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A Literature Review of Infection with ESKAPE Pathogens in Oral and Maxillofacial Region

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Odontogenic infection in the oral and maxillofacial regions caused by bacteria (mostly of oral origin) is one of the most common diseases encountered by dentists. Localized infection can easily be treated with incision and drainage followed by antibiotics. Emergence of multidrug resistant (MDR) bacteria called "Superbacteria" has become one of the serious problems in modern society, due to its small window of opportunity for treatment and high casualty. The acronym "ESKAPE", encompassing the common and serious MDR pathogens stand for *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. Literature search was performed in Medline, PubMed and Google Scholar ranging from 2012 to 2020. ESKAPE patient's infection period was longer than that of non-ESKAPE group, and the treatment method due to antibiotic resistance was also complicated. The purpose of this study is to investigate infection caused by ESKAPE pathogens in the oral and maxillofacial regions through literature review and to inform dental surgeons of the danger of ESKAPE pathogens and to suggest viable treatment options. Many studies worldwide reported infections associated with ESKAPE pathogens, but only limited number of studies targeted infection in oral and maxillofacial regions. Further research is required with more data on ESKAPE bacteria and their infection, especially in oral and maxillofacial regions.

Key Words: Abscess; ESKAPE; Infections; Methicillin-resistant *Staphylococcus aureus*; Osteomyelitis

INTRODUCTION

Odontogenic infection in the oral and maxillofacial regions caused by bacteria (mostly of oral origin) is one of the most common diseases encountered by dentists [1]. Localized infection can easily be treated with incision and drainage (I&D) followed by antibiotics. However, it can spread rapidly to other spaces and cause severe problems such as sepsis, airway obstruction, necrotizing fasciitis and mediastinitis [2-4]. Odontogenic infection is polymicrobial in nature, comprising of various facultative anaerobes, such as the *viridans* group, *streptococcus* species, and strict anaerobes, especially anaerobic *cocci*, *prevotella* and *fusobacterium* species [5,6]. Emergence of multidrug resistant (MDR) bacteria called "Superbacteria" has become one of the serious problems in modern society, due to its small window of opportunity for treatment and high mortality. The acronym "ESKAPE", encompassing the common MDR pathogens stands for *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. [7] and they are responsible for causing nosocomial and opportunistic infections in hospitals. ESKAPE species has characteristic of healthcare-acquired infection that can pose a great threat to human health and become increasingly more resistant to commonly used antibiotics [8]. These resistant

bacteria are mainly responsible for pneumonia, bloodstream infection, sepsis, surgical site infection (SSI), and urinary tract infection [9]. Likewise, there are many medical reviews of ESKAPE pathogens, but few in oral and maxillofacial regions. The purpose of this study is to investigate infection caused by ESKAPE pathogens in the oral and maxillofacial regions through literature review and to inform dental surgeons of the danger of ESKAPE pathogens and to suggest viable treatment options.

MATERIALS AND METHODS

Literature search was performed in Medline, PubMed and Google Scholar ranging from 2012 to 2020, using keywords, including "ESKAPE pathogens", "*K. pneumoniae*", "*A. baumannii*" "*P. aeruginosa*", "*S. aureus*", "*E. faecium*", "*Enterobacter* species", and "Infection in orofacial or oral and maxillofacial". The criteria included types of study, clinical diagnosis, bacteria species (especially, ESKAPE pathogens), treatment approach, respect of infections, characteristics of patients and other clinical parameters. In addition, references of all retrieved articles were checked for further relevant literature with this topic.

