Low-count bacteriuria in refractory idiopathic detrusor overactivity versus controls

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Abstract

Background. Previous studies suggest an association between idiopathic detrusor overactivity (IDO) and *high-count* bacteriuria (>10^5 CFU/mL). Recently, the importance of *low-count* bacteriuria (10^3-10^5 CFU/mL) in dysuric women with has been recognised. However, the optimal microbiological threshold for women with overactive bladder (OAB) symptoms remains unclear.

Design and Methods. A 2-year prospective cohort study, to examine the incidence of *low-count* and *high-count* bacteriuria in women with refractory IDO (RIDO) *vs* a control group without OAB symptoms. Women with dysuria, voiding dysfunction or recent urethral instrumentation were excluded. Mid-stream urine (MSU) specimens were collected during acute symptomatic exacerbation in the IDO group and cultured at the 10^3 CFU/mL threshold. Statistical analysis was performed using Statsdirect statistical package 2.7.2.

Results. Between November 2007 and November 2009, 218 study MSU specimens were collected. Both the overall incidence of any significant bacteriuria ≥10^3 CFU/mL (P<0.0001) and the incidence of *low-count* bacteriuria (P=0.0091) were significantly higher in the RIDO women than the controls. There were no baseline differences in age, menopausal status or prior continence surgery between the groups. In the RIDO group, specimens positive for *low-count* bacteriuria only were less likely to be associated with significant pyuria P<0.0001) and were cultured from younger women (P=0.0009), than specimens positive for *high-count* bacteriuria.

Conclusions. The prevalence of bacteriuria in women with RIDO during symptomatic exacerbation is 40%, which is significantly higher than the incidence in similarly-aged women without OAB. One-third of positive cultures show *low-count* bacteriuria only. The management of women with RIDO should include a search for bacteriuria, including *low-count* bacteriuria.

Introduction

Since the diagnosis of the *unstable bladder* was introduced in the 1970s by Bates and others,[1,2] continence clinicians have been puzzled by the etiology of this condition. Over the decades, theories on the underlying cause for idiopathic detrusor overactivity (IDO) have ranged from a psychosomatic disorder[3] to alterations in neuropeptide distribution[4,5] and urothelial dysfunction.[6] Most studies on the etiology of IDO have been conducted in patients with *refractory* IDO (RIDO), that is, those women who do not respond to conventional anti-cholinergic therapy.[7] Although there is little consensus on the precise definition of *refractory*, longitudinal studies provide evidence that a substantial proportion of patients with IDO do not respond to standard management.[8,9]

With the introduction of the broader term *overactive bladder (OAB)*, the exclusion of significant bacteriuria became an essential diagnostic criterion for this syndrome. However, there has been considerable evolution in the diagnostic criteria for *significant bacteriuria* in recent years, with increasing recognition of the importance of *low-count* bacteriuria (10^3-10^5 CFU/mL.[10] Indeed, both the Infectious Diseases Society of America and the European Association of Urology have stipulated that the quantitative threshold for significant bacteriuria in acutely dysuric women should include low bacterial counts.[11,12]

However, the appropriate microbiological threshold in excluding significant bacteriuria in women the OAB syndrome without dysuria remains unclear. Two recent studies have demonstrated a substantial 25-30% incidence of bacteriuria ≥10^3 CFU/mL in women with OAB.[13,14] The background comparative incidence of l*ow-count* bacteriuria in control women without OAB symptoms was not reported by these authors. The present study was carried out in a tertiary urogynecology center, in which IDO has been the major focus of research for almost two decades. This study was precipitated by the anecdotal finding that many women with RIDO who presented with an acute exacerbation of their urge incontinence symptoms, but no dysuria, were found to have bacterial cystitis. In view of the recent shift in focus towards *low-count* bacteriuria, we undertook a prospective comparative analysis of *low-count* and *high-count* bacteriuria in women with RIDO *vs* a control group of women without OAB symptoms.

