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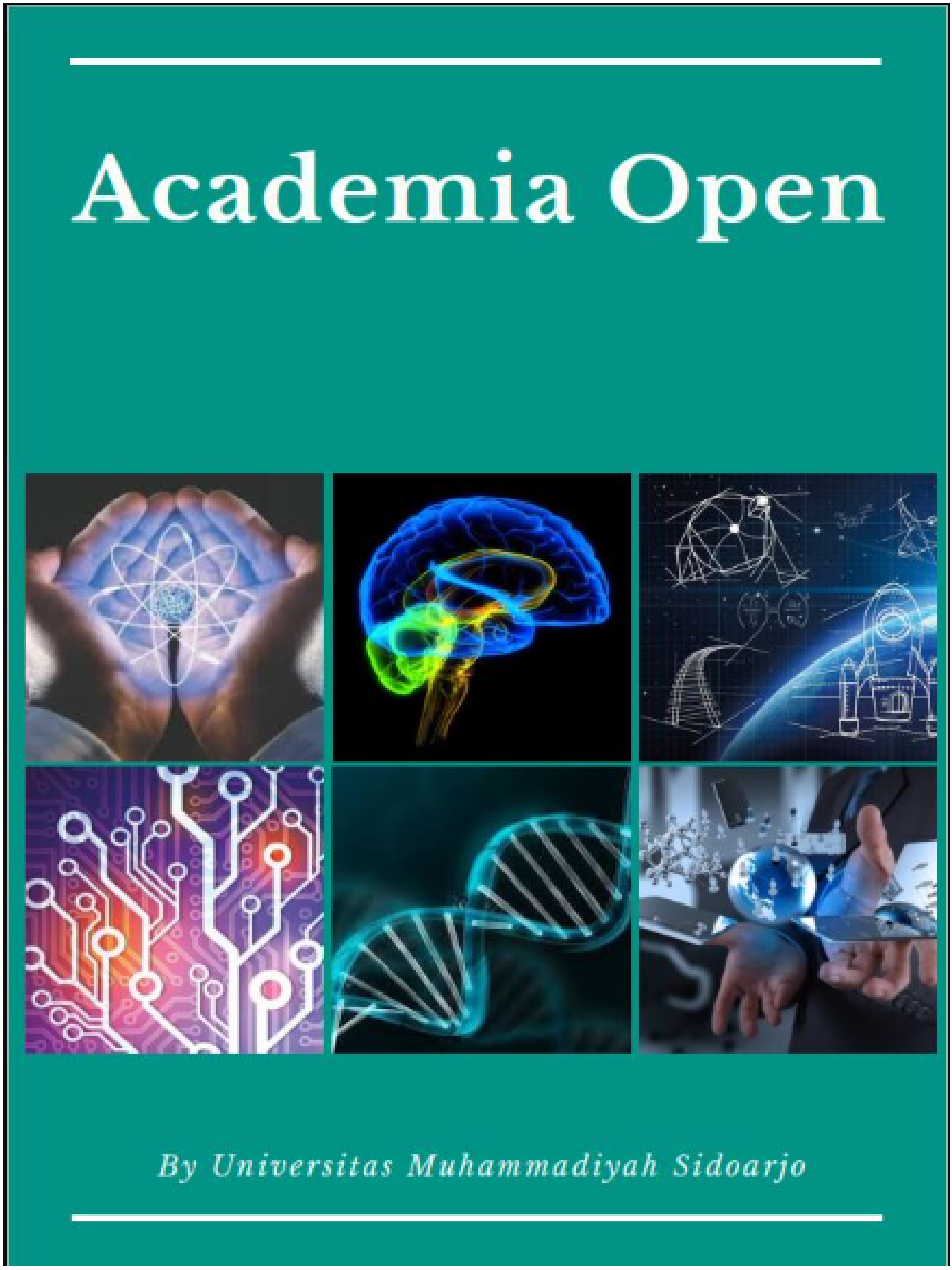


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# Molecular and Cellular Mechanisms Underlying Recurrent Urinary Tract Infections Caused by Pseudomonas aeruginosa in Women

