The clinical importance of emerging ESKAPE pathogens in nosocomial infections

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ABSTRACT

In the last decade, along with the problem of nosocomial infections, multidrug-resistant bacteria in community and hospitals have soared. High frequencies of multidrug-resistant bacteria have been grouped under the acronym ESKAPE: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter spp*. The ESKAPE pathogens are responsible for the majority of nosocomial infections and capable of 'escaping' the biocidal action of antimicrobial agents. The objective of this review is to consider the clinical importance of emerging of ESKAPE pathogens in nosocomial infections to prepare feasible data about tracing and treatment of infection related to ESKAPE pathogens that may be beneficial to clinicians at the bedhead. It can be said that healthcare-associated, community-acquired, and nosocomial infections should be clearly considered annually. The awareness of residential antimicrobial resistance can support selecting a convenient empirical therapeutic diet in diseases due to ESKAPE pathogens.

Keywords: Nosocomial infection; ESKAPE pathogens; Antibiotic resistance

INTRODUCTION

One of the most important health concerns is antimicrobial resistance. In the last decade along with the problem of nosocomial infections, the presence of multidrug-resistant bacteria in community and hospitals has been increased. High frequencies of multidrug-resistant bacteria have been grouped under the acronym *ESKAPE: Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter spp*. (1-3). The *ESKAPE* pathogens are responsible for the majority of nosocomial infections and capable of 'escaping' the biocidal action of antimicrobial agents. [2, 4, 5] Antibiotics have greatly influenced life on earth since 1930s. Four decades of extravagant antibiotic utilization had practicable selective pressure on high-level antimicrobial resistance and multiple-drug resistance (MDR) antibiotics caused threats to the end of the "antibiotic period". [2- 5] The common response to rising resistance has been followed by the proper preface of a novel class of antibiotics production. In a fundamental decrease in new antimicrobials production, generation rate currently fails to keep rise in resistance worldwide. [7]It has been predicted that the lack of proper combination of antibiotics would have miscellaneous ramifications on universal criteria, public health, security and international political consistency. [8]Health authorities, such as the Infectious Diseases Society of America (IDSA), the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization (WHO), have enhanced industrial incentives in an attempt to arouse research into novel antimicrobial combination, ameliorate antibiotic surveillance force to cover the remaining therapeutic options to physicians and encourage a focused, concerted endeavor against life-threatening infections due to multidrug-resistant (MDR) and pandrug-resistant Gram-negative bacteria. [4, 8-12]Empiric antibiotic

therapy can ameliorate patients with infections due to these microorganisms. [13, 14] Yet, most studies indicated that improper antimicrobial therapy can be decreased through using an empiric combination therapy. However the combination therapy consist the potential for a synergistic consequences and detention of resistance appearance. [15- 18]Synergy is a microbiological description well-known in in-vitro study. Prohibition of subsequent resistance in some pathogens such as *Pseudomonas aeruginosa* can be postponed by the use of the in-vitro combinations of levofloxacin and imipenem (IMP).[19, 20]No clinical studies on combination therapy in infections due to Gram-negative bacteria have formally tested or demonstrated this hypothesis. [21]Combination diets that contain aminoglycosides have been shown to develop for

Enterococcus faecium

Enterococci are gram positive cocci that distribute extensively in nature such as grounds, water, plants, and food, and are normal flora of human and animal enteric tract. [24] Due to their capability to survive under contrary environmental conditions, Enterococci have an accepted function in meat and dairy products and is used as probiotics in food and biological maintainer. [25, 26] Enterococci are opportunistic bacteria which cause severe infectious diseases. [27]Some strains of this genus are resistance to a broad number of antimicrobial drugs; these strains show inherent and acquired antimicrobial resistance. [28] The resistance characteristics can transfer intragenus horizontally or phylogenetically between related genus. [29]Enterococci can obtain resistance to erythromycin, glycopeptides, tetracycline, vancomycin (vancomycin - resistant enterococci; VRE), aminoglycosides (high-level resistance; HLR), gentamicin (high-level resistance gentamicin; HLGR) and streptomycin (high-level resistance streptomycin; HLSR. [30]In Europe, HLR enterococci have been recovered from dairy and meat products as well as strains with multiple antimicrobial resistances, containing vancomycin. [31-33]Various reports have demonstrated that *Enterococcus faecalis* and *Enterococcus faecium* can cause several infections including septicemia, higher toxicity rates in patient such as nephrotoxicity than monotherapy diet. In patients with sepsis due to Gram-negative who are often volume depleted, metabolic acidosis is present and they are faced with other nephrotoxic agents. [22]

