Sex and other host factors influencing urinary tract infection pathogenesis

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Abstract

Biological sex represents the most important host factor that influences urinary tract infections (UTIs), which are most commonly caused by uropathogenic *Escherichia coli* (UPEC). UTI susceptibility varies by sex and age throughout the patient lifespan, although the disease disproportionally afflicts women throughout the middle ages. Substantial male patient populations are also affected, and morbidity in complicated UTI is higher in men. This review highlights sex-related discrepancies in the disease, and how sex may influence the pathogenesis, outcomes, and treatment of ascending UTI.

Keywords: urinary tract infection, sex differences, androgens, testosterone, estrogen, pyelonephritis, cystitis, renal abscess

1 Introduction

“From womb to tomb” *it matters*, argues the 2001 Institute of Medicine report [1]; biological sex should be a fundamental consideration in human health and disease. Indeed, a number of human diseases manifest profound sex-based differences in prevalence, incidence, severity, and response to treatment. Yet, sex as a biological variable has long been ignored experimentally in the biomedical sciences and clinically in the application of evidence-based medicine [2], [3]. Research and medicine in the US and other countries are currently on the verge of a paradigm shift in which sex should and will increasingly be considered from bench to bedside [2], [3], [4].

Such a sex bias is well entrenched in our understanding of urinary tract infections (UTIs), a collection of diseases which have been both prejudiced and understudied because of their disproportionate affliction of women and long-standing experimental and clinical sex biases. UTIs are among the most common bacterial infections that plague humans. On an epidemiologic basis, community-onset UTI is widely viewed as a disease only of women; indeed, its occurrence between 2 and 60 years of age is almost exclusive to females, and it is estimated that at least half of American women will suffer a UTI during their lifetimes [5]. However, in certain populations the incidence of male UTI matches or exceeds that in females; epidemiologic data also suggest a sex difference in morbidity from upper-tract UTI [6], [7], [8], [9]. To better understand resistance and susceptibility mechanisms to UTI, it is important that we consider age- and sex-related discrepancies that are evident in the disease, and how sex and other host factors may influence the pathogenesis and outcomes of ascending UTI.

2 Host factors influencing UTI

Though contemporary and emerging technologies will enable further investigation of the presumed sterility of the urinary tract, microbiologic health of the urinary tract depends on multiple host factors, including a finely tuned innate inflammatory response, which act to eliminate potential uropathogens from the bladder and kidneys [10], [11], [12], [13]. Despite repetitive exposure of this potentially hospitable, nutrient-rich environment to bacterial pathogens (e.g., following sexual intercourse [14]), bacteriuria in the otherwise healthy human host usually is transient [15], [16], [17]. Host traits that compromise the defenses of the urinary tract augment disease susceptibility, severity, and progression. Forward flow of urine provides a formidable mechanical defense; dysfunctional voiding and other urodynamic abnormalities are clearly associated with increased susceptibility to UTI in children and adults [18]. Such conditions in the adult female likely include pregnancy, which also predisposes to UTI [19]. Factors which increase the hospitability of the bladder microenvironment to infection, such as glycosuria associated with diabetes

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mellitus, likewise increase susceptibility to UTI [20]; hyperglycemia may also additionally compromise the activity of phagocytes. Finally, impairment of the innate immune response either by immunosuppression or genetic defects in innate components lead to increased frequency of UTI [12]. Multiple efforts to define human genetic variation imparting susceptibility to UTI have been modestly successful. Attention in this realm has been focused largely on host innate immune genes. However, it has also become clear that susceptibility is both polygenic and environmental, and that genetic determinants of distinct clinical syndromes (asymptomatic bacteriuria, cystitis, and pyelonephritis) must be pursued independently.

3 Sex and UTI

However, the host trait that is most influential in the development of UTI is undeniably biological sex. The frequency of UTI changes drastically across the lifespan and varies by sex [21]. As mentioned previously, the occurrence of UTI in middle age is almost exclusive to females. However, certain populations show an increased risk of male UTI.