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Design and Methods

A 2-year prospective cohort study of women aged 18-80 years with *refractory* IDO. RIDO was defined as *failure to respond to ≥2 anticholinergic agents coupled with out-patient bladder training for ≥1 year, with persistent disabling symptoms on frequency-volume char.*[15] All study participants had urodynamically-proven DO without neurological disease. Eligible women were recruited and asked to submit a standard mid-stream urine (MSU) specimen for culture and sensitivity whenever their OAB symptoms (frequency, urgency, nocturia, urge incontinence) were acutely exacerbated. Women with co-existent stress incontinence were not excluded, provided the patient reported OAB symptoms to be the most bothersome. Full inclusion and exclusion criteria are detailed in Table 1. Women attending our unit with pure stress incontinence or mild pelvic organ prolapse, who denied all OAB symptoms on direct questioning, were asked to supply control MSU specimens for comparative analysis. All women with IDO in our unit are initially managed with lifestyle advice and bladder training, with anti-cholinergic medication added in as required. Peri- and post-menopausal women are treated with regular topical vaginal estrogen. All study patients

were instructed on clean-catch MSU collection according to a standard regime to minimise contamination. Briefly, the urethral meatus is cleansed, the labia parted, voiding commenced and a sterile container is inserted into the urinary stream and removed, without interruption to the stream. Each MSU specimen was refrigerated at 4°C immediately after collection and transported to the laboratory in a refrigerated container within 2 hours. The study was performed in collaboration with our Microbiology department and MSU specimens from study participants were cultured at the 10^3 CFU/mL threshold (to include *low-count* bacteriuria) rather than the usual 10^5 CFU/mL. Specimens were cultured using Horse Blood Agar incubated at 35°C in 7% CO_2 and McConkey's agar incubated at 35°C in air. These culture media grow all known pathogens and contaminants. Pyuria was determined using haemocytometer counts on uncentrifuged urine specimens, with counts of >10 white blood cells (WBC)/μL considered significant. Any bacteriuria ≥10^3 CFU/mL was considered a positive urine culture, in accordance with recent guidelines.[12] Specimens with bacteriuria <10^3 CFU/mL were considered sterile. Women with positive cultures received 5 days of appropriate oral antibiotic therapy, according to sensitivity testing.

Categorical data were analysed using Fisher's exact test. Data collated for age showed evidence of non-normality using the Shapiro-Wilk's test. As such, median age was compared using the Mann-Whitney test for non-parametric data. Two-tailed P values were used throughout and the 5% level was considered significant. Statistical analysis was performed using Statsdirect statistical package 2.7.2 (Statsdirect Ltd, Cheshire, UK).

Results

Between November 2007 and November 2009, 50 women with urodynamically-proven non-neurogenic DO, who met our strict criterion for *refractory*, were recruited into the study. Fifty control women, who denied all OAB symptoms, were also recruited. There were no differences in age (P=0.15), menopausal status (P=0.50) or history of prior continence surgery (P=0.17) between the RIDO and control groups (Table 2). The median duration of OAB symptoms for the RIDO women was 10 years and they had trialled a median of 3 anti-cholinergic medications. Over the 2-year study period, 168 MSU specimens were provided by the RIDO group and 50 MSU specimens from the control group, for a total 218 study urine specimens. Women with RIDO provided a median of 3 urine samples during the study period and control women provided one MSU per patient.

The incidence of any bacteriuria ≥10^3 CFU/mL was significantly higher in the MSU specimens obtained from women with RIDO compared to those without OAB symptoms (P<0.0001, Table 3). Analysis of *low-count* (10^3-10^5 CFU/mL) bacteriuria only also demonstrated a significant difference between groups (P=0.0091, Table 3). Overall, at least one positive culture was obtained from 56% (28/50) of women with RIDO. *E. coli* was the predominant microbiological organism cultured from women with RIDO, accounting for 58% (38/65) of total positive cultures (Table 4). Subset analysis by bacteria showed that the only significant difference was with streptococci; the proportion of specimens positive for streptococci was higher in the *low-count* specimens (6/21) *vs* the *high-count* specimens (2/44; P=0.01; Table 4). In the RIDO group, specimens positive for *high-count* bacteriuria were more likely to be associated with significant pyuria (84%; 37/44) than those positive for *low-count* bacteriuria (23%; 5/21) only (P<0.0001; Table 4).

