KLEBSIELLA OXYTOCA: CLINICAL SIGNIFICANCE, VIRULENCE FACTORS AND DEVELOPED ANTIMICROBIAL RESISTANCE

Abdolmajid Ghasemian[1,2], Ashraf Mohabati Mobarez[1*], Reza Hosseini Doust[3]

[1]*Department of Bacteriology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran*

[2]*Department of Microbiology, Fasa University of Medical Sciences, Fasa, Iran*

[3]*Department of Microbiology, Faculty of Advanced Medical Sciences, Islamic Azad University, Tehran, Iran*

ABSTRACT

The opportunistic *Klebsiella oxytoca* (*K. oxytoca*) strains colonize as a normal flora of the intestine, urethra and the skin of approximately 10% of individuals. This bacterium can multiply following the decrease in the number of the microbial flora of the intestine. Those toxigenic strains are mostly associated with antibiotic associated hemorrhagic colitis (AAHC) and there is a significant relationship between their isolation and the use of penicillins, cephalosporins, carbapenems and fluoroquinolones. *K. oxytoca* toxins known as tillivaline and kleboxymycin cause the cell apoptosis. In the process of pathogenesis, adhesion molecules, such as Pilli and Fimbria (type 1 and type 3 fimbria), and capsule are the most important factors in bacterial attachment and producing the biofilms. On the other hand, development of extended-spectrum β-lactamase (ESBL) and carbapenemase-producing *K. oxytoca* (CP-*K. oxytoca*) strains isolated from healthcare and community settings is a concern. However, other mechanisms of drug resistance have not been widely reported among these strains. Prevention of outbreaks, early detection, surveillance and control and prevention of the spread of pathogenic and drug-resistant *K. oxytoca* strains are of high importance.

Keywords: *Klebsiella oxytoca*, virulence, drug resistance, cytotoxicity.

REZUMAT

Tulpinile oportuniste de *Klebsiella oxytoca* (*K. oxytoca*) colonizează intestinul, uretra și pielea a aproximativ 10% dintre indivizi. Această bacterie se poate înmulți ca urmare a modificărilor cantitative ale florei intestinale. Tulpinile toxigene sunt în mare parte asociate cu colita hemoragică cauzată de antibiotice (AAHC), existând o relație semnificativă între izolarea acestora și utilizarea penicilinelor, cefalosporinelor, carbapenemelor și fluoroquinolonelor. Toxinele tulpinilor de *K. oxytoca*, cunoscute sub numele de tilivalină și kleb oximicină, provoacă apoptoză celulară. În procesul de patogeneză, moleculele de adeziune, cum ar fi pili sau fimbriile (fimbriile de tip 1 și tip 3), și capsula bacteriană sunt factorii cei mai importanți în atașarea bacteriană și producerea biofilmelor. Pe de altă parte, constituie o preocupare dezvoltarea unor tulpini de *K. oxytoca* (CP-*K. oxytoca*) producătoare de beta-lactamaze cu spectru extins (ESBL) și carbapenemază, izolate din sistemul unităților sanitare și din comunitate. Cu toate acestea, alte mecanisme de rezistență la medicament nu au fost raportate pe scară largă printre aceste tulpini. Prevenirea focarelor, depistarea precoce, supravegherea și controlul și prevenirea răspândirii tulpinilor *K. oxytoca* patogene și rezistente la medicamente au o importanță deosebită.

Cuvinte-cheie: *Klebsiella oxytoca*, virulență, rezistență la medicamente, citotoxicitate.

The members of the *Klebsiella, Enterobacter, Serratia, Pantoea, Cronobacter* and *Hafnia* genera belong to the tribe *Klebsielleae*. *K. oxytoca* similar to several other species such as *K. pneumoniae* sub-species *pneumonia, K. ozaenae, K. rhinoscleromatis, K. ornithinolytica, K. planticola* and *K terrigena* are found in environments such as forests, soils and often in the digestive tract of humans and animals, among which *K. pneumoniae, K. ozaenae, K. rhinoscleromatis* and *K. oxytoca* are clinically important. The species of this genus are facultative aerobic or anaerobic bacilli. The Indo-Ornithine (MIO) agar, which is a semi-solid medium, is useful for differentiating the *Enterobacter* and *Klebsiella* species [1, 2]. *K. oxytoca* mostly cause AAHC by producing cytotoxins and following decrease in the microbial flora and consumption of antibiotics [3]. Development of drug resistance among *K. oxytoca* strains from

**Corresponding author:* Ashraf Mohabati Mobarez, E-mail address: mmobarez@modares.ac.ir, Address: Tarbiat Modares University, Al-e Ahmad Exp., Tehran, Iran. Tel: +98 (21) 8288 3862, Fax: +98 (21) 8288 4555

various clinical sites and community origins is a concern and necessitates implementation of proper surveillance and infection control strategies [4-6].

