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# ESKAPE PATHOGENS: A GLOBAL THREAT AND THEIR ROLE IN HAIS

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## ABSTRACT

Microorganisms have developed resistance to many available therapeutic agents through various protective mechanisms in order to counteract the harmful effects of antibiotics, thus eventually resulting in loss of inhibitory potential of antibiotics. The phenomenon of multidrug resistance among the bacterial pathogens particularly in ESKAPE pathogens poses a major risk to the human health. The ESKAPE term includes 6 pathogens - *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp*. The looming health threat caused by these pathogens causing Hospital acquired infections and the demand for better patient care has stimulated interest for understanding the mechanisms of drug resistance acquired by these pathogens and the improvement of therapy through novel drugs. Hence there is an urgent need to focus research to develop various strategies in order to overcome their drug resistance and to discover new antibiotics that act against ESKAPE pathogens. This review paper gives an overviewof ESKAPE pathogens and their prevalence at global level and discusses their drug resistance mechanisms and various strategies employed to combat ESKAPE pathogens.

**Keywords: ESKAPE pathogens, antimicrobial resistance, AMR Surveillance, multidrug resistance, Hospital Acquired Infections**

## 1. INTRODUCTION

Hospital-acquired infections (HAI) are nosocomial infections that are acquired in the hospital by a patient admitted for a reason other than the infection in context. The infection should not be present prior to admission and the symptoms should appear at least 2 days after admission **[1]**. These infections mostly include Catheter Associated Urinary Tract Infections (CAUTI), Bloodstream Infections (BSI), Surgical Site Infections (SSI) and Ventilator- Associated Pneumonia (VAP). Cough, breathlessness, abdominal pain, altered mental status, palpitations, polyuria and dysuria are a few symptoms that favour HAIs. Approximately 7% of patients in developed countries and 10% in developing countries are infected with HAIs at any given time as reported by World Health Organization (WHO). Hospital-acquired infections may contribute to lengthier hospital stays, increased treatment-related expenses causing a huge economic burden to the hospital and a high mortality rate of 10% or more **[2, 3**).

Bacteria, Fungi, Viruses, Parasites and other microbes are the causative agents of various nosocomial infections. The transmission of these infections could be due to interpersonal communications between patients or with healthcare providers, through contaminated equipment or lack of proper sterilization measures **[4, 5]**. These nosocomial infections may be endogenous or exogenous in origin. Majority of them are endogenous and result from own normal flora invadingthe patient's body during some instrumental handling or surgical operations. Exogenous sources are from the healthcare workers, patients or hospital environment sources such as air, water and food and most importantly inanimate objects such as medical equipment bedpans, surfacescontaminated by patients' excretions, blood and body fluids **(Figure 1)**. The principal factors that determine the likelihood that a given patient would acquire a HAI and promote their spread are immune status, hospital environment, hospital organisms, diagnostic or therapeutic interventions such as insertion of a central line or urinary catheters or endotracheal tube, transfusion of blood, blood products and intravenous fluids and poor hospital administration. The factors which enhance the risks of incidence of HAIs are old age, lowered immunity status, more frequency of visits to healthcare facilities, period of stay in the hospital especially in an ICU (IntensiveCare Unit), multiple underlying comorbidities, mechanical ventilatory support, invasive procedures and indwelling devices such as catheters **[6]**.