The median age of women with RIDO in this study was 62.5 (Inter-quartile range 53-70) years. Overall, among the women with RIDO, bacteriuric urine specimens were collected

Table 1. Study inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Female aged 18-80 years	Current dysuria or fever
Idiopathic DO	Voiding dysfunction (post-void residual bladder volume ≥100 mL)
Pure DO or mixed incontinence with OAB symptoms most bothersome	Suspicion of neurogenic or post-surgical DO
Refractory to anti-cholinergic therapy	Pregnancy or <6 weeks post-partum
English-speaking	Recent (<2 weeks) urethral instrumentation

DO, destrusor overactivity; OAB, overactive bladder.

Table 2. Baseline demographic data.

	Refractory IDO	Controls	P
Median Age (IQR)	62.5 (53-70)	56.5 (48-67)	0.15
Post-menopausal % (n)	76 (38/50)	68 (34/50)	0.50
Prior continence surgery % (n)	32 (16/50)	18 (9/50)	0.17

IDO, idiopathic destrusor overactivity; IQR, inter-quartile range.

Table 3. Results of formal culture at 10^3 CFU/mL threshold.

	Refractory IDO	Controls	P
Study participants	50	50	-
Study MSU specimens	168	50	-
Sterile (<10^3 CFU/mL)	61% (103/168)	94% (47/50)	-
Bacteriuria ≥10^3 CFU/mL	39% (65/168)	6% (3/50)	<0.0001
-High-count bacteriuria (>10^5 CFU/mL)	26% (44/168)	4% (2/50)	0.0003
-Low-count bacteriuria (10^3-10^5 CFU/mL)	17% (21/124)*	2% (1/48)*	0.0091

IDO, idiopathic destrusor overactivity; MSU, mid-streamurine; CFU, colony-forming units; *low-count bacteriuria calculated as percentage of women without high-count bacteriuria.

Table 4. Bacterial etiology by quantity of bacteriuria in women with refractory idiopathic destrusor overactivity.

Bacteria	*Low-count* (10^3-10^5 CFU/mL)	*High-count* (>10^5 CFU/mL)	P
E. coli	11 (1)	27 (23)	0.59
Streptococci	6 (1)	2 (1)	0.01
Klebsiella	1 (1)	6 (5)	0.41
Pseudomonas	1 (0)	3 (3)	>0.99
Enterococcus	1 (1)	5 (4)	0.65
Other	1 (1)	1 (1)	-
Total	21 (5)	44 (37)	-

CFU, colony-forming units.

from older women when compared to specimens which were sterile (67 years *vs* 63 years respectively; P=0.04). However, within the positive specimens, those which grew *low-count* bacteriuria were collected from significantly younger women than those which grew *high-count* bacteriuria (58 years *vs* 67 years respectively; P=0.0009).

Among women with RIDO, 32% (16/50) had a history of previous continence surgery, who supplied 63 study urine specimens. MSU specimens obtained from women with previous continence surgery were significantly more likely to grow bacteriuria ≥10^3 CFU/mL (35/63) compared to those from women with RIDO and no history of continence surgery (30/105; P=0.0006), despite no difference in PVR between the sub-groups (P=0.24) and PVR<100 mL in all women with RIDO.

All women with cultures positive for *low-count* or *high-count* bacteriuria received a course of antibiotic therapy. Although the severity of urgency was generally reduced on frequency-volume chart in the RIDO group following antibiotics, formal assessment of urgency symptoms was not undertaken in this study.

Discussion

Extensive research into the etiology of IDO has been undertaken in recent decades but the underlying cause remains elusive. An association between OAB symptoms and bacterial cystitis has been postulated.[16-18] The concept of *refractory* IDO is frequently mentioned in the literature but poorly defined.[7] A longitudinal study of Australian women found a 65% rate of *non-responders* to treatment at a median follow-up of 8 years.[8] A recent long-term study of UK women reported an 88% rate of persistent IDO on urodynamics at ≥10 years following instigation of treatment.[9] Clinical management of this refractory group is moving towards sacral neuromodulation and intravesical neurotoxin.[19] These interventions are invasive, expensive and not without risk to the patient, making the identification of potentially-treatable exacerbating factors, such as bacteriuria, imperative.

