



## *Proteus mirabilis* as a pathogenic organism

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### Abstract

*Proteus* is the member of family *Enterobacteriaceae*. They are gram negative, facultative anaerobic and rod shaped bacteria. *Proteus mirabilis* caused wounds infection, urinary tract infection, rheumatoid arthritis and meningitis in infants. Pathogenicity of *Proteus mirabilis* is facilitated by their unique virulence factors like adhesins, flagella, toxins, quorum-sensing, enzymes and immune invasion. The ability of urease gene of *Proteus mirabilis* that breakdown the urea into ammonia and carbon dioxide that increase the pH of urine resulting adherence, colonization, and biofilm formation. *Proteus mirabilis* are sensitive to most of  $\beta$ -lactams containing antibiotics but also show resistance against broad spectrum  $\beta$ -lactamases, and AmpC enzymes when they acquired  $\beta$ -lactamases genes. *Proteus mirabilis* has been increased extended-spectrum  $\beta$ -lactamase (ESBL) production. The most predominant enzymes of *Proteus mirabilis* such as TEM, CTX-M, VEB- and PER are less common. *Proteus mirabilis* express number of virulence factors that promote pathogenicity. This information about *Proteus* virulence will help to a better understanding of infectious processes and will allow to develop new effective procedure for prevention and clinical treatment.

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## Introduction

*Proteus mirabilis* was first discovered by Gustav Hauser in 1885. The name of *Proteus* comes from poem Homer's *Odyssey* by their shape-shifting character because the *Proteus* has ability to change their rod-shaped vegetative cell in to elongated and highly flagellated cell that has swarming motility (Mobley and Belas, 1995). *Proteus* is the member of family *Enterobacteriaceae*. The tribe *Proteeae* is grouped along with *Morganella*, *Providencia* genera (Antoni *et al.*, 2012). This study is conducted to identify the virulence factors involve in pathogenesis of *Proteus mirabilis*.

### *Pathogenesis of Proteus mirabilis*

*Proteus mirabilis* under suitable conditions has opportunity to cause wound infections, urinary tract infections, rheumatoid arthritis and meningitis in infants (Janda and Abbot, 2006). Pathogenicity of *Proteus mirabilis* is facilitated by their unique virulence factors and increase stay in human host (Christopher *et al.*, 2000).

### *Virulence factor of Proteus mirabilis*

*Proteus mirabilis* expresses several virulence factor involved in infection like adhesins, flagella, toxins, quorum-sensing, enzymes and immune invasion (Baldo and Rocha, 2014).

### *Fimbriae and adherence ability*

Bacterial attachment to the epithelial surfaces play important role in virulence of urinary tract infections. Genomic analysis revealed that total of 17 potential fimbrial adhesins of *Proteus mirabilis* but, only 5 fimbriae have been studied (Pearson *et al.*, 2008). Mannose-resistant/Proteus-like (MR/P), *Proteus mirabilis* fimbriae (PMF), uroepithelial cell adhesion (UCA), ambient-temperature fimbriae (ATF) and *P. mirabilis* P-like pili (PMP) (Rocha *et al.*, 2007).

The important fimbriae of *P. mirabilis* is MR/P fimbriae. The MR/P gene is a group of two transcriptional genes *mrpI* and *mrpABCDEFGHIJ* (*mrp* operon). The main structural subunit protein of *Proteus mirabilis* is MrpA protein.

PMF fimbriae having five functional genes *pmfACDEF*. The occurrence of mutation is less important than its parent strain in uroepithelial cells, although colonization in kidney was not affected by *pmfA* mutation (Nielubowicz, 2010). The UCA/NAF fimbria has highly flexible rods that play an significant role in colonization of the urinary tract. The UCA operon has five genes PMIO532-PMIO536 of the genome sequence of HI4320 (Pelegriño *et al.*, 2013). The ATF are important fimbriae in *Proteus mirabilis*. ATF fimbria show expression in 23°C and there is no difference between mutant and wild-type strain in urinary tract infection. Both of these fimbriae are not important in *P. mirabilis* host colonization (Zunino *et al.*, 2000).

### *Enzymes*

Urease is important enzyme in pathogenesis of *Proteus mirabilis*. Urease enzyme has ability of the formation of kidney and bladder stones and also block urinary tract. (Coker *et al.*, 2000). The cluster of urease gene (*ureRDABCEFG*) that breakdown the urea into ammonia and carbon dioxide and increase the pH of urine. The change in pH can facilitate *P. mirabilis* adherence, colonization, and biofilm formation (Nicholson *et al.*, 1991).