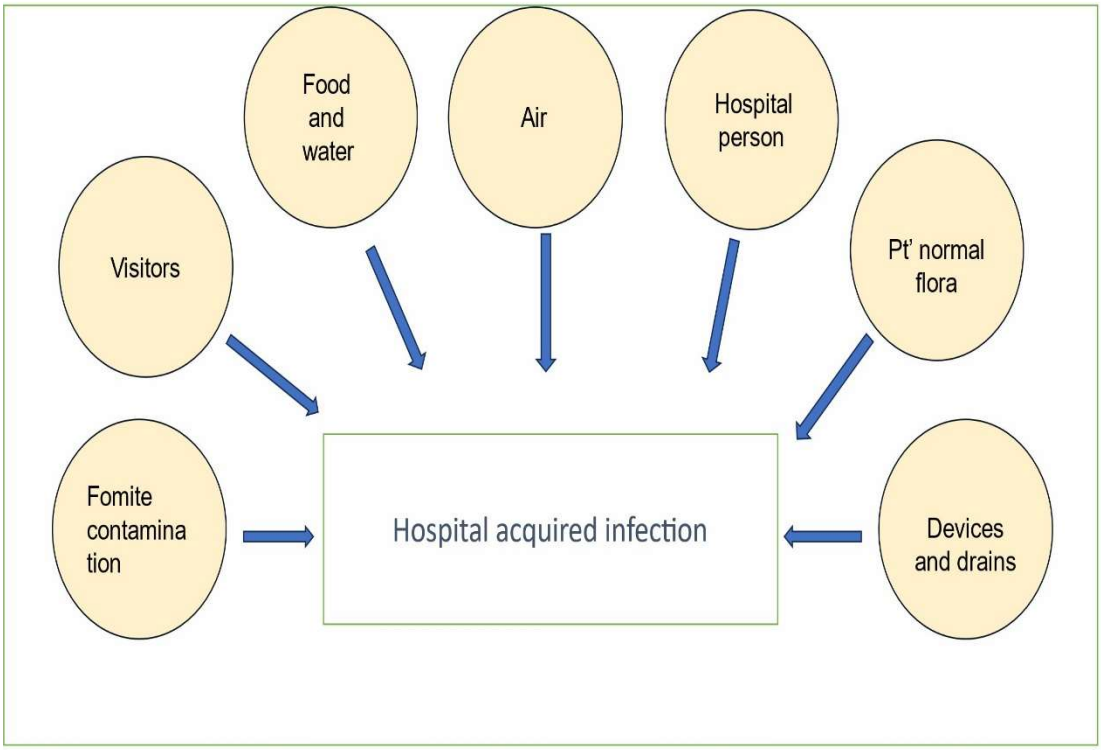


**Figure 1: Sources of Hospital Acquired Infections**

## 2. REVIEW METHODOLOGY

A thorough search of databases was performed for extraction of data from various databases - PubMed, Web of Science, Science Direct and Google scholar. A combination of the following terms was used to search the bibliographic databases: ESKAPE pathogens AND *Enterobacter* species AND *Staphylococcus aureus* AND *Klebsiella pneumoniae*, AND *Acinetobacter baumannii* AND *Pseudomonas aeruginosa* AND *Enterobacter* spp. The scope of the literature searches was restricted to papers written in the English language and released after 2000. Duplicate records were eliminated after compiling the search titles and abstracts from the databases. The titles and abstracts were subsequently subjected to an eligibility screening, employing the inclusion criteria such as Peer-reviewed English articles and those that report on the prevalence rates of the ESKAPE pathogens. After screening the titles and abstracts, the full texts of the eligible studies were evaluated based on year of publication and prevalence of ESKAPE pathogens in different countries or at global level. Thus, screening and data analysis was attempted to include potentially relevant articles based on their relevancy and thus the appropriateness of papers for inclusion in the

review was determined **(Figure 2)**.

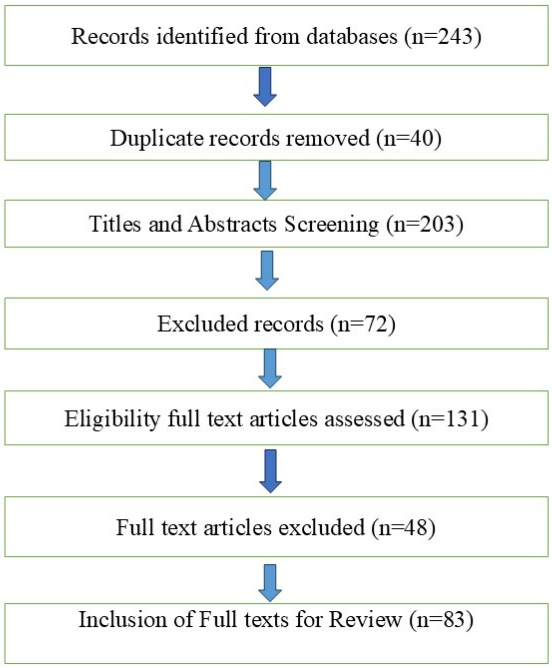


**Figure 2: Flow diagram demonstrating the search and selection process used in this review on ESKAPE pathogens**

## 3. THE ESKAPE PATHOGENS

The acronym ESKAPE is given by Louis B. Rice and encompasses six nosocomial pathogens: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* spp. A substantial percentage of nosocomial infections are caused by ESKAPE pathogens that exhibit multidrug resistance and virulence. They have emerged as a potential threat to public health, particularly in case of healthcare-associated infections. These bacteria exhibit different mechanisms of drug resistance, thereby making treatment options limited, contributing to increased morbidity, mortality, and increased hospitalization times and healthcare costs worldwide. Their resistance is largely due to their adaptive mechanisms, such as gene acquisition, biofilm formation, and efflux pumps, which enable them to evade the effects of common antibiotics. They are the causative agents of serious nosocomial infections particularly in immuno-compromised as well as critically ill patients in hospitals **[7, 5]**. ESKAPE pathogens were designated by WHO as "priority status" for which development of new antimicrobial therapy is urgently needed **[8-10]**.

