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The unexplored relationship between the urinary tract infections and the autonomic nervous system

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Abstract

Urinary tract infections (UTIs), the majority of which are caused by uropathogenic *E. coli* (UPEC), are extremely common infections that preferentially effect women. Additional complicating factors, such as catheterization, diabetes, and spinal cord injuries can increase the frequency and severity of UTIs. The rise of antimicrobial resistant uropathogens and the ability of this disease to chronically recur make the development of alternative preventative and therapeutic modalities a priority. The major symptoms of UTIs, urgency, frequency, and dysuria, are readouts of the autonomic nervous system (ANS) and the majority of the factors that lead to complicated UTIs have been shown to impact ANS function. This review summarizes the decades long efforts to understand the molecular mechanisms of the interactions between UPEC and the host, with a particular focus on the recent findings revealing the molecular, bacteriological, immunological and epidemiological complexity of pathogenesis. Additionally, we describe the progress that has been made in: i) generating vaccines and anti-virulence compounds that prevent and/or treat UTI by blocking bacterial adherence to urinary tract tissue and; ii) elucidating the mechanism by which anti-inflammatories are able to alleviate symptoms and improve disease prognosis. Finally, the potential relationships between the ANS and UTI are considered throughout. While these relationships have not been experimentally explored, the known interactions between numerous UTI characteristics (symptoms, complicating factors, and inflammation) and ANS function suggest that UTIs are directly impacting ANS stimulation and that ANS (dys)function may alter UTI prognosis.

Keywords

urinary tract infection; uropathogenic *E. coli*; autonomic nervous system; complicated UTI; therapeutics

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1. Epidemiology, symptomatology, and clinical classifications of UTI

UTIs are one of the most common infections in the United States, leading to at least 10.5 million clinical visits per year (Foxman, 2014). UTIs preferentially affect women, who have a 60.4% lifetime risk of developing a UTI (Foxman, 2014). Uncomplicated bacterial cystitis is the most common manifestation of UTI with the majority caused by UPEC, defined as a subset of extra-intestinal pathogenic *E. coli* with urovirulence (Hooton, 2012). Recurrent UTI (rUTI) is also common with a 20–30% probability of at least one recurrence within six months of the initial infection (Geerlings et al., 2014). The high rate of recurrence, coupled with the rise in antimicrobial-resistant uropathogens and the ability of these organisms to persist chronically, make UTIs an increasingly troubling healthcare problem (Mabeck, 1972; Ferry et al., 2004; Totsika et al., 2011).

Clinically, UTIs are predominantly detected through the occurrence of specific patient-reported symptoms. Both cystitis and pyelonephritis are characterized by some combination of frequency, urgency and dysuria, each of these symptoms is associated with ANS control of bladder function (Ochodnick et al., 2013; Foxman, 2014). Pyelonephritis is also commonly, associated with fever, back and flank pain, and malaise (Foxman, 2014). The definitive diagnosis of UTI requires the detection of bacteria in the urine, however, a positive urine culture in the absence of symptoms, defined as asymptomatic bacteriuria (ABU), is a common condition where bacteria colonize the bladder in high numbers without causing disease (Trautner et al., 2014). Additionally, both symptomatic UTIs and ABU are characterized by inflammatory markers in the urine including pyuria.

While little work has been done to delineate the mechanisms of sensation in the context of UTI, the symptoms of frequency, urgency, and dysuria are readouts of stimulation of the ANS. It is well established that in healthy bladders the sympathetic branch of the ANS suppresses the contraction of bladder detrusor muscle while increasing contraction of bladder neck sphincters, allowing bladder filling and preventing incontinence (Ochodnick et al., 2013). Conversely, parasympathetic stimulation of pelvic nerves causes the bladder to contract and the bladder neck sphincters to relax, resulting in micturition (Ochodnick et al., 2013). Thus, sympathetic stimulation is predominant in bladder filling and parasympathetic stimulation is responsible for voiding (Ochodnick et al., 2013). Additionally, the bladder is enervated by the afferent nerves of the ANS, which sense bladder pressure and noxious stimuli (Ochodnick et al., 2013). Thus, the defining symptoms separating UTI from ABU, frequency, urgency, and dysuria, are all modulated by the ANS (Figure 1).

