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Epidemiology, Pathogenesis and Management of *Proteus mirabilis* Infections

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Abstract **Review Article**

Proteus mirabilis belongs to Enterobacteriaceae family, it exhibits negative response to Gram staining, produce energy under facultative anaerobic conditions. They are motile (swarming), capable of self-elongation and produce polysaccharides that enable them to adhere different materials such as intravenous lines, catheters, and various clinical instruments. The most commonly utilized mode of diagnosis for *P. mirabilis* is a morphological, biochemical, and serological tests. *Proteus mirabilis* is frequently responsible gastroenteritis, wound infections, catheter-related urinary tract infections, and, in other situations, bacteremia. The morphological properties of *P. mirabilis* are: production of several adherence fimbriae and, release of hemolysin and urease, swarming motility. Therapeutic approaches for include involves a course of three days of sulfamethoxazole plus trimethoprim or an oral intake of ciprofloxacin.

Keywords: *Proteus mirabilis* Infections, Gram staining, *P. mirabilis*, morphological, biochemical, and serological tests.

INTRODUCTION

Proteus mirabilis is a member of the Enterobacteriaceae family of bacilli. It is a gram-negative facultative anaerobe that can ferment maltose but not lactose. Additionally, *P. mirabilis* exhibits swarming motility and self-elongation upon surface contact— secreting a polysaccharide that aids in attachment and surface movement, such as along medical equipment. The motility of *P. mirabilis* is facilitated by its flagella; this not only supports colonization but also contributes to biofilm formation (which, in turn, leads to resistance) as well as suggested host defense resistance via production when some antibiotics are induced (Marcon *et al.,* 2019).

Swarming motility and urease activity are common features among most Proteus mirabilis strains, which often lead to catheter-associated urinary tract infections (CAUTIs) that are polymicrobial in nature. These infections can trigger urolithiasis, a condition where stones are formed in the bladder or kidneys due to the alkalinization of urine from urease-catalyzed urea hydrolysis; this is accompanied by the development of fimbriae. P. mirabilis uses 17 different fimbriae for adherence, with MR/P fimbriae being the most notable one. In an agar plate setting, P. mirabilis transitions into a flagella-expressing filamentous swarmer cell with hundreds of flagella upon reaching swarming maturity: when different strains meet on swarming plates, each strain kills neighboring cells through its type VI secretion system resulting in formation of a Dienes line. The murine model has shown MR/P fimbria-based vaccines using MrpH adhesin to be efficacious in prevention and/or treatment of UTI and review information on both historical perspectives as well as current advances associated with urinary tract infections is provided here (Armbruster *et al.,* 2018).

Ninety percent of Proteus infections are community-acquired and primarily caused by P. mirabilis. While Proteus species are not common nosocomial infection agents, they have been found to cause infections among hospital or long-term care facility patients from colonized skin and oral mucosa. Infections acquired in the hospital or recurrently by patients indicate a higher risk of acquiring a Proteus infection along with other organisms such as Enterococci, Staphylococci, Pseudomonas, Enterobacter, and Klebsiella (Wang *et al.,* 2020).

Risk factors for UTIs involving Proteus would be sexual activity in both men and women, unprotected anal intercourse in men; uncircumcised penis, or immunodeficiency are some of the factors. In addition to these, other contributors that could increase the risk of

infection by P. mirabilis in females might include longer duration catheterization period; improper catheter cleaning or care due to an underlying illness and lack of availability systemic antibiotics (Jamil *et al.,* 2023).

Epidemiology

Proteus mirabilis is commonly implicated in burn infections, wound infections, prostatitis, pyelonephritis, cystitis, catheter-associated UTI, and community-acquired infections. It also surfaces as the culprit for meningoencephalitis and meningitis. Furthermore, it contributes to eye infections (endophthalmitis) and even respiratory tract infections. Notably, it is often identified as a common source of bacteremia subsequent to catheter-associated UTIs; although seldom reported— osteomyelitis plus empyema along with mastoiditis endocarditis and cellulitis have been attributed to it. In addition to these conditions, there has also been speculation regarding P. mirabilis playing a role in inducing rheumatoid arthritis (Nakamura *et al.,* 2019).