***2.1. Enterococcus faecium:*** Enterococcus species are facultative anaerobic Gram positive cocci in pairs or chains. The most clinically significant species among the Enterococcus group are *E. faecium* and *E.faecalis* species. These are primarily associated with HAIs such as CAUTIs, SSIs and BSIs. *Enterococcus faecium* although exists as a commensal in the GIT (Gastrointestinal Tract) of humans and animals, it may be pathogenic causing neonatal meningitis or endocarditis. The transmission of *E. faecium* infections from person to person may occur due to poor hygiene, faeces, food, fomites as doorknobs, telephones and computer keyboards **[11]**. Most Enterococcus infections are either acquired from endogenous sources or cross-infections in hospitalized patients. *Enterococcus faecium* is a prominent cause of health care-associated infections and are increasingly resistant to vancomycin and ampicillin **[12-14]**. Vancomycin-resistant enterococci(VREs) emerged in the 1980s and are a major cause of deaths in HAIs and declared as one of the high-priority pathogens by WHO **[10]**.

***2.2. Staphylococcus aureus:*** *S. aureus* is a Gram-positive cocci arranged in bunches that exists as a normal flora of humans located on the skin and mucous membranes most often in the nasal area as well as found in the environment. *S.aureus* is a skin commensal and causes multiple human infections, including bacteremia, infective endocarditis, osteomyelitis, septic arthritis, pulmonary infections, skin and soft tissue infections like impetigo, folliculitis etc. **[14]**. This is considered as a major pathogen that causes both community- acquired and hospital-acquired infections. These infections possess high transmission rate and the major routes of transmission are either direct contact or airborne. Traditionally, penicillin G was used in the treatment of *Staphylococcus* infections; however, penicillin resistant *Staphylococcus* isolates emerged owing to excessive and unnecessary use of these antibiotics and in more than 65–85% of the clinical isolates, the resistance was attributed to the production of $\beta$-lactamase **[4]**. Around 1960, the first semi-synthetic antistaphylococcal penicillins were created and then the problem of resistance to Methicillin emerged leading to the discovery of Methicillin Resistant *Staphylococcus aureus* (MRSA) in 1961 **[9]**. The treatment of infections caused by *Staphylococcus* became the most challenging task due to the emergence of multi-drug resistant MRSA. The high prevalence and clinical relevance of MRSA declared this pathogen as one of the high-priority by WHO **[15, 16]**.

***2.3. Klebsiella pneumonia****: Klebsiella pneumonia*, a member of the family *Enterobacteriaceae*, is a natural inhabitant of the intestinal tract microbiome of healthy humans and animals. It is a non-fastidious, gram-negative, capsulated bacillus and is major cause of HAIs and antimicrobial resistance-related deaths globally. This pathogen may be acquired either from endogenous source or by direct contact and causes hospital-acquired surgical wound infections, gastrointestinal infections and community-onset infections, which can cause outbreaks of nosocomial infections. *Klebsiella pneumoniae* is a highly diverse human pathogen and is categorized into 2 categories: (i) classical *K. pneumoniae* (cKP) isolates that cause nosocomial infections in immunocompromised patients (ii) hypervirulent *K. pneumoniae* (hvKP) isolates that causecommunity-acquired, disseminated infections in healthy, immunocompetent individuals **[17, 18]**. *Klebsiella pneumoniae* is a major threat in hospital environments due to its natural resistance to various antibiotics and its ability to acquire resistance through the production of β-lactamase enzymes. These enzymes break down the β-lactam structure of antibiotics such as penicillins, cephalosporins, and carbapenems, rendering them ineffective. K. pneumoniae strains that produce extended-spectrum β-lactamases (ESBLs) are particularly concerning, as they can resist a wide range of β-lactams **[10, 19]**. Additionally, carbapenem-resistant K. pneumoniae (CRKP) strains, which produce carbapenemases, are especially dangerous as they resist carbapenems, a class of antibiotics often used as a last line of defense. This resistance makes CRKP strains a significant clinical challenge and a major cause for concern in hospital settings, where they can lead to serious infections with high rates of morbidity and mortality **[4]**.

***2.4. Acinetobacter baumannii*** :

*Acinetobacter* species are commonly found in the environment, and especially prevalent in hospital settings. The most significant human pathogen in this genus is *Acinetobacter baumannii* , a Gram-negative coccobacillus from the *Moraxellaceae* family. *A. baumannii* is known for its high rates of cross-contamination in hospital environments due to its ability to survive on human hands for extended periods. It mainly affects critically ill, immunocompromised patients, leading to a variety of hospital-acquired infections such as ventilator-associated pneumonia, urinary tract infections, gastrointestinal infections, meningitis, sepsis, and skin or wound infections. A notable feature of *A. baumannii* is its rapid development of resistance, making

it a significant global health threat and a challenge for treatment **[20]**. This pathogen is often resistant to multiple antibiotics, especially in surgical and intensive care units **[4]**. While the incidence of *A. baumannii* infections is lower than that of other ESKAPE pathogens, 45-90% of global isolates are classified as multidrug-resistant (MDR), approximately four times higher than in *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* **[21-23]**. The WHO identified carbapenem-resistant *A. baumannii* as a critical pathogen requiring urgent action, including enhanced surveillance and the development of new therapies to prevent a potential global epidemic.

