Review

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Host-Pathogen Interactions in Urinary Tract Infections

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Urinary tract infections (UTIs) are classified by the host condition. Uncomplicated infections are caused most commonly by uropathogenic *Escherichia coli* (UPEC) and affect otherwise healthy people, whereas complicated infections are commonly caused by species, such as *Proteus mirabilis*, and affect patients with underlying difficulties, such as a urinary tract abnormality or catheterization. The outcome of infection caused by these bacteria is dictated by the immune response to the UTI and the host factors that influence the susceptibility to disease. This review focuses on the host pathogen interactions in UTI, including an identification of additional virulence factors and therapeutic or prophylactic targets, particularly by UPEC and *P. mirabilis*.

Keywords: Host-pathogen interactions; Immunity; Urinary tract infections

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INTRODUCTION

Urinary tract infection (UTI), one of the most common bacterial infections, affects approximately 150 million people annually worldwide [1]. Clinically, UTIs are categorized as uncomplicated or complicated. Uncomplicated UTIs occur in relatively healthy individuals, whereas complicated UTIs occur in patients, who have structural or functional abnormalities in their urinary tract, are immunocompromised, undergoing long-term catheterization, or suffering from other illnesses. In more than 80% of cases, uncomplicated UTIs are caused by *Escherichia coli*.

On the other hand, complicated UTIs, particularly those associated with long-term catheterization, are often polymicrobial, generally caused by *Proteus mirabilis, Providencia stuartii, Morganella morganii, Klebsiella pneumonia,* and *Pseudomonas aeruginosa* [2-4]. These bacterial infections manifest as a series of measures and countermeasures by the host and pathogen that eventually settle the course of the disease. Strong host defense mechanisms stimulate changes in the expression of virulence factors in bacteria, which further promote new host defenses. One goal of a pathogen is to resist the host defense mechanisms and establish a persistent infection. To prevent clearance by innate or adaptive defenses, microbes must either avoid immune recognition or resist the antibacterial mechanisms utilized by the host. Irrespective of the mechanism, for survival, the bacteria must adapt to the environment produced by host pathogen interactions [2]. This review focuses on the host pathogen interactions in UTI, particularly by uropathogenic *E. coli* (UPEC) and *P. mirabilis*, as the archetypal pathogens causing uncomplicated and complicated UTI, respectively.

MECHANISM OF INFECTIONS AND VIRULENCE FACTORS

Both *E. coli* and *P. mirabilis* can be detected in the

intestinal tract, which is the likely source of organisms infecting the urinary tract. UPEC are a specific subset of extraintestinal pathogenic *E. coli*; not all strains of *E. coli* cause UTI [5]. On the other hand, all strains of *P. mirabilis*, regardless of isolate origin, can cause UTI [6]. Horizontally acquired genetic elements have been identified in both species; UPEC strains have up to 13 pathogenicity islands [7], and an integrative and conjugative element was recently identified in *P. mirabilis* [8]. Horizontal gene transfer is associated with bacterial pathogenesis because these horizontally transferred genes often encode traits that contribute to virulence, niche specificity, or antibiotic resistance [9].

Recent studies have used RNA sequencing to analyze uropathogens directly from the urine of women undergoing symptomatic UTIs. These studies, together with basic science and improved animal models, have helped better understand the common strategies of pathogenesis by both UPEC and *P. mirabilis*, such as adherence, motility, acquisition of metals, toxin production, and immune evasion. Therefore, these studies have revealed key virulence factors that can be aimed at counteracting the pathogens and preventing UTIs [10,11].

1. UPEC

1) Adherence and colonization

During UTIs, UPEC pathogenesis includes the following: (1) colonization of the periurethral, urethral, and vaginal areas; (2) ascent into the bladder lumen and growth as planktonic cells in urine; (3) adherence to the surface and interaction with the bladder epithelium defense system; (4) biofilm formation; (5) invasion and replication by forming bladder intracellular bacterial communities (IBCs), where quiescent intracellular reservoirs form and reside in the underlying urothelium; and (6) kidney colonization and host tissue damage with an increased risk of bacteremia/septicemia [12].

