

## Underlying causes of chronic bladder dysfunction

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### Abstract

General practitioners and family physicians frequently encounter patients suffering from voiding disorders. Various underlying causes such as spinal cord injury, cerebrovascular accidents, traumatic brain injury and several neurological diseases including Parkinson's disease, dementia, multiple sclerosis and vitamin deficiencies have been implicated. Chronic bladder conditions may cause social embarrassment and decrease quality of life in affected individuals. It is important to identify the most common underlying causes of bladder dysfunction and have adequate knowledge regarding the primary treatment and prevention of complications in order to reduce the economic burden created by this group of disorders.

**Keywords:** Chronic bladder conditions; interstitial cystitis; painful bladder syndrome; chronic urinary tract infection; urinary incontinence; hematuria; bladder cancer

### Introduction

The identification and appropriate management of chronic bladder conditions remains one of the most challenging obstacles urologists, gynaecologists and general practitioners are faced with in current medical practice. Urological disorders are present from the earliest stage of human development, and continue until the end of life.<sup>1</sup> Urological complaints mostly affect individuals' quality of life, resulting in a substantial economic impact for patients and their families, employers, healthcare funders and society at large. Bladder control problems require medical attention for several reasons. They may be indicative of certain underlying medical conditions such as diabetes, renal failure, spinal cord injuries, Parkinson's disease, dementia or multiple sclerosis. In addition, the social and psychological consequences of bladder dysfunction may be a cause of great discomfort, shame, loss of self-confidence, restriction of physical activities and withdrawal from social interactions.<sup>2</sup>

The most common chronic bladder conditions according to the Urologic Diseases in America Project include interstitial cystitis/painful bladder syndrome, chronic urinary tract infections, urinary incontinence and hematuria. Other chronic bladder conditions less frequently encountered incorporate bladder prolapse, neurogenic bladder syndrome, bladder fistula and diverticulum, bladder enlargement (augmentation), and bladder extrophy.<sup>1</sup> Chronic conditions of the prostate, kidney, male health, paediatrics and uncomplicated urinary tract infections are not discussed in this review.

### Interstitial cystitis/Painful bladder syndrome (IC/PBS)

Interstitial cystitis and painful bladder syndrome (IC/PBS) is a debilitating heterogeneous chronic bladder disorder with multiple proposed pathophysiological mechanisms. It involves dysfunction of the urothelial barrier and associated

glycosaminoglycan lining, local inflammation of the bladder and lower urinary tract, and sensory changes in the central nervous system. It is often associated with other chronic pain conditions such as chronic functional fatigue syndrome, fibromyalgia and irritable bowel syndrome.<sup>3-5</sup> IC/PBS is more common in females than males (5:1) and ordinarily presents with chronic suprapubic pain, nocturia, urinary frequency and urgency.<sup>6</sup> Diagnosis remains challenging because of overlapping symptoms with various other urological and gynecological conditions. The global incidence of IC/PBS in the general population is approximately 17.3%, but shows significant variation between different countries and regions. Diagnosis involves contemporary diagnostic algorithms (duration of pelvic pain; discomfort accompanied by urinary symptoms; exclusion of other conditions by i) cystoscopy, ii) hydrodistension with bladder volume measurement, iii) bladder biopsy).<sup>7</sup> IC/PBS has a pronounced adverse effect on psychosocial and sexual well-being. The psychological impact is often neglected by healthcare practitioners due to the lack of existing evidence in effective treatment protocols.<sup>8</sup>

Pharmacological management should be individualised for each patient in the absence of recommended guidelines. Currently patients with IC/PBS are treated symptomatically with anti-spasmodic agents, anti-constipation agents, anti-inflammatory medications, tricyclic anti-depressants and botulinum toxin.<sup>9</sup> Recent literature evidence suggests that administration of exogenous intravesical hyaluronic acid, alone or in combination with chondroitin sulphate, may be a safe and effective option for treating IC/PBS.<sup>10</sup> Proposed future research approaches include systemic treatment with anti-nerve growth factors (elevated levels of nerve growth factors are present in bladder inflammation),<sup>11</sup> anti-TNF alpha agents (proinflammatory cytokine release during chronic bladder urothelium inflammation),<sup>12</sup> P2X3 receptor antagonists

(P2X3 receptors modulate bladder activity via afferent fibers),<sup>13</sup> and alpha1 adrenoreceptor antagonists ( $\alpha$  receptors increase pain in chronic stress disorders).<sup>14</sup> Preclinical studies have shown that local treatment with Toll-like receptor (TLR) antagonists may protect the host body against invading pathogens or inflammatory disorders, including autoimmune disorders and cancer. These experimental immunomodulatory drugs may provide the additional advantage of fewer systemic side effects and decrease the progression of adaptive immunity.<sup>9,15</sup>

### Chronic urinary tract infections

Urinary tract infections (UTIs) account for nearly 25% of all infections encountered by healthcare providers.<sup>16</sup> UTIs are more common in females, and it is estimated that approximately 40% of all women will experience at least one such episode during their lifetime. These infections are largely caused by uropathogenic *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Staphylococcus sp* and rarely *Pseudomonas* or fungal elements, depending on the regional or geographical incidence pattern. Appropriate antimicrobial treatment with various agents ranging between quinolones, nitrofurantoin, fosfomycin, penicillin and sulphonamides are used as first and second line therapy in uncomplicated cases. UTIs are uncommon in males and therefore considered to be complicated if they occur.<sup>17</sup> Complicated UTIs require specialist urological assessment to exclude structural or functional abnormalities since complications such as bacteremia, sepsis or even death may occur.