Combination therapy is mostly used in the clinical workout and depends on the orientation of infectious disease doctors, combining the antimicrobial treatment, especially over tuberculosis, HIV infection, brucellosis, *C. difficile*-associated colitis, enterococcal endocarditis, and *Helicobacter pylori* infection. [23]The objective of this review is to consider the clinical importance of emerging ESKAPE pathogens in nosocomial infections to prepare the feasible data on tracing and treatment of infections related to ESKAPE pathogens . urinary tract infections, endocarditis, bacteremia, wound infections, meningitis, and neonatal sepsis [34-36]. Moreover, the simultaneous emergence of VRE and HLAR is a persisting clinical problem in health care facilities. [37-39]

There are nine vancomycin resistance genes including *van* A, B, C, D, E, G, L, M, and *van* N in Enterococci. *Van* A is the most common type worldwide [41-45] mainly related to vancomycin resistant *Enterococcus faecium*, allowing a great rate of vancomycin and teicoplanin resistance [46] and *Van* B causes a high degree of vancomycin resistance, yet susceptible to other glycopeptides such as teicoplanin [47,48]. Nosocomial infections due to Enterococci have been introduced extensively all over the world. The Significant reason for long-term permanence of enterococci in the hospital is their inherent resistance to multiple antibiotics generally used and the resistance to novel generation of antibiotics via either gene mutation or transmission of plasmids and transposons. Moreover, enterococci can transfer the vancomycin resistance genes to another species as well as to other genus. Also, the transmission of vancomycin resistant gene from *Enterococcus* to *S.aureus* has been detected in the laboratory. The emergence of vancomycin- intermediate (VISA) and vancomycin-resistant *Staphylococcus aureus* (VRSA) can produce important problems to the

treatment of *S.aureus*. since vancomycin has been considered as a drug of choice for treatment of enterococcal and MRSA infections.*Enterococcus faecium* also causes nosocomial infections. Emergence of vancomycin resistant strains has been related to further charge on the patients, physicians and health setting. Appropriate application of antibiotics against vancomycin resistant *Enterococcus faecium* (VREF) would help designing methods for pathogens control. [49] Recently, there is no current therapy that consistently provides bactericidal activity for critical infections due to VRE. The efficacy of therapy remains problematic because VRE is frequently related to violent underlying diseases and can be a part of polymicrobial infection. [50, 51]

Staphylococcus aureus

Nearly 25 - 30% of skin or noses of healthy people are colonized by *Staphylococcus aureus*. Methicillin-resistant *S. aureus* (MRSA) is resistant to certain antibiotics, such as methicillin, dicloxacillin, oxacillin, cloxacillin, nafcillin, and closely related class of drugs, such as cephalosporins. The use of more powerful drugs than necessary for less serious infections may be some of the causes of the MRSA expansion.

MRSA isolates which are susceptible only to glycopeptides antibiotics, such as vancomycin, are becoming multidrug-resistant. [52] Now, low level resistance to vancomycin is emerging and increasing .[53]