***2.5. Pseudomonas aeruginosa****: P. aeruginosa* is a facultative anaerobe, Gram negative rod that exists as normal flora of intestine. *Pseudomonas aeruginosa* typically thrives in moist environments, making it common in settings like chronic wounds, respiratory support equipment, urinary tract devices, and various healthcare environments. In these areas, biofilm formation promotes the bacteria's persistence, immune evasion, and resistance to antimicrobial treatments **[24, 25]**. While transmission rates are low in the general population, they are higher among hospital inpatients, particularly in immunocompromised. Infections are usually acquired from external sources, (direct / indirect contact) rather than from the patient's own microbiota. *P. aeruginosa* is an opportunistic pathogen responsible for approximately 10% of all hospital-acquired infections, including respiratory infections, ventilator-associated pneumonia, urinary tract infections, bloodstream infections related to central lines, and surgical site infections **[10, 26]**. It poses a significant burden in healthcare settings and also in some community-acquired infections. This bacterium is naturally resistant to many antimicrobial agents and has developed resistance to several antibiotic classes, particularly carbapenems **[4, 27]**. The genetic flexibility of *P. aeruginosa,* driven by many regulatory genes, is a major factor in its ability to persist in the host and evade antibiotic treatments **[28]**. Multiple drug resistance along with wide virulence factors helps the organism to survive host immunity and difficult to treat. WHO prioritised and listed carbapenem-resistant *P. aeruginosa* as one of the critical pathogens.

***2.6. Enterobacter:*** *Enterobacter* species, belonging to the Enterobacteriaceae family, are non-fastidious, capsulated Gram-negative bacilli. There are over 22 species of Enterobacter, but only a few are pathogenic and clinically significant species responsible for nosocomial outbreaks include

*Enterobacter cloacae*, *Enterobacter asburiae*, and *Enterobacter hormaechei*, they exist as normal flora of gut and can cause opportunistic infections and can be easily transmitted among patients in hospitals especially in immunocompromised hosts. Enterobacter species are common causes of nosocomial infections, and less frequently cause community-acquired infections, such as UTI, RTI, SSI, soft tissue infections, bacteraemia, osteomyelitis, endocarditis and other device related infections **[10]**. *Enterobacter aerogenes* and *Enterobacter cloacae* are the most prevalent species in hospital-acquired infections, posing significant risks to neonatal units and intensive care patients, particularly those on mechanical ventilation. These pathogens possess numerous antibiotic resistance mechanisms, and the rise of these two species as MDR pathogens is a growing concern for HAIs **[29]**.

## 3. GLOBAL PREVALENCE OF ESKAPE PATHOGENS

ESKAPE pathogens pose a substantial threat globally, particularly as healthcare systems worldwide face increasing rates of antibiotic resistance. ESKAPE pathogens have been implicated in majority of HAIs and arelargely present in clinical settings where patients are exposed to invasive procedures and immunocompromised environments, which facilitate transmission. A study in U.S. hospitals reported nearly 60% of hospital-acquired infections are caused by ESKAPE pathogens, contributing to significant patient morbidity and healthcare burden **[30]**. The impact of these pathogens is even more pronounced in places with less stringent infection control practices. A systematic review by WHO (2014) underscores the global spread of these pathogens, emphasizing the need of coordinated efforts by international bodies to combat their spread **[31]**.

A review study made during 2014 -2024 on the prevalence of ESKAPE pathogens in Africa revealed that *S. aureus* was the most prevalent species (79.5%), followed by *A. baumannii* (27.6%), *K.pneumoniae* (24.2%), *Enterobacter* spp. (20%), *P. aeruginosa* (9.0%), and *E. faecium* (5.1%) **[32]**. A retrospective study conducted in India during 2010–2020 reported different infections caused by ESKAPE pathogens and revealed a global increase in antimicrobial resistance exhibited by both Gram-negative and Gram-positive ESKAPE pathogens. This analysis showed that *A. baumannii* was the predominantspecies (35.9%), followed by *P. aeruginosa* (25.3%), *K.pneumoniae* (19.5%), *S. aureus* (16.3%), *E. faecium* (2.6%), and

*Enterobacter* spp. (0.4%) **[33]**.