RESULT

This study found 16 articles from 2012 to 2020 in Medline, PubMed and Google Scholar and performed comparative analysis. As shown in Tables 1 and 2, articles discussed various bacterial infection on different sites. This study specifically focused on ESKAPE bacteria. Of the 16 articles reviewed in this paper, 11 articles studied medical and systemic infection, and only 5 articles studied oral and maxillofacial infection, mostly of dental origin (Tables 1, 2). Empirical antibiotics were first administered, and culture was performed to identify bacteria type and antibiotic sensitivity. With the result of culture test, carbapenem was most commonly used, and vancomycin was mainly used in *E. faecium* and *S. aureus* infection. In addition, it was confirmed that postoperative infection occurred in 31% of the papers and 68% showed that the infected patients stayed in the hospital for a long time, which continued to increase the risk of infection. Analysis showed that ESKAPE infection route was mainly nosocomial infection rather than community infection. The healing period of patient with ESKAPE was longer than that of non-ESKAPE group, and the treatment method was also complicated because of its antibiotic resistance.

DISCUSSION

The problem of infection has continued to exist even after the introduction of antibiotics and the emergence of antibiotic resistant bacteria (ARB) has become a worldwide issue that threatens individual healthcare, economic and social welfare [10-12]. Despite increased efforts in recent years, the problem of ARB continues to grow [9,13]. Especially, ESKAPE pathogens are mostly resistant to antibiotics and the risk of infection is growing due to mechanisms including inactivation or alteration of antimicrobial molecule, modification of the site of action, inhibition of cell membrane function, and reduction of antibiotic penetration/accumulation [11,14,15]. Extensive resistance to antibiotic requires discreet infection prevention, development of new antibiotics and treatment methods. Most previous studies reported on systemic infections in medical field caused by ESKAPE pathogens and different antibiotics that effectively treat ARB.

Only a few researches have been performed on ESKAPE infection and treatment of oral and maxillofacial region. Among the various bacteria, *S. aureus* was mainly observed among ESKAPE pathogens. *S. aureus* consists normal human flora, including nose, oral cavity and perineum and may lead to opportunistic infection in both hospital and community [16]. With regards to oral infections, a review on orofacial bacterial infections diseases reported that, *S. aureus* was also associated with a bullous type of facial infections around the nose and the mouth of patients with dry mouth and denture [17,18]. In the nares, *S. aureus* interacts with nasal mucosa's epithelial cell ligands and colonizes the area [19]. Hands serve as the main transporter from the nose to other locations in the body [20]. Oral cavity has been identified as a significant reservoir of *S. aureus* in an acute hospital by healthcare worker, extensive patient [21]. *S. aureus* is an opportunistic pathogen that is not a problem in normal situation. Traditionally, infections have

Table 1. Description of eligible paper included in this review

Study (y)	Type of study	Clinical diagnosis	Bacteria species (ESKAPE)	Treatment approach	Respect of infection	Patients character	Reference
1. Li et al. (2016)	Retrospective cohort study	SSI	*Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter baumannii*	Vancomycin, piperacillin, tazobactam, carbapenem	HAI	Open reduction and internal fixation of mandibular fracture	[26]
2. Xiao et al. (2019)	Case report	Meningitis	*A. baumannii*	Aminoglycosides, cephalosporin, carbapenem, glyconpetides	HAI	History of neurosurgery	[45]
3. Park et al. (2017)	Retrospective cohort study	Urinary tract infections	*Escherichia coli, Enterobacter* species, *Klebsiella* species, *S. aureus*	Carbapenem, fluoroquinolones, cephalosporin (3rd generation)	BSI		[34]
4. Gudiol et al. (2013)	Prospective observational study	SSI	*Enterococcus faecalis, Enterococcus faecium*	Carbapenem, glycopeptides (vancomycin, teicoplanin)	BSI-endogenous source & followed by catheter infection	Hospitalized and immunosuppressed patients with cancer	[42]
5. Batabyal et al. (2012)	Prospective study	SSI	MRSA	Linezolid (oxazolidinones), carbapenem, rifampicin	Post-operative surgical infection	Patient after surgery	[31]
6. Barlean et al. (2019)	Retrospective study	SSI	*K. Pneumoniae, S. aureus, A. baumannii, P. aeruginosa*	Linezolid (oxazolidinones), glycopeptide (vancomycin, teicoplanin), colistin	HAI	Patient with tumor pathology surgery	[35]
7. Oh et al. (2019)	Retrospective cohort study	Septic infection	*A. baumannii, Pseudomonas* spp., *Klebsiella* spp., *Enterobacter* spp.	Carbapenem and colistin	HAI	Patients who underwent lung transplantation due to underlying lung disease	[36]
8. Candevir Ulu et al. (2015)	Retrospective cohort study	Catheter-associated BSI, urinary infections and soft-tissue infections	*K. pneumoniae*	Cephalosporin (3rd generation), carbapenem	Intensive care unit	Patient with nasogastric catheter and being admitted to the neurosurgical intensive care unit	[43]
9. Bilal et al. (2014)	Retrospective cohort study	Septic infection	MRSA	Linezolid (oxazolidinones), glyconpeptides (vancomycin, teicoplanin)	HAI	Patients after plastic surgery	[37]

