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Pathogenesis of *Proteus mirabilis* in Catheter-Associated Urinary Tract Infections

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Proteus mirabilis · Catheter-associated urinary tract infections · Pathogenesis · Urinary tract infections · Catheters

Abstract
Proteus mirabilis (PM) is a Gram-negative rod-shaped bacterium and widely exists in the natural environment, and it is most noted for its swarming motility and urease activity. PM is the main pathogen causing complicated urinary tract infections (UTIs), especially catheter-associated urinary tract infections. Clinically, PM can form a crystalline biofilm on the outer surface and inner cavity of the urethral indwelling catheter owing to its ureolytic biomineralization. This leads to catheter encrustation and blockage and, in most cases, is accompanied by urine retention and ascending UTI, causing cystitis, pyelonephritis, and the development of bladder or kidney stones, or even fatal complications such as septicemia and endotoxic shock. In this review, we discuss how PM is mediated by a catheter into the urethra, bladder, and then rose to the kidney causing UTI and the main virulence factors associated with different stages of infection, including flagella, pili or adhesins, urease, hemolysin, metal intake, and immune escape, encompassing both historical perspectives and current advances.

Introduction

Urinary tract infection (UTI) is one of the most common bacterial infections, and in the world, each year about 150 million people are affected by this [1]; it is an important cause of infection in male infants of all ages and elderly men and women and can cause serious complications, including frequent recurrence of infection, pyelonephritis with sepsis, infant kidney injury, premature delivery, and complications from frequent use of antibiotic drugs (such as severe antibiotic resistance and *Clostridium difficile* infection) [2]. UTI is divided clinically into uncomplicated and complicated UTI. Uncomplicated UTI usually affects other aspects of patients without urinary tract structural or neurological abnormalities [3–5]; complicated UTI is defined as an infection associated with hazards to the urinary tract or host immune factors, including urinary obstruction, urinary retention due to neurological diseases, immunosuppression, renal failure, kidney transplantation, pregnancy, and presence of foreign bodies such as stones, indwelling catheters, or other drainage devices [6]. UTI caused by *Escherichia coli* and others has been extensively studied. However, complicated UTIs, especially those caused by *Proteus mirabilis* (PM), pose increasing medical challenges.

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PM, originally discovered in 1885 by Hauser, is a kind of motile Gram-negative bacteria in the Enterobacteriaceae family; due to the growth of a solid surface and its shape which can show a sharp change from short rod "swimming" cell differentiation for the expression of thousands of flagella and highly elongated cell "group", it was named after a Greek god. PM is widely distributed in the environment, mainly in water, soil, and human and animal gastrointestinal tracts [7]. It is an opportunistic pathogen that accounts for <0.005% of the human intestinal flora in healthy subjects [8]. PM is a common cause of complicated UTI in patients with anatomical or functional abnormalities of the urinary tract, particularly in patients with long-term indwelling catheters, who may develop catheter-associated UTI (CAUTI) [9]. In the USA, PM accounts for about 3% of all hospital infections and 44% of CAUTI [10–12]. These infections, due to the unique ability of PM to form crystalline biofilms, eventually lead to crusts and obstruction on the surface of the catheter [13], which can then lead to urinary retention and reflux and potentially fatal complications such as sepsis and septic shock if the infection goes up and causes cystitis and pyelonephritis [14]. In addition, urethra and bladder mucosa may be damaged when the crystalline catheter is removed [15].