A retrospective study made over 5 years during 2016–2020 in a Romanian infectious disease hospital assessed the antimicrobial resistance of ESKAPE pathogenic isolates from the patient's biological samples revealed 97% of the ESKAPE pathogens and the the most prevalent strains were identified as *E. coli* (38.26%*)* and *Staphylococcus aureus* (26%) **[34]**. Another retrospective study conducted in Hungary at a tertiary-care ED over 5 years focusing on epidemiology and resistance patterns of ESKAPE bacteria revealed 72.22% of ESKAPE pathogens. The study demonstrated *E. coli* as the most frequent isolate (44.1%), followed by the *Klebsiella* genus (13.4%) and *S. aureus* (11.3%). The study also indicated that multi-drug resistance (MDR) was present in 23.8% and was most prevalent in *A. baumanii* (65.5%), *P. mirabilis* (42.7%), and *K. pneumoniae* (32.6%) **[35]**. A retrospective cross-sectional study conducted during 2021-22 year on patients infected with ESKAPE pathogens in Palestine revealed 90.5% of them had MDR infections. The study demonstrated that *A. baumannii* was the most prevalent MDR pathogens accounting to 95.6% of ESKAPE pathogens, majoritybeing Carbapenem-resistant strains. The study also found that 83.8% of the clinical isolates were *K. pneumoniae* with more than 90% strains exhibiting extended-spectrum cephalosporin resistance. This was followed by 68.2% of isolates as *S. aureus* with oxacillin-resistance, 40% of *E. faecium* isolates showing vancomycin resistance and 22.6% of isolates as *P.aeruginosa* majorly showing carbapenem resistance **[36]**.

A study was conducted during 2014 to 2018 in USA to analyze and evaluate the prevalence of ESKAPE pathogens revealed that 42.2% of species isolated were ESKAPE pathogens, the most prevalent being *S. aureus* accounting to 21.9%*, K. pneumoniae* 7.5%, and *P. aeruginosa* being 7.2% of the total bacterial isolates. The most prevalent non-ESKAPE pathogens were identified to be *E. coli, E. faecalis,* and *P. mirabilis* **[37]**. Another study conducted in a tertiary universityhospital in Tehran, Iran during 2020 to 2021 showed 30% of the ESKAPE isolates were *S. aureus*, 22% of *A. baumannii*, 17% of them as *P. aeruginosa*, 13% of *K. pneumoniae*, 10.3% of *E. aerogenes* and 7.7% of them were identified as *E. faecium*. Most of the ESKAPE pathogens isolated were found to be multidrug resistant (MDR) and extensively drug resistant (XDR), majorly being resistant to methicillin and vancomycin **[38]**. Another study conducted on Urinary tract infections in paediatric population in the South-East of

Gabon from 2018 to 2021 demonstrated that 89% of the uropathogens belonged to the *ESKAPE* group which was much higher than non-*ESKAPE* group (11%). 75% of the *ESKAPE* bacterial isolates were Gram-negative and were thus found to be more prevalent than the *ESKAPE*-Gram-positive group (14%). The study also revealed that the *E. coli* (46%) and *K. pneumoniae* (45%) were predominant among the *ESKAPE*-Gram-negative uropathogens **[39]**.

**4.AMR IN ESKAPE PATHOGENS**

Since the discovery of the penicillin in the year 1928, there has been a tremendous progress in the field of modern medicine. Many antimicrobials were discovered and introduced into modern medicine between the years 1940 to 1965 and considered as the golden era in the field of antibiotics **[5]**. These newly discovered antibiotic drugs were principally used for the treatment of bacterial diseases, thus leading to the revolutionization of modern medicine. Unfortunately, irregular intake and/or excessive usageof antibiotics led to the emergence of antibiotic-resistant microorganisms. The phenomenon of antibiotic resistance has amplified to a great extent and is currently at an alarming pace and has become a major global health concern. ESKAPE pathogens frequently associated with the hospitals exhibit various mechanisms of drug resistance such as (i) drug inactivation/alteration commonly caused by an enzyme catalysed irreversible cleavage (ii) modification of drug binding sites(iii) reduced antibiotic penetration/accumulation as a result of the reduced permeability or increased drug efflux (iv) bacterial biofilms providing mechanical protection **[4, 40]**. The continued use of antibiotics has led to the rise of MDR and XDR bacteria, which make even the most potent antibiotics ineffective **(Table 1)**. The development of MDR bacteria is largely due to factors such as prolonged antibiotic use, self-medication, and exposure to infections in hospital settings, contributing to 15.5% of healthcare-associated infections (HAIs) worldwide.

