The pathophysiology of urinary tract infections

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Abstract

Urinary tract infections are amongst the most bacterial infections. They can occur in either an uncomplicated host setting, where there is no underlying structural or functional abnormality of the patient's genito-urinary tract, or complicated, where there is. For the latter, common predisposing factors are the presence of a foreign body, including urinary catheter, or disruption of normal urinary flow by obstruction or retention. Bacteria vary widely in their ability to successfully invade the urinary tract; the vast majority of such infections being due to a small number of species. The route is usually ascension from the urethra. Certain uropathogenic strains of *Escherichia coli* are the most proficient as measured by their frequency of being the identified cause. Such strains display a number of virulence factors which enable them to occupy this niche – which with increasing understanding, may promote different methods of treating. Other species are often implicated only in the presence of an underlying urological abnormality. The presence of a urinary catheter, or other urine drainage device, provides a ready scaffold for organisms to develop a biofilm, which in turn shields them from being eradicated successfully. Renal calculi similarly can be linked to biofilm production.

Keywords Biofilm; catheter; cystitis; *Escherichia coli*; pyelonephritis; urease

Introduction

Urinary tract infection (UTI) is one of the most common bacterial infections, particularly affecting women. Up to half of women will suffer at least one episode of UTI in their lifetime and one in four of these women will develop a recurrence.[1,2] Signs and symptoms differ according to the site of infection; upper UTI (pyelonephritis) classically presents with fever and flank pain whilst lower UTI (cystitis) typically presents with some or all of the following: dysuria, frequency, haematuria and suprapubic tenderness. Here we examine the mechanism of UTIs and the host and microbiological factors associated with these infections. Key predisposing host factors involved in complicated UTIs are either obstruction of normal urinary flow, such as by congenital anomalies, renal calculi or prostate enlargement; or the presence of a foreign body – such as a urethral or suprapubic catheter.[2]

Practical interpretations of commonly used terms[2–4]

Cystitis: bladder inflammation. Clinical syndrome of dysuria, urinary frequency and urgency, which may be accompanied by supra-pubic tenderness. The commonest cause of the inflammation is infection, but not exclusively. These symptoms and signs can be termed those of the 'lower urinary tract', and the infection has not ascended beyond the bladder.

Urethritis: inflammation of urethra, usually due to infection. Associated symptoms may mimic those of cystitis. Infective causes, such as *Neisseria gonorrhoeae* or *Chlamydia trachomatis*, are usually acquired during sexual contact and do not ascend to the bladder, so although the urethra is normally the final passageway for urine from the body (and the primary route for organisms to gain access to the bladder and beyond), specific urethral infections are not usually included in the term UTI.

Acute urethral syndrome: the typical symptoms of cystitis in the absence of a 'significant' bacteriuria. Some of these patients still have bladder involvement but with relatively low pathogen counts, whilst in a proportion, the inflammation and associated uropathogen (usually *Escherichia coli*) is genuinely limited to the urethra. (NB: these symptoms can also be caused by sexually transmitted pathogens.)

Acute pyelonephritis: this describes the symptoms and signs which are generated when a kidney (the 'upper urinary tract') is infected – such as flank pain and tenderness, and pyrexia. Non-infectious causes, such as renal stone or infarction, can mimic this presentation. Upper urinary tract involvement is also usually accompanied by lower urinary tract symptoms and signs.

Uncomplicated UTI: infection in a normal urinary tract, both structurally and neurologically.

Complicated UTI: symptomatic infection of the bladder or kidneys, in the presence of a structural or functional abnormality of the genitourinary tract. Common factors include presence of a foreign body (e.g. in-dwelling urinary catheter or other drainage device or renal calculus); disruption of normal urinary flow (e.g. by obstruction or urinary retention) or immunosuppression. Infection in children or men should be assumed to be complicated unless confirmed to the contrary.

Recurrent urinary tract infection: a further symptomatic episode following previous resolution of a UTI. It can reflect either re-infection or bacterial persistence. Significant recurrent UTI is defined as three or more episodes of UTI within a 12-month period.[5]

Significant bacteriuria: bacteriuria is the presence of bacteria in urine. Urine in the bladder is normally sterile – however, low numbers of organisms in a urine sample may be due to contamination by normal anterior urethral flora. A significant bacteriuria is one where the bacterial count is sufficiently great to

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indicate a genuine bladder bacteriuria. Historically, this has been defined as a count $\geq 10^5$ colony forming units (cfu) of the 'same' organism per mL of urine in two consecutive clean-catch, voided urine samples in women. In men, a single sample of clean-catch voided urine with a count of $\geq 10^5$ of one species is sufficient. It is important to recognize that symptomatic infections can still be associated with lower counts – notably if a pure growth of a well-recognized uropathogen. Conversely, significant bacteriuria in the absence of symptoms often does not require treatment (see below). For samples derived via a urinary catheter, a lower threshold may be applicable due to the reduced risk of contamination. For practical laboratory testing purposes, $\geq 10^3$ cfu/mL of ≥ 1 bacterial species in a single catheter-derived sample is a useful cut-off.