On clinical, we found that a long-term indwelling catheter will often cause the clogging of the catheter and UTI, most confirmed by the urine culture are major PM infection, the conventional antibiotics do not respond well, and infections are prone to recur, so understanding the the pathogenic mechanism of PM in CAUTI is the basis for the prevention and treatment of the disease. By reading the literature (we used UTI, CAUTI, and PM for keywords to retrieve a large number of relevant literature on PubMed), we found some unique characteristics of PM such as the production of urease and swarming motility, the formation of biofilms, and various virulence factors encoded by genes. We all know that a normal urethra with urine flushing action is less susceptible to bacterial infection, but UTIs are generally considered to be bacterial retrograde, so in the patients with a urethral catheter, how PM is mediated through the catheter into the bladder and even to the kidney aroused our great interest. After further reading of the UTI-related literature, we are well aware of the different stages of infection where bacteria colonize from contaminated urethral openings to catheter adhesion, then to the bladder, and finally to the kidneys, causing cystitis and pyelonephritis. At different stages of this retrograde infection, things like clogged catheters, cystitis, pyelonephritis, and urinary stones can occur, all of these are related to the characteristics and virulence factors of PM. Therefore, we decided to review the mechanism of PM in CAUTI by taking the process of UTI as a clue and combining with the role of the bacterial virulence factor in different stages.

The PM Enters the Urethra and Bladder

To establish UTI, PM must first enter the urethra. Because PM mainly exists in the soil and in the human in the gastrointestinal tract, urinary tract intermittent colonization of the surrounding area has a repository from the gastrointestinal tract bacteria. In a study by Mathur et al. [16], urine bacteria in patients with PM were also matched with fecal isolates, so it can be speculated that UTI usually begins with the presence of urinary pathogens in the intestine that contaminate around the urethra. During catheter insertion and indwelling of the catheter, the catheter becomes contaminated with bacteria, and the organism enters the urethra, followed by urethral colonization and subsequent migration of pathogens to the bladder. If there are any urine tube or other obstacles, it will hinder the normal urine flushing action of pathogens; while the catheter continuous bladder drainage leads to the capacity or power not enough to flush the urethra bacteria effectively, PM can bypass the natural host defense system into the urethra and bladder. Traditional Foley catheters and drainage tubes are designed to leave between 10 and 100 mL of urine in the bladder, which also provides a reservoir for bacterial replication [17].

PM Adheres to the Catheter

Adhesion and colonization are key events that initiate each step in the pathogenesis of UTI and require appendages, such as pili or adhesins. Roberts et al. [18] confirmed the adhesive effect of PM on catheters in vitro and found that different materials of catheters had significant effects on bacterial adhesion, and PM was the bacterium with the strongest adhesion to catheters among Gram-negative bacteria, especially on the inner and outer surfaces of red rubber catheters and silicone catheters with serum and urine. In contrast, in serum conditions, PM did not adhere to teflon catheters, and in the presence of urine alone, PM poorly adhered only to the interior of these catheters and not externally. Subsequent experiments also demonstrate that, during the initial stage of adhesion, PM attaches the pili to a humoral protein-derived coating

on the catheter surface [19] or directly attaches to the catheter material [20].

Whole genome sequencing in the PM genome identified at least 17 pilus operons, and this number is the most in all the bacterial genome sequencing [21, 22]. The strongest adhesion to catheter surfaces in Gram-negative bacteria also clearly reflects this [18], but little is known about the contribution of bacterial pili to catheter adhesion and colonization. We know that PM can secrete mannose-resistance/*Klebsiella* hemagglutinin (MR/KH). In an earlier study, Mobley et al. [23] demonstrated that *Providencia stuartii* and *Proteus penneri* secreted MR/K pili that were related to the adhesion of siliconized-latex catheters [24]. Considering the fact that PM also produced MR/KH, we speculated that MR/KH might contribute to the adhesion and colonization of PM on the catheter surface. Some studies show that ambient temperature fimbria (ATF) does not promote the colonization of the urethra in mice, but expressed at optimal temperature, and thus may affect the colonization of catheters [25, 26]. Like other bacteria that cause UTI, PM infection of the urinary tract is not considered to be through blood-borne pathways.

