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ESKAPE pathogens and their potential in antimicrobial resistance: A Review

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Abstract
ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.) are the predominant cause of nosocomial infections all over the world. The bacteria have been popular for their notoriety due to their ability to render the highest class of antibiotics ineffective and have been therefore accredited as the priority pathogens by the World Health Organization (WHO). The remarkable presence of virulence factors along with the development of multi-drug resistance emphasizes an urgent need for development of new therapeutics against these pathogens. This review intends to highlight the critical importance of the ESKAPE pathogens with respect to their potential in development of antimicrobial resistance (AMR).

Keywords: Antimicrobial resistance, ESKAPE pathogens, extended spectrum beta lactamases, multi-drug resistance, Enterobacteriaceae

Introduction
The current research studies have envisaged the potential of subset of bacteria (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.) acronymically dubbed as 'the ESKAPE pathogens', manifesting multi-drug resistance (MDR) against biocidal action of antibiotics and illustrating an exemplified dissemination across the globe. The indiscriminate use of antibiotics, self-prescription, inadequate dosage regimens and infections acquired from hospital premises (nosocomial infections) have been a major cause of emergence of MDR bacteria, accounting for 15.5% hospital acquired infections (HAIs) in the developing world (Rice 2008; Allegranzi *et al*., 2011 and Pendleton *et al*., 2013) [29, 1, 27]. ESKAPE pathogens play a pivotal role in causation of nosocomial infections (Rice, 2008 and Navidinia, 2016) [29, 25], accounting to highest risk of mortality and subsequently high expenditure on health care (Founou *et al*., 2017) [10]. Consequently, in February 2017, the World Health Organization listed ESKPAE pathogens among the top twelve priority pathogens against which new therapeutics are immediately needed (Tacconelli *et al*., 2018) [35]. Inadequate and unsolicited use of antibiotics and meagre presence of new antimicrobials have challenged the researchers with the problem of antimicrobial resistance (AMR). While, AMR remains a looming threat for the present and future, the discovery of new antimicrobials seems like a conundrum due to the reduced incentives and regulatory challenges for the pharmaceutical companies. Additionally, the spurious use of antimicrobials in human and animal health sectors, development of new resistance mechanisms by the bacteria and widespread dissemination of AMR bacteria across the world further escalates the burden of AMR. The present review highlights the significance of ESKAPE pathogens and explores their potential with respect to AMR.

Enterococci
Enterococci are a group of gram positive, facultative commensal bacteria found in gut of both humans and animals, however under immune-suppression they can produce a range of infections *viz*., intra-abdominal infections, urinary tract infections, pelvic/soft tissue infections and bacteremia or endocarditis. Being a part of normal microflora of GIT of mammals, the pathogen is commonly found in soil, water and food, however, their capability to colonize gut and skin alike *Enterobacteriaceae* and *Staph. aureus* and environmental persistence like *Cl. difficile* make them a successful "triple-threat" pathogen (Bonten *et al*., 1996) [4].

The pathogen evolved as a serious superbug, when antimicrobial resistance against ampicillin, the available drug of choice was reported. The pathogen is unique and mischievous due its innate low-level resistance against beta lactams, aminoglycosides and macrolides. The natural resistance against the beta lactams is majorly attributed to the production of low affinity penicillin binding protein (PBP5) and rarely due to the production of beta lactamases. The resistant *Enterococci strains* are treated by glycopeptide group of antibiotics, which include Vancomycin, however reports of vancomycin resistance have persuaded the clinicians to highlight the need for new therapeutics against *Enterococcus* spp. Vancomycin resistance is a result of reduced binding of antibiotic to their target due to the activity of VanA or VanB ligase, with VanA resistance being the highest in prevalence. Moreover, many new Van variants (VanC1/C2/C3, VanD, VanE, VanG, VanL, VanM, VanN) with lower prevalence have also been described. Additionally, VRE isolates possess "pathogenicity island" (Shankar *et al*., 2002) [32], which code for an enterococcal surface protein (ESP) responsible for biofilm formation. The expression of ESP is however dependent on temperature, that helps *Enterococci* to alternate its niches between environmental reservoir and a human host. The capability to form biofilm in indwelling and implanted medical devices in addition to colonization of skin and gut makes *Enterococcus* spp. a successful nosocomial pathogen (Van *et al*., 2007) [37].