Currently more than 17 interpretations regarding recurrent (chronic) urinary tract infection (RUTI) are specified in the biomedical literature. Many features overlap, but inconsistencies regarding urinary symptoms, culture specific thresholds, bacterial species identification and number of infections per year contribute to this lack in formulating a homogeneous definition.<sup>18</sup> Clinically, RUTIs indicate two or more infections in a six month period, or three or more infections in a year. It is important to differentiate between re-infection and relapse. Recurrent UTIs may be regarded as a re-infection if the responsible microorganism is different from the one responsible for the original infection. Considering rectal, introital, and periurethral colonization of the original responsible pathogen, re-infection may also be diagnosed if a period of at least two weeks elapse following successful antimicrobial treatment.<sup>19</sup> These types of re-infection are regarded as uncomplicated (permitting an absence of anatomic or functional abnormalities of the urinary tract), and are not associated with long-term consequential co-morbid conditions such as hypertension or renal disease. In contrast, most physicians consider a relapsing UTI to occur within two weeks after prosperous antimicrobial treatment for the same infecting microorganism. Relapsing infections requires a more comprehensive urological evaluation, longer duration of therapy, and occasional surgical intervention. As mentioned above, the administration of exogenous intravesical hyaluronic acid markedly reduces recurrences of chronic urinary tract infections, although not currently available in South Africa.<sup>10</sup>

Worsening of chronic urinary frequency or urgency is generally associated with asymptomatic bacteriuria (ASB) in approximately 10% of pregnant women, and 20% in women older than 70 years by virtue of the changing female urinary microbiota.<sup>20</sup> Elderly men have an incidence of about 6%. Other special population groups with an increased susceptibility to ASB are those with immunosuppressant conditions (diabetes, HIV/AIDS, cancer), patients with catheters or spinal cord injuries, children under the age of 1 year, and those with multiple sclerosis.<sup>16</sup> Changes in diet, previous drug or antibiotic use, surgery or urological instrumentation are additional contributing factors. Other symptoms may include nocturia, dysuria, suprapubic tenderness, costovertebral angle pain and incontinence. The absence of fever or signs of debilitating ill health demonstrates the challenges in identifying and treating this condition. It is therefore of clinical importance for the general practitioner or family physician to perform side-room urinalysis in these special population groups to prevent complicated lower urinary tract disorders and limit future hospitalizations by opportune referral to specialist urological professionals.

### Urinary incontinence and overactive bladder

Urinary incontinence represents one of the most vexing chronic conditions affecting physical and social functioning. Owing to its embarrassing nature, only 25–60% of symptomatic patients seek medical care.<sup>21</sup> It is estimated that 41% of women over the age of 40 years and 11.2% of men above 45 years suffer from urinary incontinence.<sup>22, 23</sup> For both males and females the incidence increases with age and does not vary by race or ethnicity. Individuals residing in nursing homes show a prevalence of between 45–72% compared to those living in community settings.

The involuntary leakage of urine is classified according to the anatomical and physiological defects responsible for maintaining continence and micturition. These involve lower urinary tract, pelvic and neurological components. Functional (psychological) mechanisms are also implicated. The main types of urinary incontinence include stress, urgency and overflow incontinence, although a significant overlap between the different types often exists.<sup>24</sup> Stress incontinence results from urethral hypermobility or intrinsic sphincteric deficiency where there is insufficient support of the pelvic floor muscles to the urethra and bladder neck, or the loss of urethral muscular tone to keep the urethra closed. It is generally associated with childbirth or direct trauma to the pelvic muscles. Any sudden increase in the intraabdominal pressure (sneezing, laughing or coughing) result in spontaneous passage of urine.<sup>25</sup>

The terms 'urgency incontinence' and 'overactive bladder syndrome' are often used interchangeably, although the latter may or may not be associated with leaking of urine. Nocturia and frequency are the principle characteristics and occur in nearly 20% of elderly patients. Pathophysiology includes detrusor overactivity leading to uninhibited detrusor muscle contractions and the passage of small amounts of urine. Urgency incontinence may

be secondary to neurological disorders, bladder abnormalities, or the alteration of normal bladder microflora.<sup>26</sup>

Overflow incontinence embodies the continuous leakage or dribbling of urine in the setting of incomplete bladder emptying. Bladder outlet obstruction or detrusor underactivity occurs in approximately 5–10% of elderly patients. Impaired urothelial sensory function or ineffective detrusor muscle contraction triggers symptoms similar to stress or urgency incontinence. Various etiologies of detrusor underactivity have been reported, and consist of low estrogen levels, smooth muscle fibrosis, diabetes mellitus, alcoholism, vitamin B12 deficiency and other neuropathic conditions.<sup>27</sup> Less common causes include external masses or tumors, urethral stricture and pelvic organ prolapse.