The emergence of antimicrobial-resistant ESKAPE pathogens poses a significant global health threat. These pathogens are responsible for a majority of hospital-acquired infections and have the ability to "escape" the lethal effects of antimicrobial agents **[41, 42]**. These bacteria share several key biological features including adaptations for survival in the modern health-care settings, diverse methods for acquiring resistance determinants and the dissemination of successful high-risk clones all over the globe. The development of methicillin resistance in *Staphylococcus aureus* (MRSA) is through the mecA gene,

while *Enterococcus faecium* often displays vancomycin resistance (VRE), associated to the vanA and vanB genes. *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are recognized for producing extended-spectrum beta-lactamases (ESBLs) and carbapenemases, enzymes that degrade many beta-lactam antibiotics, rendering treatment more challenging **[43]**. ESKAPE pathogens often develop resistance to one or both antibiotics in combination, not only through natural selection of resistant strains but also via horizontal gene transfer to susceptible strains. These pathogens may be intrinsically resistant to certain antibiotics or carry antimicrobial resistance genes within their bacterial chromosomes or on mobile genetic elements such as plasmids, transposons, insertion sequences, integrative and conjugative elements, and other genomic islands. Through genetic mutations and the acquisition of these mobile elements, ESKAPE pathogens have gained resistance to a wide range of antibiotics, including oxazolidinones, lipopeptides, macrolides, fluoroquinolones, tetracyclines, β-lactams, β-lactam-β-lactamase inhibitor combinations, and even last-resort antibiotics such as carbapenems, glycopeptides, and polymyxins **[9, 44-50]**. The spread of AMR genes among ESKAPE pathogens has severely limited treatment options for serious infections, contributing to higher disease burdens and mortality rates due to treatment failures, thus highlighting the urgent need for coordinated global efforts in AMR surveillance.

**Table 1: ESKAPE Pathogens and their Antibiotic Resistance Profiles**

| Bacterial Species | Clinical manifestation | Resistant drugs | Treatment |
|---|---|---|---|
| ***Enterococcus faecalis*** | **Catheter associated UTI, abdominal infection, pelvic infection** | **Vancomycin, linezolid Teicoplanin, piperacillin, cephalosporin.** | **Nitrofurantoin, Fosfomycin, Daptomycin, Chloramphenicol** |
| ***Staphylococcu s aureus*** | **Bacterial skin infection, pneumonia, osteoarticular infection, endocarditis.** | **Aminoglycosides, Chloramphenicol, trimethoprim, Fluoroquinolones.** | **Vancomycin clindamycin daptomycin tedizolid trimethoprim** |
| ***K. pneumonia*** | **Pneumonia, pyogenic liver abscesses, soft tissue infection, blood stream infection.** | **Cephalosporin, meropenem, ciprofloxin, aminoglycosides, tetracycline.** | **Aminoglycosides, polymyxin combination therapy, tigecycline, meropenem, imipenem.** |
| ***Acinetobacter baumanii*** | **Ventilator associated pneumonia, central line blood stream infection, nosocomial meningitis.** | **Carbapenems, polymyxin, tigecycline, Ceftazidime, fourth-generation cephalosporin.** | **Colistin, tigecycline** |
| ***P. aeruginosa*** | **Blood stream infection, ventilator associated infection, chronic respiratory infection.** | **First and second- generation cephalosporin, piperacillin-tazobactam, aminoglycosides.** | **Piperacillin- tazobactam, ceftolozane- tazobactam.** |
| ***Enterobacter species*** | **Blood steam infection, neonatal pneumonia, skin and soft tissue infection.** | **Carbapenems, fourth-generation cephalosporin, fluoroquinolones, polymyxin** | **Cefepime, ceftriaxone, gentamycin, meropenem** |

**Source: Adapted from De Oliveira *et al*. 2020**

## 5. STRATEGIES TO COMBAT ESKAPE PATHOGENS

To mitigate the impact of ESKAPE pathogens, hospitals and healthcare systems have adopted several strategies of rigorous infection control practices such as hand hygiene, antimicrobial stewardship programs and isolation of diseased patients. These efforts aim to stop the spread of ESKAPE pathogens within healthcare settings, though challenges persist because of the pathogens' ability to persist on surfaces in the hospital environments. Advanced diagnostics and rapid molecular testing have been instrumental in identifying these pathogens quickly, thus allowing for better targeted interventions and improved patient outcomes **[51]**. Future directions and challenges in combatting ESKAPE pathogens requires continued research into novel antibiotics and alternative therapies and improved diagnostic methods.

### 5.1. Antibiotics Therapy

The discovery of new antimicrobial drugs is a significant challenge, and the growing rise of antimicrobial resistance (AMR) is diminishing the effectiveness of existing antibiotics. The misuse of antibiotics has contributed to the reduction in their ability to combat pathogens, leading to an increase in antibiotic-resistant bacterial populations (Aloke & Achilonu 2023). In 2018, three new antibiotics—plazomicin, eravacycline, and omadacycline—emerged from clinical trials and were approved by the U.S. FDA. These drugs had potential in treating serious bacterial infections, particularly those caused by ESKAPE pathogens **[9]**.

