Review

Urinary Tract Infection in Parkinson's Disease

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Abstract. Urinary tract infection (UTI) is a common precipitant of acute neurological deterioration in patients with Parkinson's disease (PD) and a leading cause of delirium, functional decline, falls, and hospitalization. Various clinical features of PD including autonomic dysfunction and altered urodynamics, frailty and cognitive impairment, and the need for bladder catheterization contribute to an increased risk of UTI. Sepsis due to UTI is a feared consequence of untreated or undertreated UTI and a leading cause of morbidity in PD. Emerging research suggests that immune-mediated brain injury may underlie the pathogenesis of UTI-induced deterioration of PD symptoms. Existing strategies to prevent UTI in patients with PD include use of topical estrogen, prophylactic supplements, antibiotic bladder irrigation, clean catheterization techniques, and prophylactic oral antibiotics, while bacterial interference and vaccines/immunostimulants directed against common UTI pathogens are potentially emerging strategies that are currently under investigation. Future research is needed to mitigate the deleterious effects of UTI in PD.

Keywords: Parkinson's disease, urinary tract infection, delirium, falls, exacerbation

INTRODUCTION

Urinary tract infection (UTI) is a leading cause of acute hospitalization in patients with Parkinson's disease (PD) [1, 2]. In this comprehensive review, we summarize research related to the epidemiology, clinical impact, and pathogenesis of UTI in PD. We further provide a detailed review of current and emerging management strategies to mitigate the risk of UTI-induced neurological deterioration in patients with PD.

EPIDEMIOLOGY AND CLINICAL IMPACT

Patients with PD are twice as likely to be admitted for UTI compared to non-PD controls (48.6% vs. 23.3%, $p < 0.001$) [3]. Although the risk of UTI increases with age and is generally more common in women, PD-associated UTI occurs in relatively equal proportions between older men and women, consistent with the notion that PD, and the secondary effects inherent to the disease, supersede sex as a risk factor for UTI [1]. PD-associated UTI is likely underreported, as it is often classified as a urinary disorder rather than as an infection [2]. Furthermore, the reason for hospitalization in patients with PD and UTI may be categorized under a related incident, such as

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a fall secondary to UTI, rather than the UTI itself [4, 5], thus underestimating the actual incidence and significance of PD-associated UTI. PD is the second most common neurodegenerative condition after Alzheimer's disease and is the fastest growing neurologic condition overall [6]. With PD cases expected to double by 2030 [7], PD-associated UTI is expected to only increase in importance to health care providers and planners in the coming decades.

UTI is a leading cause of acute hospitalization in patients with PD [8, 9]. Even when not the primary cause for admission, UTIs are often found incidentally at higher rates in patients with PD compared to the general population [10]. Patients with PD who undergo surgeries, both elective and emergency, are also known to be at higher risk of UTI [11]. In one review of nine retrospective studies of 433 patients with PD, UTI was reported to be one of the most frequent orthopedic postoperative complications, in frequencies up to 49% [12]. The risk of UTI is elevated in patients with PD following total hip arthroplasty (OR = 1.39; 95% CI, 1.09–1.76; $p = 0.007$) [11, 13], while one-third of patients with PD develop UTI after total knee arthroplasty [13, 14]. These studies highlight the particular risk PD patients undertake when undergoing operative admissions. As UTI-induced motoric dysfunction in PD likely contributes to an increased risk of falls [15] and PD-associated bladder dysfunction increases the risk of UTI, future studies are necessary to clarify the exact directionality of the relationship between UTI and orthopedic injury. Regardless, whether the admission is due to medical or surgical reasons, UTI is a common driver of hospitalization.

Overall, systemic infection is the single most frequent underlying cause for motoric exacerbation in PD, accounting for 25% of exacerbations [16]. UTI and pneumonia are the most frequently implicated systemic infections that contribute to worsening motoric function [12, 17–20]. This deterioration is significant, with nearly one-third of patients discharging with worse motor function with a mean increase of more than 5 points on the UPDRS-III [20]. Worse motor outcomes lead to increased long-term care placement, increasing the risk for subsequent UTI [21] and potentially leading to a vicious cycle of infection and deterioration. Cognitive deterioration can be equally deleterious and patients with PD and UTI have an increased susceptibility to developing delirium, which may explain why patients with PD have, on average, longer hospital stays than patients without PD (17.8 days vs. 15.4 days, $p < 0.001$)

[3, 22]. UTI is also associated with psychosis in PD, which increases the risk for subsequent nursing home care [8].

Sepsis due to UTI, often from *Escherichia coli*, *Streptococcus spp.*, and *Klebsiella pneumoniae,* is a feared consequence of untreated or undertreated UTI and a leading cause of morbidity in PD [3, 23]. There is a clear increase in the trend of PD patients being admitted with unspecified sepsis and UTI [7], which is of concern as PD patients are twice as likely to stay in the hospital for longer than 3 months. Additionally, PD hospital mortality rates are 1.5 times higher than controls (3.9% vs. 2.5%) in the US [7, 24] and 2.5 times higher in the UK [25, 26]. These factors combine to increase the need for new interventions for PD-related UTI as demographic and epidemiologic factors are driving a massive increase in the burden of this treatable disease on an already overtaxed healthcare system.