There are several categories of UTI, depending on host characteristics and the location of infection. In addition to uncomplicated cystitis and pyelonephritis, numerous other conditions alter UTI by changing the functional and environmental characteristics of the bladder. These complications include Catheter-associated UTIs (CAUTI), structural abnormalities of the urinary tract, diabetes, neurogenic bladder, pregnancy, and age (Chenoweth et al., 2014; Dielubanza et al., 2014; Foxman, 2014; Nicolle, 2014). The mechanisms by which these complications contribute to UTI propensity and severity are just beginning to be investigated. Further increasing the potential mechanistic diversity of UTI is the wide range of potential bacterial and fungal uropathogens. While UPEC account for

~80% of all uncomplicated community acquired UTIs, the remaining 20% are caused by a range of *Candida* sp., Gram-positive and Gram-negative bacteria including *Staphylococcus saprophyticus* and *Klebsiella pneumoniae* (Hooton, 2012; Kauffman, 2014). Unfortunately, while there are clear mechanistic connections between the ANS and UTI symptomology, alterations of ANS function have been understudied in relation to UTI risk. Additionally, though connections between UTI complicating factors and the ANS have been drawn, a role for the ANS in increasing susceptibility to infection and disease severity in complicated UTI has not been considered.

2. Model systems of uncomplicated UTI: disease complexity and therapeutic development

Extensive studies have characterized the molecular mechanisms by which model UPEC strains cause disease in a murine infection model. These studies revealed numerous bacterial virulence factors, including pili, adhesins, toxins, iron acquisition systems, capsular structures, flagella, pathogenicity islands and factors important for biofilm formation to establish and maintain infection within the host (Nielubowicz et al., 2010; Hadjifrangiskou et al., 2012; Ulett et al., 2013). These studies elucidated that cystitis is not necessarily characterized by the simple luminal growth of pathogens in the urine, but rather, involves complex population dynamics including occupation of extra- and intracellular niches with selective pressures and bacterial population bottlenecks during colonization and infection that impact disease outcome (Chen et al., 2006; Chen et al., 2009; Schwartz et al., 2011; Schwartz et al., 2013). Upon introduction into the bladder, UPEC bind either mannosylated uroplakin plaques or $\beta 1$ – $\beta 3$ integrin receptors on the urothelial surface via FimH, a chaperone/usher pathway (CUP) pilus-associated adhesin and invade the urothelium (Wu et al., 1996; Mulvey et al., 1998; Kline et al., 2010). As mechanisms of host defense, UPEC can be exocytosed in a TLR-4 dependent manner (Song et al., 2007). Additionally, the host can exfoliate superficial facet cells to shed attached and invaded bacteria into the urine for clearance (Mills et al., 2000). UPEC can subvert these innate defenses by escaping from the endocytic vesicle into the host cell cytoplasm, where they replicate into biofilm-like intracellular bacterial communities (IBCs) containing 10^4 – 10^5 bacteria (Anderson et al., 2003; Schwartz et al., 2011). Following IBC maturation, UPEC flux out of the superficial facet cell and filament, avoiding the bactericidal action of neutrophils (Justice et al., 2004). These newly luminal bacteria can reinitiate the IBC cycle in any remaining superficial facet cells. Additionally, IBC formation and the innate immune response of cytokine secretion and exfoliation have been observed in all tested mouse strains, but the long-term outcome of infection differs (Hannan et al., 2012). In addition, a wide collection of clinical isolates were all found to form IBCs and filaments after infection of many different mouse strains (Garofalo et al., 2007). Thus, IBC formation is part of a mechanism UPEC uses to colonize and replicate in the bladder.

Several features of acute UTI in the mouse model have subsequently been observed in human clinical samples. Evidence of IBCs and bacterial filaments have been observed in women suffering acute UTI, one to two days post self-reported sexual intercourse, but not in healthy controls or infections caused by non-IBC forming Gram-positive organisms (Rosen

et al., 2007). IBCs have also been observed in urine from children with an acute UTI (Robino et al., 2014). The successful use of mice to generate testable hypotheses, subsequently observed in humans, suggests that this system could be employed to examine the role of ANS function and dysfunction in UTI disease progression.