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## Abstract

**General Background:** Recurrent urinary tract infections (rUTIs) in women represent a persistent clinical problem with substantial healthcare burden and frequent relapse episodes. **Specific Background:** *Pseudomonas aeruginosa* has emerged as an opportunistic uropathogen characterized by advanced molecular and cellular strategies, including quorum sensing, biofilm formation, virulence factor expression, and intracellular persistence within bladder epithelial cells. **Knowledge Gap:** Despite increasing recognition of its role, the precise mechanisms underlying persistence and recurrence, particularly host–pathogen interactions and immune dysregulation, remain incompletely understood. **Aims:** This narrative review aims to synthesize current evidence on the molecular and cellular pathways driving recurrent infections caused by *P. aeruginosa* in women. **Results:** The findings highlight interconnected mechanisms, including quorum sensing systems (Las, Rhl, Pqs), biofilm-mediated protection, secretion systems (Type III and VI), intracellular reservoirs, and altered innate immune responses involving Toll-like receptors and inflammasomes, alongside host-related factors such as hormonal and genetic influences. **Novelty:** This study integrates microbiological, immunological, and clinical perspectives into a unified framework explaining recurrence dynamics. **Implications:** Improved understanding of these mechanisms provides a foundation for identifying therapeutic targets and guiding the development of strategies to prevent recurrence and improve clinical management of rUTIs in women.

**Highlights:**
• Intracellular Bacterial Reservoirs Enable Persistence and Relapse After Apparent Clearance
• Coordinated Signaling Systems Regulate Virulence Expression and Adaptive Survival Strategies
• Host Immune Dysregulation and Hormonal Factors Contribute to Susceptibility in Female Patients

**Keywords:** Pseudomonas Aeruginosa, Recurrent Urinary Tract Infections, Biofilm Formation, Quorum Sensing, Host Pathogen Interactions

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## Introduction

Urinary tract infections (UTIs) are one of the most common bacterial infections among women, ranking only behind upper respiratory tract infections in frequency of occurrence. While typically uncomplicated, they can still lead to substantial medical burden, such as emergency physical visits and antibiotic prescriptions, particularly if they are recurrent. Pseudomonas aeruginosa is emerging as an important determinant of recurrent urinary tract infection in women. Despite representing a small percentage of the overall UTI population compared with E. coli and other uropathogenic species, P. aeruginosa is associated with increased likelihood of recurrence and diminished time to repeat infection. Recurrent UTIs as defined in clinical literature do not merely represent re-infection by the same or different pathogen, but rather depend on microbial, host, and treatment-based considerations. These encompass parameters such as strain type, tissue origin, and the time interval between therapy completion and clinical relapse [1,2].

Studies on intracellular reservoirs indicate that after acute urinary tract infection due to P. aeruginosa, bacteria can survive within bladder epithelial cells in the form of intracellular bacterial communities, where they remain protected from both the host immune response and antibiotic treatment. Similar phenomena have been described in the case of UPEC; however, the underlying host-pathogen interactions within the bladder epithelium differ greatly between these two uropathogen types, underscoring the need to investigate different uropathogenic agents individually. Formation of intracellular bacterial communities appears to be coupled to a distinctive shift in the transcriptomic landscape of both host and pathogen [3,4].

## Methodology

In this Narrative Review, our methodology consisted of a thorough search and synthesis of peer-reviewed scientific literature examining the molecular and cellular mechanisms of recurrent urinary tract infections (rUTIs) in women caused by Pseudomonas aeruginosa. A systematic review was performed of relevant clinical, experimental and molecular studies exploring the intricate host–pathogen interactions involved in the persistence and recurrence of bacteria. The recognition of the first major pathogenic mechanisms such as quorum sensing systems, biofilm formation, controlling essential virulence factors (e.g. type III and type VI secretion systems) that drive epithelial invasion, immune evasion, and tissue damage are discussed in the review. The method also assesses the ability of P. aeruginosa to form intracellular reservoirs in bladder epithelial cells for prolonged survival and recurrent infection. Host immune responses, especially innate immune signaling pathways [Toll-like receptor (TLR) and other], inflammasome activation and antimicrobial peptide production, were also evaluated. The study also integrates mechanisms of bacterial antibiotic resistance, including intrinsic resistance, biofilm-associated tolerance, and persister cell formation. In addition, the authors reviewed host-related factors, this includes genetic predisposition, hormonal factors, and differences in teh microenvironment of he urothelium, that could contribute to the occurrence of recurrent disease. This approach combines data from microbiological, immunological and clinical angles into a comprehensive framework, providing a global view of the multifactorial aspects of recurrent P. aeruginosaUTIs and indicating directions for better uropathogen diagnosis and reconception of treatment.