Group Movement and Flagella

Once attached to the urethra, PM must pass through the urethra to enter the bladder. PM is a motile organism that has peripheral flagella and is capable of differentiating from a single short rod-like "swimming cell" into multicellular elongated "colony cells" that are sequentially arranged to form rafts of cells that can move rapidly across solid surfaces in a coordinated manner [27, 28]. Therefore, movement in groups may promote the migration of PM from the area around the urethra along the surface of the catheter into the urethra and the bladder leading to CAUTI [29]. In addition, groups of cells generally exhibit higher expression of virulence factors, including ZaPA protease and hemolysin, which further enhance their ability to adhere to the duct surfaces and bladder epithelium [30, 31].

Swimming movement is thought to contribute to transmission within the urethra, particularly from the bladder to the kidneys and between the kidneys. For example, immune stimulation to produce antibodies that immobilize PM prevents the spread of bacteria directly inoculated into the medullary tissue of the kidney to the opposite kidney [32]. "Colony cells" are also thought to contribute to kidney colonization and the development of pyelonephritis, especially during prolonged infection, as swarms of cells have been seen in the renal parenchyma [33, 34]. However, in the mouse model of UTI, "colony cells" were rarely observed in the 4-day infection study [35]. Therefore, although flagella clearly contribute to the pathogenesis of PM, the importance of swimming movement and "colony cell" differentiation for disease progression and severity remains to be fully elucidated.

One of the most striking features of population multicellularity is the overproduction of flagella, which in "swimming cells" may play an important role in the vigorous movement of bacteria from the urethra to the target tissue of the bladder and in close contact with the bladder epithelial cells. In contrast to movement of other bacteria, all the flagellate components and chemotactic proteins of PM are encoded in a single locus on the chromosome, which spans about 54 kB [21]. In this region, the 2 flagellin genes encoded by PM were *flaA* and *flaB* [36]. FlaA appears to be the primary flagellin produced by PM, but recombination between FlaA and FlaB may occur, resulting in occasional hybrids [37, 38]. Because the flagellum proteins can be identified by the host immune response and cause inflammatory reaction, so the antigenic variation flaAB and flaAB hybrids may be in the process of infection from immune [39, 40], and PM isolated from infected mice urine produced mainly hybrid flagella protein, and this shows that the flagellum protein gene rearrangement may be PM's immune escape mechanism. Flagella are not an absolute requirement for establishing UTI because naturally occurring nonmotile strains and PM flagella mutants in the experimental model are still able to colonize in the urethra [41, 42]. However, there is clear evidence of the contribution of flagella to pathogenesis, and studies of homogene nonmotility flagellate-negative mutants (flaD mutations) have shown that their ability to settle the urethra of mice is significantly lower than that of their parents [43]. To some extent, the production of flagella also promotes the invasion of PM on human renal proximal renal tubular epithelial cells in the kidney, which enables the bacterial cells to be very close to the host cells [43].

Fimbriae and Adhesin

Fimbriae extending from the surface of bacteria, usually a hair-like protein structure, and once in the bladder, the PM can produce various fimbriae and adhesins, can specifically combine with urinary tract mucosal epithelium, including combining with bladder mucosa epithelial cells; even when lost 2 different types of pili, PM still retains the adhesion in the bladder cells and the ability to establish a UTI, although its level decreased [44]. PM can

code various fimbriae, and among them, the most widely researched fimbriae are the MR/PM fimbriae, MR/KH [45], PM fimbriae [46], the nonagglutinating fimbriae (also known as the urethroepithelial adhesin [UCA] fimbriae) [47], and ATF [48], the other fimbriae encoded by PM have relatively poor characteristics.