UPEC colonize the bladder using diverse virulence factors that play critical roles in the pathogenesis of UTI: surface structural components, such as lipopolysaccharide (LPS), polysaccharide capsule, flagella, pili, non-pilus adhesins, curli, outer-membrane vesicles, outer-membrane proteins, secreted toxins, secretion systems, and TonB-dependent iron-uptake receptors, including siderophore receptors [13].

LPS are amphipathic molecules, consisting of fatty acids lined to an oligosaccharide core, stuck to a long polysaccharide chain, commonly called the O antigen. LPS mediate multiple aspects of the UPEC life cycle, including the ability to acutely colonize bladders, fashion reservoirs, and arouse the innate and adaptive immune responses [14]. Moreover, LPS provides resistance against hydrophobic antibiotics, such as some antibiotics and bile salts, which form when LPS is decreased at the cell surface [15].

In UPEC, the fim operon encodes type 1 pili exhibiting mannose-sensitive hemagglutination, whereas the pap operon encodes P- or Pap-pili that are capable of interacting with the digalactoside unit in the P-blood group antigen. The chaperone-usher pathway (CUP) assembles the pili. Type 1 pili are tipped with the adhesin FimH, which recognizes mannosylated uroplakins and $\alpha1\beta3$ integrins with stereochemical specificity, initiating colonization and invasion into umbrella cells [16]. Type 1 pili, combining these cells, triggers a signal transduction cascade, activating Rho GTPases, such as those from the Rac family, causing actin rearrangement, and internalization of UPEC via a zippering mechanism composing a plasma membrane sheathe that engulfs the bacterium [17]. Moreover, the expression of type 1 pili is administered stringently by a phase variation, which reversibly diverts between the type 1 pili active expression (Phase-ON, piliated cells) and a loss of expression (Phase-OFF, non-piliated cells). Environmental signs within the urinary tract, such as salt growth conditions and acidic pH, manage stringently the molecular pathways involved in reversible diverting between the ON-OFF Phases [18].

Unlike the mannose-binding adhesion (FimH) of type 1 pili, the adhesin of P pili (PapG) sticks globosides containing glycolipids that are present in the kidneys [19]. In addition, PapG modulates the local secretory-antibody immune response by interacting with TLR4 to reduce the level of polymeric immunoglobulin receptor expression, impairing immunoglobulin (Ig)A transport through the lamina propria and epithelial cells to the kidney lumen. This mechanism helps UPEC evade a key host protective mechanism, allowing the establishment of ascending infection [20].

Curli are bacterial surface appendages that secrete subunits from the cell as soluble monomeric proteins and possess the typical structure and physical characteristics of amyloid fibrils. In UPEC, proteins encoded in the csgDEFG operon organize curli formation. The operon accessory proteins, CsgE, CsgF, and CsgG, are required to promote the secretion

of CsgA, whereas CsgB nucleates CsgA subunits into curli fibers [21].

While pili are involved in the first attachment of UPEC to the urinary tract mucosa, UPEC employs several other afimbrial adhesins. The adhesin TosA was found in approximately 30% of urinary tract isolates [22]. Another adhesin FdeC aided colonization of the kidneys and bladder in a mouse infection model [23], whereas the iron-regulated adhesin (Iha) mediates adherence to bladder epithelial cells [24].

2) Other toxins

UPEC fabricates three main types of toxin: α-hemolysin (HlyA), cytotoxic necrotizing factor 1 (CNF1), and secreted autotransporter toxins [9]. HlyA forms pores in the umbrella and promotes their lysis, facilitating iron and nutrient acquisition by the bacteria. HlyA also triggers exfoliation, exposing deeper layers of the uroepithelium for colonization and promoting bacterial spread to other hosts following cell expulsion in the urine [25,26]. CNF1 influences actin remodeling in the host cell through three small RHO GTPases: RAC1, RHOA, and cell division control. CNF1 enters the host cell in endocytic vesicles, by sticking to the basal cell adhesion molecule receptor, constitutively initiating RHO GTPases via the deamination of a glutamine residue; this generates actin cytoskeletal rearrangements and membrane ruffling, guiding increased bacterial internalization [27]. CNF1 is not necessary for infection but might be a fitness factor [9]. UPEC also secretes autotransporter toxins. Sat (secreted autotransporter toxin) is a serine protease that intercedes in the cytopathic effects on the kidney and bladder cell lines in vitro and causes tissue damage and immune responses in infected mice [28]. The autotransporter, Pic, with serine protease activity, is expressed during infection, but it does not aid in colonization. Another autotransporter Tsh, which lacks detectable serine protease activity, is expressed during infection in mice [29].