## Result and Discussion

### 1. Epidemiology and Clinical Burden of Recurrent UTIs in Women

Urinary tract infections (UTIs) are one of the most common infections in women, with Pseudomonas aeruginosa being one of the key pathogens responsible for recurrent UTIs (rUTIs)—defined as infections occurring three or more times a year or two or more times over six months [5,6]. A month after a declared UTI, 24% of women experience another one; 34% for a declared cystitis; and 68% for the first episode encountered within the past year. The incidence of rUTIs is higher for women than for men (about 80%) at all ages, and rUTIs already occur in 23.1% of confirmed cases among children and in 44.2% among adolescents. Due to this biological aspect, the clinical burden due to rUTIs is higher in this gender, especially in women, since a larger portion of the global population falls in this susceptible group [7,8]. Understanding the mechanisms of rUTIs by P. aeruginosa may help in the development of improved therapies against these infections [9].

### 2. Pseudomonas aeruginosa: Microbiology and Virulence Factors

Pseudomonas aeruginosa is a ubiquitous, opportunistic pathogen which causes urinary tract infections (UTIs) in humans, among other infections. It is one of the most frequently recovered pathogens from urine samples in hospitalized patients and accounts for approximately 5-10% of the UTIs reported worldwide 10. Although P. aeruginosa is an important UTI pathogen, the epidemiology, clinical burden, and molecular-pathogenic mechanisms employed by this pathogen to elicit recurrent UTIs are poorly understood [10,11]. P. aeruginosa is a metabolically versatile, ubiquitous ɣ-proteobacterium often present in soil, water, plants and various commercial and industrial products found in households. The wide-spread presence of P. aeruginosa in the environment, coupled with the unique and rich nutrient composition of urine provides an ecological niche for this pathogen. Textbook-adopted culture-based methods and accompanying genomic-sequencing approaches have established P. aeruginosa as the prototypical model organism to study both fundamental biological mechanisms as well as complex pathogenic-processes from the single to population level. Research on this organism has further illuminated the major virulence traits commonly exploited in the human host [12]. P. aeruginosa deploys an array of virulence factors such as various toxins, secretion systems, biofilm-formation, and intrinsic resistance to multiple antibiotics to establish infection, among others [13,14].

### 3. Host-Pathogen Interactions in the Urinary Tract

The urinary tract mucosal barrier represents the first line of defense against microbial pathogens. Epithelial cells lining the urinary tract are critical for maintaining host–pathogen interactions. Surge of recurrent urinary tract infection (UTI)-causing bacterium, Pseudomonas aeruginosa, indicates establishment of dual infection cycle in the urinary tract after initial UTI clearance. Traces of recurrence, in order of several weeks post-initial infection, indicates full colonization-evasion regarding the host epithelial barrier [15,16]. Epithelium-unstable traces hint utilization of the intracellular reservoir also seen in persisting bladder intracellular reservoir. The epithelial cell surface-expressed receptors are at the first line of adhesion recognition. Three classes of glycoproteins are recognized by pathogen: heparan sulfate-like glycosaminoglycan chains, sialoglycoconjugates, and terminal glucose-specific receptors. Utilizing notable P. aeruginosa adhesins lectin-like PA-IL (also referred as LecA) and Galactophilic lectin PA-IL (LecB) accompany by the respective signals Passive E-cadherin, cytoskeletal involvement by the protein E-cadherin-serum response factor-β–actin precursor A, persistent touch, and non-cyclic adhesion induced cytotoxicity suggests the process of establishment of recurrent cycle through full dual-pathogen cycle stimulation and abdication of the UTI cycle [17,18].

The factors that influence the epithelial response to P. aeruginosa determine the potential for persistence in the human urinary tract. Moreover, P. aeruginosa pathogenicity yellow signal and red signal virulence factors are injected into the host cells through the type III and type VI secretion systems, respectively, playing an important role in the recurrence of P. aeruginosa UTI. Pseudomonas aeruginosa can survive intracellularly within human bladder epithelial cells and can establish a persistent intracellular reservoir in urinary tract infections. The intracellular population is antibiotic-tolerant and may serve as a reservoir that leads to the emergence of antibiotic-resistant variants [18].