Staphylococcus aureus

Staphylococci represent the class of gram-positive bacteria that are common inhabitants of skin and external nares of humans and other mammals. *S. aureus* predominates *Staphylococci* spp. in causing wide range of clinical and sub-clinical infections in humans, consequently making 60% and 20% human population as intermittent and persistent carriers respectively (Kluytmans *et al*., 1997) [16]. Despite being an opportunistic wound pathogen, *S. aureus* is capable of producing both acute and chronic infections because of the biofilm forming ability. However, it was in the year 1960 that *Staph. aureus* garnered the prime attention of researchers when methicillin resistant Staph aureus (MRSA) was first reported. MRSA is defined as any strain of *Staph aureus* that manifests resistance against beta lactam antibiotics *viz*., penicillins, cephalosporins and carbapenems via expression of mecA or mecC gene, which encode for a low affinity penicillin binding protein (PBP 2a) which aid in resisting the action of beta lactam antibiotics. These genes are part of a mobile genetic element (staphylococcal cassette chromosome (SCC) which is integrated in bacterial chromosome. The SCC is composed of a mec operon and ccr (cassette chromosome recombinase gene), with a magnitude of both mec operon and ccr gene combinations. Presently thirteen different SCCmec types are described and reported in the literature. Infections by MRSA are treated using high class drugs- glycopeptides, with Vancomycin being the first choice for treatment. However, undue selective pressure over MRSA has resulted in emergence of Vancomycin-intermediate and resistant *Staph aureus* (VISA & VRSA respectively) (Chambers and Deleo, 2009) [7]. VISA strains are a result of unavailability of vancomycin at the target bacterial site due to alteration in thickness of bacterial cell wall (Appelbaum, 2007) [3]. However, VRSA strains are relatively less common in abundance and have been derived by interspecies transfer of vancomycin resistance genes from Vancomycin resistant enterococci (VRE).