3) Flagella-mediated motility

Similar to adherence, motility is another trait often associated with bacterial virulence. Complex surface structures called flagella mediate motility. UPEC is capable of flagella-mediated motility, which contributes to the fitness of UPEC during a UTI and the ascension of infection [30].

4) Metal acquisition

Iron, an essential nutrient, is isolated by the host, and successful bacterial pathogens must have the means to acquire it. Therefore, iron acquisition is a crucial requirement for UPEC survival. Consequently, IBC UPEC often shows the upregulation of redundant systems for iron acquisition. Siderophores are small molecule iron chelators provided by UPEC strains to scavenge ferric ions (Fe^{3+}). UPEC produces several siderophores, of which aerobactin and yersiniabactin are essential in the urinary tract [13,31]. Aerobactin is expressed strongly, stable at low pH, and displays higher iron sticking capacity than enterobactin. Yersiniabactin is important in bio-film formation in urine and protects against intracellular killing by copper stress because it sequesters host-derived copper [32].

Pathogens can usually scavenge Fe from precursors, such as heme and hemoglobin. UPEC contains two outer membrane heme receptors, ChuA and Hma. Heme uptake via these receptors contributes to fitness during a UTI; the *hma* mutant outcompetes the *chuA* mutant, indicating that ChuA is the predominant heme transporter [33]. Moreover, ChuA aids in the intracellular growth of UPEC in bladder epithelial cells. During intracellular growth, *chuA* is expressed strongly, and its mutant fails to grow at the wild-type level. Heme uptake systems contribute to fitness during extracellular and intracellular growth in UPEC [34].

Similarly, zinc is another essential nutrient sequestered by the effectors of nutritional immunity. Two distinct zinc import systems, ZnuACB and ZupT, operate in UPEC. Indeed, the high-affinity zinc-transport system, ZnuACB, contributed to the fitness of UPEC during experimental UTI [35,36].

5) Strategies for evading the host defenses

Another important factor that supports host colonization is the ability to evade the host immune response. Iron is a crucial nutrient that must be obtained by UPEC during an infection, and enterobactin represents one mechanism of iron procurement. On the other hand, the host protein lipocalin-2 issued by neutrophils specifically sticks to, and sequesters enterobactin, making it unable to provide UPEC with iron. Interestingly, UPEC can revise enterobactin by glycosylation; glycosylated enterobactin, known as salmochelin, are not identified and sequestered by lipocalin-2, enabling UPEC to escape the host defense mechanism mediated by lipocalin-2 [9,37].

In addition, some UPEC strains encode the proteins, SisA and SisB, which suppress the host inflammatory response during the early stages of infection. A deletion of functional copies of these genes in UPEC causes significantly more inflammation in the host. Furthermore, a phase variation of type 1 fimbrial genes might assist UPEC in evading the immune system [38].

2. *Proteus mirabilis*

1) Adherence

After the first attachment, *P. mirabilis* produces mannose-resistant *Proteus*-like (MR/P) pili (CUP pili) that activate biofilm formation and colonization of the kidney and bladder; these are critical for catheter-associated biofilm formation. The most understood are possibly MR/P pili, which are synthesized in vivo, eliciting a strong immune response during infection; these have been implicated in auto aggregation and biofilm formation, contributing to virulence [39]. Other CUP pili encoded by *P. mirabilis* include *P. mirabilis*-like fimbriae (PMF), which are important for bladder and kidney colonization, non-agglutinating fimbriae (NAF) for attachment to uroepithelial cells in vitro, and *P. mirabilis* P-like fimbriae, which are recognized from a canine UTI isolate. Interestingly, the genes encoding this fimbria have also been found in human clinical isolates. On the other hand, the in vivo mechanistic roles of PMFs, NAFs, and their receptors remain unclear [40,41].

2) Toxins

P. mirabilis fabricates two toxins: hemolysin (HpmA) and *Proteus* toxic agglutinin (Pta), which have been implicated in tissue damage and dissemination to the kidneys, initiating acute pyelonephritis [42]. Boht HpmA and Pta induce tissue damage during infection. On the other hand, Pta alone promotes the ability of *P. mirabilis* to colonize the urinary tract [43].

