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Review

# Is chronic urinary infection a cause of overactive bladder?

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ABSTRACT

Overactive bladder (OAB) is a diagnosis resulting from a combination of multiple underlying factors. Current traditional treatments are based on anticholinergic blockade which have marginal benefits and are associated with poor tolerability and continuation rates. There is mounting evidence that chronic low grade bacterial bladder colonisation may exacerbate OAB symptoms and may explain why the current treatment strategies are not always successful. However, standard diagnostic laboratory tests to identify the presence of such bacterial infection are unreliable. Newer technologies such as RNA sequencing and extended culture techniques, show that urine is not sterile and organisms that are found in urine may be responsible for OAB symptoms. This article aims to review the current evidence suggesting that micro-organisms in urine may be important in the aetiology of OAB or may exacerbate OAB symptoms.



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## Introduction

Overactive bladder (OAB) is a common and distressing condition affecting up to 20% of the ambulant adult female population [1]. OAB is a syndromal diagnosis and there are probably multiple factors that combine together to result in the clinical syndrome. Targeting treatments at the appropriate causative factors is likely to result in more successful outcomes. Current therapies are based on antimuscarinic receptor blockade and are mostly aimed at the final common pathway of detrusor muscle contraction. These treatments have marginal benefits over placebo with poor tolerability and poor continuation rates.

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There is mounting evidence that chronic bacterial infection may be a co-factor or subtype of OAB or may exacerbate OAB symptoms. Certainly the belief that urine is sterile does not seem likely. This article aims to review the current evidence suggesting that infection may be an aetiological factor or may exacerbate OAB. Infection as a cofactor could be a reason why current treatment strategies are not always successful.

## Current investigations

A joint report on terminology defines OAB as 'urinary urgency, usually accompanied by frequency and nocturia with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology' [2]. However, diagnostic tests to identify infection have limited sensitivity and specificity in the context of over active bladder and may fail to identify infection. This can result in patients with undiagnosed infection being treated with anticholinergics.

### *Urinalysis*

Dipstick urinalysis testing for the presence of nitrites and leucocyte esterase is the routine initial investigation recommended by the National Institute for Health and Care Excellence (NICE) in the initial evaluation of uncatheterised patients with lower urinary tract symptoms where a UTI may be implicated. However, in this scenario many studies have shown a wide range of sensitivity and specificity [3–6].

A meta-analysis of 70 publications conducted by Deville et al. demonstrated that the sensitivity of the urine dipstick for diagnosing a UTI in an unselected population (nitrites) was low ranging between 45% and 60% with a specificity ranging between 85% and 98%. The dipstick test sensitivity of leucocyte esterase for diagnosing a UTI ranges between 48% and 86% with a specificity between 17% and 93%. The specificity and sensitivity of these tests increase if they are used in combination [6]. Unsurprisingly in patients with symptoms of OAB, the situation is similar; the urine dipstick test has been shown to have a sensitivity of 44% and a specificity of 87% for the correct identification of a urinary tract infection when compared to urine culture obtained by catheter [7]. The use of urine dipstick analysis as a screening tool in OAB to decide whether to initiate culture will miss significant numbers of women with underlying infection.

### *Role of pyuria in OAB and urinary culture*

Pyuria is defined as the presence of 10 or more white blood cells (WBC)/$mm^3$ in fresh uncentrifuged urine. A large case–control study by Kunin et al. showed that urine samples with bacterial counts of $>10^5$, $10^4$, $10^3$ and $10^2$ correlated with pyuria 85%, 72%, 56% and 28% of the time respectively [8]. Hence a low bacterial count infection may not show pyuria [9].

Pyuria rates fluctuate following urine collection due to the rapid destruction of WBCs. The WBC count decreases to about 60% of the original in the first 2 h after collection. Though refrigeration and boric acid delays this destruction, 40% of white cells are still lost by 4 h. As most studies conducted their microscopic examinations 3 or 4 h after collection, there has been an overall underestimation of pyuria [10]. Any administrative delay may easily result in a prolongation of the time taken to process the specimen e.g. night time prior to specimen processing. This might be less important but many laboratories use the presence of pyuria as a threshold for full culture. Hence if there is no pyuria the sample will not undergo plating, culture and sensitivity and will be discarded and reported as showing no infection. Some laboratories report "microscopy falls below the threshold for culture". This management strategy has the potential to underdiagnose urinary tract infections in OAB.