The expression of MR/KH has been associated with the adhesion of PM on the catheter surface, thus initiating biofilm formation during CAUTI [10]. However, whether MR/KH is mediated by a specific type of fimbriae or by more than one type of fimbriae is unknown, and the exact nature of the gene associated with MR/KH has not been determined [49]. It has been found that both MR/P fimbriae and PM fimbriae play an important role in the selective adhesion of PM to the bladder epithelium [50, 51]. The Jansen research team has found that MR/P fimbriae are unnecessary and not enough to trigger a biofilm formation [52], but compared with wild-type strains, the MR/P mutant has less biofilm formation, which proved that the MR/P in PM has the key role of biofilm formation. On the contrary, the same study reported that the PM fimbriae with biofilm formation in the enhanced mutant gene cannot be expressed [22]. PM fimbriae have been shown to contribute to bladder, kidney, or both infections and also contribute to adhesion during CAUTI, but its receptor has not been identified [53]. UCA fimbriae are structurally homologous to the fimbriae of intestinal colonies of *E. coli* [54], thus suggesting that they promote PM colonization in the intestinal tract and thus may cause CAUTI [55].

Recently, Wurpel et al. [56] found a new UCA-like fimbria in uropathogenic *E. coli*, and the authors demonstrated its ability to promote biofilm formation on abiotic surfaces and to participate in the binding of uropathogenic *E. coli* to urethroepithelial cells. Meanwhile, the UCA mutant PM that grows in artificial urine has a lower ability to form biofilms than wild-type strains [22]. Although ATF was initially reported to have no role in PM-induced UTI [26], Scavone et al. [22] subsequently demonstrated its role in abiotic surface adhesion and biofilm formation, which may be related to their role in environmental survival, as implied by their optimal expression temperature (23°C) [57].

Urease and Stone Formation

PM is known for its ability to produce urease (urease amylase), a 250-kDa polymeric nickel metalase whose synthesis is induced by the presence of its substrate urea, which catalyzes the hydrolysis of urea into ammonia and carbon dioxide [58, 59]. During infection, ammonia produced by urease increases the pH of the local environment in the urinary tract, followed by the precipitation of polyvalent ions (Mg^{2+} and Ca^{2+}), which are usually soluble in urine. Ammonia accumulation can also be toxic to urinary epithelial cells, leading to direct tissue damage [55]. In addition, it is worth noting that in individuals with catheter insertion, PM is often one of the most common organisms in microbial colonization and CAUTI, and coculture with other urinary pathogens has been found to enhance the ability of PM to produce active urease [60]. The most common CAUTI pathogens are *Enterococcus* species or enterococci, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, all of which can enhance the activity of PM urease by multiple isolates [61].

PM urease is clearly associated with infection-induced stone formation and is known as urolithiasis [62]. Urea is a nitrogenous waste of mammals, urease catalyzes the hydrolysis of urea, and ammonia produced from the decomposition of urea will lead to a sharp increase in urine pH. Soluble polyvalent anions and cations will precipitate under high pH to form guano (magnesium ammonium phosphate) and carbonate apatite (calcium phosphate). In vitro studies on urine inoculation of PM showed that increasing the concentration of magnesium, calcium, and phosphate ions would enhance the strength of crystallization [63]. These crystals are incorporated into developing biofilms in a process called urea demineralization [64]. Stone formation is a hallmark of PM infection and offers a number of benefits to microorganisms, including, but not limited to, protecting the bacteria from the host's immune system (the bacteria are trapped in the pores of the stone and can replicate). Antibiotics and immunoglobulin are unable to reach the bacteria hiding in the stone, urine is blocked from entering the ureter, ammonia is toxic to host cells, and direct tissue damage occurs, all of these events form a microenvironment that is protective and nutrient rich for bacteria.

Biofilm Formation

Biofilms are adherent microbial communities, and one of the characteristics of PM is the formation of crystalline organisms. PM-mediated CAUTI depends on the initial attachment of MR/P fimbriae and the formation of biofilms in the catheter and bladder. The ability of PM to form biofilms on the surface of catheters has been well demonstrated [65]. What is not fully understood is

whether biofilms can form within the urethra and to what extent they cause disease.