RISK FACTORS

Patients with PD are susceptible to UTI due to several modifiable and non-modifiable risk factors (Fig. 1). In this section, we will explore underlying risk factors that increase the risk of UTI in PD.

Disease progression, care-setting, and dementia

Several clinical features of PD account for the increased risk of UTI, including both progressive motor and non-motor dysfunction and, in particular, autonomic nervous system dysfunction. Autonomic dysfunction of the bowel, for example can lead to constipation, fecal impaction, urinary retention and UTI [27] and can also directly impact the urinary system by precipitating neurogenic bladder [28]. Death of dopaminergic neurons in the substantia nigra and the ventral tegmental area are thought to degrade the frontal-basal ganglia D1 dopaminergic circuit, thereby impairing suppression of the micturition reflex and causing loss of bladder control, compounding the risk of UTI [29]. The severity of urinary symptoms, in particular storage symptoms, has been associated with greater nigrostriatal dopaminergic degeneration in early PD [29]. Lower [123I]-FP-CIT SPECT binding in the non-dominant putamen ipsilateral to the side of greater motor deficit has been associated with worse storage symptoms (r = –0.172, $p = 0.004$) and worse voiding symptoms (r = –0.119, $p = 0.049$), while severity of bladder dysfunction correlates with degeneration of the caudate [30].
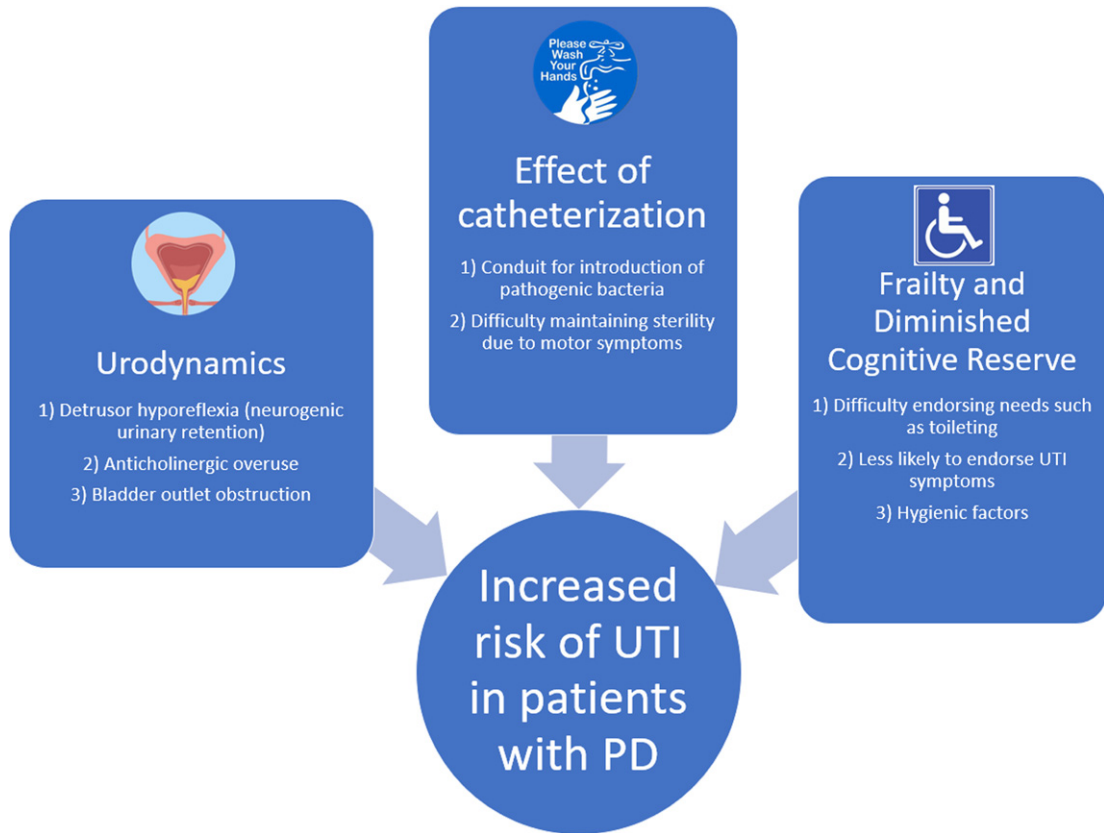
Fig. 1. Risk factors for UTI in Parkinson's disease.