The possible predisposing factors of MRSA emergence are: consumption of antibiotics without medical prescription, lack of awareness, receipt of antibiotics before coming to the hospital, long duration of hospitalization, etc. [54] Infected patients and health care providers' carriers play a significant role in spreading and transferring this badbug in hospitals. [55] Studies on MRSA surveillance in hospitals and communities represent the main challenges of the healthcare setting .[56] Unfortunately, penicillin resistant bacteria can spread in healthcare setting and in the community. Methicillin narrow spectrum semi-synthetic penicillin was introduced to overcome infections due to beta-lactamase-producing *S. aureus*. *Strains* isolate from the hospital are named as hospital acquired *S. aureus* (HASA). [57, 58]Clindamycin, a macrolide-lincosamide-streptogramin B (MLSB) antibiotic, is a good substitute to treat these infections. Unfortunately,a diversity of *erm* genes, with either constitutively (MLSBc phenotype) or inducibely (MLSBi phenotype) expression can cause resistance to macrolide (MLSB). Active efflux pump, produced by *msr*A gene (MS phenotype), is another resistance mechanism. The treatment of serious bacterial infections with clindamycin may result in failure, therefore detection of this resistance by D test (double disc diffusion test) is a neccesity. Laboratory susceptibility test for clindamycin cannot detect routinely inducible clindamycin resistance and erythromycin resistant - clindamycin sensitive strains. [59, 60]*Staphylococcus* aureus causes atopic dermatitis (AD) and induces skin inflammation by secreting superantigens following a chronic relapsing course and defects in innate and acquired immune response resulting in a heightened susceptibility to bacterial, viral and fungal infections .[61-67] The high rate of *S.aureus* colonization in the nasal cavity and skin lesions of AD patients has been reported, especially in ranges between 76–100%, compared to 2–25% in healthy people .[68-70]It might be so that a combination of host factors containing skin barrier disorders and impaired host immune responses in AD patients are the major factors in this respect.[71, 72]Oxacillin–resistant staphylococci are resistant to all beta-lactam antimicrobial drugs except newer cephalosporins with anti-MRSA activity. Thus, susceptibility or resistance to a broad spectrum of beta-lactam drugs may be decreased due to susceptibility tests such as penicillin, cefoxitin or oxacillin. Routine testing of other penicillins, cephems, beta-lactam/beta-lactamase inhibitor combination, or carbapenems is not recommended.A forecast of the existance of *mec*A-related oxacillin resistance in *S.aureus* and *S.lugdunensis*, examination of either cefoxitin disk diffusion or cefoxitin MIC tests can be used. The cefoxitin disk diffusion test is preferred for the purpose of detecting of *mec*A-mediated oxacillin resistance for coagulase – negative staphylococci except *S.lugdunensis*. Cefoxitin is a substitute for tracing of oxacillin resistance, reporting oxacillin as susceptible or

resistant based on cefoxitin results. If a penicillinase –stable penicillin is examined, oxacillin is the preferred agent, and results can be used to the other penicillinase -stable penicillins, dicloxacillin, flucloxacillin and cloxacillin. [73]

Klebsiella pneumonia

Klebsiella pneumonia belonged to the Enterobacteriaceae family that frequently causes lower respiratory tract infection and catheter-associated urinary tract infection.

Klebsiella pneumonia is progressively resistant to penicillin and ampicillin because of its beta-lactamases. In addition, the bacterium belongs to the extended-spectrum beta-lactamase or ESBL strains and is increasingly multidrug-resistant to a wide spectrum such as cephalosporin or ceftazidim. [74]

The emergence of *Klebsiella pneumonia* isolates producing carbapenemases (KPCs) has become a major obstacle in the last 5 years. Carbapenemases are able to destroy the carbapenems and cause resistance against a wide spectrum of antibiotics. [75-78] Recently, many areas in the world have been affected and KPC-producing strains have now been detected from many countries such as China, France, Norway, Brazil, Sweden, Scotland, Trinidad, Colombia, Poland and Tobago, Columbia, occupied Palestine, Greece and Puerto Rico. [79-89] KPC-1 beta - lactamase was created because of a great plasmid that was responsible for the resistance carbapenems, extended-spectrum cephalosporins and aztreonam. **[**90,91**]**The fast propagation of bacterial resistance is perhaps due to the *bla*- KPC gene carriage on plasmids. Plasmid-mediated imipenem-hydrolyzing enzyme (KPC-2) among multiple carbapenem resistant bacteria is increasing. [92]

Currently, a predominant isolate and sequence type 258(ST258) is identified to cause about 70% of *K. pneumoniae* infections .[93]It is forecasted that resistance due to KPC will be a mechanism of multidrug-resistance in Gram-negative bacilli in the nearby future. [94,95]The increasing interest on combination therapy for *K. pneumoniae* infections is due to its ability to obtain resistance to distinct classes of antibiotics, containing carbapenems, with limited accessibility of impressive agents. The increasing rate and high mortality of infections have prompted physicians to consumption combination therapy even more often for the handling of infections because of such bacteria. [96]