UTI in young children is common [22], [23]. The sex ratio in UTI incidence among infants is approximately 2:1 – still favoring females, but at a much lower ratio than in later childhood and beyond. In fact, many studies have shown that male UTI cases outnumber females within the first 3–6 months after birth [24], [25], [26], [27], [28], [29], [30], [31]. Thereafter, UTI susceptibility wanes in males throughout later infancy. Infants and young children thus may represent a unique patient population in which to investigate sex differences in UTI. Clinically, prompt diagnosis and treatment of UTI in infancy is necessary to prevent renal scarring and potential long-term complications [32]. Interestingly, a history of maternal UTI during pregnancy has been associated with up to a 5.9-fold higher risk of UTI in both sexes during infancy [33], [34]. It is unclear if this risk arises from inheritance of genetic predisposition to UTI, intrapartum or postpartum transmission of virulent uropathogens from the maternal genitourinary tract to the microbiota of the infant, or other environmental factors.

Though women represent >90% of UTI patients between early childhood and late middle age [5], [35], [36], complicated UTI manifests in both sexes across this time frame in patients with indwelling urinary catheters, diabetes mellitus, spinal cord injuries, immunosuppression, and structural or urodynamic abnormalities. Notably, while female cases of complicated and upper-tract UTI (pyelonephritis) outnumber male cases overall, men carry an increased risk of mortality from these infections [6], [7], [8], [9]. Thousands of men, particularly those of advancing age, also suffer from acute and chronic bacterial prostatitis, a clinical diagnosis with signs, symptoms, and etiological pathogen profiles that overlap substantially with those of lower UTI in females [37], [38]. The incidence of UTI in males increases substantially after 60 years of age, largely because of abnormal voiding patterns due to acquired urodynamic abnormalities (e.g., benign prostatic hyperplasia) [5], [21], [39]. In total, UTIs comprise debilitating diseases with substantial morbidity and occasional mortality among males [37], [38].

Though a number of distinct bacterial pathogens may cause UTI and prostatitis, uropathogenic *Escherichia coli* (UPEC) predominate among etiological agents in both sexes, causing >80% of community-onset UTI, roughly one fourth of hospital-acquired UTI, and >70% of infectious prostatitis [5], [21], [40]. Our knowledge of the molecular details of UPEC pathogenesis has been developed largely in an exclusively female murine model. In this widely used model of bacterial cystitis, female mice are briefly catheterized and uropathogenic bacteria inoculated into the bladder lumen; however, the bladders of male mice are not reliably accessed by catheter, precluding studies of male cystitis and pyelonephritis using this method. Upon delivery to the female bladder, UPEC and other uropathogens first encounter the stratified transitional epithelium, lined by a single layer of large, multinucleated superficial facet cells apically coated with an array of integral membrane proteins known as uroplakins [41]. UPEC exploit mannose moieties decorating these uroplakins as the receptor for their major virulence determinant, adhesive type 1 pili [42], [43]. Following type 1 pilus-mediated attachment to the uroepithelium, UPEC are rapidly internalized into superficial facet cells [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60], [61]. After a single bacterium has invaded a facet cell, it may then rapidly replicate in the host cell cytoplasm, initially forming loose collections that subsequently coalesce into densely packed intracellular bacterial communities (IBCs) [50]. Infected bladder epithelial cells may be exfoliated, eliminating some IBCs in the urine [62], [63]; meanwhile, a subset of UPEC may flux from the mature IBC, assume a filamentous morphology that resists neutrophil phagocytosis, and initiate further rounds of IBC formation by invading nearby naive epithelial cells [64], [65]. Murine and *in vitro* evidence for this IBC cascade has been corroborated by detection of shed IBCs in female human urines [66], [67], suggesting that the murine IBC pathway recapitulates acute cystitis in women.