Klebsiella pneumoniae

K. pneumoniae is an opportunistic lactose fermenting, non-motile bacillus inhabiting the environment and gastrointestinal tract (GIT) of humans and animals. Apart from the GIT, the organism colonizes the nose and throat of apparently healthy individuals. The successful bacterial colonization is attributed to the presence of a thick polysaccharide capsule, which helps the organism in evading host's immune response. The phylogenetic studies reveal that *K. pneumoniae* can be classified into three phylogroups *viz*., *K. pneumoniae* (KpI) (Fevre *et al*., 2005) [9], *K. quasipneumoniae* (KpII A-B) (Brisse *et al*., 2014) [5], and *K. variicola* (KPIII) (Rosenblueth *et al*., 2004 and Maatallah *et al*., 2014) [30,20], of which KpI is observed to be frequently associated with infection in humans (Holt *et al*., 2015) [11]. The infections are further classified as community acquired (CAI) or hospital acquired (HAI) infections, wherein HAIs are associated with bloodstream infections along with infections of abdominal cavity, surgical site, soft tissues, meninges, respiratory and urinary tracts, especially in immunocompromised patients (Janda, 2015) [14]. However, a new hypervirulent (hypermucoviscous) strain of *K. pneumoniae* possessing specific capsule serotypes K1, K2 along with presence of many siderophores has been circulating worldwide (Shon *et al*., 2013) [34]. Apart from the many virulence factors, the acquisition of AMR genes via plasmids, bacteriophages, insertion sequence and integrative conjugative elements (ICEs) enhance the pathogenic potential of the bacterium when compared to other gram-negative bacteria (Ramirez *et al*., 2014; Holt *et al*., 2015 and Mathers *et al*., 2015) [28, 11, 21]. Previously during 1980s and 2000s, *K. pneumoniae* was profoundly known for carrying plasmids encoding resistance against aminoglycoside, fluoroquinolones and beta lactams, with more consideration given to the production of extended spectrum beta lactamases (ESBLs) enzymes against the beta lactam antibiotics *viz*., penicillins, cephalosporins and oxy-iminobactams. The ESBLs are encoded by variety of genes namely, TEM, SHV, CTX-M, OXA, AmpC etc. The wide spectrum of multi-drug resistance manifested by the bacterium compels the use of carbapenems as an available therapeutic choice against infection. However, there has been an unprecedented rise in carbapenem resistance encoded by *bla*NDM, *bla*KPC, *bla*IMP, *bla*OXA and *bla*VIM genes since 2000s (Zheng *et al*., 2016) [41]. Additionally, transmissible colistin resistance genes *mcr*-1 (Liu *et al*., 2016) [17], *mcr*-2 (Xavier *et al*., 2016) [38] and *mcr*-3 (Yin *et al*., 2017) [39] have also been identified in *K. pneumoniae.* Although polymixins and tigecycline are presumed to be treatment of choice for carbapenem resistant *Enterobacteriaceae* (CRE) infections, the emergence of colistin resistance has narrowed down the treatment options to tigecycline alone (Liu *et al*., 2016 and Sheu *et al*., 2019) [17,33]. Moreover, a widely circulating plasmid-borne efflux pump type tigecycline resistance determinant has been recently identified from food producing animals (Lv *et al*., 2020) [19].

Acinetobacter baumannii

A. baumannii is an opportunistic gram negative aerobic, non-motile bacillus, particularly dangerous for immunocompromised individuals, especially those on a prolonged hospital stay (>90days) (Montefour *et al*., 2008) [23]. The bacterium has demonstrated a shift in its niche from

hot and /or humid climate to temperate climate, attributed to its environmental persistence and development of multi-drug resistance (MDR). While being ubiquitous in aquatic environment (Turton *et al*., 2006) [36], it is predominantly isolated from the skin, respiratory and oropharyngeal secretions of the infected patients (Sebeny *et al*., 2008) [31]. Even though the rates of infection with *A. baumannii* are relatively low compared to other ESKAPE pathogens, approximately 45% of all globally isolated *A. baumannii* demonstrate multi-drug resistance which makes the bacterium a serious cause of concern. The propensity to develop antibiotic resistance has led to the emergence and vast dissemination of MDR isolates, with globally 30% increase in rate of identification from year 2011-2016. The bacteria has gained particular attention in conflict zones of Iraq, where serious incidences of MDR bacteremia among military troops are observed, thus popularizing it to be named as "Iraqibacter" (Howard *et al*., 2012) [12]. While the clinical symptoms are a result of infection and colonization of respiratory tract, urinary tract, surgical sites, pleural cavity, CNS, skin, eyes and blood, the patients with indwelling medical devices such as catheters, endotracheal tubes are at a higher risk to counteract serious infections due to the biofilm forming property of the bacterium (Lorente *et al*., 2002) [18]. The virulence potential of the bacterium resides with the presence of surface protein, OmpA (outer membrane protein) and production of phospholipase D and C, which aids in biofilm formation, complement evasion (Choi *et al*., 2005) [8], epithelial cell evasion and enhanced toxicity to epithelial cells (Camarena *et al*., 2010) [6] respectively. With regard to AMR, all the genomic variants contain a non-inducible AmpC cephalosporinases, popularly known as Acinetobacter-derived cephalosporinases (ADCs) (Hujer *et al*., 2005) [13]. *A. baumannii* however, intrinsically possess class D- OXA beta lactamase belonging to OXA-51 group of enzymes which weakly hydrolyze penicillin and carbapenems (meropenem and imipenem), however, carbapenem resistance is mostly mediated by production of *bla*OXA-23, *bla*OXA-40 and *bla*OXA-58. The advanced surge in resistance against last resort antibiotics *viz*., carbapenem lead to origin of carbapenem resistant *A. baumannii* (CRAb), a critically acclaimed pathogen capable of causing huge mortality, morbidity and global pandemic.