### 3 .1. Mucosal Barrier and Innate Immune Responses

The urinary tract epithelium is the host’s primary barrier against infection, facing mechanical stresses during urination yet maintaining preservation of integrity. Several cellular components build the structural framework of maintaining the bladder barrier, including the expression of tight junction proteins such as claudin-2 and zonula occludens-1 19 ; production of tight junctions on luminal surface with cytokeratin-18; and the formation of cytoplasmic lamellar bodies, which can be secreted as a lipid bilayer structure for high-molecular-weight proteins 20. Urothelial cells secrete antimicrobial peptides such as interleukin (IL)-18, IL-1β, β-defensin-1, β-defensin-2, and secretory leukocyte protease inhibitor via various signaling pathways; antibacterial factors secreted in the urine can directly eliminate uropathogenic microorganisms without damaging urothelial cells [20,21]. The mechanism of a Toll-like receptor (TLR)-mediated inflammatory response relies on activating nuclear factor-κB (NF-κB) signal pathways; furthermore, secretion of pro-inflammatory mediators (e.g., CCL2, CCL5, CXCL1) as TLR4 downstream effectors is rapidly induced by P. aeruginosa colonisation via TLR4 on epithelial cells, contributing to inflammatory responses, leukocyte infiltration and ultimately promoting UTI recurrences [22,23].

### 3 .2. Epithelial Receptors and bacterial Adhesion

In the urinary tract, the pathogen most commonly responsible for recurrent infections is Escherichia coli. Nevertheless, an increasing number of clinical studies indicate that the non-fermentative Gram-negative bacterium Pseudomonas aeruginosa may also cause this reoccurring disease in females. Similar to E. coli, P. aeruginosa likely establishes inside the urinary bladder epithelial cells and persists there, allowing asymptomatic re-emergence weeks to months after apparent eradication is achieved. The sustained intracellular existence of P. aeruginosa in the urinary tract, and of E. coli in uncomplicated cases, offers a viable explanation for the continuous return of these pathogens after the therapy of a recurrent urinary tract infection (UTI) [24,25].

Jung and colleagues demonstrated that P. aeruginosa retained its ability to repeatedly infect the urinary bladder despite the phagocytic activity of neutrophils and the rapid clearance stimulated by the previous exposure to E. coli. This finding suggests that the organism can readily invade bladder epithelial cells and survive thereafter inside intracellular reservoirs that remain undetected by the host’s defense system [26,27]. The observation that a single inoculation of P. aeruginosa can lead to recurrent infections even when identified as an initial pipeline pathogen indicates that mechanisms underlying recurrence have probably been conserved between the two species [28,29].

### 3 .3. Intracellular Reservoirs and Quiescent Host Cells

Pseudomonas aeruginosa can invade and survive within the endosomal compartment of bladder epithelial cells. These intracellular reservoirs potentially form a persistent, antibiotic-tolerant population that allows reactivation of infection after catheter removal 1. Bladder specimens from patients with recurrent UTI caused by antibiotic-resistant P. aeruginosa contained non-culturable intracellular bacteria with a lineagespecific transcriptional signature indicative of prolonged residence within the host. This adaptation to the intracellular milieu relies on the type III secretion system (T3SS) and its effector ExoU, which promote invasion of epithelial cells and confer a significant advantage during the early phase of acute infection [30,31].

## 4. Molecular Pathways Driving Recurrence

The two major mechanisms driving recurrent urinary tract infections (rUTIs) due to Pseudomonas aeruginosa in women have been mapped: the reactivation of previously established intracellular reservoirs and repeated ascent from external sources. To understand how these two pathways operate, three key details are of particular interest: 1) P. aeruginosa elaborates a complex array of signalling molecules that coordinate adaptive responses through quorum-sensing circuits; 2) the Type III and Type VI secretion systems inject a battery of effectors into host cells, modifying multiple aspects of cell

function according to an evolving pathogenic programme; and 3) both intrinsic and acquired determinants support broad-spectrum antibiotic resistance, whereas persister cells and the biofilm state enable long-term survival and tolerance to treatment [32,33].

Quorum sensing is a universal mechanism enabling individual bacteria to monitor and respond to fluctuations in population density. After a low-density lag phase, P. aeruginosa releases the N-acyl homoserine lactones (AHLs) N-butanoyl and N-hexanoyl, which bind to the cytoplasmic receptor RhlR and activate the transcription of rhlA. This enzyme generates the signal required to switch to the high-density mode, triggering the expression of additional genes, including those needed for biofilm formation, motility and virulence factors [34,35]. At high population densities, the signal 3,5-dimethylpyrazin-2(3H)-one (3,5-DMP), synthesised in upstream competitions by LasR-active strains, stimulates the production of pyocyanin. This toxin amplifies the response itself through yet another circuit, highlighting the interconnected nature of the various systems and the importance of inter-strain competition in the formation of community structures [36,37].