PD-related dementia increases the risk of inadequate self-hygiene, and likelihood of urinary catheterization [31], which can contribute to persistent bacteriuria and lower the threshold for UTI [31]. PD patients, especially those with advanced disease and dementia, are often housed in long-term care facilities where antibiotic resistant bacteria are common [32, 33]. Decreased physical ability, overall poorer health, and reduced ability to perform self-care further increase the risk of UTI [34, 35] and compound over the course of the disease, rising with disease duration and severity [8, 36]. However, the relationship between PD-related cognitive impairment and risk of UTI is complex. First, PD-related cognitive impairment is associated with more severe Hoehn and Yahr disease stage [37], making confounding variables likely in any retrospective analysis. One recent study of 58,000 patients diagnosed with UTI in the ED controlled for age, sex, catheter use, recurrent UTI and SNF residence, found that patients with dementia are more than twice as likely to be diagnosed with UTI versus those without

dementia [38]. However, this study did not categorize type and severity of dementia, the presence of urinary/fecal incontinence or mobility status.

In practice, patients with cognitive impairment may have difficulty endorsing symptoms typically associated with UTI. This may lead to an overdiagnosis of UTI and overtreatment of asymptomatic bacteriuria in the acute setting. On the other hand, this relationship could be causal and cognitive impairment may be an independent risk factor for UTI due to more issues with poor hygiene and infection control. In the second circumstance, PD-related cognitive impairment and its hygienic sequelae may be potentially modifiable risk factors that can be pre-emptively addressed in the outpatient setting. Although formal studies on this topic are lacking, from a practical standpoint the combined motor, dysautonomic, and cognitive burden of PD can be expected to place patients at a higher risk of UTI than in patients with cognitive decline alone; however, more research is needed on the association between PD-related dementia and UTI versus other types of

dementia and, in particular, to the discrete physiological risks of UTI in PD compared to other etiologies of dementia.

Urodynamics

Incomplete bladder emptying results in urinary retention and stasis which can predispose to bacteriuria and UTI [39, 40]. In the context of neurologic disorders, this is termed neurogenic urinary retention. Detrusor hyporeflexia and detrusor-sphincter dyssynergia are two principal mechanisms by which patients can develop neurogenic urinary retention [41, 42] yet surprisingly, these two findings are rather uncommon in urodynamic studies of patients with PD, with reported rates of detrusor hyporeflexia ranging from 0–16% and dyssynergia from 0–3% [43–46]. When present in patients with PD, it may be associated with advanced disease [46] or the use of anticholinergic medications. In contrast, neurogenic urinary retention is highly prevalent in multiple system atrophy and can be used to distinguish it from PD in atypical cases of Parkinsonism [47, 48].

Detrusor overactivity due to a neurologic disorder is termed "neurogenic detrusor overactivity" and results in storage symptoms including urinary urgency and urge incontinence. Neurogenic detrusor overactivity is the most common cystometric abnormality in PD and is estimated to occur in 45–95% of patients with PD, with higher frequency in older patients with worse motor and autonomic involvement [46, 49–51]. It is theorized that dopaminergic cell loss in the basal ganglia leads to loss of D1-mediated inhibition of the pontine-sacral micturition pathway and subsequent detrusor overactivity [49, 52]. This can lead to a "spastic" bladder that contracts at low volumes, which clinically presents as nocturia, urinary frequency and urgency. These symptoms are the most common urologic complaints in patients with PD and are usually treated with anticholinergics, such as solifenacin [53, 54], as first-line therapy, which can inadvertently increase the risk of UTI [55].

Bladder outlet obstruction is important to consider as an alternative cause of irritative lower urinary tract symptoms in patients with PD because it can mimic neurogenic detrusor overactivity and predispose to UTI and nephropathy. Antimuscarinic drugs may mask the urgency symptoms in these patients but worsen the underlying urinary retention and increase the risk of UTI. Obtaining a post-void residual before prescribing antimuscarinics can help distinguish these two syndromes in patients with PD [56]

and referral for urodynamic testing is suggested in patients with complicated lower urinary tract symptoms or those who fail to respond to first-line therapy with anticholinergics [57].

Effect of catheterization

Urinary catheterization can introduce pathogenic bacteria into the normal urinary bacterial microbiome and cause local mucosal injury, which can predispose to catheter-associated UTI. The need for catheterization in patients with neurogenic urinary retention predisposes many patients with PD to UTI. It is well-known that long-term catheterization is a major risk factor for catheter-associated UTI [58]. In cases where catheterization is necessary in patients with PD, intermittent straight catheterization is preferred. One recent meta-analysis of 2321 patients with neurogenic bladder, independent of PD, suggested that use of intermittent straight catheterization is associated with lower rates of UTI compared to indwelling urinary catheterization [59, 60]. However, depending on the severity of their motor symptoms, it may be difficult for patients with PD to maintain sterility while performing self-catheterization and they may require caregiver assistance to maintain sterility even in the early stages of disease. To our knowledge, there are no available data comparing rates of UTI in patients with PD who use intermittent straight catheterization versus indwelling urinary catheterization. Further research is needed in the area.