HpmA is a Ca^{+}-dependent pore-forming cytolysin that destabilizes the host cell by inserting itself into the cell membrane, causing Na^{+} efflux [5]. On the other hand, the surface-associated cytotoxic protease, Pta, is functional only in alkaline pH, such as that generated by the activity of *P. mirabilis* urease. In the proposed mode of action, Pta penetrates the host cell membrane, causing osmotic stress, the leakage of cytosol, and the depolymerization of actin filaments. Therefore, the structural integrity of the cell is compromised, resulting in kidney and bladder damage. Moreover, Pta induces bacterial cell-cell interactions via autoaggregation [5,41,44].

3) Flagella-mediated motility

Perhaps the most defining hallmark of *P. mirabilis* is swarming motility, a specialized form of flagella-mediated movement that requires the differentiation of cells into an elongated morphotype teeming with flagella. These elongated cells appear to be limited during infection, but *P. mirabilis* is capable of swarming across the surface of urinary catheters. Swarming and swimming motility during infection are difficult to distinguish because both are flagella mediated. Strains lacking flagella were weakened in a murine model, indicating a role for flagella during ascending UTI. On the other hand, a strain of *P. mirabilis* lacking flagella has been separated from a human patient, suggesting that flagella are not mandatory for its virulence [9,45].

4) Metal acquisition

Historically, it was believed that *P. mirabilis* did not produce siderophores, unlike other members of the *Enterobacteriaceae* family. On the other hand, a microarray-based transcriptional study of *P. mirabilis*, cultured under Fe-limited conditions, revealed genes involved in Fe uptake, including siderophore systems, heme receptors, and receptors for exogenous siderophores. This study also led to the identification of proteobactin, a novel siderophore system, and a yersiniabactin-related siderophore system in *P. mirabilis* [46], which were developed for Fe^{3+} acquisition. The yersiniabactin-related siderophore was originally recognized in a signature-tagged mutagenesis screen designed to detect the virulence factors in a murine UTI model and found to induce the successful colonization of the urinary bladder [34]. Moreover, *P. mirabilis* utilizes HmuR1 and HmuR2, which are outer membrane receptors that activate heme import. A loss of HmuR2 attenuated this process in both the kidney and bladder in a murine UTI model [47].

Similar to UPEC, the ZnuACB high-affinity zinc transport system promotes Zn uptake in *P. mirabilis*, both in vitro and in vivo. A *znuC* mutant with a Zn^{2+} limitation was damaged during growth and contained a fitness defect during a UTI in a mouse model. Overall, Zn^{2+} uptake by the ZnuACB system is involved in urofitness in both UPEC and *P. mirabilis*

[48].

5) Strategies for evading host defenses

At least three mechanisms are used by *P. mirabilis* for immune evasion during a UTI. The first is the production of ZapA, a zinc metalloprotease capable of cleaving several host proteins, including serum and secretory IgA1, IgA2, and IgG, antimicrobial peptides (AMPs), and complement proteins [49]. ZapA activity was detected in the urine of infected patients, probably helping *P. mirabilis* colonize the urinary tract [9,49]. In the second mechanism, *P. mirabilis* possibly utilizes MR/P fimbriae, which are capable of undergoing phase variation, to facilitate immune response avoidance. In the third mechanism, flaA is the predominate version of flagellin expressed by *P. mirabilis*, whereas flaB is normally silent. On the other hand, upon recombination of these genes, *P. mirabilis* produces antigenically distinct flagella, enabling it to subvert the immune response [5,9].

6) Urease production

UTI caused by *P. mirabilis* is characterized by urolithiasis and is affected by urease, a Ni^{2+}-dependent metalloenzyme crucial for colonization of the kidney and bladder [39,41]. The *P. mirabilis* urease is expressed constitutively during growth in urine. The urease actively hydrolyzes urea into ammonia and carbonate several times faster compared to those by other species, such as *Proteus vulgaris, Providencia rettgeri*, and *M. morganii*. The highly active *P. mirabilis* urease produces rapid crystal formation, which is trapped within the polysaccharides produced by the attached bacterial cells. They form crystalline biofilms on catheters [50], affording protection to *P. mirabilis* from the host immune system and antibiotics. Moreover, these structures block urine drainage from the ureters, potentially resulting in reflux and activating the progression to pyelonephritis, septicemia, and shock [41].