PM is readily adherent to a variety of surfaces, including clinically relevant materials such as silica gel, latex, glass, and polystyrene. In the presence of urine, the guanosite and apatite minerals are deposited between the colonized PM surfaces, and extracellular polymers produced by bacteria attached to the ducts capture these crystals and add them to the polysaccharide capsules to form crystalline biofilms [66]. Antibiotic resistance of urethral pathogens increases as biofilms mature because they provide a physical barrier to the entry of antibiotics. Crystals build up in the catheter's biofilm and eventually block the lumen, blocking the flow of urine and leading to complications such as urinary incontinence and painful bladder distension (caused by urinary retention), which in turn leads to vesicoureteral reflux, bacteriuria, increased infection, pyelonephritis, and possible septicemia [67].

In addition, the formation of crystalline biofilms is generally considered to increase the risk of bladder stones, as one study found that 62% of patients with crystal catheters also had bladder stones, and PM infections were detected in the majority (65–79%) of patients with blocked catheters. Both infectious calculi and crystalline biofilms are dense and complex bacterial communities, in which urease and MR/P fimbriae are involved [68].

Bacterial Toxins

PM produces 2 toxins, namely, hemolysin (HpmA) and *Proteus* toxigenin (Pta), which are associated with tissue damage and renal transmission, leading to acute pyelonephritis [10, 69]. HpmA is a Ca^{2+}-dependent pore-forming toxin that destabilizes host cells by inserting itself into the cell membrane and causing Na^{+} effervescent expulsion [10]. In contrast to surface-related cytotoxic proteases, Pta functions only at alkaline pH, such as pH induced by PM urease activity [70]. Pta will puncture the host cell membrane, causing leakage of cytoplasm, destruction of osmotic pressure, and depolymerization of actin filaments, and help colonization in the bladder and kidneys, and it can spread to the spleen (in the UTI mouse model) [71]. It is interesting to note that HpmA and Pta are toxic to cells during in vitro, and experimental UTI has a cumulative effect, especially for cystitis and possible interstitial nephritis, but Pta seems to be the most effective toxin in experimental infection because the effect of the destruction of the Pta on infection is much larger than the loss of HpmA [72].

PM also can produce zinc metalloproteinases (ZaPA) with a broad range of specificity; the metalloproteinase can disintegrate IgA and IgG in serum and cleave complement components (such as C1q and C3), cellular matrix components (such as collagen fibronectin and laminin), cytoskeletal proteins (such as actin and tubulin), and some antimicrobial peptides [73]. Thus, ZaPA may help evade innate immune responses during infection.

Metal Collection

Bacterial pathogens compete with hosts for micronutrients, and one way that hosts fight pathogens is by isolating these nutrients to starve the bacteria of these ions; hence, the bacteria that colonize the urinary tract epithelium have evolved the ability to capture these elements (including iron, zinc, and nickel) [74, 75]. The most intensively studied nutrient competition system is iron, and since the urinary tract is an iron-limited environment, iron is essential for many protein and enzyme functions, including the production of cytochrome, which is essential for effective growth and metabolism. Bacteria produce iron carriers that chelate iron and transport it back to cells at very low iron concentrations. Competition for iron between host and bacteria occurs in bacterial infections, where the survival of bacteria depends on iron acquisition, so the bacteria use specialized systems to obtain iron from the host. PM was initially thought to be iron deficient because of its poor performance in iron chelation tests compared to other bacteria and its negative performance in the iron carrier assay [76, 77]. In addition, PM's ability to establish infection was inhibited in iron-deficient rat pyelonephritis [78], leaving considerable confusion in our understanding of how this species persists in the urinary tract. However, we now know that PM has at least 3 methods of iron acquisition: the protein bacteriocin, the nonribosomal peptide synthesis system, and alpha-ketoic acid [76, 79]. It can also use Enterobacteriaceae, an iron carrier produced by other intestinal bacteria, although this strain cannot make its own [80].