The Type III secretion system delivers at least twenty distinct effectors into the cytoplasm of target cells, altering a diverse range of host cellular activities. Such modification may restore water and ion homeostasis, counter inflammation, promote cell survival and ultimately facilitate reactivation of quiescent intracellular reservoirs. The Type VI secretion system injects an arsenal of additional toxic effectors into neighbouring bacterial cells, thereby favouring clonal expansion and reinforcing the competitive advantage once gained [38].

### 4.1. Quorum Sensing and Biofilm Formation

Biofilm formation and the accompanying emergence of chronic infections have long been associated with the exponential growth and interplay of bacterially produced virulence determinants such as toxins, polysaccharides, and effector proteins, which attend the expression of specific mutations and metabolic adaptations 39. Advances in the understanding of P. aeruginosa both as a common organism associated with urinary tract infection (UTI) in women overall and as a hard-to-erradicate, recurrent pathogen in particular have made note of the pivotal role of collective behaviour in establishing and re-establishing recurrent, chronic, or late-onset UTI, as well as drawing attention to the specific molecular pathways by which this bacterium hijacks host tissues. Since the distinct transition and emergent brief changes in these states have already been reviewed in detail regarding other aspects of the P. aeruginosa lifecycle, at least some of this other material will be cited as well [40,41].

### 4.2. Type III and Type VI Secretion Systems

Pseudomonas aeruginosa possesses multiple secretion systems that play a pivotal role in its pathogenesis, among which type III secretion systems (T3SS) and type VI secretion systems (T6SS) mediate eukaryotic cell targeting. A T3SS injectisome allows direct translocation of effectors into host cells, causing cellular damage and evasion of innate defense mechanisms 42. Various T3SS effectors modulate cell signaling, promote cytoskeletal rearrangements, and trigger apoptosis to favour colonization and persistence [42,43]. T6SSs function as bacterial nanoweapons to deliver both prokaryotic and eukaryotic effectors, facilitating competition with other species and contributing to virulence. These secretion systems are subject to complex regulatory networks and are associated with increased pathogenicity and transmission during chronic lung infections in cystic fibrosis patients [44,45].

### 4.3. Antibiotic Resistance Mechanisms and Persistence

Antibiotic resistance is of concern in the treatment of infections caused by Pseudomonas aeruginosa, a pathogenic bacterium implicated in recurrent UTIs in women. The various mechanisms of resistance available to this opportunistic pathogen have been summarized in detail 46. Pseudomonas aeruginosa may possess intrinsic and acquired resistance mechanisms and can exhibit multidrug tolerance during biofilm growth. Intrinsic resistance mechanisms include reduced outer membrane permeability, overexpression of multidrug efflux pumps, and inactivation of many classes of antibiotics [46,47]. The bacterium also employs strategies to acquire resistance determinants, such as plasmids, that encode antibiotic-modifying enzymes, alternative drug targets, and efflux pumps. Further, Pseudomonas aeruginosa can survive antibiotic exposure in a viable but nonculturable state without acquiring a stable resistant genotype. This adaptive resistance can occur due to stress conditions that are not limited to antibiotic exposure and vanishes when the stress is removed. Pseudomonas aeruginosa persisters can survive lethal antibiotic concentrations and retain their sensitive phenotype after prolonged antibiotic treatment [48]. These cells can be eliminated by agents that target metabolic activity or biofilm-associated stress responses [49,50].

## 5. Host Genetic and Hormonal Factors Influencing Susceptibility

Pseudomonas aeruginosa infections are often associated with patients suffering from cystic fibrosis (CF), immunocompromised individuals, burn victims, and ventilated patients. However, in women of reproductive age, the recurrent urinary tract infection (rUTI) caused by P. aeruginosa is the most common type of resistance. Several studies have reported human genetic polymorphisms that alter immunity against P. aeruginosa and/or modulate its response. Among these polymorphisms, interleukin (IL)-10 and transforming growth factor beta 1 (TGF-β1) may modulate the inflammatory response to aggravate urinary incontinence by promoting biofilm formation but diminishes the severity of acute pyelonephritis [51,52].

Compared with P. aeruginosa non-recurrent strains, recurrent P. aeruginosa strains are associated with polymorphisms in

two genes (TGF-β1: C−988T; CXCR1: A−1015G) segregating within the same family and the urická level 51. In women suffering from rUTI at the progeny level, the risk is 70% for the first-born daughter and 50% for subsequent daughters. The severity of acute bacterial cystitis mainly depends on host inflammatory responses. When the bladder escape is associated with a cystitis episode, the rUTI risk increases. The urinary tract is intimately exposed to oestrogens (unlike the respiratory tract), which potentiate the rUTI risk. Yet, the role of oestrogens in rUTI development still requires further elucidation [53].