MECHANISM OF THE HOST DEFENSES

1. Urine Flow and Cell Exfoliation

Uropathogens must defeat the mechanical force of the flow of urine. Paradoxically, the shear stress of urine flow improves the sticking interactions of FimH and UPEC. Superficial umbrella cells in the bladder are covered with membrane proteins known as uroplakins. Type 1 pili of UPEC bind to uroplakin-1a, triggering exfoliation of the bladder epithelium, thereby detaching bacteria. On the other hand, it permits access to underlying tissue that is normally unexposed despite the rapid differentiation of these underlying cells into superficial facet cells in response to exfoliation. During a UPEC infection, this exfoliation results from an apoptosis-like mechanism that is promoted by FimH [9,51].

2. Innate Immune Response to UTI

AMPs are short, positively charged peptides that bind to and disrupt the bacterial membranes. For example, β-defensin 1 and cathelicidin LL-37 have been implicated in the response to UTI. Recent discoveries on the AMP cathelicidin and the erythropoietin and P2Y receptors have revealed new aspects of defense against UPEC. The production of cathelicidin constrains UPEC in the bladder and is boosted by vitamin D, representing a potential new adjunct for the prevention of UTI [52]. The Tamm-Horsfall protein (uromodulin), a high molecular weight glycoprotein present in human urine, binds to type 1 pili, thereby limiting the interaction of UPEC with the host receptors. Moreover, it acts against *P. mirabilis* [53].

Multiple cytokines and chemokines are upregulated in response to a UPEC infection. Both kidney and bladder cell lines secrete interleukin (IL)-8, the main neutrophil attractant in humans, in response to UPEC. Indeed, neutrophils are the most rapid and robust responders to UTI, and their movements to the site of UPEC infection in the urinary tract is dependent on IL-8 [9]. Moreover, IL-17 and IL-10 have protective roles in UPEC infections. Both cytokines, such as granulocyte-colony stimulating factor (G-CSF), are formed following a UPEC infection, but unlike G-CSF, they appear to limit the ability of UPEC to sustain a bladder infection [54,55]. The functions of IL-17 and IL-10 in cell recruitment and immune regulation suggest that these cytokines potentially fine-tune the innate cellular defenses against UPEC in the bladder [56].

Toll-like receptors (TLRs) play an important role in the pathogenesis of a UTI. The TLR signals induce an inflammatory response via the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which induces the secretion of cytokines (IL-1β, IL-6) and tumor necrosis factor-alpha. As immunomodulation elements, TLRs are closely related to pathogen identification and host defense in UTI [57]. TLR receptors TLR2, TLR4, TLR5, and TLR11 promptly

recognize and defend the pathogenic invasion of bladder epithelial cells [58].

3. Adaptive Immune Response to UTI

In general, data regarding the adaptive immune response to UTI are sparse. Thumbikat et al. [59] reported that the protection originated from infection is antibody-mediated. In addition, evidence implies that UPEC clearance is antibody-mediated. On the other hand, it is unclear if the immune response is skewed toward a T_H1-mediated or T_H2-mediated response, and the role of T_{REG} cells is unclear [9,59].

TREATMENT OF UTI

Antibiotics will continue to be an unavoidable treatment for UTI. On the other hand, the increasing rates of antibiotic resistance, high recurrence rates, and long-term interference with intestinal microbiota, mandates a search for alternative remedies. Ideally, such remedies should be recalcitrant to the development of resistance. Many promising approaches are being developed from leveraging what has been learned regarding the basic biology of UTI pathogenesis to target virulence pathways specifically. These antivirulence treatments should theoretically enable an effective attenuation of UTI pathogens, without altering the gut commensal microbiota Antivirulence treatments target processes that are essential for UTI pathogenesis but are not for growth and cell division, which are the targets of conventional antibiotics.

Here, the following briefly summarizes the progress made towards the improvement of antivirulence therapeutics and the approaches for improving the current therapeutic options for UTIs with a special focus on vaccines.