Acute infection in the absence of effective treatment can lead to one of three potential outcomes in mice: i) chronic cystitis; ii) resolution with complete clearance from the bladder; iii) resolution with the establishment of quiescent intracellular reservoirs (QIRs). Chronic cystitis is characterized by persistent high titer bacteriuria ($>10^4$ CFU/ml), chronic inflammation, and high bacterial bladder burdens ($>10^4$ CFU) two or more weeks after inoculation (Hannan et al., 2010). During chronic cystitis, persistent lymphoid aggregates, urothelial hyperplasia and a lack of terminally differentiated superficial facet cells are hallmark features (Hannan et al., 2010). These histological findings have also been observed in humans suffering persistent bacteriuria and chronic cystitis (Schlager et al., 2011). Infected mice initially experience urinary frequency and dysuria as determined by reaction to noxious stimuli and nerve responses during acute infection; however, the symptoms mice experience during chronic cystitis have not been examined. Interestingly, elevated serum levels of interleukins (IL) 5 and 6, keratinocyte cytokine (KC/CXCL1), and granulocyte colony-stimulating factor (G-CSF) in C3H/HeN mice 24 hours post infection predicted the development of chronic cystitis suggesting that a host-pathogen checkpoint during acute infection determines disease outcome (Hannan et al., 2010; Hannan et al., 2012). While acute UTI often self-resolves in mice, these resolved infections frequently result in the formation of QIRs, small collections of non-replicating intracellular bacteria in LAMP1 positive vesicles (Mysorekar et al., 2006). QIRs are resistant to antimicrobial treatment and are capable of reemergence, seeding subsequent infections (Blango et al., 2010; Guiton et al., 2012a). Thus reservoir formation following UTI resolution could contribute to recurrence.

The mouse UTI model is also being used to examine other risk factors for the development of rUTI, including host genetic susceptibility, the impact of prior UTI incidence on subsequent UTI frequency, and the role of sexual activity in UTI frequency. To model host genetic diversity, numerous mouse strains and mutants have been tested for their susceptibility to acute cystitis, pyelonephritis, and chronic cystitis (Hannan et al., 2010; Godaly et al., 2015). One notable pattern is that defects in the toll-like receptor 4 (TLR4) mediated response to the UPEC lipopolysaccharide (LPS) leads to decreased inflammation and reduced UTI severity while defects further down this innate immune signaling cascade result in abrogated bacterial clearance and exacerbated disease progression (Godaly et al., 2015). A prior history of UTI is one of the highest risk factors for the development of subsequent UTI episodes. This can be recapitulated in the mouse model, where a previous chronic infection was shown to greatly increase the sensitivity of mice to future infections thus establishing a relevant model to study the impact of UTI history on rUTI (Hannan et al., 2010; O'Brien et al., 2015). Frequent sexual intercourse is another established risk factor for the development of UTI, likely through the mechanical introduction of uropathogens into the bladder which has been modeled by a successive inoculation technique termed superinfection. Interestingly, 30% of the otherwise resistant C57BL/6J mouse strain developed chronic cystitis if superinfected. Serum elevations of IL-6, KC, and G-CSF prior

to superinfection predicted the development of persistent bacteriuria in C57BL/6J mice similar to singly infected C3H/HeN mice. Superinfecting C3H/HeN mice also increased the proportion of mice experiencing chronic cystitis (Schwartz et al., 2015). These studies demonstrate that animal models of UTI are relevant and flexible platforms for examining the molecular mechanisms of host-pathogen interactions.