### 6. Diagnostic and Analytical Approaches for Recurrent Infections

Recurrent urinary tract infections (rUTIs) have been defined as two or more uncomplicated UTI episodes in six months or three or more episodes in a year 54. This term primarily surrounds young women who generally possess an uncomplicated urinary tract. In the United States, over 50% of women will experience at least one UTI in their lifetime, and approximately 20-30% will go on to develop rUTIs. Women who suffer from rUTIs often experience recurrent cystitis and commonly visit emergency rooms and family care physicians for UTI management. rUTI is a condition that negatively impacts quality of life and contributes to significant healthcare expenditures. In addition, over 35 million women a year are estimated to suffer from six or more UTI episodes, further contributing to the high healthcare costs associated with rUTIs [54].

In general, rUTIs are a condition that remains poorly understood, and the specific mechanisms underlying the recurrence of UTI in women need further elucidation. Studies indicate that there is also fundamental research to explore the genomic, proteomic, and metabolomic aspects of UTI and rUTI 7. Urinary tract infections (UTIs) are the second most common bacterial infectious disease and cause significant morbidity internationally, especially among women. Several hypotheses have been proposed to explain the recurrence of UTI, but most, if not all, fail to account for several major observations. In a recent study of the Pseudomonas aeruginosa UTI pathogen, multiple attendant mechanisms have been elucidated that could explain the unique characteristics of recurrent UTI, particularly among women. Therefore, understanding the potential mechanisms that drive the recurrence of UTI in women infected with P. aeruginosa and their organelle and cellular characteristics represents an urgent scientific need [55],[56].

### 7. Therapeutic Implications and Future Directions

Despite the chronic burden of recurrent urinary tract infection (rUTI), few therapeutic solutions addressing the underlying mechanisms responsible for recurrence exist. Management of rUTI continues to rely on conventional approaches, including augmented prophylactic regimens, combination treatments, or nonantibiotic agents to mitigate unintended bacterial selection. Although several promising targets are emerging to disrupt the interplay between uropathogens and host, these strategies remain largely investigational and do not incorporate patient-specific factors critical for optimal intervention design [57],[58].

Thus, a greater appreciation for patient heterogeneity and a deeper mechanistic understanding of recurrent infection are needed to optimize current therapies, establish the scope of additional targets, and identify relevant biomarkers to guide treatment selection [59],[60]. Recurrence may result from low-density reinfection or dormant bacteriuria instead of relapse, suggesting limited utility of current culture and molecular methods to discriminate between these events. Early diagnosis of rUTI preemptively directs appropriate remedial measures; however, personalized approaches to therapy are counterproductive when reinfection identifies the predominant mechanism of persistence [61],[62]. Infection with uropathogenic strains evolving heightened resistance determinants, including increased biofilm formation, Quorum Sensing or Type III Secretion System Class II silencing, or hypermutation, may also inform therapeutic selection [63].

## Conclusion

Recurrent urinary tract infections (UTIs) remain a significant health problem for women. Pseudomonas aeruginosa is an uncommon but growing UTI pathogen and is increasingly recognized as a cause of recurrent UTI. Enhanced appreciation of the persistence and recurrence mechanisms of this opportunistic pathogen is essential to understanding the drivers of UTI recurrence in women. P. aeruginosa can survive intracellularly within human bladder epithelial cells, contributing to persistent intracellular reservoirs that may be antibiotic-tolerant and promote resistant infections. Such reservoirs impair the response to antibiotics and are likely relevant in patients with catheterization or chronic UTIs. Bacterial adaptation to intracellular niches may promote the persistence of UTI-causing pathogens, a phenomenon also seen with other uropathogens 1. An important step during recurrent UTI caused by P. aeruginosa is the formation of a biofilm that protects the bacteria from the immune system and antibiotics. Understanding the environmental signals leading to biofilm formation, the composition of the biofilm matrix, and the role of the quorum sensing system in biofilm development is critical to the design of therapies able to prevent recurrence. The current paradigm defines recurrent UTI as the occurrence of two or more episodes of UTI within six months or three or more episodes within a year and suggests a fundamental shift in understanding of UTI pathogenesis. Such an alternative perspective provides further insights into the mechanisms used by P. aeruginosa to mount recurrent infections and can help guide the development of effective preventative therapies.

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