDR isolates of *C. freundii* resistant against quinolones, aminoglycosides, tetracycline and sulfonamides mediated by plasmids have been reported [69,72]. Based on limited therapeutic options for treating current MDR *Citrobacter* infections, selecting the appropriate antibiotic is imperative. The current treatment recommendation is with meropenems as first choice and fluroquinolones (moxifloxacin, ciprofloxacin) as alternatives [65].

2.5. Polymyxins and AMR bacteria implicated in HAIs

Polymyxins are a group of antibiotics of clinical importance in treating Gram-negative bacterial infections. They are natural

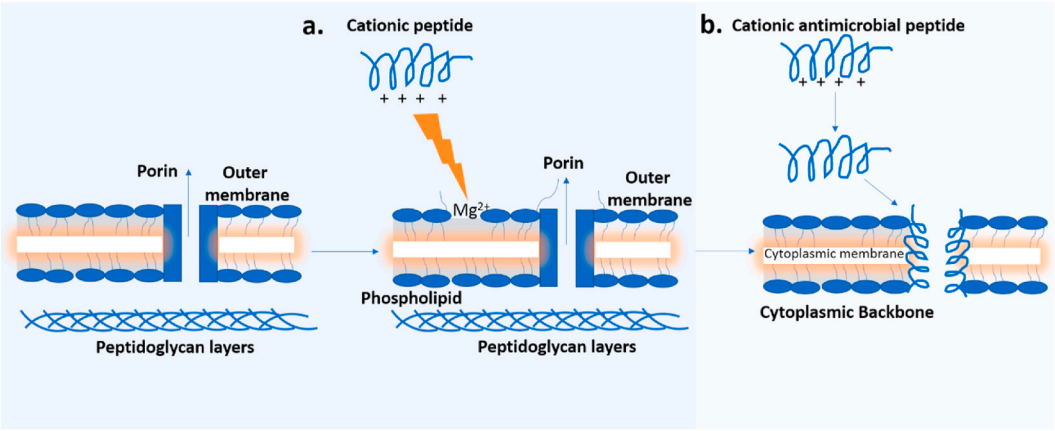

Fig. 3. The self-promoted uptake of cationic peptides across the outer membrane of Gram-negative bacteria**, (a.)** The cationic peptide competitively displaces Mg^{2+} from the LPS causing outer membrane disruption and uptake of antibiotic; (b.) **Mechanism of bacterial killing by cationic peptides:** the positively charged peptides bind to the negatively charged LPS leading to thinning of the bilayer (cytoplasmic membrane). Membrane potential generated inserts peptide into the membrane to form channels leading to leakage of cytoplasmic molecules and cell death. Figure adapted from (1) [86].

products first isolated from *Bacillus polymyxa* in 1947 [73,74]. Polymyxin use declined in the 1970s due to toxicity concerns and the availability of effective and broader spectrum alternative antibiotics [75]. The rise of MDR pathogens and lack of new antibiotics has necessitated reconsideration of the therapeutic use of polymyxin B and colistin E [75]. Polymyxins are active against *P. aeruginosa*, *A. baumannii* and some *Enterobacteriaceae*; however, *Proteus* spp., and *Serratia marcescens* are intrinsically resistant [76]. Polymyxins disrupt the outer membrane integrity of bacterial cells in a poorly-understood way [77,78]. The current toxicity reports of polymyxins show less incidence of nephrotoxicity [79,80]. Following reduction in clinical use, polymyxins were reserved for management of cystic fibrosis, ear and eye infections [81]. However, due to the recent emergence of MDR pathogens, polymyxins B and E have resurfaced as a single dosage and in combinations with other antibiotics (meropenem, imipenem/cilastatin, ampicillin/sulbactam) for clinical use [76].

2.6. Structure and mechanism of action

The polymyxins are five structurally different compounds (A, B, C, D and E), with polymyxin B/E in clinical use [79]. The physicochemical properties of polymyxins are similar to cationic antimicrobial peptides such as defensins of the eukaryotic innate immunity [82]. Polymyxins are non-ribosomal, cyclic lipopeptides and contain a mixture of D and L-amino acids as a general characteristic of most peptide antibiotics. They possess a heptapeptide ring of amino acids and a fatty acid attached to a tripeptide side chain through an amide bond [83]. The amino acid component of polymyxin B includes D-phenylalanine, L-threonine and six 2, 4-diaminobutyric acid residues. Colistin has D-leucine in place of D-phenylalanine. This mixture of lipophilic and hydrophilic groups confers an amphiphilic nature to polymyxins, giving them their bactericidal activity [84].