Pseudomonas aeruginosa

P. aeruginosa is a gram-negative opportunistic pathogen mostly associated with severe respiratory infections in immune-compromised individuals and accounting for around 10% nosocomial infections. The patients with chronic lung disease *viz*., cystic fibrosis (CF) are at a major health risk due to the colonization and biofilm forming ability of *P. aeruginosa* in the lungs thereby evading host's immune response and treatment with antibiotics. The genome plasticity and adaptability augment the pathogen's ability to escape the antibiotic treatment and persist as chronic pathogen in the infected host (Moradali *et al*., 2017) [24]. The intrinsic resistance against a repertoire of antibiotics aids in the development of multi-drug resistant infections. Globally, patterns of AMR in the bacterium varies extensively, however, lineages ST235 and ST175 have emerged as major cause of HAIs. The highest AMR in isolates of *P. aeruginosa* has been observed from Western and Central Europe, North, Central and South America, China, India and Southeast Asia.

***Enterobacter* spp.**

Historically, past thirty-five years have witnessed an unprecedented rise in infections in neonatal wards and intensive care units by *Enterobacter aerogenes* (renamed as *Klebsiella* aerogenes) and *E. cloacae*. While, *E. aerogenes* predominated the clinical episodes of nosocomial infections from early 1990s to 2003, it was superseded by *E. cloacae* in the year 2010 due to its extensive distribution in the natural environment and clinical settings. *E. cloacae* complex (ECC) is an amalgamation of 22 species of gram-negative rod-shaped *Enterobacter sp.* (Mishra *et al*., 2020) [22]. The members of ECC were first accredited as nosocomial pathogens in 1970s and are presently the third most important etiological agents of HAIs among all *Enterobacteriaceae* (Jin *et al*., 2018) [15]. The organisms are responsible for causing variety of infections viz., urinary and respiratory tract infections, soft tissue infections, meningitis and septicemia (Zhao *et al*., 2020) [40]. With regard to AMR, the members of ECC are believed to be second most common beta lactam resistant bacteria belonging to *Enterobacteriaceae* (Peirano *et al*., 2018) [26], by the virtue of intrinsic resistance to first and second generation cephalosporins via production of class C beta lactamases and overexpression of efflux pumps (Jin *et al*., 2018) [15]. Moreover, acquisition of other ESBL (*bla*TEM, *bla*SHV, *bla*CTX-M) and carbapenemase encoding genes (*bla*OXA-48, *bla*VIM, *bla*IMP, *bla*KPC and *bla*NDM-1) *via* horizontal gene transfer (HGT) strengthens their role in dissemination of AMR. Carbapenem resistance in *Enterobacter* strains has now been reported from all WHO health regions. However, the characterization and transmission potential of carbapenamase among ECC strains still remains a less explored topic, which needs prime attention before any pandemic occurs in future (Annavajhala *et al*., 2019) [2].

Conclusion

The rapid progression and dissemination of antimicrobial resistance along with the absence of new antimicrobials has posed a major challenge before the clinicians. While AMR infections are treated using high class of antibiotics, the resistance against these last resort antibiotics leaves no choice for the treatment. The ESKAPE pathogens alone account for majority of nosocomial infections with a moderate to high risk of morbidity and mortality mostly among immune-compromised individuals. Despite being claimed as the priority pathogens by the WHO, there are limited studies on their surveillance and development of newer antimicrobials against them which creates a critical gap for the researchers and pharmaceutical companies.

Conflict of interest

The authors declare no conflict of interest.

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