Carbapenems were once considered the most effective treatment option for infections caused by ESKAPE pathogens, especially those belonging to the *Enterobacteriales* order. However, the widespread use of carbapenems in clinical settings has led to the emergence of carbapenem-resistant pathogens. This highlights the urgent need for the discovery and development of novel therapeutics to treat drug-resistant infections, particularly those caused by ESKAPE pathogens. New drug development strategies should focus on alleviating the growing dependence on last-resort antibiotics, by exploring antibiotic-antibiotic potentiator combinations and reducing hospital stay lengths to minimize further complications. The combination of two or more antibiotics may be a good therapeutic approach, it is not always effective, underscoring the need for extensive research into alternative strategies. Non-drug therapies such as bacteriophage therapy, drug repurposing, vaccine development, photodynamic therapy,

antimicrobial peptides, and nanoparticles are emerging as promising approaches to tackle the AMR crisis.

**5.2.Combination of antibiotics therapy**

The novel and effective antimicrobial drugs also often failed to overcome the bacterial infections especially the emergence of antimicrobial-resistant (AMR) strains. This issue can be overcome by adopting various strategies such as pairing the existing antimicrobials either with other antimicrobial drugs or non- antimicrobial compounds. Researchers have tested antibiotic combinations as a treatment approach, as pathogens are less likely to develop resistance to a combination of two drugs than to a single drug. Drug combinations also broaden the spectrum of coverage and have been beneficial in treating severe bacterial infections caused by multiple pathogens **[40, 52-54]**. Antibiotic hybrids, which combine different biologically active agents into a single, heteromeric entity, represent a promising alternative to traditional antibiotics or their combinations. These hybrids are designed to retain the biological activities of the individual components, offering hope for more effective treatments in the future **[55-57]**.

**5.3. Drug repurposing**

Repurposing the existing drugs offers a promising alternative to the traditional process of de novo discovery, significantly reducing the time, cost and risks associated with the process of innovation and developing new drugs **[9]**. Drug repurposing has proven effectiveness against a wide range of Gram-positive and Gram-negative ESKAPE pathogens. For example, Glatiramer acetate (Copaxone), commonly used to treat multiple sclerosis, has demonstrated antibacterial activity against *E. coli, A. baumannii*, and *P. aeruginosa* strains **[58]**. Similarly, in vivo studies have shown that the synthetic anti-inflammatory drug Ebselen, and the oncology drugs adarotene and floxuridine, are bactericidal against methicillin resistant and vancomycin resistant *Staphylococcus aureus* **[9, 59, 60]**.

**5.4. Bacteriophage Therapy**

Since the discovery of Bacteriophages in 1915, they have been used in the treatment of several bacterial infections of animals and humans. Bacteriophages offer several advantages for therapeutic use, including high host specificity, which helps protect the normal flora and prevents infection of eukaryotic cells, as well as the ability to be administered in low doses, and their rapid proliferation within host bacteria **[53, 61]**. Despite their potential in treatment, the genomic characterization of bacteriophages is

crucial to ensure their safety. Since bacteriophages can act as vectors for horizontal gene transfer, they could facilitate the exchange of virulence or antimicrobial resistance (AMR) genes between bacteria, potentially making them more pathogenic or resistant to antibiotics **[53, 62, 63]**. While phage therapy holds promise, it does have some limitations, though these can be addressed through appropriate modifications.

**5.5. Vaccine development**

Bacterium-targeted vaccine therapies offer a promising approach to reduce reliance on existing antibiotics while also providing herd immunity, protecting both vaccinated and unvaccinated individuals. However, vaccines for infections caused by ESKAPE pathogens are not yet available, as many vaccine candidates have failed to induce a protective immune response in clinical trials **[64, 65]**. Among the limited number of ESKAPE pathogen-targeted vaccines that have undergone clinical trials, the *S. aureus* 4-antigen vaccine stands out as one of the few candidates shown to be effective in preventing invasive *S. aureus* infections in humans. Vaccines have been highly successful in reducing the incidence of other AMR pathogens, such as *Streptococcus pneumoniae* and *Haemophilus influenzae* type b **[9]**. Although there are currently few clinical trials for vaccines targeting ESKAPE pathogens, some recent preclinical studies have demonstrated the in vivo efficacy of vaccines against *Klebsiella pneumoniae, P. aeruginosa*, and *A. baumannii* **[65-67]**. The growing AMR threat posed by ESKAPE pathogens could be significantly mitigated through the development of new ESKAPE-targeted vaccines, which would complement existing therapies and enhance efforts to control these resistant infections.

**5.6. Photodynamic Therapy**

The photodynamic therapy (PDT) is another strategy employing non-invasive technique which uses the combination effect of non-deleterious photoactivatable compound/dye referred to as photosensitizer as well as a low-intensity visible or near-infrared light sources and molecular oxygen usually seen in the biological target **[68, 69]**.