### *Mid-stream urine microscopy and culture*

In current clinical practice, the confirmation of urinary tract infections hinges on a positive MSU growth of $>10^5$ colony forming units per millilitre (CFU/ml) – the results of which will guide the need for, and choice of antimicrobial therapy. Current guidelines for the laboratory processing and reporting of MSUs may lead to under diagnosis of infection in the context of OAB. The diagnosis of a urinary tract infection by MSU culture is defined by the isolation of $\geq 10^5$ CFU/ml of a single species of bacteria from direct-plating of the urine sample to the culture medium [11]. However, the use of a single threshold to diagnose all urinary tract infections was challenged as far back as 1993 [8]. In patients with frequency and dysuria (non OAB patients) a more appropriate level is probably $\geq 10^2$ CFU/ml [12]. This has since been supported by multiple studies which have demonstrated that a significant proportion of women with identical symptoms of acute UTI had bacterial counts of less than $10^5$ CFU/ml, grew the same organisms (predominantly *Escherichia coli*) and responded to antimicrobial therapy [13–17].

The $10^5$ CFU/ml threshold may miss a proportion of patients with a UTI as a cause for their OAB symptoms. Khasriya et al. demonstrated this when the lower cut-off identified more than doubling of the bacterial isolation rate using the $\geq 10^2$ CFU/ml level [18].

In the United Kingdom, routine hospital MSU culture is performed on media selective for *Enterocbacteriaeceae* species under aerobic culture conditions. However, some aerobes require longer than conventional incubation times and anaerobic cultures are not usually performed [19]. Bacteria adhere to urothelial cells. Routine urine cultures use uncentrifuged urine specimens where such urothelial cells settle to the bottom of the sample once left to stand for more than a few minutes and hence may not be sampled during the plating process. The volume of urine inoculated on the plate may also influence whether a bacteria is grown. It has been argued that these factors taken in combination would suggest that current culture methods might miss many low-grade infections or those due to anaerobic organisms. This has the potential to fail to diagnose infection and ultimately failure to treat patients appropriately.

Mixed growth samples are also routinely rejected as contamination. Khasriya et al. showed that *Lactobacillus*, a common vaginal commensal organism, was more common in catheter specimen of urine (CSU) than MSU samples suggesting that they were not contaminants from the vagina [19,20]. It is likely that multiple bacterial species regarded as contaminants may cause lower urinary tract symptoms.

In addition to the concerns raised above regarding dipstick testing, our current standard for excluding infection by MSU ($10^5$ CFU/ml) may be inadequate. It is possible that many cases of low-count bacteriuria are under-recognised and thus under-treated in women attending with symptoms of OAB.

## Is conventionally diagnosed infection more common in patients with OAB?

An association has been shown between detrusor overactivity and positive urinary cultures when patients are first assessed. A conventional $10^5$ CFU/ml positive culture is seen in 6% of women with OAB compared to only 1% of women with stress incontinence acting as a control group [21]. CSUs were performed on nondysuric patients who did not have foul smelling urine scheduled to undergo urodynamics at later date. If the $\geq 10^2$ CFU/ml threshold was used, more patients would have "positive" cultures and would

be treated with appropriate antibiotic therapy. These patients would otherwise receive treatments such as anticholinergic therapy.

Rodrigues et al. demonstrated that in patients with recurrent UTI, 84% demonstrated involuntary detrusor contraction compared to 32% of the control group [22]. Walsh et al. demonstrated that during flare-ups of OAB symptoms, MSU samples demonstrated bacteruria in 39% of patients compared to 6% of controls [23].

## Is *E. coli* the most common pathogen?

*E. coli* is the most prevalent bacterial species associated with UTIs [24]. *E. coli* was not the most common organism identified in OAB patients conducted by both Hilt and Khasriya who used directly-plated urine and centrifuged urine sediments respectively. This suggests that causative agents of lower urinary tract symptoms in OAB may be more diverse and different from those of acute UTIs [19,25]. *Staphylococus*, *Streptococcus* and *Lactobacillus* were commonly isolated. However, there was some variation in species isolated in both studies. Multiple organisms are commonly cultured.