2.7. Polymyxin interactions with LPS-divalent cations

Polymyxin B interacts with the LPS of the outer and potentially LPS precursors in the inner membrane [77] of Gram-negative bacteria by competitively displacing divalent cations ($Ca^{2+}$and Mg^{2+}) from the negatively charged phosphate group of lipid A. This ultimately results in disruption of the barrier function of the outer membrane [77], as well as depolarization of the inner membrane [85]. This process is described as a self-promoted uptake pathway, where the break in membrane results in passage of various molecules including the cationic peptides (polymyxin). The interaction of the divalent cations on the polypeptide, whose binding affinity is three orders greater than the affinity of the native cations, competitively displaces cations on the binding surface of the LPS. The bulky nature of the polypeptide also disrupts the normal barrier property of the outer membrane (Fig. 3.) [86]. The divalent cations displacement weakened the outer membrane resulting in membrane leakage/breakage. Subsequently, the fatty acid chain of the peptide is directed towards the interior of the cell membrane allowing the heptapeptide ring of amino acids to form an inward channel to further disrupts the membrane integrity leading to bacterial cell death [86,87]. The high transmembrane potential, high negatively charged lipids, lack of cationic lipids and cholesterol generated enhances polymyxins selectivity for bacterial pathogens to eukaryotic hosts [86].

2.8. Bacterial mechanisms of resistance to polymyxins

Resistance to polymyxin has been reported in a number of bacterial pathogens, especially MDR bacteria that used to be sensitive,

Table 1
Mechanisms of polymyxin resistance.

Bacteria	Polymyxin Mechanisms of Resistance	References
Klebsiella pneumoniae	• Expression of phoP/phoQ and pmrA/pmrB • Point mutations within *pmrA/B* upregulation of the operon *arnBCADTEF and pmrC* • Production of capsular polysaccharide (CPS) inhibits binding of polymyxins to lipid A • *KpnEF* and *AcrAB* encodes efflux pumps • Mutations in *KpnEF* and *AcrAB*	[82,92,93]
Acinetobacter baumannii	• Mutations in *pmrA* and *pmrB* genes • Upregulation of the *pmrCAB* operon resulting in transcription of *pmrC* encoding EptA • Mutations in *lpxA, lpxB* or *lpxC* involved in lipid A biosynthesis pathway	[92]
Pseudomonas aeruginosa	• Five Two-Component Systems (PmrAB, PhoPQ, ParRS, ColRS and CprRS) in *P. aeruginosa* influence L-Ara4N modifications on the lipid A • Outer membrane protein (OprH or H1) of *P. aeruginosa* binds to the phosphate groups on the LPS hindering polymyxin binding	[82,93]
Enterobacter	• Mutation in *phoP* • Inactivation of the *mgrB* gene • Ecr transmembrane protein acts on the *phoPQ* component system to activate the *pbgP* operon leading to increase in LPS modification • Heteroresistance to polymyxin	[94–96]
E. coli	• Modification of the PmrAB • *arnT* gene encode a glycosyltransferase catalysing the transfer of L-Ara4N to a phosphate group of lipid A • Polymyxin efflux activity involving *marRAB, sap* AcrAB-TolC efflux genes	[74, 97–99]
Proteus	• *Proteus* spp. exhibit natural resistance to polymyxins due to the presence of L-arabinose-4-amine attached to the Kdo (3-deoxy-D-manno-oct-2-ulosonic acid) residue on the lipid A moiety of the LPS • EptC gene involved in modification of the LPS with PEtN addition	[100,101]
Citrobacter	• Mutations in the TCS sensor kinase *pmrB* • *MgrR* negatively regulates *eptB* to mediate the modification of the outer Kdo residues of LPS with PEtN.	[82,95]