Acinetobacter baumannii

Acinetobacter baumannii is an opportunistic bacterial pathogen with the power of causing hospital acquired infections, individually in intensive care units, urinary tract infection, bacteremia, meningitis, pneumonia, wound infections, healthcare-related infections (HAIs) with myltiple outbreaks. [97-102]

From January 2002 to August 2004, bloodstream infections due to *A. baumannii* were detected among 85 soldiers in Afghanistan and the Iraq/Kuwait area. A total of 35 % of the strains were susceptible to just one class of antibiotics and 4 % were resistance to all standard drugs.[103] The epidemic potential and the clinical severity of *A. baumannii* infections are primarily related to the capability to survive and propagation in healthcare setting and to expand resistance to a diversity of antimicrobial agents, containing fluoroquinolones, broad-spectrum beta-lactams, and carbapenems.[107-109]

Antimicrobial resistance causes major limits to treatment options in infected patients, particularly in isolates with carbapenems resistant. Other therapeutic options contain aminoglycosides, sulbactam, tigecycline, and polymixyns. [110,111] Spread of *A. baumannii* in a hospital setting is facilitated both by tolerance to desiccation and development of bacterial resistance through antibiotic selective pressure. [112] Antimicrobial resistance causes major limits to the choice of antibiotics in patients infected by carbapenems resistant isolates.[113]MDR *A.baumannii* is resistant to 3 or more several classes of antibiotics containing beta-lactams, aminoglycosides, fluoroquinolones, and 3rd generation of cephalosporin .[114] Pan-drug resistance (PDR) *A.baumannii* was described as the strains that were resistant to all examined antibiotics exclude colistin and tigecycline .[115]

Pseudomonas aeruginosa

One of gram negative bacteria that has intrinsic resistance characteristic is *Pseudomonas aeruginosa.* Low antibiotic susceptibility in this bacteria is due

to low penetrance of the bacterial cellular envelopes, function of multidrug efflux pumps, mutations in targets of antibiotics and the horizontal gene transfer of antibiotic resistance determinants. [116-120]

The outcomes of infection caused by MDR *Pseudomonas* may be related to enlarge morbidity and mortality, which can cause narrow effective antimicrobial choices as resistance to at least three classes of antibiotics, mainly carbapenems, antipseudomonal penicillins, cephalosporins, aminoglycosides, and fluoroquinolones. [120-122]

One of the most common lethal genetic diseases due to *Pseudomonas aeruginosa* in the white population is cystic fibrosis (CF), with the prevalence of 1 case per 90,000 in Asia .[123-125]

If this disorder is almost treated, the average prospects of life expectanye of CF patients would increase more than 35 to even 50 years. [126] *P. aeruginosa* that infects CF patients has serious implications for infection control in the hospital **.[**127**]**

Wide range of antimicrobial resistances in MDR *P. aeruginosa* mainly cause the dose limits for remediation such as polymixyns and aminoglycosides. Recent studies have reported that these agents may or may not be as efficient as first-line drugs; and yet, they may also be related to more serious detrimental effects (such as neurotoxicity, ototoxicity and nephrotoxicity). [128-137]

P. aeruginosa is the most studied pathogen about the priority of combination diet over monotherapy. [138-140] Other prospective studies and meta-analysis have been unsuccessful to demonstrate the priority of the combination therapy versus monotherapy for the treatment of *P. aeruginosa* infections. [141–143]

Serious infections such as burn wounds due to by *Pseudomonas aeruginosa* are treated through the combination of a beta-lactam drugs and an aminoglycoside. The emergance of MDR in *Pseudomonas aeruginosa* containing resistance to β-lactams, aminoglycosides, and fluoroquinolones is extremely problematic to the treatment of burn patient. So, the recognition of drug resistance patterns in *P. aeruginosa* and tracing of pan-resistant producing bacteria are of major importance in prevention and control of infections in burn center ward. [144]

Enterobacter spp.