Urinary tract infections (UTIs) are the primary clinical presentations of Proteus infection. Typically, UTIs prevail more among individuals ranging from 20 to 50 years of age with women being the majority at this age bracket. Among healthy women, the contribution of Proteus to all UTIs is between 1% and 2%— E. coli being the most common in such cases while in hospital-acquired UTIs, it is 5%. Complicated UTIs (like those induced through catheterization) bear an even higher prevalence of association with Proteus: ranging from 20% to 45%. In the United States, gram-negative bacteremia due to genitourinary tract infections occurs in about 35% of patients — portraying another dimension for these alarming statistics that can result from such infections and impact different populations within a society (Ahmad-Mansour *et al.,* 2021).

The staphylococcal strains of S. aureus play a major role in wound infections, burns, and other skin conditions among humans. Also counted among the most common agents responsible for food poisoning: these bacteria cause urinary tract infections, pneumonia, meningitis and mastitis (a condition that affects women's breasts or domestic animals' mammary glands). Apart from these localized infections leading to toxic shock syndrome — which is often fatal due to the release of a toxin into the circulation — other staphylococcal infections are responsible for such diseases as well (Britannica *et al.,* 2014).

Pathogenesis

In Proteus mirabilis infections, the battle between the pathogen and host immune defenses is pivotal. The outer membrane of Proteus species is part of their extracytoplasmic space— a common feature among gram-negative bacteria, consisting of lipids, lipopolysaccharides, polysaccharides, and lipoproteins. These components play a role in interactions with the host defense mechanisms that determine the organism's pathogenicity. Moreover, the size of the infecting population is directly proportional to the severity of infection; this inoculum size determines whether P. mirabilis can successfully attach itself onto host tissues via its fimbriae or pili— small surface projections containing specific compounds at their tips that

When Proteus species make contact with the host cell, an event sequence is triggered— including IL-8 and IL-6 secretion within the host cell (that promote inflammation) alongside apoptosis leading to cell death and desquamation. The production of urease by Proteus contributes to a higher likelihood of upper UTIs and pyelonephritis, as well as ammonia through urea hydrolysis to alkalinize urine: by creating these conditions through its own survival mechanism. Moreover, alkaline urine will reduce struvite stone formation due to low solubility, which is commonly composed of calcium carbonate-apatite and magnesium ammonium phosphate (Armbruster *et al.,* 2017).

In the case of Proteus species and other gram-negative bacteria, endotoxin (which is part of their cell wall) is released into the bloodstream when they invade it. This triggers host inflammatory responses leading to sepsis or systemic inflammatory response syndrome (SIRS)— a life-threatening condition with mortality rates ranging from 20% to 50%. Clearly, P. mirabilis is highly equipped with virulence factors. It produces an abundant number of fimbriae and adhesins, among which MR/P fimbria stands out for its phase variable expression and high virulence. Various toxins and proteases further contribute to its virulence. Apart from the Enterobacteriaceae members, P. mirabilis also possesses several secretion systems such as types VI, V, III, and I— serving different functions including providing cofactors and regulating intracellular metabolism (Armbruster *et al.,* 2018).

A Proteus infection can manifest in various ways in individuals including urethritis, cystitis, prostatitis or pyelonephritis. A chronic Proteus infection might be suggested by a history of frequent renal stones as urethritis typically presents with dysuria and pyuria and sometimes without urethral discharge or increased urinary frequency. Symptoms of the former are often mild and ignored whereas cystitis is more acute, presenting with hematuria — dark urine — small volume urine — back pain — suprapubic urgency — frequency of urination — dysuria; also, a fever signifying more severe conditions (imminent sepsis, bacteremia or pyelonephritis) may be observed. (Belyayeva *et al.,* 2022; Li and Leslie, 2023).

Acute prostatitis presents more acutely in men than cystitis, sharing a similar set of symptoms— although it can also present with fever and chills. The onset of prostatitis is often age-related, typically affecting older men. In cases where there is an associated

obstruction, patients might additionally report perianal pain. A palpable finding during physical examination is a diffusely swollen and tender prostate. It's thus easy to diagnose acute prostatitis based on these signs and symptoms noted on clinical presentation.

Pyelonephritis develops secondary to either of those two conditions, so a patient might present with symptoms related to urethritis or cystitis. Other symptoms more specific to pyelonephritis include: vomiting, nausea, flank pain — which is demonstrated by hematuria — fever and costovertebral angle tenderness; occasionally palpable as an enlarged kidney (Armbruster *et al.,* 2018; Li and Leslie, 2023).