Deepening our understanding of the complex host-pathogen interactions during UTI, and elucidating the molecular mechanisms of disease has led to the development of multiple potential therapeutics that function independently or synergistically with antimicrobials. UPEC adherence via CUP pili is crucial to the establishment of UTI. Detailed studies outlining the structural and molecular basis of pilus biogenesis and ligand binding have resulted in small molecule inhibitor development targeting CUPs (Kline et al., 2010; Kostakioti et al., 2013). Mannosides, synthetic mannose analogues, that bind to the type 1 pilus adhesin, FimH, have been shown to be efficacious in the treatment and prevention of UTI and to potentiate the activity of antimicrobials (Han et al., 2010; Klein et al., 2010; Cusumano et al., 2011; Guiton et al., 2012a). Further, vaccination with recombinant FimH protein imparts protective immunity to UPEC UTI in both mice and Cynomolgus monkeys (Langermann et al., 1997; Langermann et al., 2000). Numerous studies, both molecular and epidemiological have demonstrated the importance of iron acquisition for successful UTI pathogenesis (Garcia et al., 2011). Immunization with the iron uptake components, including the most promising iron uptake vaccine candidate, FyuA, provided some protection against pyelonephritis in mice (Brumbaugh et al., 2013). Additionally, recent studies have demonstrated that mitigating the host immune response to reduce the severity of inflammation had profound impacts on decreasing the susceptibility to rUTI and/or chronic cystitis (Hannan et al., 2014). Further, a small clinical study suggested that administration of the anti-inflammatory ibuprofen to UTI patients results in similar outcomes to antimicrobial treatment (Bleidorn et al., 2010). In addition to mediating bladder function, stimulation of both the sympathetic and parasympathetic branches of the ANS modulates the activity of the immune system (Koopman et al., 2011). While pharmacological modulation of the ANS during uncomplicated UTI has not been studied, the stimulation of voiding through the administration of bethanechol chloride was necessary to potentiate the antimicrobial combination trimethoprim/sulfamethoxazole (TMP-Sulfa) during the treatment of *E. coli* associated urinary malakoplakia (Qualman et al., 1984). In this study, treatment with TMP-Sulfa resulted in sterile urines but failed to kill plaque resident bacteria, leading to immediate recolonization of the urine upon cessation of therapy, indicating that both antimicrobial treatment and stimulation of the ANS were necessary to clear the bacterial colonization (Qualman et al., 1984). If manipulation of the ANS could alleviate disease symptoms and facilitate bacterial clearance while also reducing counterproductive inflammation, it would make pharmacological modulation of the ANS a novel avenue for the development of alternative therapeutics to improve patient prognosis without exerting selective pressures on the uropathogens.

3. Host and pathogen diversity suggest variation in pathogenic mechanisms

While 60% of women present with at least one UTI during their lifetime and 20–30% of these women will experience one or more recurrences, the remaining 40% of women never present with a UTI (Foxman, 2014). This range of susceptibilities suggests a genetic basis underlying host resistance to UTI. Indeed, human gene association studies revealed numerous polymorphisms in several innate immune pathway genes, most frequently TLR genes, correlating with altered propensity for different manifestations of UTI (Godaly et al., 2015). These findings agree with the varying susceptibilities of mouse strains to the development of chronic cystitis, pyelonephritis, and ABU (Hannan et al., 2010; Godaly et al., 2015; O'Brien et al., 2015).

In addition to host variation, the role of bacterial diversity in UTI is becoming more acutely appreciated. *E. coli* is genetically versatile, possessing ~2200 “core” genes conserved throughout the species and an additional 2000–3000 variable “accessory” genes in each *E. coli* strain, resulting in an expansive pan-genome (Chaudhuri et al., 2012). Phylogenetic analysis of core genes separated *E. coli* into multiple clades that are only marginally predictive of pathogenic characteristics (Chaudhuri et al., 2012; Hazen et al., 2013). It is generally appreciated that the severity of UPEC UTI is weakly predicted by the virulence factor profile of the infecting organism (Brzuszkiewicz et al., 2006; Norinder et al., 2012; Srivastava et al., 2014). Additionally, the phylogenetic diversity of UPEC is exceptionally broad with documented UTIs being caused by strains originating from nearly all *E. coli* clades (Chen et al., 2013; Bielecki et al., 2014). These findings, combined with the diversity of uropathogenic microorganisms, each causing UTI with similar symptoms, suggest that the limited symptomatology associated with UTI may obfuscate an array of novel molecular mechanisms and that better characterization and differentiation of these mechanisms could facilitate the development of targeted therapeutics to improve the treatment and prevention of UTI. The division of diarrheagenic *E. coli* into pathovars on the basis of their disease characteristics, including symptomatology and histological hallmarks, results in a classification that tracks weakly with the phylogenetic structure of the core genes but rather, is predictive of the presence of sets of virulence factors that mediate the specific disease properties of the infecting organism (Chaudhuri et al., 2012; Hazen et al., 2013). By analogy to UPEC, research into the diarrheagenic *E. coli* would be greatly confounded if all episodes of diarrhea caused by *E. coli* were assumed to function via a single mechanism. The assumption of a single unifying molecular mechanism used by UPEC to cause UTI has likely inhibited the discovery of a set of pathogenic mechanisms that would better explain the diverse and currently unpredictable nature of UTI in the clinic (Figure 2).

4. Models of complicated UTI

Though uncomplicated UTI has received the most research attention, models of complicated UTI have also been developed. A silicone implant-based CAUTI model has been used to characterize molecular interactions and host processes resulting from implantation that facilitate sustained bladder colonization by *E. faecalis*, a prominent causative agent of

CAUTI (Guiton et al., 2010; Guiton et al., 2012a; Guiton et al., 2012b). A follow-up study identified fibrinogen deposition on the catheter and increased urine protein concentrations as the key factors potentiating *E. faecalis* CAUTI. This led to the development of a novel vaccination strategy to prevent *E. faecalis* CAUTI (Flores-Mireles et al., 2014).