Enterobacter spp. is significantly responsible for some important nosocomial infections, representing wide MDR through plasmid-encoded ESBLs and KPC carbapenemases,metallo-β-lactamase, even OXA and metallo-β-lactamase-1. Although few antimicrobials such as colistin and tigecycline are influenced by these resistant bacteria and also against many of the other ESKAPE pathogens, there is little or no drugs in the 'pipeline', being remarkably effective in addressing this mounting health crisis.[6,145-146] In veterinary medicine, fluoroquinolone resistance is becoming more common. This Resistance is caused by both chromosomal and plasmid-mediated fluoroquinolone resistance (PMQR) mechanisms which are co-located with other antimicrobial resistance genes including β-lactamases. The genes' relationship with PMQR can cause resistance to fluoroquinolone when joined with topoisomerase mutations and efflux**.** [147]

In some situations, examination of subsequent strains to find resistance that may have expanded might be warranted before three to four days. The decisions to do so require knowledge of particular condition and the intensity of patient condition such as *Enterobacter cloacae* isolated from a blood culture of premature infants. CLSI protocol to carry out susceptibility experiment on repeat isolates should be defined after negotiation with medical personnel. Some strains of *Citrobacter*, *Providencia* and *Enterobacter* spp. have been presented to give false-susceptible outcomes when tested by disk diffusion with cefdinir and loracaebef strains of these genera should not be examined by disk diffusion with agents. [71]

DISCUSSION

Health crisis of ESKAPE pathogens seems overwhelming. There are comprehensive guidelines for antibiotic resistance control and for a coordinated holistic medicine to uniform industrial and governmental organizations.[4,148-151]In the short run, with treatment options diminishing, it is necessary that the last remaining

antimicrobial agents be protected via intellectual choice and ameliorated infection control. The call for antibiotic superintendence has been mentioned for several years by health authorities to temper the expansion of resistance mechanisms versus the recent persisted antimicrobial agents. [152-154]

Selection of suitable guidelines is readily accessible and accurate prescribing protocols have been successfully implemented worldwide. [155]Prescription of the most suitable antimicrobial agents at the right dose and period, and for an appropriate time has consistently improved sick people outcomes and has decreased antibiotic resistance appearance. [156-157]The campaign of "Clean your hands" in the UK displayed how public intermediation for control of infection one behind another follow with a high profile governmental force can decrease selected HAIs (healthcare-related infections). [158]

In the same case, common notification campaigns, such as the European Antibiotics Awareness Day (EAAD) can support and emphasize the foundation sequences of consecutive antibiotic abusage in both medical profession and in agronomy by the suitable political and financial patronage as the crisis expands and common knowledge enhances. [159]

Louis Pasteur's and Robert Koch's pioneering methodologies appointed the arena of classical microbiology and organized the basis of antimicrobial susceptibility examination over 150 years ago till now. [71,160] However, some microbiologists suggest more complex biofilm manner in distinction for the more lightly reproducible planktonic manner which has mislead research generations .[161,162] Bacterial biofilms provide a distinguished survival benefit versus antimicrobial agents in comparison with their planktonic counterparts, by a 1000-times augmentation in some agents concentration Biofilm development is the underlying basis for persistent HAIs related to installing medical devices in the greater numbers, made possible by ESKAPE pathogens.[163-167]Based on standard guidelines to make proper and practical antibiotic susceptibility testing, the number of agents examined should be confined. CLSI have lists of those agents that perform the fundamental prescriptions for routine utilization in most clinical laboratories. The tables have columns based on particular organisms or organism groups; several antibiotics are recommended in preference for experiment to help laboratories in their conventional testing batteries selection. This means that major errors are less than 3% and minor errors are fewer than 10%, based on an examination of great collection of accidental clinical strains. Moreover, to determine for an "or word in report of antibiotic susceptibility testing, at least 100 strains with resistance to the agents in question must be examined, and a result of "resistant" must be gained with all agents for at least 95% of the strains.[149]

To sum up, it can be said that healthcare-associated, community-acquired, and nosocomial infections should be carefully considered . In this review, the alarming frequency and increasing tendency of extremely resistant ESKAPE pathogens in the worldwide is highlighted. The awareness of residential antimicrobial resistance can support the selection of a convenient empirical therapeutic diet in which diseases occur due to ESKAPE pathogens. [168]

It should be mentioned that the clinical response of a patient after receiving antibiotic does not always correlate with the laboratory reports. Even so, it should be noted that description of pathogens antimicrobial resistance patterns needs a consecutive update. [128] We must increase hospital infection-control practices for the purpose of restricting the spread of resistance. This procedure will ensure a steady stream of newantibacterials to meet the needs of current patients .

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