Frailty and urinary retention

Immobility in patients with PD likely plays a large role in the development of urinary retention and associated UTI. A large retrospective study of over one million female Medicare beneficiaries showed that a diagnosis of urinary retention was positively associated with spinal cord injury, MS and "frailty" [61], a category which includes patients with PD, other neurodegenerative disorders and nursing home residents. Patients diagnosed with urinary retention were 2.5 to 4.5 times more likely to have one or more of these underlying conditions [62]. As expected, a history of UTI was also associated with a diagnosis of urinary retention. Interestingly, patients with frailty and retention did not have a significantly higher rate of catheterization than the total population of patients with retention. This suggests that the higher rate of UTI in PD patients may not be fully explainable by higher rates of catheterization. Rather, immobility

and mild or sub-clinical urinary retention may be independent risk factors for development of UTI in this population. Araki et al. demonstrated a positive correlation between PD severity and post-void residual urine volume [46]. Even asymptomatic retention defined as post-void residual volume > 150 mL has been associated with higher rates of UTI in a large screening study [63]; however, the risk-benefit balance of active interventions to maintain lower post residual volumes has not been established. Additional research needs to be done to explore how immobility modifies the risk for urinary retention, catheterization and UTI in patients with PD.

PUTATIVE BIOLOGICAL MECHANISMS

Urinary retention and stasis

As previously mentioned, advanced PD may predispose to urinary retention through a variety of mechanisms. One Korean study of 197 PD patients found that 8.9% had increased post-void residual volumes over 100cc, a well-established risk factor for UTI [64]. Another potential mechanism involves motor dysfunction itself, as patients with advanced PD may have severe rigidity/akinesia preventing access to toileting. Additionally, as PD patients may be at higher risk for urinary incontinence, they may be prescribed anticholinergics, which may independently contribute to an increased risk of UTI [55]. Caution should be taken when titrating antimuscarinic agents on patients with advanced PD and PD dementia to avoid the risk of drug-induced urinary retention. PD patients with cognitive impairment and spastic bladder may benefit from timed or prompted voiding to prevent episodes of urinary incontinence and avoid the need for antimuscarinic therapy, as discussed in further detail below under *Management strategies to prevent UTI in PD*.

Introduction of bacteria via catheterization

Indwelling urinary catheterization provides a direct pathway for pathogenic bacteria to ascend from the external environment to the lower urinary tract. There are three possible mechanisms by which catheterization may lead to bacterial colonization of the lower urinary tract and subsequent infection [65–67]. First, bacteria may be introduced directly during catheter insertion if aseptic technique is not observed. Secondly, bacteria may travel along the outside of the catheter, between the urethral mucosa and the exterior of the catheter. Lastly, bacteria may ascend directly along the interior lumen of the catheter. Overall, extraluminal tracking of bacteria seems to be the predominant pathophysiologic mechanism of catheter-associated UTI [67], with biofilm formation playing a role in some cases [68]. Bacteriuria is virtually guaranteed with indwelling urinary catheterization and is more likely with prolonged duration of catheterization.

Pathogenesis of urinary tract infection in PD

The pathogenesis of UTI is complex and depends on multiple factors involving both the host and pathogen. Even a healthy person's urine is not completely sterile, so various host factors likely contribute towards the pathogenesis of UTI. Age, sex, host immune function, e.g., immune senescence in elderly patients with PD, and general illness can all predispose to the development of UTI. Additionally, structural abnormalities of the lower urinary tract including calculi, benign prostatic hyperplasia, and pregnancy are associated with increased risk of UTI [69].

The urinary microbiome is an emerging area of study in the development of UTI [70]. Multiple recent studies have demonstrated that the urinary microbiome profiles differ significantly between healthy controls, patients with asymptomatic bacteriuria and those with chronic lower urinary tract symptoms [71–73]. One recent study examined urine samples from patients with neurogenic bladder from spinal cord injury using 16s rRNA sequencing and found that the presence and duration of neurogenic bladder and methods of catheterization are associated with asymptomatic overgrowth of pathologic bacteria in the lower urinary tract [74]. As the duration of neurogenic bladder increased, patients' urinary microbiomes shifted away from commensally present *Corynebacterium* and *Lactobacillus* species towards the typical pathogenic *Enterococcus* and *Enterobacterales* species. A healthy urinary microbiome may be necessary to control the proliferation of pathogenic bacteria via competition for nutrients or uroepithelial binding sites [75]. In theory, catheterization and antibiotic overuse would disrupt the healthy urinary microbiome and possibly contribute to recurrent UTI. Additionally, pathogen-specific factors may negatively affect patients with PD, as demonstrated in a recent study in MPTP-lesioned mice that demonstrated that oral administration of *Proteus mirabilis*, a common UTI pathogen, damages dopaminergic

neurons and worsens motor function [76]. However, it remains unknown whether urinary infection with *Proteus mirabilis* or related organisms may have a similar neurotoxic effect on PD pathology and phenotype. Despite the potential relevance of the urinary microbiome in patients with PD, we found no PD specific studies on this topic, potentially representing an important research gap and area for future investigations.