In parallel with the work on the etiology of IDO, our understanding of what constitutes *significant* bacteriuria in the diagnosis of urunary tract infection (UTI) has developed considerably. The traditional definition of significant bacteriuria [>10^5 colony-forming units (CFU) per milliliter) was described in 1957 by Edward Kass, a Harvard nephrologist.[20] However, Kass was mainly interested in a practical threshold which could be used to distinguish probable infected specimens from those likely to be simply contaminated, at a time when pyelonephritis was a major source of mortality.[20,21] He did acknowledge that lesser degrees of bacteriuria may be associated with infection. Since then, the focus has shifted towards women with lower urinary tract symptoms; numerous studies have found that 30-50% of urine cultures from acutely dysuric women fail to meet Kass' microbiological standard.[10] Expert guidelines now support the inclusion of *low-count* bacteriuria in women with acute dysuria.[11,12] In contrast, there is a paucity of data on the incidence of bacteriuria 10^3-10^5 CFU/mL in women with IDO without dysuria. Previous studies linking female urinary incontinence and bacterial cystitis were performed using Kass' older, less sensitive microbiological definition. Moore *et al.* reported bacterial cystitis in 6% of women with DO undergoing urodynamics, compared to 1% in stress incontinent controls.[16] A study of 913 post-menopausal women found the basal rate of incontinence to be higher for women who experienced UTIs, even after controlling for the acute incontinence surrounding an infective episode.[17] Neither of these studies considered low-count bacteriuria. The presence of bacteriuria also impacts on the accuracy of urodynamic testing. Bhatia *et al.* performed repeat urodynamic studies on 15 women who had significant bacteriuria (≥10^5 CFU/mL) during initial cystometric testing. They found that the incidence of DO fell by 50% after eradication of the UTI, although urodynamic parameters such as first desire to void and maximum cystometric capacity were unchanged.[18]

Currently, there is a dearth of evidence on the significance of bacteriuria, particularly *low-count* bacteriuria in women with frequency/urgency/nocturia. Khasriya *et al.* reported on 470 women with lower urinary tract symptoms (LUTS) without dysuria.[13] By incorporating *low-count* bacteriuria, the incidence of positive specimens increased from 15% (using the traditional culture threshold of 10^5 CFU/mL) to 29%. However, this study was primarily examining the role of dipstick urinalysis and the specimens were obtained from a wide range of women without urodynamic diagnoses. A similar German study reported an almost identical 28% incidence of bacteriuria ≥10^3 CFU/mL in women with OAB without symptoms of acute UTI (dysuria, fever or haematuria).[14] However, neither study presented a suitable control group to allow comparative analysis (although the former paper does include a small, mixed-gender control group). Thus, while an incidence of 28-29% appears high (and likely is), background data regarding the incidence in the general female population is not, to our knowledge, available.

The aim of the present study was to examine the incidence of bacteriuria and *low-count* bacteriuria among a severely affected group of women with RIDO, compared to the incidence in women without OAB symptoms. Only women with IDO were recruited as, compared to women with OAB syndrome without DO, women with urodynamically-proven DO have more incontinent episodes and earlier abnormal sensory symptoms.[22] Furthermore, this group would generally be considered candidates for sacral neuromodulation or intravesical neurotoxin, which may be inappropriate if bacteriuria has not been excluded. The present study finds that, in women with RIDO, the incidence of bacteriuria during an episode of symptomatic exacerbation, using a sensitive microbiological threshold, is 39%. This is considerable and is higher than similar incidences quoted for women with OAB symptoms only.[14] Furthermore, our data show that the comparative incidence amongst similarly aged women without OAB symptoms is significantly lower (6%, Table 3), which has not previously been reported.

The European Association of Urology has recently published guidelines which support the treatment of low bacterial counts in acute UTI.[12] These echo guidelines published in 1992 by the Infectious Diseases Society of America (IDSA).[11] However, it was also noted that a marginally higher threshold (≥10^3 CFU/mL) improved specificity (90% *vs* 85%) with little loss of sensitivity (80% *vs* 95%) compared to ≥10^2 and, in addition, could be more easily identified by routine microbiological techniques.[12] Despite these expert guidelines, many laboratories continue to use the traditional threshold of ≥10^5 CFU/ml when determining bacteriuria that requires treatment.[23] Indeed, the recent joint consensus document on the terminology of pelvic floor dysfunction by the International Continence Society/ International Urogynaecological Association, endorses a threshold of >10^5 CFU/ml for voided specimens in the diagnosis of UTI.[24] The present study shows that, among women with RIDO, one-third of bacteriuric specimens grow *low-count* bacteriuria only, which would be missed if a >10^5 CFU/mL threshold is maintained.