Models examining UTI in the context of type 1 diabetes, age, parity, and neurogenic bladder following spinal cord injury have also been developed. Mice treated with streptozocin to induce uncontrolled type 1 diabetes demonstrated susceptibility to lower inoculum sizes, increased bladder and kidney burdens of the alternative uropathogens *K. pneumoniae* and *E. faecalis*, and manifested biofilm-like colonization of the renal tubules by UPEC (Rosen et al., 2008). These findings recapitulate the clinical observations of increased UTI diversity and susceptibility in diabetic individuals. Epidemiological studies have associated advanced age, pregnancy and increased parity, with a higher risk of UTI complications (Bachman et al., 1993; Rowe et al., 2014). These risk factors were examined by determining bladder and kidney bacterial burdens of retired breeder and age-matched nulliparous mice (7–11 months old) and compared to standard young (7–9 week old) nulliparous mice. While mice develop resistance to UTI as they age, increased parity counteracts much of this resistance (Kline et al., 2014). These data partially recapitulate the clinical observations, but increased resistance to UTI with advanced age directly conflicts with these observations, necessitating further model optimization (Kline et al., 2014).

Disruptions to the neurological control of bladder function, such as traumatic spinal cord injury (SCI) or spina bifida, lead to neurogenic bladder, a condition characterized by impaired somatic/ANS coordination leading to aberrant bladder emptying and increased residual urine retention (Hou et al., 2014; Nicolle, 2014). The urine retention observed in this population is believed to contribute to the increased UTI frequency (Nicolle, 2014). This was tested in SCI rats, which develop increased average urine retention volumes, however the severity of the UTI did not correlate with retention volume (Balsara et al., 2013). Conversely, SCI rats developed bacteriuria with substantially lower doses of UPEC and exhibited an exaggerated immune response to lower inocula (Balsara et al., 2013; Chaudhry et al., 2013). These studies suggest that physiological or neurological alterations to the bladder in addition to urine retention contribute to the increased sensitivity of this population to infection. Neurogenic bladders have altered ANS receptor density but the functional consequences of this alteration with regard to UTI susceptibility are unknown (Ochodnick et al., 2013).

5. UTI symptomatology suggests disruption of the ANS during disease

While interactions between the ANS and UTI have not been examined, studies addressing the bacterial and immunological mechanisms of bladder pain during UTI have been conducted. Employing a method for measuring the pain experienced during UTI in a mouse model it was determined that TLR4 mediated recognition of LPS mediates the pain sensation (Rudick et al., 2012). Interestingly, pain sensation appears to be tied to O-antigen modifications attached to LPS and not exclusively to inflammatory TLR4 stimulation by the lipid A LPS core (Rudick et al., 2012). This suggests that UPEC encoding particular O-antigen structures that impact pain sensation may contribute to the different symptomatology

experienced by individuals with ABU versus UTI, thus linking bacterial structures to nervous stimulation (Rudick et al., 2012).

In the animal models of UTI, the role of the immune system has regularly been assessed. These experiments addressed the impacts of different mechanisms and degrees of immune activation on the severity and outcome of disease and have implicated immunomodulation as a promising therapeutic avenue (Bleidorn et al., 2010; Hannan et al., 2014). Conversely, little work has assessed the impact of the ANS and urinary tract enervation on UTI, nor has the impact of UTI on the ANS been intensively studied. This is unfortunate as several studies suggest important roles for the ANS both in the diagnosis and control of UTI. The primary diagnostic symptoms of UTI are patient-reported frequency, urgency and dysuria, each of which is a manifestation of feedback through the ANS. A better understanding of the impact of UTI on these ANS functions could lead to better diagnostic methods and facilitate rationally designed treatment modalities. The conditions associated with complicated UTI are also likely to impact the ANS. Multiple studies have shown that diabetes, aging, pregnancy, and neurogenic bladder all alter ANS receptor density or function (Lepor et al., 1989; Levin et al., 1991; Yoshida et al., 2001; Wuest et al., 2005; Ochodnický et al., 2013). While little work has been done to examine the impact of catheterization on the enervation of the bladder, the functional changes that result from implantation in the mouse model are similar to the conditions above, particularly dysfunctional bladder emptying, suggesting that catheterization could impact ANS mediated control of bladder function (Guiton, P.S., Flores-Mireles, A.L., Hibbing, M.E. and Hultgren, S.J. unpublished results). Finally, noninfectious inflammation in the bladder has been shown to increase ANS receptor density or sensitivity (Giglio et al., 2005; Ikeda et al., 2009). All of these findings imply direct connections between the complicating factors of UTI and the ANS.