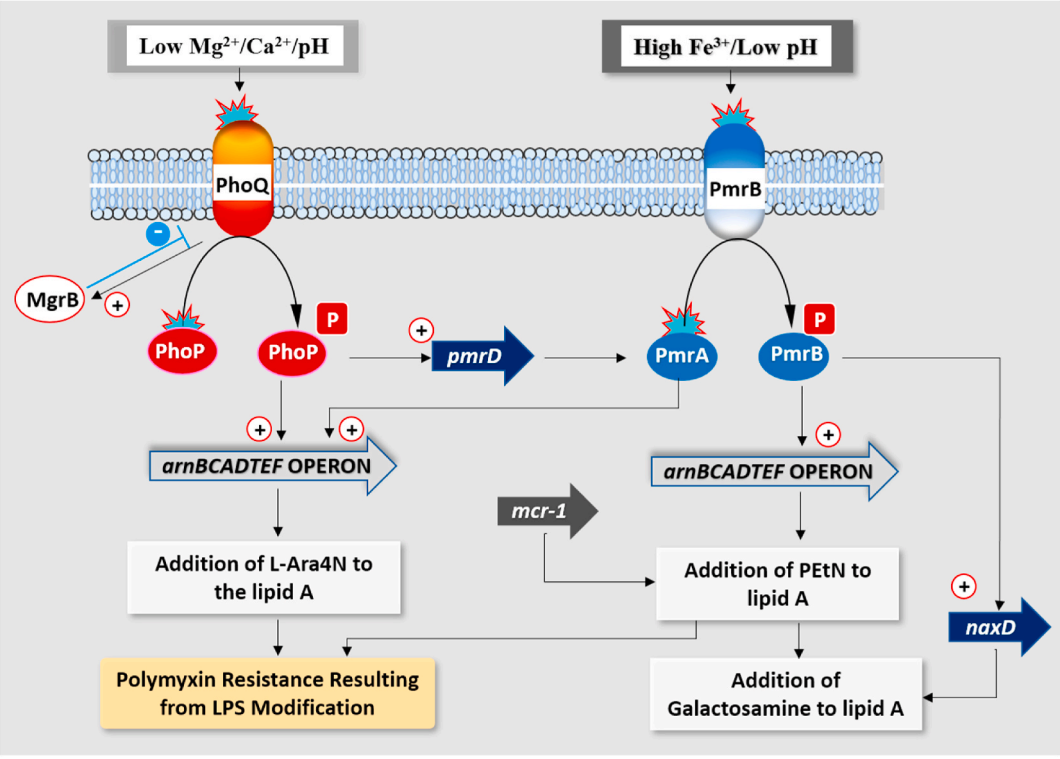

Fig. 4. Schematic overview of mechanisms of LPS modification involved in polymyxin resistance in Gram-negative bacilli (Adapted from Ezadi et al., 2019). [104].

but became polymyxin resistant after their reintroduction [88]. This emerging resistance is attributed to the increased and inappropriate use of polymyxins globally [89,90]. Investigating polymyxin resistance has led to the detection of diverse mechanisms, including modification of LPS, loss of LPS, efflux pump activity, capsule formation and overexpression of outer membrane protein (OprH) [82]. These resistance mechanisms are either intrinsic (such as in *Proteus* spp., *Serratia* spp., *Morganella morganii*, and *Burkholderia* spp.), mutational, acquired or adaptive [91] (Table 1).

The majority of the resistance mechanisms target the lipid A of LPS, the initial site of action of polymyxin [74]. Two major two-component systems (TCS) (PhoPQ and PmrAB) play crucial roles in regulating gene expressions for lipid A modification in Gram-negative bacteria [94]. In some *Enterobacteriaceae,* the LPS is targeted by modification of lipid A moiety with 4-amino-4--deoxy-L-arabinose (L-Ara4N) or phosphoethanolamine (PEtN) [77]. In environments with low Mg^{2+} and Ca^{2+}, PhoQ is activated leading to activation and phosphorylation of cytoplasmic *phoP,* promoting transcription of the *pmrD* gene. The *pmrD* product activates PmrAB at a posttranscriptional level ensuring phosphorylation of PmrA to mediate synthesis or incorporation of L-Ara4N into the lipid A moiety of LPS [102] (Fig. 4.). In some *Enterobacteriaceae,* like *E. cloacae,* the L-Ara4N modification is exclusively controlled by the PhoPQ system [103].

2.9. Role of the mgrB gene in bacterial resistance to polymyxins

MgrB [105] is a small regulatory transmembrane protein with 47 amino acids whose function inhibits the kinase activity of PhoQ or stimulates its phosphatase [106] (Fig. 3b). MgrB thus represses PhoQ activity post-translationally and inactivation of MgrB therefore results in high baseline activation of the PhoPQ signalling pathway. Consequently, PhoPQ-controlled OM modifications are also induced, resulting in high Polymyxin resistance. Mutations in MgrB have been observed in clinical isolates displaying colistin resistance, implicating the *mgrB* gene in clinical treatment failure [107,108]. Mutations include frameshifts, deletion of gene segments, amino acid substitutions, nonsense mutations and inactivation; the most frequently reported is by transposition of insertional sequences [105]. MgrB is conserved particularly in *Klebsiella* pneumoniae [109], *E. coli* [106] and *Enterobacter* spp [110].