The impact of age on rates of bacteriuria in this study is notable. In general, positive urine cultures were obtained from older women, which is consistent with previous reports.[25] However, amongst the positive cultures, those positive for *low-count* bacteriuria only were obtained from significantly younger women than those with *high-count* bacteriuria. Several theories have been proposed to explain the phenomenon of *low-count* bacteriuria, including urinary dilution, an early phase of infection, the presence of an inhibitor or following antibiotic therapy.[26] An interesting Israeli study examined the natural history of *low-count* and *high-count* UTI over 2 days without antibiotic treatment. Among women

with a baseline *low-count* UTI, 50% had progressed to a high-count infection after 48 hours, which substantiates the theory that *low-count* bacteriuria simply represents an earlier stage in the infective process.[27] To our knowledge, a possible association between low bacterial counts younger aged women has not previously been suggested.

Pyuria has traditionally been used to distinguish true infection from colonisation. Most women with bacteriuria >10^5 CFU/mL will have pyuria. Recent expert guidelines include pyruia as part of the diagnostic algorithm for UTI.[12] However the relationship between bacteriuria 10^3-10^5 CFU/mL and pyuria is less clear. The previous study of 470 women with OAB by Khasriya *et al.* noted a trend towards reduced pyuria in low-count compared to high-count bacteriuria (P=0.078).[13] Another study, on bladder biopsies from patients with the OAB syndrome, found that the presence of significant pyuria in urine did not predict the histological finding of chronic cystitis.[28] Furthermore, the high rate of natural progression of *low-count* to *high-count* bacteriuria suggests that low bacterial counts, even in the absence of pyuria, cannot be dismissed as clinically insignificant.[27]

In the present study, bacteriuria 10^3-10^5 CFU/mL was significantly less likely to be associated with pyuria (P<0.0001). It is notable that destruction of urinary leukocytes begins almost immediately after specimen collection. We refrigerated our specimens immediately at 4°C and transported them to the laboratory within 2 hours in all cases. However, refrigeration slows but does not eliminate WBC lysis. White cell destruction in refrigerated specimens is approximately 20% in the first 2 hours after collection,[29] which may have impacted on the rates of pyuria reported here although one would expect all specimens to be equally vulnerable to this effect.

We acknowledge a number of limitations with the present study. Firstly, microbiological analysis was performed on MSU specimens rather than CSU, which may overestimate the incidence of bacteriuria. However, most women with IDO will continue to provide midstream, rather than catheter, specimens at times of worsening OAB symptoms, thus enhancing the clinical applicability of our findings. Secondly, although anecdotal evidence suggested an improvement in IDO symptoms following antibiotic treatment of bacteriuria, formal assessment of patients' symptoms pre- and post-treatment was not undertaken. Statistical evidence of symptomatic improvement following antimicrobial therapy of women with IDO and bacteriuria will likely require a randomized placebo controlled trial. Finally, the debate regarding the clinical importance of *low-count* bacteriuria without pyuria will continue. Although several studies have consistently demonstrated reduced rates of pyuria in lower bacterial counts, objective evidence of symptomatic improvement will be needed to substantiate the notion that, among women with IDO, bacteriuria without pyuria is clinically meaningful.

Conclusions

A substantial proportion of women with IDO are *refractory* to standard treatment and contemporary management of these cases may include invasive neuromodulation and intravesical neurotoxin. Recent expert guidelines endorse the inclusion of low bacterial counts (10^3-10^5 CFU/mL) in the diagnosis of acute UTI but the incidence of this *low-count* bacteriuria in women with refractory IDO is poorly studied.

In the present study, we were quite surprised to find that almost 40% of women with RIDO and an acute exacerbation of symptoms had significant bacteriuria on MSU. For the first time, we can report that this incidence is significantly higher than among a control group of similarly-aged women without OAB symptoms. One-third of positive cultures grew *low-count* bacteriuria only. *Low-count* bacteriuria was seen in younger women and was more likely to resolve following appropriate antibiotic therapy. The management of women with RIDO experiencing an acute worsening of symptoms should include a search for bacteriuria and a *low-count* microbiological threshold should be considered.

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