Antimicrobial photodynamic therapy (aPDT) is the widely employed to treat dental, skin, and soft tissue infections **[70, 71]**. One approach to enhancing the delivery of photosensitizers involves using nanoparticles, which are co-administered to facilitate their entry across bacterial membranes or to generate a synergistic reactive oxygen species (ROS) response, resulting in an antimicrobial effect. Photodynamic therapy is especially effective for topical applications and holds

promise as a viable treatment option for infections caused by ESKAPE pathogens. When PDT is combined or conjugated with antibiotics, antimicrobial peptides, nanoparticles, or efflux pump inhibitors, a synergistic effect is often observed, enhancing its efficacy against these resistant pathogens **[53]**.

**5.7.Antimicrobial peptide therapy**

Antimicrobial peptides (AMPs) are short, positively charged, host defense oligopeptides produced by a wide range of organisms, including protozoa, bacteria, archaea, fungi, plants, and animals **[72]**. Due to their ability to interact with bacterial cell membranes and induce cell lysis, AMPs are considered as a promising alternative to combat multidrug-resistant (MDR) pathogens **[73]**. In addition to their in vitro effectiveness, AMPs also demonstrate significant in vivo activity against ESKAPE pathogens. Their broad-spectrum antibacterial properties, both in vitro and in vivo, make AMPs a hopeful alternative to conventional antibiotics **[53]**. Further, their stability can be improved and toxicity can be reduced through the development of peptide mimetics or by utilizing effective delivery systems, such as liposome encapsulation **[74]**.

**5.8. Silver Nanoparticle therapy**

Owing to their unique physical and chemical properties, Metal nanoparticles (NPs) have extensive applications in biomedical field and are employed as effective antimicrobial agents and thus emerged successfully in treating the drug-resistantpathogens **[75-77]**. Amongst all metal nanoparticles, silver nanoparticles (AgNPs) are well known as strong antibacterial agents and show extensive inhibitory activity against nearly 650 kinds of microorganisms and even antibiotic-resistant bacteria. Silver nanoparticles (AgNPs) can be produced using physical, chemical, or biological methods and have demonstrated significant antibacterial potential due to their ability to target multiple sites within pathogens **[78-82]**. Studies have shown that sunlight-synthesized AgNPs effectively inhibited biofilm formation in a *Staphylococcus aureus*-infected zebrafish model, thereby lowering the likelihood of resistance development **[53]**. Additionally, in vitro experiments confirmed that incorporating AgNPs into polymer dressings, such as those made from chitosan, nylon, or collagen, exhibited robust antibacterial activity against ESKAPE pathogens **[83, 84]**. Moreover, antimicrobial coatings utilizing these polymer-based nanomaterials and metallic nanoparticles on medical devices like catheters and implants play a crucial role in preventing infections.

## 6. CONCLUSION

ESKAPE organisms present a significant global health threat, causing severe challenges in both community and clinical settings. These pathogens are a leading cause of nosocomial infections, exemplifying issues of antibiotic resistance, virulence, and disease transmission. Despite genetic diversity among ESKAPE pathogens, they share common mechanisms for emergence and persistence, including drug inactivation and chemical modification of antibiotic targets, which complicate treatment efforts and heighten public health concerns. AMR (Antimicrobial resistance) in these pathogens has become a major threat to global health systems and seems to upsurge in the near future due to ever changing antibiotic resistance profiles. This results in the scarcity of potential therapeutic agents which is a cause of real concern. Hence research should be triggered and focussed on the development of novel antibiotics or new approaches to control the infections produced by drug resistant pathogens especially ESKAPE pathogens. To combat against the threatening antimicrobial resistance of ESKAPE organisms, various novel strategies are utilized such as repurposing of drugs, monoclonal antibody therapy, vaccine development, bacteriophage therapy, probiotics, therapeutic antibodies, fecal microbiota transplantation. However, the development and implementation of these therapies face regulatory and financial challenges. These novel tools, combined with advancements in antimicrobial resistance (AMR) surveillance, improved diagnostics, and enhanced patient education, offer promising avenues for controlling AMR in ESKAPE pathogens and thus provide a hope for the prevention and effective treatment of nosocomial infections.

As the search for alternative therapies intensifies, research into combinatorial approaches—leveraging the synergistic effects of dual or multiple therapies—has garnered significant attention for improving efficacy and clinical translation. Future studies should prioritize optimizing existing therapeutic agents to address current limitations and developing novel antimicrobials to tackle the challenges posed by drug-resistant ESKAPE pathogens.

Given the global significance of ESKAPE pathogens and their AMR, collaborative efforts are crucial. Hence collaborative efforts are to made in policymaking, funding, guidelines for appropriate use of antibiotics, diagnostics, and treatment at regional and global level to overcome the antimicrobial resistance and combat the the proliferation and spread of these life-threatening ESKAPE pathogens.

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