1. UPEC Vaccines

To date, probably the most successful vaccine targeting UPEC is Uro-vaxom (OM Pharma, Geneva, Switzerland), a daily oral capsule including membrane proteins from 18 *E. coli* strains. On the other hand, no licensed UPEC vaccine currently is available in the United States, and active research toward this goal is ongoing [60].

Strategies to fight UTIs have focused on the development of vaccines based on the bacterial elements or specific UPEC factors as vaccine antigens. Potential candidate antigens are adhesins, AMPs, and siderophores [61]. Vaccines, however, may alter the intestinal microbiota, and pathogens may device alternative strategies to reach the bladder lumen. Furthermore, vaccines might treat upper UTIs rather than lower UTIs more effectively [62]. Recently, vaccination using a bioconjugate vaccine, including the O-antigens of four *E. coli* serotypes, induced significant IgG responses for all serotypes in healthy adult women with a prior medical history of recurrent UTI.

Moreover, the vaccine group identified significantly lower UTIs induced by UPEC of any serotype compared to the placebo group [63]. An alternative strategy to derive protective immunity is to select small molecules as antigens, rather than proteins or peptides. The use of siderophore-protein conjugates was reported to elicit immune responses targeted to bacterial siderophores and successfully protect against UTI [64].

2. *P. mirabilis* Vaccines

In addition to the UPEC adhesins, those from *P. mirabilis* have been utilized as vaccine targets [65]. In a mouse model of UTI, vaccination with the *P. mirabilis* MR/P pilus adhesin, MrpH, reduced the bacterial burdens compared to those of unvaccinated controls, similar to the results observed with UPEC in the FimH vaccine trials [5,65]. Several urease inhibitors have been developed as potential drugs for the treatment of UTI, of which the best characterized one, acetohydroxamic acid (AHA), successfully treated UTIs caused by urease-producing organisms, such as *P. mirabilis*. AHA works by preventing urine alkalization and was approved by the U.S. Food and Drug Administration in 1983.

On the other hand, many of these inhibitors exhibit severe side effects related to toxicity [66]. Another group of urease inhibitors, phosphoramidites, exhibited potent activity against *P. mirabilis* urease in a mouse model. These elements, however, displayed low stability in the low pH of gastric juice, making them impractical [5,66]. Finally, an immunoproteomic screen was performed to show the outer membrane proteins of *P. mirabilis* that could derive an immune response in infected mice [67]. These proteins are exciting new potential vaccine candidates because they are expressed in vivo and are exposed to the surface, where they can potentially interact with the host. Indeed, immunization with one of these proteins, Pta, protected mice from a subsequent transurethral challenge [41].

CONCLUSIONS

UPEC and *P. mirabilis* are common pathogens of bacterial UTI in humans. Proteins that contribute to the virulence of these pathogens have been identified, increasing the understanding of the mechanisms of pathogenesis. Such virulence or fitness factors contain pili (such as type 1 and P pili in UPEC and MR/P pili in *P. mirabilis*) that mediate attachment to the host tissues, toxins (such as hemolysins and autotransporter toxins in both species), flagella, iron acquisition systems, and proteins that function to evade the host immune response. In addition, each pathogen has unique traits; UPEC can produce IBCs, and *P. mirabilis* produces urease, whose action leads to urolithiasis, blocking the flow of urine through catheters. To colonize and persist in the host successfully, these uropathogens must overcome the host defenses mediated by the innate and adaptive immune systems.

The identification of virulence determinants, specifically those crucial for the first attachment (adhesins) and the subsequent establishment of disease (siderophores and urease), has permitted the development of targeted therapies that effectively attenuate pathogenic bacteria. By targeting the initial steps of infection or by vaccination with adhesins or siderophore receptors, these therapies can prevent uropathogens from gaining a foothold in the urinary tract. Therefore, there is interest in the generation of vaccines against both uropathogens. Although several studies focused on the development new strategies for the treatment and prevention of UTIs, more work is required. In addition, further studies will be needed to elucidate adaptive immune responses in the urinary tract. These findings will help better understand the disease process and provide new insights into novel therapeutic or prophylactic strategies in UTI.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

P.H.S. participated wrote the manuscript. P.H.S., Y.H.K., and J.Y.C. participated in the study design. Y.H.K. helped to draft the manuscript. All authors read and approved the final manuscript.

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