UTI-induced neurotoxicity

Infection is a well-known trigger of acute cerebral dysfunction and has been implicated in the pathogenesis of delirium. Mild infection such as UTI can trigger inflammatory upregulation which is likely a key step in the behavioral alterations seen in delirium. This can occur independently of blood-brain-barrier disruption via endothelial cell signaling and/or via
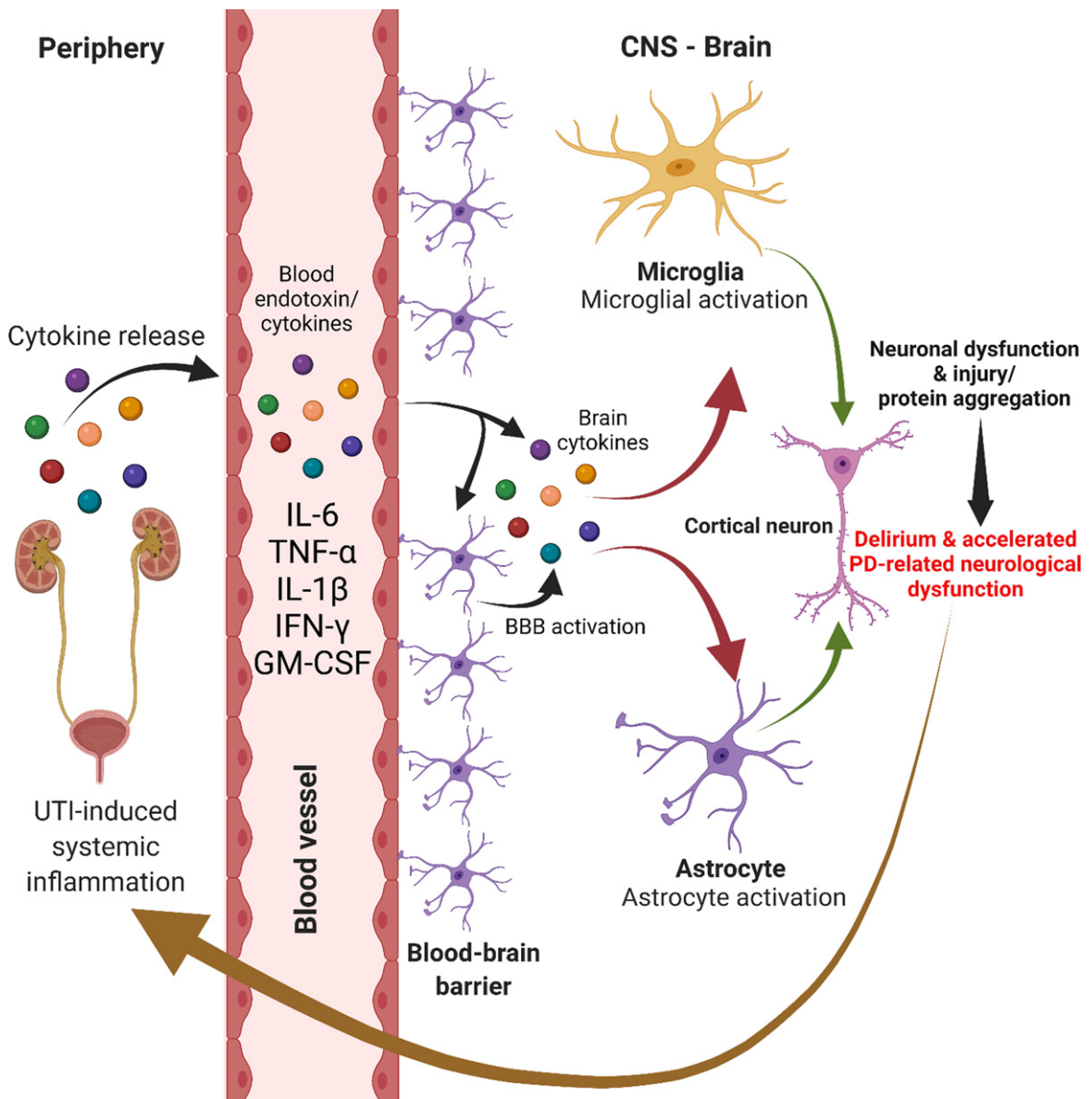

Fig. 2. UTI-induced immune-mediated neurological dysfunction.

areas without a blood-brain barrier [77]. Animal models of UTI demonstrate that the cytokine interleukin-6 mediates neuronal dysfunction of the frontal cortex and hippocampus leading to delirium-like behavioral states [78]. Indeed, it has been proposed that bacterial endotoxins may interact with aggregable proteins to produce neurodegenerative diseases such as PD [79]. Supporting this theory, endotoxins do appear capable of influencing α-synuclein production and aggregation [80, 81] and can contribute to substantia nigra dopaminergic neuronal loss [82, 83]. The possibility that bacterial endotoxins can directly contribute to disease pathogenesis only increases the need for a better understanding of UTI-related neurotoxicity and delirium states (Fig. 2). Indeed, there is evidence that other infections, such as influenza, may precede the diagnosis of PD [84]. Amongst the other studied infections, only urinary tract infection had an increased odds for PD more than 10 years later (increase of 19% [OR, 1.19; 95% CI, 1.01–1.40] for urinary tract infection as compared with increase of 73% [OR, 1.73; 95% CI, 1.11–2.71] for influenza) [84]. The authors suggest that this could be due to early unrecognized autonomic symptoms of PD increasing the risk for UTI, but given the systemic effects of UTIs, it is possible that UTIs could contribute to PD onset due to neuroinflammatory mechanisms.