This paradigm, in which cystitis pathogenesis depends on an intracellular cascade, has been recently expanded to male hosts. The technical barriers to modeling UTI in male mice have long been simply

accepted in the field, with the rationalization that females comprise the important population of UTI patients anyway. To overcome the technical hurdles, we recently devised and optimized a strategy to induce UTI via mini-surgical inoculation of the bladder in both sexes of mice. Acute UPEC cystitis in male mice recapitulated the intracellular bacterial community pathway previously shown in females [68]. Intracellular bacteria have also been recently identified within exfoliated bladder epithelial cells from the urine of infected male infants [69]; these findings collectively suggest that the IBC cascade is important for the development of acute bacterial cystitis in both sexes.

The sex discrepancies seen in UTI epidemiology have been traditionally attributed to anatomic (and less conclusively, hygienic) factors, including the permissiveness of the surrounding vaginal and perineal environments to microbial colonization, a shorter distance from the anus to the urethral meatus, and shorter urethral length in females. Our data demonstrating similar bladder infectivity between male and female mice after direct inoculation [68] offers empirical data to support this long-standing hypothesis that UTI risk in females is potentiated by these anatomic features, and is not driven by intrinsic epithelial receptivity or comparatively diminished immune resistance within the urinary tract of women. Conversely, normal anatomy represents a key defense against ascending bacterial infection in boys (past infancy) and men [68].

4 Male UTI

Unfortunately, the epidemiology, diagnosis, and treatment of UTI in male populations have been poorly described compared to the robustly studied female populations, although substantial differences exist between them [70]. Infections of male accessory organs, including prostatitis, epididymitis, orchitis, and seminal vesiculitis, can also be classified as exclusively male forms of UTI. UTI in adult male patients is often viewed as “complicated,” if only because of the relative paucity of cases in men compared to women.

Males also exhibit an increase in some specific risk factors that potentiate UTI. A lack of circumcision increases risk for UTI in both infants [71], [72], [73] and adult men [74]. Men have a striking predilection for spinal cord injury, outnumbering female cases four to one; chronic, recurrent UTIs present a difficult and often lifelong challenge in patients with neurogenic bladder arising from such injuries and other causes [75]. Complicated UTI also manifests in hospitalized males with indwelling urinary catheters, those receiving immunosuppression, and those with structural abnormalities (particularly in infancy).

Optimal treatment regimens (antibiotic choice and duration) for uncomplicated UTI in females have been the subject of numerous clinical trials, and the contemporary clinician can rely on published guidelines for these patients [76], while evidence supporting proper choice of antimicrobial agents and duration of therapy for men is less clear. Many expert recommendations call for extended (14 days or longer) courses of antibiotic therapy to treat male UTI [39], [77], [78], [79]. However, a recent study found no differences in acute resolution or recurrence rate between male UTI patients treated for <7 days versus those treated for >7 days; moreover, longer-duration therapy was associated with the subsequent development of *Clostridium difficile* infection [80]. Ongoing studies and clinical trials are expected to inform the development of more evidence-based and specific recommendations for treating male UTI [81].

5 Hormones

Developing evidence suggests that hormonal milieu, specifically estrogen and testosterone influence, may impact UTI susceptibility and severity. Our increasing knowledge of this field is particularly interesting as it may ultimately inform approaches that represent alternatives to antibiotic treatment.