### *Toxins*

#### *Hemolysin*

Hemolysin is a toxin that enter into host cell membranes and create pore in the membrane, resulting host cell damage (Braun and Focareta, 1991). This toxin facilitate *Proteus* in the kidney and also cause pyelonephritis in urinary tract. *P. mirabilis* has two hemolysin genes *hpmA* and *hpmB*. *HpmA* is present in the periplasm spaces, whereas *HpmB* is most likely present in outer membrane of host cell where it is involve in *HpmA* secretion process (Lukomski *et al.*, 1991). However, the virulence of hemolysin is not completely understood (Mobley *et al.*, 1991).

#### *Proteus toxic agglutinin*

This toxic protein is present in outer-membrane that facilitates cell to cell aggregation and the  $\alpha$ -domain of

*Proteus* toxic agglutinin also has ability to lyse kidney and bladder cells. PTA gene of *P. mirabilis* had decrease pathology as well as, important colonization in the bladder, kidneys and spleen ( Alamuri and Mobley, 2008).

#### *Immune evasion*

The presence of bacteria within host cell must evasion of primary and secondary immune responses. *Proteus mirabilis* encodes ZapA, that breaks the chain of immunoglobulins A1 (IgA1), IgA2 and IgG (Walker *et al.*, 1999)

Mutation in zapA genes can decrease the immune system to find *Proteus mirabilis* in a host cell. Thus bacteria has ability to express different kind of fimbriae like MR/P and flagellin that increase adherence of bacteria to epithelial cell ( Bahrani and Mobley, 1994).

#### *Swarming ability*

Swarming behavior of *proteus mirabilis* is mediated by *rsbA* gene which RsbA may function as a protein sensor of environmental conditions (Manos and Belas, 2006). RsbA gene is also responsible in biofilm formation and extracellular polysaccharide formation (Liaw *et al.*, 2004).

#### *Biofilm formation*

Biofilm formation due to *Proteus mirabilis* in urinary tract can increase the length of infection, and slow down activity of antibiotics and immune response. Thereby the bacteria is able to adhere uro-epithelial surfaces of host cell resulting accumulation of ammonia in uro-epithelial cells that becomes toxic and caused direct tissue damage (Sara, 2014). Stone formation by *P. mirabilis* in urinary tract can block the flow of urine through the catheter, bladder or kidneys that caused serious problems and also formation of pyelonephritis, septicemia, and shock. Diseases related to biofilm formation are chronic wounds infection, endocarditis, urinary tract infection, cystic fibrosis and periodontitis. biofilm formation can also weaken the immune system, thus bacteria can easily evade within the host. The PM1

strain has been shown to be able to form biofilm faster than PM2, and also is able to stimulate a lower inflammatory response ( Parsek and Singh ., 2003).

#### *Serotyping*

The important virulence factor of *Proteus mirabilis* is lipopolysaccharide. The lipopolysaccharides some time explain the serology of bacteria. *Proteus mirabilis* are grouped into 80 O-serogroups. The OPS is acidic in all O-serogroups, by the presence of amino acids, uronic acids, phosphate, altruronic acid and other acidic nonsugar components (Knirel, 1999). *Proteus mirabilis* have branched or linear polysaccharides that madeup of repeating units oligosaccharide. However, *P. mirabilis* strains is belong to different serogroups such as, O3, O10, O11, O13, O23, O27, and O30 (Kaca *et al.*, 2011).

#### *Proteus mirabilis in urinary tract infection*

*Proteus mirabilis* is capable to cause urinary tract infection such as cystitis, pyelonephritis and asymptomatic bacteriuria, mostly in type 2 diabetes patients. The infections of *Proteus mirabilis* also responsible for bacteremia and development of life-threatening urosepsis. Furthermore, *Proteus. mirabilis* can cause the formation of urinary stones ( Matthews *et al.*, 2011).

#### *Proteus mirabilis in wound infection*

*Proteus mirabilis* can cause wounds infection, specially in diabetic wounds along with *Klebsiella* species, *E. coli*, *Enterobacter* species and *Serratia marscens* ( Mutta *et al.*, 2003). *Proteus mirabilis* are found in nosocomial infection. *Proteus mirabilis* cause clinical infections, so there is difficulty to eliminate bacteria from host cell with complicated wounds infection, underlying diseases and the immuno-compromised patients (Auwaerter, 2008).