Delirium that arises in the context of systemic infections such as UTI is an independent predictor of long-term cognitive decline and dementia [85, 86]. An interesting question can be raised regarding this observation: does this demonstrate a reduced cognitive reserve and reflect "subclinical" dementia, or does delirium result in direct neuronal damage, and can delirium accelerate neurodegeneration? There is a limited amount of observational evidence comparing biomarkers such as S100B [87] and interleukins [88] and brain volumetric analysis [89, 90] with and without the presence of delirium. Overall, delirium is associated with higher degrees of inflammation within and outside the CSF, brain atrophy and worse clinical outcomes.

Delirium may have a deleterious impact on clinical outcomes in patients with PD. Two recent review articles found that delirium is associated with worsening cognitive and motor functioning in PD [91, 92]. The biochemical basis of this potentially causative association is unclear but has been explored. Cytokine activation caused by systemic inflammatory stimuli induces degeneration of nigrostriatal dopaminergic neurons in animal models [93, 94]. The authors in

this study posited that abnormally primed microglial cells, in the presence of neurodegeneration, were triggered by the presence of an inflammatory insult to increase translation of pro-inflammatory cytokines, inducing local tissue damage via free radicals and nitric oxide. Could recurrent UTI in the absence of acute delirium predispose to cognitive and functional decline through these same mechanisms? Given the association between UTI and delirium in the PD population, more research is needed on the effect of UTI on long-term clinical outcomes in PD.

MANAGEMENT STRATEGIES TO PREVENT UTI IN PD

Although there is little in the way of high-quality data to prevent UTI in PD, several measures can be considered as part of a multifaceted approach. In general, all patients with PD and urinary retention should be counseled on maintaining adequate hygiene including perineal cleanliness and, if required, aseptic catheterization techniques (discussed below). In addition, regular scheduled bladder and bowel emptying should be encouraged to reduce urinary retention and inadvertent fecal contamination from stool incontinence. There should be a low threshold to treat

Table 1
Concomitant conditions that lead to recurrent UTI and recommendations for prevention [145]

Concomitant conditions	Prevention
Postmenopausal	Vaginal estrogen
Intermittent or indwelling urinary catheter	Catheter care, aseptic procedure
Poor bladder emptying	Refer to specialty care to facilitate better bladder emptying
Benign prostatic outlet obstruction	Consider alpha-blockers or 5-alpha reductase inhibitors until transurethral resection of the prostate (TURP)
Diabetes	Manage hyperglycemia, glucosuria; assess bladder emptying
Advanced uterine prolapse	Surgical correction; vaginal pessary
Enterovesical fistula	Consider suppressive antibiotic until surgical correction
Nephrolithiasis	Consider stone removal, increased fluid intake
Urethral diverticulum	Consider suppressive antibiotic until surgical correction

comorbid medical conditions that increase the risk of urinary retention and UTI, such as benign prostatic hyperplasia or diabetes, and adjustment of medications that promote urinary retention (Table 1). More PD-specific research is urgently needed to address this important issue.

Preventative supplements

Estrogen

Estrogen has a key role in modulating the natural defenses of the lower urinary tract against UTI by promoting vaginal colonization with lactobacilli [95] and regulating cell growth and differentiation [96]. In one randomized controlled trial, the incidence of UTI was significantly lower in women who received topical estrogen compared to placebo (0.5 versus 5.9 episodes per patient-year ($p < 0.001$)). Another multi-center, randomized, open, parallel-group study showed that the cumulative proportion of UTI-free women was significantly higher in the topical estrogen group (45%) compared to the placebo control group (20%) ($p = 0.008$) [97]. These findings derived from general populations strongly suggest that topical estrogen may reduce the risk of UTI in women with PD.

Cranberry products

Though cranberry products are routinely used to prevent UTI, few studies have asserted their beneficial effects [98, 99]. A meta-analysis of 24 studies showed that compared with placebo, water, or no treatment, cranberry products did not significantly reduce the occurrence of symptomatic UTI (RR 0.86, 95% CI 0.71 to 1.04) [100].

Vitamins and other supplements

Similarly, although prophylactic supplements such as ascorbic acid (vitamin C), D-mannose, methenamine hippurate, chlorhexidine, and probiotics are widely used to prevent recurrent UTI, support for their use is not as well-established in clinical studies [101]. However, given the relative safety of these measures, they may be reasonable to consider on a case-by-case basis.