It is important for the general practitioner to pro-actively assess and enquire about urinary continence in all patients above the age of 40 years. Initial non-pharmacological treatment of urinary incontinence includes lifestyle modifications (weight loss, dietary changes, smoking cessation, avoidance of constipation), and pelvic floor muscle (Kegel) exercises for at least 6 weeks before drug therapy should be attempted.<sup>28</sup> Pharmacotherapy consists of antimuscarinic agents (darifenacin, oxybutynin, solifenacin, tolterodine, trospium) and beta-3-adrenergic agonists (mirabegron). The antimuscarinics are the most commonly prescribed and act by increasing bladder capacity and decreasing urgency through blockade of muscarinic acetylcholine stimulation during bladder storage.<sup>29</sup> Therapy should be tailored according to the risks and side-effect profile of each individual drug. Mirabegron presents an alternative to patients not responding to anticholinergic therapy, where the selective stimulation of beta-3 adrenoreceptors in the detrusor muscle enhances smooth muscle relaxation.

## Hematuria

Blood in the urine is a sign, and not a disease. Therapy should therefore be directed at the cause and not the symptoms. Hematuria is a common complaint encountered by approximately 4–20% of patients presenting to healthcare professionals. Urological causes for hematuria can be excluded in nearly 60% of cases, most of which often remain unidentified. In the majority of occurrences, the presence of gross hematuria may be explained by indisputable underlying conditions such as cystitis (20–25%), urethral stones (2–20%), anticoagulant therapy or in menstruating and postpartum women. Current best practice in the evaluation of hematuria includes urinalysis. Hematuria with unilateral flank pain may be indicative of obstructive nephrolithiasis and requires radiological imaging (radiography, ultrasound or non-contrast computed tomography). Hematuria suggestive of acute kidney injury (gross hematuria without visible clots) may indicate glomerular bleeding and requires additional cystoscopy. Microscopic hematuria as a result of menses, vigorous exercise or trauma could be excluded by history taking, followed by a repeat investigation after six weeks. Transient or persistent hematuria, especially in individuals over the age of 35 years, warrant a focused urological assessment to exclude any malignant cause.<sup>30</sup> The presence of microscopic

hematuria carries a risk of less than 1% of associated renal or upper tract tumors.

## Bladder Cancer

The prevalence of bladder cancer increases with age, and is characterised by either gross or microscopic hematuria. Bladder cancer is regarded as the ninth most frequently diagnosed cancer worldwide, and rated thirteenth as the overall cause of mortality.<sup>31</sup> It is estimated that around 12% of elderly patients presenting with hematuria may have bladder cancer.<sup>30</sup> This high global incidence reflects the prevalence of tobacco smoking in industrialised countries. Exposure to carcinogenic chemicals used in the manufacturing of plastic and rubber (such as polyethylene or arylamine derivatives) may contribute towards developing transitional cell carcinoma (TCC) of the bladder.<sup>32</sup> In contrast, squamous cell carcinoma (SCC) has a poor prognosis, and is essentially observed in developing African countries, where infection with endemic schistosomiasis (*bilharzia*) is implicated in the pathophysiology of bladder cancer. Increased urbanization, industrialization, obesity and cigarette smoking however complicate this generalization for the South African population, where an almost equal amalgamation between TCC and SCC exists.<sup>33</sup> The 5-year survival rate is approximately 54% in patients with TCC and 27% in those with SCC of the bladder.<sup>34</sup>

## Conclusion

Chronic bladder dysfunction is associated with multiple comorbidities that have a widespread economic impact. The multifaceted heterogeneity of the underlying pathophysiology presents a challenge to the general practitioner in adequate identification and treatment of chronic bladder disorders. History and physical examination are the cornerstones of evaluation in patients with urinary tract symptoms. Complex symptomatology warrants specialist referral and investigation. This information is preeminent to formulate a long-term management plan and prognosis. Laboratory testing is necessary to diagnose and classify chronic urinary tract infections. The general practitioner should embrace every opportunity to investigate the cause of hematuria and refer all episodes not explained by an acute UTI, medication or menses for specialist urological investigation to exclude malignancy. Knowledge of the urinary microbiota, including insight into high-risk population groups, may be beneficial in the advancement of prevention, diagnosis and precision treatment of chronic lower urinary tract conditions. Being aware of this additional information may provide an opportunity to enhance clinical care without the (indiscriminant) use of antibiotics or anti-cholinergic agents.

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