PM must ingest zinc to colonize the host, and the zinc in the bacteria is at least involved in the synthesis of flagella and zinc metalloproteinases (ZaPA). Compared with the laboratory culture, UTI induced high-affinity zinc into the gene *ZnuACB* [81], which can be recognized by the human immune system [39]. Nielubowicz's team [82] by inserting a gene containing ZnuC to interrupt a copy of the strain to study the role of it in PM found that ZnuC::Kan mutants are more sensitive to zinc limit than

the wild type, it showed stronger competition ability than the wild type, swimming and cluster motion decreased, and the expression of the FlaA transcript and flagella protein was less in microelement medium. In addition, the presence of TPEN, a transition metal chelator, can also inhibit group movement, further supporting the role of zinc in movement. ZaPA is a member of the zinc metalloproteinase family and has a conserved zinc-binding motif; although this clearly indicates that ZaPA needs zinc, it has not been directly tested [73].

Nickel is an important component of catalytic active urease in addition to other bacterial enzymes. However, there have been few experimental studies on the homeostasis of nickel in PM, and the host isolation of nickel as a defense strategy for pathogens has also been proposed, but has not been conclusively confirmed [83]. In the CAUTI's model, uptake of nickel was not found to be essential, but nickel excretion was, because high transition metal concentrations interfered with the redox potential of cells and produced oxygen-free radicals that damaged cells [53]. Thus, nickel homeostasis appears to be important during infection, but the balance between enzyme demand and metal toxicity may be affected by indwelling catheters and other bacterial competing nutritional requirements.

Immune Escape

After entry into the host's urinary tract, PM has a remarkable ability to survive, persist, and cause disease, despite antibiotic treatment and the replacement of the catheter, depending on its ability to evade innate and adaptive immune responses. PM is generally resistant due to its ability to kill antimicrobial peptides (especially polymyxin) [84]. Two components of this resistance are ZaPA metalloproteinases (biodegradable antimicrobial peptides) and lipopolysaccharides modified to alter the surface charge [85]. It should be noted that different types of *Pseudomonas* lipopolysaccharide O antigens induce different proinflammatory cytokine IL-8 responses in cultured urothelial and renal cells [86]. Urinary calculi can also prevent the invasion of white blood cells or antibiotics [49]. In addition, PM produces a lysozyme inhibitor called PliC [87]. Finally, at least 2 major antigenic proteins (MR/P fimbriae and flagella) on the surface of the bacteria undergo phase transitions [88]. Thus, bacteria that produce altered flagellin or diminishing MR/P pili may evade innate and adaptive immune responses.

Conclusion

CAUTIs are common in patients with long-term urological intubation. Catheters are the preferred breeding environment for PM, and the bacterium usually coexists with several other members of the microbiome. Years of research has been confirmed in the urinary tract pathogen virulence factors and pathogenesis and has made significant progress, especially in the CAUTI; understanding the pathogenic mechanism and virulence factor of PM in each phase of the CAUTI can be used in the clinical work for us to diagnose, treat, and prevent the disease to provide the corresponding basic knowledge. But for PM, the study of the virulence factors, such as urea enzyme, 17 different kinds of fimbriae, the secretion of cell death and dissolve toxins and protease, used in iron and other metal ions to capture the extensive network, and flagella, is more concentrated in a single bacterial infection model; however, actual catheter-related infections usually contain more bacterial infection. With the development and innovation of biotechnology and the establishment of biological models of multibacterial infection, more studies have proved that the actual mechanism of infection may be more complex than currently recognized, and more in-depth and perfect mechanism studies will further open the door to the development of research on the treatment of PM-related infections.

Statement of Ethics

This study does not involve ethical issues.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

F.Y.: manuscript writing; Z.H.: manuscript editing and review; T.Y.: literature collection and review; G.W.: review; P.L.: project development; B.Y.: literature collection; J.L.: review. Fei Yuan and Ziye Huang contributed equally to this work. All authors approved the final manuscript.

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