2.10. Plasmid-mediated polymyxin resistance

Resistance to polymyxin was historically linked to chromosomal-related mechanisms with no reports on horizontal gene transfer. However, a plasmid-mediated colistin resistance gene encoding a PEtN transferase was detected in *E. coli* strains from animal sources in China [111]. The modification with PEtN is not a novel mechanism of resistance; rather, the transferability of the gene among bacteria especially MDR strains, represents a challenge for polymyxin treatment. This plasmid-borne mobile colistin resistance gene (*mcr-1*) has been reported in more than 30 countries [112], in species of *Klebsiella, Enterobacter*, *Citrobacter*, *Proteus, Salmonella* and *E. coli* [113]. Currently, new *mcr*-like genes have emerged with *mcr*-2 [114], *mcr*-3 [115], *mcr*-4 [116], *mcr*-5 [117], *mcr*-6 (3) [118], *mcr*-7 [119], *mcr*-8 [120], *mcr-9* [121] and *mcr-10* [122] currently in circulation. These genes have variations compared to the *ancestral mcr-1,* with about 30 SNPs in *mcr-3* [123]. *Mcr-2, 3, 4, 5, 6, 7, 8, 9* and *10* share 81%, 32.5%, 34%, 36.1%, 83%,35%, 31%, 36% and 29.31% amino acid sequence similarity with MCR-1 respectively [122,124,125]. The presence of *mcr* genes on conjugative plasmids replicon such as IncI2, IncHI2, IncX4 and IncF have been confirmed [113,125]. The origin of the *mcr-1* gene is unclear; however, the chromosomal region in a *Moraxella porci* displays significant homology to the *mcr-1* structure [118]. The gene is also flanked by insertion sequence (ISApl1) with the transposon Tn6330 as the key element mediating the translocation of *mcr-1* into various plasmids [126]. Although *mcr* genes were initially mainly reported as plasmid-mediated, the ISA*pl*1 and the *mcr-1* cassette has been found on the chromosome of *E. coli* suggesting its integration into the bacterial chromosome [127,128]. The *mcr-1* is currently the predominant gene circulating globally with prevalence in the environment (22%), animals (11%) and humans (2.5%) [128] necessitating investigations into its epidemiology and the resistance mechanisms to improve clinical treatment.

2.11. Bacterial phenotypic mechanisms of survival against polymyxins

Host organisms utilize diverse defence mechanisms to reduce the burden of infections from bacterial pathogens. They avoid exposure to pathogens (barriers for protection), resist infections (host immunity) or tolerate the presence of the pathogen [129]. However, bacteria alter their lifestyle in response to these host survival mechanisms [130]. These responses include gene expression and protein activity, lifestyle switch from avirulent to more virulent forms within the hosts, biofilm formation/swarming and other adaptive mechanisms [131]. As a particularly well-understood example, bacterial LPS modifications promote bacterial survival against host immunity factors like antimicrobial peptides [132]. The O antigen of the LPS complex has repeating oligosaccharide units that are highly variable immunologically and block the initiation of the complement system of the host innate immune system [133], while the non-repeating lipid A core strengthens the integrity of the outer membrane [133].

3. Discussion

The hospital is characterized as a high health risk environment particularly with reports of HAIs within developed and developing countries [134]. The burden HAIs poses ranges from elevated financial burden, increase in disease severity, high incidence of antimicrobial resistance, morbidity and elevated rates of mortality. Within the hospital setting, bacterial pathogens are associated with nosocomial infections with majority displaying resistance to conventional and last resort antibiotics [4]. Members of ESKAPE pathogens are high-risk pathogens and majorly implicated in HAIs with increased tendency to display multidrug resistance. They are

Table 2
Strategies to combat AMR in ICUs.