Asymptomatic bacteriuria: bacteria may be isolated from urine at significant counts, in the absence of any accompanying symptoms. This is more common with increasing age – being reported to be present in a tenth of men and a fifth of women over the age of 65.[2] Unlike in younger adults, where significant bacteriuria is 30 times more common in women than men, there is a progressive decrease in the ratio of women to men with this phenomenon with increasing age. Factors which make older men more prone to bacteriuria include reduced bactericidal activity of prostatic secretions, and prostatic enlargement leading to urinary retention. In both genders, there is a high rate of spontaneous clearance of bacteriuria – followed by subsequent reinfection. Antimicrobial treatment of asymptomatic bacteriuria in adults is rarely warranted; and is more likely to be associated with patient 'harm' than benefit and so should be avoided. This includes people of either gender over the age of 65; catheterized individuals; and younger women who are not pregnant. The two groups of adult patients with asymptomatic bacteriuria in whom treatment is recommended are pregnant women and those prior to a urological procedure where mucosal bleeding is anticipated.

Pyuria: presence of a raised count of polymorphonuclear leukocytes (PMLs) in urine (e.g. ≥ 10 PMLs per mm^3 of urine), but unit of measurement and definition vary with counting method used. This is indicative of an inflammatory response in the urinary tract – however, it is neither specific for infection, nor for symptoms in the presence of a bacteriuria. Ninety per cent of asymptomatic elderly institutionalized patients with a bacteriuria will also have a pyuria. Pyuria in the absence of bacteriuria can be associated with other pathologies, such as renal stone disease, malignancy and tuberculosis of the renal tract, which should be considered depending on the clinical scenario.

Mechanism of infection

Ascending infection

The most common route of infection is ascension of bacteria from the urethra to the bladder. Early animal studies supported this, showing that if bacteria were directly instilled into the bladder, and one ureter was ligated, the unligated kidney was more likely to develop pyelonephritis.[6] The most common bacterial causes of UTI are the same bacteria that colonize the gut and they enter the urinary tract following colonization of the peri-urethral area.[7] Once within the bladder, bacteria may then multiply and ascend the ureters to cause upper UTI.

Haematogenous infection

Less commonly, upper UTI can be a result of haematogenous spread of bacteria, for example in prolonged bacteraemia, often associated with a deep source of infection such as endocarditis. Direct animal studies support this, showing that intravenous injection of *Staphylococcus aureus* can result in pyelonephritis.[8] However, it is more difficult to produce pyelonephritis in similar models with Gram-negative bacteria, suggesting that this is not the common route of infection for most pathogens.

Host factors in urinary tract infections

Women

UTIs are more common in women because of their anatomy; the shorter urethra and the relative proximity of the urethra to the anus. Several other factors have also been shown to increase the risk of UTI in women: particularly sexual intercourse and the use of spermicide,[9] which is thought to affect the vaginal microbial flora resulting in a reduction in lactobacilli allowing for an increased proportion of potentially pathogenic Gram negative bacteria, such as *E. coli* to colonize the genital tract.[10] Postmenopausal women are particularly prone to recurrent UTI. Reduced oestrogen levels increase the risk of vaginal atrophy, which results in vaginal dryness and increased pH, which in turn alters the vaginal microbial flora, reducing the proportion of ('protective') lactobacilli.[11] In addition, low oestrogen levels are associated with post-voiding residual urine in the bladder, which is a further risk factor for UTI.

Genetic factors

Recurrent UTIs in women are more common in those with a family history, suggesting a genetic pre-disposition. Host factors to protect against UTI include physical barriers (such as unidirectional urine flow), proteins that hinder bacterial adhesion and the cells of the innate immune system, including neutrophils. Polymorphisms of various genes have been found to be associated with recurrent UTI.[12] CXCR1 and 2 are IL-8 receptors that play a role in neutrophil recruitment and reduction in CXCR1 expression has been associated with recurrent UTI in children.[12] CXCR2 levels have been shown to be lower in women with recurrent UTI compared to controls.[13]

Structural abnormalities

Certain renal tract pathologies increase the risk of recurrent UTI. Conditions resulting in a residual volume of urine post voiding, for example neurogenic bladder, reduce the protection of the unidirectional flow of urine and so increase the risk of UTI. The same applies to the increased risk of UTI associated with vesicoureteric reflux. Renal stone disease is also associated with UTI. The foreign material provides a surface for bacteria to form a biofilm. This prevents bacteria from being easily removed from the urinary tract by the flow of urine and renders the bacteria more difficult to eradicate by the host immune response.

Catheterization

Indwelling catheters are well known to increase the risk of recurrent UTI, by enabling bacteria to form biofilms, providing a

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