Table 1. Continued

Study (y)	Type of study	Clinical diagnosis	Bacteria species (ESKAPE)	Treatment approach	Respect of infection	Patients character	Reference
10. Kang and Kim (2019)	Retrospective cohort study	Infections in the oral and maxillofacial regions	*K. pneumoniae, P. aeruginosa, A. baumannii, S. aureus*	Metronidazole or amoxicillin+clavulanate, cephalosporins, clindamycin, quinolone	OI		[3]
11. Amin et al. (2021)	Retrospective cohort study	Lip infections	MRSA	Vancomycin, cephalosporin (3rd generation), metronidazole	CAI	Immunocompromised patient	[38]
12. Valderrama-Beltrán et al. (2019)	Retrospective cohort study	Skin and soft tissue infections	MRSA	Penicillin, cephalosporins, vancomycin	CAI & HAI	Most of patients with purulent cellulitis and previous antimicrobial outpatient treatment	[39]
13. Brito et al. (2017)	Retrospective cohort study	Deep cervical abscesses	*S. aureus, E. faecium, K. pneumoniae*	Amoxicillin+clavulanate, cephalosporins, carbapenem	OI & bacterial tonsillitis	Most of patients with various medical history	[40]
14. Hwang et al. (2015)	Retrospective cohort study	Chronic suppurative otitis media	MRSA	Aminoglycosides (arbekacin), glycopetides (vancomycin), cephalosporins	Not reported	Patients with otitis media older than 18 ages	[27]
15. Serra et al. (2015)	Review	Chronic leg ulcers	*S. aureus, P. aeruginosa*	Piperacillin-tazoactam, glycopeptides (vancomycin, teicoplanin), linezolid, carbapenem, fluoroquinolones	CAI & HAI	Patients with diabetic foot ulcers, pressure ulcers and chronic venous ulcers	[22]
16. Shah et al. (2016)	Retrospective cohort study	Infections in the oral and maxillofacial regions	*S. aureus, K. pneumoniae, P. aeruginosa*	Amoxicillin+clavulanate, imipenem, carbenicillin, moxifloxacin, amikacin, ceftriaxone	OI	Orofacial space infections of odontogenic origin	[41]

ESKAPE, *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp.; SSI, surgical site infections; HAI, hospital-acquired infection; BSI, Bloodstream infection; MRSA, methicillin-resistant-staphylococcus-aureus; OI, Odontogenic infection; CAI, community-associated infections.