6. Conclusions: a new avenue of inquiry

In spite of the suggestive conceptual links between the ANS and UTI, little work has been done to establish a connection between these potentially intertwined topics. The primary symptoms of UTI demonstrate that this disease impacts the ANS during acute infection as multiple aspects of urinary bladder function and sensation are disrupted and stimulation of the ANS has contributed to the clearance of one rare form of recurrent UTI. Similarly, the vast majority of complicating conditions and risk factors appear to impact bladder ANS function. This commonality has been largely ignored in the study of UTI and provides a clear and exciting new avenue for basic and translational research to determine the role the ANS plays in modulating pathogenesis and potential ways the ANS could be pharmacologically modulated to improve treatment efficacy (Figure 3).

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Highlights

- We review the epidemiology and pathogenesis of uncomplicated and complicated UTI
- ANS associated symptoms separate symptomatic UTI and asymptomatic bacteriuria
- There is a dearth of experimental or mechanistic evidence linking UTI to the ANS
- Future studies addressing the reciprocal link between UTI and the ANS are suggested

Figure 1. Clinical features of asymptomatic bacteriuria and urinary tract infections

The clinical characteristics of ASB (contained in the blue oval) represent a subset of those of UTI (contained in the red oval). The critical differentiating factors, urgency, frequency, and dysuria are all functional manifestations of ANS. Thus, ANS involvement/dysfunction is a key distinguishing feature between the benign and pathogenic states of urinary tract colonization.

Figure 2. The pathovars of diarrheagenic *E. coli* (DGEC) facilitate the molecular and epidemiological understanding of DGEC

Simple categorization systems such as grouping all DGEC or extraintestinal pathogenic *E. coli* (ExPEC) strains into large general groupings obscures mechanistic diversity and inhibits the discovery of virulence factor sets necessary for causing different forms of disease. The DGEC have been effectively subdivided into pathovars based on disease symptoms and molecular mechanisms including the attaching and effacing and Shiga toxin producing *E. coli* (AEEC and STEC), which are subsequently subdivided into the enterohemorrhagic *E. coli* (EHEC and include the O157:H7 subtype) as well as typical and atypical groups of AEEC. The currently accepted ExPEC divisions are based on the location of the infection rather than symptomatology or virulence factor profile. The result is that all UPEC are essentially grouped together with vague subdivisions that have no clear genetic basis. Thus, unknown diversity in potential pathovars of UPEC may be obscured. This may explain why attempts to identify unifying characteristics in a large group of potentially diverse ExPEC/UPEC have been met with difficulty. A hypothetical, more detailed categorization, subdividing the ExPEC/UPEC based on pathogenic characteristics and virulence factor complement would likely aid in the elucidation of novel pathogenic mechanisms and improve our understanding of this diverse group of pathogens

Figure 3. Interplay between urinary tract infection, inflammation, and the autonomic nervous system and the opportunities for pharmacological intervention

The central cycle of this figure depicts known and proposed interactions between UTIs, inflammation, and the ANS. It is well established that UTIs cause infection and that uncontrolled inflammation exacerbates UTI severity. Similarly, inflammation has been shown to impact ANS function and ANS stimulation alters inflammatory cytokine production and immune cell/organ behavior. Direct interactions between the ANS and UTI have not been experimentally examined, but, given the role of the ANS in UTI symptomatology, it is likely that UTI stimulates the ANS. Additionally while the evidence demonstrating that UTI complicating factors, such as age, pregnancy, and diabetes, alter ANS function strongly suggests that ANS dysfunction contributes to UTI susceptibility and severity. The interactions between UTIs, inflammation, and the ANS suggest avenues for actual and potential therapeutic intervention. The colored boxes indicate the proximity of the treatment modalities to clinical application red = current clinical use for cure, purple = current clinical use for symptom relief but not cure, blue = successful application in model systems, and grey = novel theoretical intervention.