Although several studies have attempted to assess the effectiveness of probiotics in preventing recurrent UTI, the data are mixed and controversial in the general patient population [102]. Although there have been a large number of observational studies done on the gut microbiome in PD [103], the same cannot be said for the urinary microbiome. Interestingly,

one recent randomized control trial ($n = 60$) demonstrated statistically significant improvement in the MDS-UPDRS and several metabolic biomarkers, including quantitative insulin sensitivity check index, homeostasis model of assessment-estimated insulin resistance, malondialdehyde, total glutathione, and high-sensitivity C-reactive protein, following three months of probiotic consumption [104]. Theoretically, positive changes in the gut and/or urinary microbiome may mediate a decreased neuroinflammatory state as host responses are downregulated. This may potentially manifest in symptom reduction and increased subjective well-being. Further research is needed to improve our understanding of the potentially bidirectional relationship between altered urinary microbiome, increased UTI risk and other clinically relevant outcomes in PD.

Bladder irrigation and clean catheterization

Bladder irrigation with various solutions such as aminoglycoside, glycosaminoglycans [105], povidone-iodine [106], chlorhexidine solution [107], and saline with acetylcysteine [108] have been advocated as a management strategy for patients with indwelling catheters or those who require intermittent catheterizations [109, 110]. Although several studies have demonstrated the efficacy of bladder irrigation with various agents [111–113], gentamicin remains the best intravesical treatment that has shown efficacy in both the prevention and treatment of recurrent UTIs [114]. Furthermore, the risk of developing antibiotic resistance and systemic adverse effects is low in patients treated with bladder irrigation with gentamicin [115].

Clean intermittent catheterization has been advocated as a quick, safe, and valuable cost-effective technique in combination with other treatment options to prevent recurrent UTI if the post-void residual is consistently more than 100 mL [116, 117]. Factors that determine the frequency of catheterizations include fluid intake, urine production, patient motivation, patient and caregiver schedules [109]. Patients and/or caregivers should be trained on the aseptic technique of catheterization: sterile gloves and catheter, non-traumatic urethral insertion, appropriate sterile lubricant, perineal hygiene, etc. An assessment of manual dexterity, anatomical, social and psychological factors is very important for patients with PD to improve adherence and prevent catheter-associated UTIs [118, 119]. Alternative bladder drainage strategies should be considered

Table 2
Summary of interventions and recommendations from European Association of Urology [120]

Interventions	Recommendation	Notes
Behavioral modifications	Made despite the absence of directly applicable quality clinical studies	Consistently documented the lack of association with recurrent UTI [146]
Hormonal replacement	Can be recommended	In postmenopausal women applied topically but not oral [137, 147]
Immunoactive prophylaxis	Can be recommended	Based on studies of OM-89 [148, 149]
Probiotics (Lactobacillus)	No recommendation	Differences in effectiveness between available preparations warrant further trials [102]
Cranberry	No recommendation	Further trials are warranted [100]
D-mannose	No recommendation	Further trials are warranted [150]
Endovesical instillation	No recommendation	Large-scale trials are urgently needed [151]
Continuous low-dose antimicrobial prophylaxis	May be given	Offer after counseling, and when behavioral modifications and non-antimicrobial measures have been unsuccessful [121, 152]
Self-diagnosis and self-treatment	Should be considered in patients with good compliance	The choice of antimicrobials-same as for sporadic acute uncomplicated UTI [153]

when patients become severely disabled and incontinence persists resulting in chronic or frequent infections, potentially via suprapubic rather than indwelling catheters [120].

Prophylactic antibiotics

Prophylaxis with oral antibiotics may be considered in highly selected patients who have frequent recurrent UTIs and in whom conservative measures, including behavioral modifications and non-antimicrobial treatments, have been unsuccessful. A double-blinded randomized clinical study evaluated the efficacy and safety of fosfomycin in the prevention of recurrent UTI and showed a significantly lower number of UTI in the antibiotic compared to the placebo group (0.14 vs. 2.97 infections/patient-year; $p < 0.001$) [121]. The potential benefits of a prophylactic antibiotic regimen should be carefully weighed against the risks, including that of producing antibiotic-resistant organisms. Additionally, the dangers of drug-drug interactions and polypharmacy need to be considered carefully. Notably, linezolid, which may be used to treat UTI, can interact with other monoamine oxidase inhibitors such as rasagiline or carbidopa-levodopa [122], and precipitate serotonin syndrome, a feared neuromedical emergency [123, 124]. Ciprofloxacin may also increase plasma levels of ropinirole and exacerbate its adverse effects, such as nausea, dizziness, hallucinations or orthostatic hypotension [125]. A close

review of potential medication interactions is warranted prior to initiation of prophylactic antibiotic therapy in patients with PD and recurrent UTIs.