A variety of other organisms have also been implicated depending on the culture methods used. These have been termed "fastidious organisms" by some researchers and include mycoplasma and ureaplasma. Longer culture cycles, specific media and anaerobic techniques may be needed. Latthe reported positive cultures for mycoplasma and ureaplasma in 34% of resistant OAB cases that were tested in a tertiary referral centre over one year [26]. There was no correlation found for co-existence of typical and atypical organisms or for sterile pyuria. They found a trend towards improvement of symptoms following long-term antibiotic treatment. There are certain limitations with arbitrary testing, the retrospective methodology and the non-consecutive nature of the study population.

Baka reported positive ureaplasma cultures in 53% of 191 cases with "chronic voiding symptoms" [27]. In summary, the data suggests that other organisms are highly prevalent in the patient groups studied. These findings need reassessment in a more generalised setting with a more rigorous methodology.

New techniques such as 16S ribosomal RNA gene sequencing suggest that the urinary tract contains microbial communities. These techniques need to be combined with extended culture techniques (expanded quantitative urine culture EQUC) to give a full appreciation of the organisms that can be found in the urine of patients with OAB [25]. These findings support our contentions that the urinary microbiome exists and that it is a reflection of living bacterial species that make up the resident flora (microbiota) in the adult female bladder. Patients with OAB have different organisms in their urine compared to patients without OAB. Urine should not be considered to be sterile but contains low levels of organisms and a microbial community that usually does not result in symptoms of infection or OAB. Screening for a specific subgroup may enable targeting of treatment.

This is not an unusual concept in other areas of medicine and has been termed the female urinary microbiome [28]. Sixteen S rRNA testing found bacteria in more than 50% of patients with OAB in a randomised trial of botox vs. placebo and anticholinergics. Urine positive for bacteria was associated with higher baseline urgency urinary incontinence episodes and responded better to treatment [29].

## Does bacterial infection cause OAB symptoms?

Assuming that the current methods of excluding infection are inadequate in OAB patients, is there any evidence that urinary infection is related to OAB?

A recent study conducted investigating the association of a positive urine culture at $10^5$ in women with lower urinary tract symptoms showed a significant correlation between bacteriuria and symptoms of nocturia, bladder pain and urgency incontinence and nocturnal enuresis. This supports a role for bacterial infection in the pathogenesis of OAB symptoms [19,30].

The mechanism by which bacterial infection results in OAB symptoms is unclear at this time. However, bacterial infection results in an increased nucleotide release from epithelium. Extracellular nucleotide signalling via P2 receptors is key in bladder sensation and can result in the release of pro inflammatory cytokines (e.g. IL-1 beta, IL-6, IL-8, and TNF alpha) which result in sensitisation of endogenous signalling mechanisms [31]. The molecular mechanisms by which a local inflammatory, directly or indirectly, increase transmitter release from bladder urothelium is currently the focus of a number of research laboratories around the world.

## Can we identify bacteria associated with OAB from other specimens taken from the bladder?

### *Intracellular bacteria*

Intracellular bacteria seem to be found more commonly in patients with OAB compared to controls. Khasriya found intracellular bacteria in 94% of a small sample of patients with OAB compared to 29% in controls [19]. Cheng employed confocal microscopy to demonstrate intracellular bacteria [32].

In acute UTIs, intracellular bacterial invasion is a probable mechanism of action, leading to treatment failure and persistence of disease [33]. However, the role of intracellular infection causing lower urinary tract symptoms is poorly understood. Intracellular bacterial colonies may be shielded from the therapeutic effects of systemic antibiotics and remain in a quiescent state [34–36].

### *Bladder biopsy culture*

When bladder biospies of patients with refractory OAB were cultured, bacterial organisms were isolated in 52% of samples. There were a wide range of organisms identified including *staphylococcus*, *enterococcus* and *E. coli* [37]. However, looking for bacteria on a biopsy is difficult. These high rates of infection suggest that OAB refractory to antimuscarinic therapy might be caused by chronic underlying infection.