#### *Proteus mirabilis in meningitis*

*Proteus mirabilis* also involved in formation of neonatal sepsis and infections of the central nervous system. It is reported that only 4% cases of neonatal meningitis due to *Proteus mirabilis* (Unhanand *et al.*, 1993). Cerebral abscess formation and

pneumocephalus has been described as also being associated with *Proteus* infections (Phan *et al.*, 2012).

#### *Antimicrobial susceptibility*

*Proteus mirabilis* are sensitive to majority of antibiotics such as penicillin, cephalosporins, aminoglycosides, rifamycin and fluoroquinolones whereas resistant to amoxicillin, cefotaxime and carbenicillin (Saurina *et al.*, 2000). *Proteus mirabilis* are sensitive to most of  $\beta$ -lactams containing antibiotics because they do not show a chromosomally encoded AmpC cephalosporinase (Park *et al.*, 2006). However, *Proteus mirabilis* show resistance against broad spectrum  $\beta$ -lactamases, and AmpC enzymes when they acquired  $\beta$ -lactamase genes (Andrea *et al.*, 2006). Resistance of amoxicillin in *Proteus mirabilis* is mostly due to the TEM-1 and TEM-2 penicillinases. *Proteus mirabilis* has been increased extended-spectrum  $\beta$ -lactamase (ESBL) production. The most predominant enzymes of *Proteus mirabilis* such as TEM, CTX-M, VEB- and PER are less common (Miro *et al.*, 2005).

#### *Antibiotics resistance gene of Proteus mirabilis*

Antibiotic resistance in human pathogens becomes a major problem in public health. Antibiotics resistance in the field of medical and agriculture is due to horizontal mobile genetic transfer elements that transmit more than one resistance genes (Shibata *et al.*, 2003).

Plasmids, transposons, and integrons play important roles in transfer antibiotic resistance gene in bacterial species (Hansson *et al.*, 2002). Antibiotic resistance of aminoglycosides, chloramphenicol,  $\beta$ -lactams, trimethoprim, erythromycin, and rifampin is due to integrons gene transfer (Patridge *et al.*, 2002).

*Proteus mirabilis* is show resistant against ampicillin, tetracycline, gentamycin, and kanamycin. This resistance is occurred due to Class 1 integrons that carrier the antibiotic resistant genes, such as *aadA1*, *aadB*, and *aadA2*. Class 2 integrons also involved in transfer antibiotic resistance gene included: *dhfr1*, *sat1*, and *aadA1*.

The mutations in *gyrA* and *parC* gene of *Proteus mirabilis* show resistance against nalidixic acid. The resistant of ampicillin in *Proteus mirabilis* is due to *bla*TEM-1. and *bla*TEM-1, that were able to transmit resistance gene from *Proteus mirabilis* into *Escherichia coli* by conjugation ( Shin-hee kim *et al.*, 2005).

#### *ESBL producer proteus mirabilis*

The production of CBLs belonging (ACC, CMY/LAT and DHA) of *Proteus mirabilis* has been reported occasionally (Moland *et al.*, 2006). *Proteus mirabilis* producing ESBL has been identified in 1997 (Endimiani *et al.*, 2005). This is the first strain of *P. mirabilis* that producing an acquired CBL (CMY-16) was identified in 2003 (Andrea *et al.*, 2006).

Increase antibiotic resistance of *Proteus mirabilis* against third generation cephalosporins was observed in community and hospitalised patients.

#### *Laboratory diagnosis of Proteus mirabilis*

*Proteus mirabilis* can be identified by their robust swarming motility and urease production in clinical and microbiology laboratories. This Gram-negative *Proteus mirabilis* are motile, indole-negative, lactose-negative, and also have ability to produces hydrogen sulfide (Hara *et al.*, 2000).

*Vaccine against Proteus mirabilis* there is no commercially available vaccines is present against *Proteus mirabilis*. However, the vaccine of *P. mirabilis* are being tested in a murine model of ascending UTI (Habibi *et al.*, 2015).

#### **Conclusion**

*Proteus mirabilis* is a pathogenic organism it caused number of infection in human. Their pathogenicity is promoted by number of virulence factors. Such as adhesins, flagella, toxins, quorum-sensing, enzymes and immune invasion This information about *Proteus* virulence will help to a better understanding of infectious processes and will allow to develop new effective procedure for prevention and clinical treatment.

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