Natural habitat

K. oxytoca is an opportunistic bacterium in the normal flora of the intestine, urethra and skin of approximately 2-10% of people and thus have the potential of causing infection. Some toxigenic strains are associated with hemorrhagic colitis [7-9]. The number of *K. oxytoca* increases by the imbalance in the intestinal microbial flora and a significant relationship has been revealed between its isolation and the use of penicillins, cephalosporins, carbapenems and fluoroquinolones [10].

***K. oxytoca* colonization factors**

Similar to other *Klebsiella* species, *K. oxytoca* contains several virulence factors, including surface adhesion structures leading to their attachment and colonization, toxins, and invasions. *K. oxytoca* is known to be the leading cause of 2% of hospital-acquired infections in the United States.

K. oxytoca is also associated with AAHC, septicemia, neonatal septicemia, nosocomial infections in ICU patients, ventilator-associated pneumonia (VAP), catheter-related urinary tract infections (UTIs) and spontaneous arthritis [11]. A high rate of these infectious processes occur due to prolonged admission of patients in the hospitals or implementation of offensive operations on patients [12]. Today, the range of infections associated with *Klebsiella* genus is changing, mainly due to the emergence of certain strains or specific clones of bacteria that have the potential for higher invasion or wider resistance to first line antibiotics such as carbapenems.

K. oxytoca is able to attach via several surface structures. The type 1 fimbria, although different from that of some of *Enterobacteriaceae* family, has similarities in terms of function. It is composed of repetitive structural subunits including FimA, and the binding the FimH tip molecule. In *Klebsiella spp*, this apparatus is encoded by an operon called "*fimABCDEFGHIK*". The FimA is a major subunit and FimG and FimF function as small subunits. Moreover, both FimB and FimE regulate fimbria expression.

Type 3 fimbria is a protein binding structure with a surface length of 0.5 up to 2 micrometers and a diameter of 2-4 nm and is able to pull and open or retract. The adhesive tip is located on the outside part and the pilus subunits are bound to each other in a three-dimensional spiral manner and form the main body of the Pilli. Some laboratory studies have shown that this pilus binds to several epithelial cells and extracellular matrix proteins in cell culture. However, its proprietary receptor has not been identified. In addition, the biofilm formation is highly related to the Type 3 fimbria, which facilitates the bacterial attachment and escape from host defense mechanisms, or possibly leading to increase in resistance to antibiotics. In *K. pneumoniae*, this fimbria has been found in conjugated plasmids and transposons in addition to the chromosomal DNA. The *mrk* gene cluster, which includes *mrkA*, *mrkB*, *mrkC*, *mrkD* and *mrkF* genes, is one of fimbria which utilizes the chaperon-Usher pathway for subunits assembly. This cluster is carried by the both chromosomal and plasmid DNA. The further analysis of this region showed that *mkK* and *mrkJ* genes function as signal sensors of the cGMP molecule. This signal changes the state of the bacteria from planktonic to biofilm mode [13]. It has been shown that *mrkB* gene plays a role in agglutination and biofilm formation in *E. coli*, *K. pneumoniae*, *K. oxytoca* and *Citrobacter koseri* urinary isolates.

The similarity between these genes in the chromosomal and plasmid types is between 69% and 96%, and the differences were most commonly observed in the MrkD protein, which is the adhesive subunit. The chromosomal type is found in most strains in the *Klebsiella* species, but the plasmid type is present only in a small percentage of strains [14-16].

The capsular antigenic compound of *K. oxytoca* is an important adhesive and antiphagocytic agent which leads to appearance of mucous colonies. This agent alongside other adhesive structures contributes to colonization of *K. oxytoca* on different areas of the human body such as the gastrointestinal (GI) tract, sterile wounds, skin and urine. The *matB* gene

which contributes to the capsular biosynthesis was amplified in all of MDR strains causing antibiotic associated diarrhea in our recent study [4].

***K. oxytoca* cytotoxins**

K. oxytoca is the only species among *Klebsiella spp* which produces and secretes a low molecular pentacyclic peptide toxin called tillivaline, which is associated with the development of hemorrhagic colitis symptoms. The tillivaline is a member of the family of Pyrrolobenzodiazepines (PBD) (13). This toxin is heat sensitive but resistant to enzymatic digestion by proteinases. Other members of this toxin family are selective DNA polymerizing agents, along with intense cytotoxic activity. The toxin production is associated with the *K. oxytoca* virulence and causes the apoptosis of the intestinal epithelial cells and destroys the epithelial cells. The cytotoxin has exhibited effects on laboratory animals including rats, guinea pigs, pigs and non-human primates. According to previous reports, the prevalence of toxin production is between 23% and 82% among *K. oxytoca* strains, however the patients population is a determining factor in this regard [17, 18]. It was demonstrated that isolates from urine and sputum samples had not cytotoxic effect on the Hep-2 cells and overall, 9/75 of *K. oxytoca* from various clinical specimens exerted the cytotoxic effects [9, 19]. Therefore, more attention is necessary among isolates other than stool specimens in terms of toxin production. A previous consumption of several antibiotics has been associated with the toxin production including amoxicillin, ampicillin, clavulanic acid, metronidazole, ceftriaxone and cephalothin [17, 20]. Recently, there was a hypothesis regarding the production of other uncharacterized cytotoxins which subsequently introduced as kleboxymycin, tricyclic PBDs indicating 9 fold higher cytotoxicity (TC_{ID50}) power than tillivaline [3].