Diagnosis

The most reliable way to evaluate an acute infection caused by P. mirabilis is to conduct a culture test. Proteus species, being gram-negative and rod-shaped bacteria, are also facultatively anaerobic. The majority of these strains do not ferment lactose and can be identified by their unique swarming motility when cultured on agar plates. However, it is essential to always relate positive culture results with the clinical presentation of the patient; only then can we arrive at an accurate diagnosis. Other tests involved in the evaluation include analyzing urine samples for pyuria and leukocyte esterase: the presence of pyuria typically indicates bacterial UTI (beyond doubt) while lack of pyuria might point towards other causes for symptoms. Although less sensitive than microscopy, leukocyte esterase dipstick can serve as an alternative diagnostic tool— particularly in resource-limited settings where microscopic examination is unavailable. Gram staining of urine may help detect microscopic bacteriuria (as evidence for infection); however, the absence of bacteriuria does not rule out the possibility of UTI since not all cases present with this finding. (Hooton *et al.,* 2010).

Management

The most effective approach to managing Proteus infections is through a collaborative effort between pharmacists, nurses, and physicians; infectious disease specialists can also contribute significantly in cases of resistance or immuno-compromised patients (Jamil *et al.,* 2023).

Management of an uncomplicated UTI caused by P. mirabilis is generally empiric (similar to other uncomplicated UTIs) and typically treated on an outpatient basis. The two options for therapy include either a 3-day course of sulfamethoxazole plus trimethoprim or an oral fluoroquinolone like ciprofloxacin. Although it can be treated on an outpatient basis, a regimen of 1-2 weeks is recommended when using fluoroquinolones to treat acute uncomplicated pyelonephritis. An alternative approach would involve a single dose of gentamycin or ceftriaxone followed by sulfamethoxazole plus trimethoprim, cephalosporin or an oral fluoroquinolone for 1-2 weeks. (Pelling *et al.,* 2019).

In a more serious condition or hospital environment, the patient will start antibiotic therapy through intravenous injection of one of the following: ztreonam, gentamycin plus ampicillin or fluoroquinolone. Also considered is gentamycin combined with ceftriaxone until the fever subsides and then shift to oral therapy with cephalosporin, an oral fluoroquinolone or sulfamethoxazole plus trimethoprim for two weeks if still warranted. For complicated UTI cases (e.g., male or female with underlying risk factors), outpatient oral antibiotic treatment can be given for 1-3 weeks provided there is good follow-up care. To avoid Proteus infection, it is important to ensure proper sanitation and hygiene practices such as adequate sterilization of medical equipment surfaces and avoidance of catheterization except as a last resort (Duarte *et al.,* 2019).

The Proteus mirabilis are associated with the development of strains that are resistant to three or more classes of antimicrobials (MDR). Resistance in extended-spectrum alpha-lactamase is uncommon, but the increasing resistance in extended-spectrum beta-lactamase (ESBL) producing strains is an emerging concern. The primary components of ESBLs resistance mechanism include β-lactamases and antibiotic modifying enzymes, which act by hydrolyzing antibiotics. Various factors such as mutation or Porin loss leading to reduced permeability, efflux pump enhancement due to increased activity levels, target site modification preventing binding of antibiotics, and lipopolysaccharide mutation causing resistance can be responsible for different mechanisms against polymyxin antibiotics (Al-Qurashi *et al.,* 2022).

CONCLUSIONS

Proteus mirabilis belongs to Enterobacteriaceae family, it exhibits negative response to Gram staining, produce energy under facultative anaerobic conditions. They are motile (swarming), capable of self-elongation and produce polysaccharides that enable them to adhere different materials such as intravenous lines, catheters, and various clinical instruments. The most commonly utilized mode of diagnosis for *P. mirabilis* is a morphological, biochemical, and serological tests. *Proteus mirabilis* is frequently responsible gastroenteritis, wound infections, catheter-related urinary tract infections, and, in other situations, bacteremia. The morphological properties of *P. mirabilis* are: production of several adherence fimbriae and, release of hemolysin and urease, swarming motility. Therapeutic approaches for include involves a course of three days of sulfamethoxazole plus trimethoprim or an oral intake of ciprofloxacin.

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