Minocycline has been suggested as possibly neuroprotective in PD by preventing nigrostriatal dopaminergic neurodegeneration in MPTP treated mice [126, 127] and has potentially positive effects on gut microbiome in PD [128]; however, animal studies have found mixed results, sometimes showing deleterious effects in PD animal models [129, 130]. Furthermore, minocycline may not be an appropriate UTI prophylactic agent due to increased rates of resistance to common UTI pathogens [131]. Ceftriaxone may also have neuroprotective effects against dopaminergic neuronal injury in 6-hydroxydopamine-lesioned rats [132], while ampicillin has been shown to prevent motor and behavioral impairments in toxic post-streptococcal A murine models and increased tyrosine hydroxylase and D1 and D2 receptors in the striatum [133]. However, no human trials in PD have directly compared the efficacy of these antimicrobial agents, thus limiting any specific recommendations.

Emerging interventions

Bacterial interference

Competitive inoculation with commensal or lesspathogenic bacteria is currently under investigation to prevent recurrent UTI. A double-blind randomized crossover trial in patients with incomplete bladder

emptying and recurrent UTI investigated if the deliberate establishment of asymptomatic bacteriuria with *Escherichia coli 83972* reduced rates of UTI recurrence [134]. The study showed that there was a delayed onset of UTI in patients instilled with *E. coli 83972* in the bladder compared to those who were instilled with saline (median 11.3 vs. 5.7 months; $p = 0.0129$). Furthermore, there were significantly fewer episodes of UTIs in patients inoculated with *E. coli 83972* bacteriuria compared to the saline group (13 vs 35 episodes; $p = 0.009$, CI 0.31–1.89). Although the use of less-pathogenic strains of uropathogenic bacteria to compete with and prevent colonization and infection with disease-causing organisms seems promising, the practicality of achieving sustained colonization with non-pathogenic organisms remains a concern.

Vaccines and immunostimulants

Recent innovative efforts have been directed towards developing vaccines against uropathogenic organisms. These vaccines are thought to stimulate immune function by activating dendritic cells, neutrophils, and T helper cells, leading to activation of T lymphocytes and B lymphocytes and associated IgA-mediated immune protection [135, 136]. OM-89 (Uro-Vaxom) is an oral capsule that is comprised of extracts from 18 strains of heat-killed uropathogenic E. coli and is currently available in Europe to prevent E. coli UTI. A systematic meta-analysis of four randomized, placebo-controlled trials of 891 patients with recurrent UTI showed that OM-89 significantly reduced UTI compared to a placebo group with a relative risk of 0.61 (95% CI 0.48–0.78) [137]. In preliminary studies, MV140 (Uromune), a sublingually administered vaccine against four common strains of inactivated uropathogens, E. coli, K. pneumoniae, P. vulgaris and E. faecalis, was shown to dramatically reduce the mean number of UTIs at 3 months compared with usual care with antibiotics (0.36 versus 1.60; $p < 0.0001$) [138]. These provocative results await confirmation in follow-up studies.

Identifying and reporting UTI in PD

Cognitively intact patients with urinary symptoms should have testing with a urinary dipstick as an initial measure to evaluate for the presence of nitrite or leukocyte esterase or, alternatively, a urinalysis to detect pyuria. Although urinary culture is not required in all cases of uncomplicated UTI, it is preferred to document speciation and susceptibility to antibiotics [139]. In cognitively impaired patients in whom self-reporting of urinary symptoms may be limited, an acute change in mental status, with or without localizable genitourinary symptoms, such as dysuria, urgency, or suprapubic pain, should prompt diagnostic testing for UTI [140]. Heightened suspicion for UTI is appropriate when these symptoms occur in combination, as demonstrated in a study of nursing home residents that showed that the combination of dysuria with either a change in the character of the patient's urine or mental status predicted the presence of bacteriuria plus pyuria in 63% of cases [141]. In the future, new technologies may evolve to allow for serial monitoring or automated detection of UTI, perhaps with the use of smart-diapers with built in urinalysis capability [142].

The accurate reporting of UTI in patients with PD is essential to enable assessment of its epidemiological impact. To minimize underestimation of UTI in PD, special care is justified in documenting UTI as a principal cause of admission, rather than as a urinary disorder [143] or urinary dysfunction [144] or to attribute the cause of admission to a consequence of UTI, such as a fall [2].

CONCLUSION

UTI is a leading cause of hospitalizations, morbidity, and mortality in patients with PD. PD is the fastest growing neurological condition and increases the risk of UTI due to a combination of urodynamic factors, cognitive decline, frailty, catheterization, and exposure to antibiotic resistant organisms in longterm care settings. UTI prevention strategies include the use of protective supplements, in particular estrogen, prophylactic treatments with oral antibiotics, bladder irrigation, and clean intermittent catheterization, while emerging strategies such as competitive inoculation and vaccine-based immunomodulatory interventions are currently being investigated. Substantial research efforts are needed to develop specific interventions that mitigate the burden of PD-associated UTI in human suffering and health care resource expenditure.

CONFLICT OF INTEREST

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