Due to the prevalence of Uropathogenic *Escherichia coli* (UPEC) as a causative agent in UTI, it remains the most widely studied uropathogen. However, it now appears that bacteria such as *Staphylococcus saprophyticus*, *Streptococcus*, *Klebsiella pneumonia*, *Pseudomonas*, *Salmonella enterica* and *Proteus* may also possess the ability to replicate within a cell. Conventional cultures will remain negative in this situation [38,39].

## Other factors

Studies have shown that both gram positive and negative bacteria (e.g. *Enterococcus faecalis* and *Pseudomonas aeruginosa*) are able to perform cell-to-cell signalling via a process called quorum sensing. This process of communication enables bacteria to express themselves as a collective to produce virulence factors only when the impact on the host is maximised [40]. The community of organisms in the bladder microbiome may be quiescent in terms of virulence but switch on virulence factors in response to changes in their environment at an optimum time [40]. This may lead to acute infection and consequently an exacerbation of lower urinary tract symptoms that is commonly seen in OAB patients.

Studies in the mouse and murine models have demonstrated that UPEC was able to invade the bladder epithelia and form intracellular bacterial colonies with biofilm-like characteristics. *E. coli* was able to persist for long period in quiescent intracellular reservoirs leading to latent, recurrent and low-level chronic infection during shedding of the epithelial lining into the urine [33]. Cheng et al. were able to identify (by microscopy and Wright staining) the presence of filamentous *E. coli*, indicative of intracellular bacterial community formation, in 58.5% of patients with DO. This was significantly more common than in patients with stress urinary incontinence [41]. The effect of chronic urinary colonisation in a quiescent state is uncertain but could conceivably cause LUTs.

This method of intracellular bacterial colonisation may occur in OAB. A subgroup of LUTS patients with overactive bladder has showed microbiological and cytological evidence of cell adhesions with *E. coli*, *E. faecalis*, *Staphylococcus*, *Pseudomonas*, *Streptococcus* and *Proteus*. In recurrent urinary tract infections in humans it has been shown that 68% of bacteriological recurrence is caused by identical bacterial strains to that of the index infection. Though, it may be possible that this may be due to re-infection, the possible of presence of a quiescent intracellular bacterial colony untouched by antibiotic treatment may be causing these same-strain infections [42]. The mechanism by which bacteria invades urothelial cells is still unknown. Further studies in this field are ongoing.

## The role of antibiotics

If we presume that infection is an aetiological factor in OAB, the symptoms of OAB should respond to appropriate antibiotic therapy. A recent pilot case series demonstrated that the use of sequential, combination antibiotic treatment (ciprofloxacin 500 mg bid; cephalexin 500 mg tds, doxycycline 100 mg bid) specific for both Gram-negative and Gram-positive organisms was associated with a significant decrease in nerve growth factor (NGF) in patients with OAB. More importantly, patients developed a significant improvement of OAB symptoms including urgency, nocturia and daytime frequency [43]. This is a potential treatment option for patients with refractory OAB. However, this treatment modality is still in its infancy and randomised trials will be required.

## Conclusion

Standard diagnostic laboratory tests to identify bacteriuria, pyuria and UTI performed in hospital may under-diagnosed the presence of bacterial infection. Dipsticks are not sensitive and not validated tools to diagnose chronic and recurrent UTIs. Current data suggests that lower urinary tract symptoms suggestive of OAB may be generated by bacterial infection. Underlying infection should be suspected in the presence of nondysuric LUTS. New technologies are required to identify the microbiology of OAB patients and randomised trials are needed to identify if antibiotic treatment results in improvement in OAB symptoms. At present, the underlying mechanisms of action of such bacterial infection in OAB are still unknown. In order to prove conclusively the presence of intracellular bacterial colonisation, an RCT will be required to corroborate existing results. These results may have far-reaching implications for our diagnosis, treatment and understanding of the aetiology of OAB.

## Author's contribution

AA Balachandran: Manuscript writing.
SS Wildman: Manuscript writing.
M Strutt: Manuscript writing.
J Duckett: Manuscript writing & Manuscript editing.

## Conflict of interest

None declared.

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