Strategies	Interventions	Relevant global guides and tools/Evidence based study/ References
Nonpharmacological/Infection, Prevention and control	1. Hand hygiene and good sanitation practices that limit transmission of infectious MDR bacteria	137–139
	2. Proper disinfection, decontamination and waste management disposal within and around ICUs	[140,141] https://apps.who.int/iris/handle/10665/312226. License: CC BY-NC-SA 3.0 IGO;
	3. Routine epidemiological surveillance of hospital environments for emerging and circulating microbes	[142]
	4. Isolation or patient cohorting systems	WHO Global strategy for containment of AMR, 2001; https://apps.who.int/iris/handle/10665/66860
	5. Development and strengthening of national reference microbiological laboratories	[143,144]
	6. Building human capacity in microbial diagnostics, testing and treatment	[143,145]
Antibiotic management	7. Establishing effective antimicrobial stewardship programs in hospitals, especially in ICUs	[144] WHO Global strategy for containment of AMR, 2001; https://apps.who.int/iris/handle/10665/66860 https://apps.who.int/iris/bitstream/handle/10665/329404/9789241515481-eng.pdf
	8. Appropriate diagnostic tests and microbial identification, antimicrobial susceptibility tests coupled with treatment of implicated microorganism	[145] https://apps.who.int/iris/bitstream/handle/10665/205912/B4691.pdf
	9. Development of guidelines for antimicrobial treatment	[146–149] https://apps.who.int/iris/bitstream/handle/10665/205912/B4691.pdf
	10. Shorter course administration of antibiotics; effective application of pharmacodynamics and kinetics dose optimization	[150,151] https://apps.who.int/iris/bitstream/handle/10665/205912/B4691.pdf

characterized as global priority pathogens as they play critical roles in increasing disease severity by compounding rates of morbidity and mortality.

The multidrug resistance phenotype exhibited by 'Global Priority Pathogens' particularly Gram-negative bacteria prompted dependence on two last resort antibiotics carbapenems and polymyxins. Between 2000 and 2010, global use of carbapenems and polymyxins increased by 34% and 14% respectively (4) [135]. However, this emergence of resistance to carbapenems and polymyxins coupled with presence of mobile genetic elements such as plasmids harboring resistant markers challenged treatment options. Gram-negative bacteria developed resistance to polymyxins following reintroduction into clinical and animal use.

Polymyxin resistance mechanisms commonly employed by bacteria were chromosomally or intrinsically mediated with mechanisms such as modification and loss of LPS, efflux pump activity, formation of capsule and overexpression of membrane outer protein. However, recent emergence of circulating plasmid-mediated colistin resistance genes in bacterial strains from animal sources has been reported in over 20 countries with Gram-negative bacteria majorly implicated [112]. The variations in the mobile colistin resistance genes (*mcr*) predominant in the environment as compared to animals and humans complicates AMR challenges and HAIs. This is further compounded by the transfer of these MDR genes as facilitated by these plasmids.

3.1. Strategies to combat AMR in ICUs

Generally, strategies to combat AMR would majorly involve Infection Prevention/Control (IPCs) and antimicrobial management strategies. By implementing IPCs and antimicrobial stewardship programs in hospital environments and ICUs, the burden AMR poses would be mitigated.

4. Infection Prevention and Control

Emergence of AMR is inevitable as bacteria develop ways to circumvent effectiveness of antibiotics. Administration of antibiotics contributes to selection of antimicrobial resistant bacteria; however, increased complications is linked with prolong antibiotic selection pressure during treatment within the ICU. In this regard, AMR is better prevented and best mitigated by nonpharmacological or Infection Prevention and Control practices (5) [136]. Also, good hygiene practices including hand washing and proper disinfection practices, frequent hospital surveillance of emerging pathogens, establishing effective patient cohorting systems, effective waste disposal protocols/systems and building infrastructural/human capacity and expertise.

5. Antimicrobial management strategies

Proper antibiotic management strategies would involve establishment of good antimicrobial stewardship program in hospitals and use of narrow spectrum antibiotics. Also, effective diagnosis coupled with treatment of infection, shorter course administration of

antibiotics and effectively applying pharmacodynamics and kinetics principles in drug administration could help mitigate the rise and spread of resistant bacteria in ICUs and within the hospital environment. Combating antibiotic resistance requires a multifaceted approach that entails international, national and individual level collaborative action to mitigate global spread. Table 2 summarizes a list of strategies to reduce the burden of AMR particularly in hospital setting.

6. Conclusion

The burden of hospital acquired infections is increasing globally. The consistent emergence of antimicrobial resistant bacteria, particularly Gram-negative bacteria is contributing to the challenge of HAIs. The plethora of innate resistance mechanisms coupled with acquired genes displayed by Gram-negative bacteria further complicates the efficiency of antibiotics, especially last-resort such as polymyxins. An understanding of the interplay of HAIs and antimicrobial resistant Gram-negative bacteria could inform effective infection control practices to enable implementation of safety protocols.

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Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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