Table 2. Characteristics, infections type, infections site and treatment approach against some of the ESKAPE pathogens

ESKAPE bacteria	Study (reference)	Infection site	Infection type	Characteristic	Treatment approach
Enterococcus faecium	[40,42]	SSI, DCA	BSI, OI	Gram-positive facultative anaerobes bacterium	Carbapenem, glycopeptides (vancomycin, teicoplanin)
Staphylococcus aureus	[3,22,26,27,31,34,35,37-41]	Septic wounds involving various regions of the body, meningitis, SSI, septic infection, infections in the oral and maxillofacial regions	HAI, BSI, ICU	Gram-positive facultative anaerobes bacterium: clinical relevance: methicillin-resistant *Staphylococcus aureus*	Linezolid (oxazolidinones), glycopeptides (vancomycin, teicoplanin)
Klebsiella pneumoniae	[3,26,34-36,40,41]	SSI, infections in the oral and maxillofacial regions, DCA	OI, ICU, CAI, HAI, BSI, OI	Gram-negative facultative anaerobes bacterium	Carbapenem, cephalosporin in combination with colistin
Acinetobacter baumannii	[3,26,35,36,45]	Meningitis, SSI, septic infection, infections in the oral and maxillofacial regions	HAI, OI	Gram-negative bacterium	Carbapenem →sulbactam or in combination with colistin Glycopetides
Pseudomonas aeruginosa	[3,22,26,35,36,41]	SSI, infections in the oral and maxillofacial regions, chronic leg ulcers	HAI, OI, CAI	Gram-negative bacterium	Carbapenem or fluoroquinolones Glycopeptides (vancomycin, teicoplanin) in combination with tigecycline/colistin
Enterobacter species	[34,36]	Urinary tract infections, septic infection	HAI, BSI	Gram-negative aerobes bacterium	Carbapenem

ESKAPE, *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp.; SSI, surgical site infections; DCA, deep cervical abscesses; BSI, bloodstream infection; OI, odontogenic infecton; HAI, hospital-acquired infection; ICU, intensive care units; CAI, community-associated infections.

responded well to penicillin treatment [11,22].

However, methicillin resistance should also be taken into consideration in clinical situation. Most common methicillin-resistant *S. aureus* (MRSA) infections in oral and maxillofacial area were postoperative to primary resections with reconstructions using free flap [23]. A few cases of osteomyelitis of jaws [24,25] and SSI by mandible fracture [26] were also reported to be related to *S. aureus* infection.

These MRSA strains are resistant to many antibiotics such as β-lactam antibiotic, aminoglycosides, macrolides, and choloramphenicol [27]. In most cases, glycopeptide antibiotics, such as vancomycin and teicoplanin, are used as first-line of antibiotics for of MRSA infections [11,28,29]. Emergence of vancomycin-resistant *S. aureus* has also been reported [22,30]. In order to treat MRSA with low sensitivity to vancomycin, costly medication such as linezolid, daptomycin, etc. can be prescribed [31].

K. pneumoniae is a gram-negative facultative anaerobes bacteria and is known to asymptomatically colonize the skin, mouth, respiratory and gastric intestinal tract [32,33]. Multiple studies reported that *S. aureus* and *K. pneumoniae* may cause bacteremia, septicemia, soft tissue infections, endocarditis, bone infections, pneumonia, blood stream infection (BSI), and SSI [3,22,26,27,31,34-43]. The ability of *K. pneumoniae* to produce extended spectrum beta-lactamase makes it resistant to all beta-lactam antibiotics except carbapenem, thereby making carbapenem preferable treatment option [44].

Like other bacteria, infection of *A. baumannii* is problematic, because of limited therapeutic options due to increasing resistance to antibiotics groups and the capacity to persist in the hospital environment, resulting in outbreaks [45,46]. The most common clinical manifestations of *A. baumannii* are ventilator-associated pneumonia and bloodstream infection. *A. baumannii* can also colonize the skin, wounds, respiratory tract and gastrointestinal tract [47,48].

Carbapenems are conventionally used to treat persistent infections caused by gram-negative bacteria and were first administered to other ESKAPE bacteria except for MRSA, and it can be used in conjunction with colistin to treat *A. baumannii* and *P. aeruginosa* [11,49]. In patient with *P. aeruginosa* infection, infection of imipenem, ceftazidime, ciprofloxacin or piperacillin resistant bacteria is associated with significantly prolonged hospitalization and increased chance of secondary bacteremia [50].