There are extensive but somewhat conflicting data on the influence of estrogen on susceptibility to UTI. Young adult women, who exhibit the highest estrogen levels, account for the majority of community-onset UTI cases, and high estrogen levels have been linked to increased UTI susceptibility [82]. However, post-menopausal females also experience an increased incidence of UTI, which in some cases has been treated with estrogen supplementation. Results from murine studies employing ovariectomized and/or estrogen-supplemented females to examine the influences of estradiol on UTI pathogenesis are likewise conflicting. Some studies have found modest increases in bladder bacterial burdens in estrogen-depleted hosts, particularly during the acute phase of cystitis [83], [84]. Conversely, we found no change in susceptibility to chronic cystitis or pyelonephritis in ovariectomized female mice [68], and Curran et al. noted an increased risk of upper-tract UTI in mice following estrogen treatment [85]. These experimental models notably bypass the vaginal and periurethral microenvironment, as mice are inoculated by transurethral catheterization of the bladder. Collectively, the available data suggest that the impact of

estrogen on bacterial pathogenesis within the urinary tract proper is likely minor. However, many have posited that estrogens may influence periurethral colonization by uropathogens and alter UTI-relevant facets of the vaginal environment (e.g., composition of the vaginal microbiome, dryness, sexual intercourse frequency). In line with this hypothesis, a Cochrane review concluded that topical estrogens show possible benefit in reducing UTI risk, albeit with a number of side effects [86]. Of note, recent evidence suggests that high estradiol levels may cause opposing changes in both bladder fortification and receptivity to infection, providing a viable hypothesis for inconsistent estrogenic influences on UTI. High estradiol levels may induce expression of major adhesive receptors for uropathogens in bladder epithelial cells *in vitro* (thereby promoting increased bacterial adherence and invasion), while a protective effect may be attributable to its ability to induce antimicrobial peptides during acute UTI [84].

The influence of testosterone on UTI susceptibility has only recently been explored. As described above, our initial investigation of sex differences in murine UTI pathogenesis revealed that susceptibility to acute cystitis remained fairly similar between sexes [68]. However, male mice displayed strikingly higher susceptibility to chronic cystitis and severe pyelonephritis, as well as formation of renal abscess – an event that is very uncommon in immunocompetent female mice [68], [87], [88]. Castration substantially abrogated male susceptibility to UTI, while provision of exogenous testosterone restored severe UTI outcomes, demonstrating a previously unrecognized role of androgens in UTI susceptibility [68]. If testosterone administration also promotes these complicated UTI outcomes in female mice, then modulation of androgens might ultimately be a viable adjunct therapy in some UTI patients. Future investigation using our model of surgical infection for sex comparisons will continue to give insight into mechanistic differences in UTI initiation, progression, and persistence in both male and female hosts [68].

6 Conclusion

Men and women display fundamental differences in their susceptibility to infectious diseases. These dissimilarities stem from a multitude of differences: in pathogen exposure, cultural and behavioral issues, anatomy, hormonal expression, treatment efficacy, socio-economic influences, and many more. Most notably, sex differences in immunity have been clearly described, with females displaying enhanced resistance to many infections because of more robust immune responses controlling pathogens [89], [90], [91]. This enhanced defense in women has been hypothesized to have evolved from the need to protect their fetuses from infection [92], and is associated with the greater frequency and severity in women of many chronic inflammatory and autoimmune diseases [93], [94].

Ascending UTI represents a contradiction to this paradigm, being one of the few infectious diseases which disproportionately afflicts females over males. In considering how biological sex influences UTI, the chief protective mechanism for males is anatomy, while repeated introduction of bacterial pathogens to the urinary tract in females necessitates a finely tuned innate surveillance and defense system as primary protection. Accordingly, traits or interventions which bypass or hamper these defenses represent risk factors for chronic and/or recurrent UTI [13]. As described above, new experimental models that bypass lower anatomic barriers will enable the study of immunologic and other sex differences in cystitis and pyelonephritis. Recent calls by the US National Institutes of Health [4] and in the basic and clinical literature [2], [95], [96] for sex-based research approaches to infectious and other diseases, including a specific focus on UTI [80], [97], should help to accelerate research progress in this arena. Continued work on studying sex differences in these conditions promises to inform the development of novel therapeutics and interventions, yielding better sex-based treatment and prevention strategies for the benefit of all patients.

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