Clinical significance of *K. oxytoca* infections

In 1970, the first observations of the isolation of *K. oxytoca* from patients with hemorrhagic colitis, which were negative for *Clostridium difficile* infection, were published, and in 2006, with experiments on Sprague Dawley rats, it was revealed that *K. oxytoca* has caused hemorrhagic colitis. This type of infection is associated with the use of antibiotics, especially penicillin derivatives such as amoxicillin and cephalosporins, and also other classes such as quinolones and clarithromycin and even non-steroidal anti-inflammatory drugs (NSAIDs) which have been associated with AAHC [21, 22].

This syndrome occurs with sudden onset of bloody diarrhea associated with severe abdominal pain mostly among people with a short period of antibiotic therapy.

Other common features of this syndrome include an increase in the number of leukocytes and the level of C-reactive protein. Risk factors for this type of colitis include the recent administration of antibiotics, the use of NSAIDs, and the presence of toxigenic *K. oxytoca* strains in the stool. In addition, colonoscopy of an infected area, in cases of hemorrhagic colitis caused by *K. oxytoca*, is helpful in the early diagnosis. This type of colitis is observed with segmented inflammation in colon and sigmoid.

Recent studies in different populations have revealed that the prevalence of *K. oxytoca* varies from 2.9% to 8.9%, and the presence of toxin-producing strains in the same groups is between 0.6 to 5% [10, 23].

Hemorrhagic colitis mostly known as AAHC by *K. oxytoca* and several other bacterial agents is followed by severe damage and loss of epithelial cells in the large intestine, including retinal (colon) and rectum (rectum). In this disease, abdominal cramps, dysentery, radiological signs and colonoscopy of mucous membranes, damage and hemorrhage occur. The underlying cause of the disease is not clear, but bacteria and viruses seem to be causing it. Also, stress and living in urban environments exacerbate the disease. This disease is also known as hemorrhagic rectocolitis or inflammation of the large intestine. A special symptom is bloody diarrhea being gradually extended. Usually there is no fever, and the mucus is small in the colitis sample [20, 22]. Although stress is considered as an important factor in the development of hemorrhagic colitis, symptoms such as the immune system and hereditary factors contribute to the

disease. However, AAHC due to *K. oxytoca* is mostly self-limited and care should be taken in children because of intrinsic penicillin-resistant *K. oxytoca* colonization.

Developed antibiotic resistance

The emergence and dissemination of drug-resistant *K. oxytoca* strains is a concern for the danger of growth of toxigenic strains in the body. The ESBL and carbapenemase-producing *K. oxytoca* which have spread in most of countries are of great concern [24]. The plasmid-encoded bla_{CTX-M}, bla_{TEM}, bla_{SHV} and DNA chromosomal bla_{OXY} (OXY1-4) type ESBLs have been increasingly transmitted among strains [25-29]. Antibiotic resistance agents such as ESBLs and carbapenemases in the clinical isolates of *K. oxytoca* have been associated with difficulties and failure in the chemotherapy. Furthermore, carbapenemase-encoding genes such as mostly important classes of bla_{KPC}, bla_{IMP}, bla_{VIM}, bla_{OXA-48} and bla_{NDM1} and likewise porin deficiency [30-39] or with co-expression of several carbapenemase genes [40, 41] have been reported among these strains. Resistance to other classes of antibiotics such as fluoroquinolones and aminoglycosides which has been less reported should be considered and these drugs must be prescribed with more precaution. The reports of MDR-*K. oxytoca* strains from community settings also highlight the possibility of spread of these strains from healthcare to community settings which is a concern [42-45]. Furthermore, the emergence of colistin resistance among Gram-negative species occurs due to the chromosomal DNA mutations and plasmid-mediated transfer of *mcr-1*, *mcr2* and *mcr3* genes [46, 47].

CONCLUSION

K. oxytoca strains have the potential of causing life-threatening infections mostly among vulnerable patients. The consumption of β-lactams, fluoroquinolones, metronidazole and NSAIDs should be considered when prescribing for treatment of gastrointestinal infections. The emergence and spread of drug-resistant and pathogenic *K. oxytoca* is a concern and there is a need of implementing infection control strategies.

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