Various antibiotics are being administered depending on the bacteria, and antibiotic resistance is developed accordingly. Inadequate use of antibiotics increases the risk of drug resistance, leading to impairment of a patient's condition. For effective treatment of ARB, early diagnosis is essential [51].

Early detection of causative agents and selection of corresponding antibiotic is stressed [12,52]. Empirical prescription of antibiotics and antibiotic-susceptibility test (culture test) should be performed [53]. Based on the results of culture testing, non-resistant and sensitive antibiotics must be selected and treated. Evaluating the patient's clinical condition is also important. If other bacteria are found in culture test, it is necessary to see if they respond to the currently prescribed antibiotics. In other words, the most appropriate antibiotics should be selected in cooperation with the Infectious Disease Department. Many papers suggest that immunosuppressed patients are more susceptible to infection [32,33]. An article studied patients with human immunodeficiency virus [38] and another article studied with diabetes mellitus [22,40]. In diabetic patients, certain infections were more predominant, and some outbreak appeared almost exclusively. Diabetes was also associated with increasing severity of the infections and increased chance of complication. Diabetic patients had compromised immune system in several aspects [54]. Accordingly, systemic conditions can influence the progress of infection, and patient's comprehensive health condition is crucial in the course of treatment.

However, according to other studies, the frequency of infection by ESKAPE pathogens is not significantly different from that of the non-ESKAPE group in terms of gender, the presence of systemic disease, and the frequency of occurrence by infection site [55,56]. However, it was found that the treatment period was longer in patients with systemic diseases of ESKAPE-group than in patient of non-ESKAPE group.

This study confirmed high rate of SSI and BSI by ESKAPE pathogens. Fifty percentage of the studies reported healthcare-associated infection that can be also affected adversely to patients who admitted to the intensive care units.

Most nosocomial infections can be derived from exogenous sources and transferred by either direct or indirect contact between patient, healthcare workers and contaminated objects [13]. As a result, clinicians should be mindful to prevent infection. Especially, dentists should take proper precautions to prevent cross contamination of bacteria in the dental clinic and hospitals, where infection is easily spread by aerosols. Infection by ESKAPE pathogens is associated with a longer treatment period, higher cost of care and a higher mortality rate compared to that of non-ESKAPE pathogens [57,58]. A systematic approach to surveillance, infection prevention, antimicrobial stewardship and clinical guidelines ensures best practice for infection control and reduces the spread of antimicrobial resistance [59]. Directing attention to the ESKAPE pathogens can better address the broader challenges of MDR.

We expect some difficulties in our study and acknowledge some limitations. First, literature reviewed in this paper did not have consensus over the definition of the outcomes. Following a single published guidance on assessment of outcomes of different infection sites should provide more statistically meaningful conclusions. Second, there was a limitation to the fundamental analysis due to lack of the number of papers on infection focused with ESKAPE pathogens in the oral and maxillofacial regions, and the gold standard treatment option cannot be proffered. Third, due to the variety of infection areas and variety of antibiotics empirically prescribed for treatment, the effect of antibiotic resistance could not be properly analyzed. Fourth, not all identified pathogens were tested against the administered antibiotics and it is difficult to analyze and compare various antibiotic resistance rates by bacteria. In the future, comparing different strains applied with the same antibiotics will yield a more meaningful conclusion. In addition, there were limitations in classifying risk factors.

CONCLUSION

Many studies worldwide reported infections associated with ESKAPE pathogens, but only limited number of studies targeted infection in oral and maxillofacial regions. Infection by ESKAPE bacteria can have fatal consequences if the cause of the infection is not properly identified and characterized in an early stage. Further research is required with more data on ESKAPE bacteria and their infection, especially in oral and maxillofacial regions.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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