Do urethral *Escherichia coli* cause abacterial cystitis?

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SUMMARY To determine whether *Escherichia coli* in or near the urethra caused symptoms of abacterial cystitis, the results of serial cultures from the vaginal introitus of 92 patients with recurrent cystitis were compared with symptoms at clinic visits when they were abacteriuric. Similar comparisons were made in 15 of these patients using cultures from the external urethral meatus and proximal urethra. *E coli* were grown from the vaginal introitus, urethral meatus and proximal urethra at 41, 66 and 26% of visits respectively. Overall they were not significantly more often isolated when patients had cystitis, and the serotype was unrelated to symptoms.

E coli was cultured significantly more often from the introital swabs of symptomatic intermittently bacteriuric (IB) women than from symptomatic persistently non-bacteriuric (NB) patients; and more often from symptomatic than from asymptomatic IB patients, although this difference was not significant. These findings were consistent with previous suggestions that symptoms of apparently "abacterial" cystitis in IB patients are due to occult coliform infection. We found no direct evidence that *E coli* were the cause of symptoms in persistently non-bacteriuric women, or that urethral colonisation caused them. However *E coli* were isolated from the introitus of control women only half as often as from both intermittently bacteriuric and persistently non-bacteriuric patients.

In only half the attacks of cystitis in women can evidence of bacterial growth in the urine be obtained using standard techniques, and the terms urethral syndrome, abacterial cystitis,¹ frequency-dysuria syndrome and symptomatic abacteriuria have been used to describe the remainder. Urinary infection with viruses, chlamydia, slow growing bacteria and low concentrations of coliforms, infection of the urethra itself, and stenosis of the urethral meatus have been suggested as possible causes of "abacterial" cystitis, the term used here. Many patients with bacterial cystitis later develop "abacterial" cystitis,² which implies that one cause may underlie both illnesses. We have examined the possibility that *E coli* within or near the urethra is responsible for the symptoms of "abacterial" cystitis.

Patients, controls, and methods

Ninety-two women, referred because of recurrent frequency and dysuria, were studied. They were reviewed at least monthly for six months, then less frequently if well. At each visit urinary symptoms

were recorded and mid-stream urine (MSU) and a low vaginal swab (LVS) were taken for culture. Urine was also collected by suprapubic aspirate (SPA) at a quarter of the visits. In 15 women additional swabs were also taken from the external urethral meatus (superficial urethral swab: SUS), from the proximal part of the urethra (deep urethral swab: DUS), and from the rectum.

As controls, MSU and LVS cultures were done from each of 100 women who presented to a general practitioner with minor illness. They had had no urinary symptoms for two years, and had not taken antibiotics for at least one week.

METHODS

Low vaginal swabs were collected by passing a swab moistened with saline around the uncleaned margin of the vaginal introitus. Superficial urethral swabs were taken from the uncleaned external urethral meatus. Deep urethral swabs were collected, after cleaning the perineum with sterile saline, by passing a fine swab through a rigid sterile polypropylene catheter which was prevented from passing more than one centimetre into the urethra by a shield. Rectal swabs were taken at the same time. LVS and MSU specimens from patients were cultured as previously described.³ Urine from control

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subjects was cultured using dipslides. SUS, DUS and rectal swabs were plated directly and incubated aerobically overnight.

Coliform bacteria were identified according to Cowan and Steel.⁴ *E coli* were serotyped using antisera to the following O antigens: 1, 2, 3, 4, 6-13, 15-25, 68 and 75.

Significant bacteriuria in patients was defined by any of the following findings: (i) Two consecutive MSU specimens culturing $\geq 10^8$ CFU/l; (ii) one MSU specimen culturing $\geq 10^8$ CFU/l, with an uncentrifuged urinary leucocyte concentration exceeding $10/\text{mm}^3$; (iii) one MSU specimen culturing $\geq 10^8$ CFU/l, collected when there was pain during micturition; (iv) one suprapubic aspirate culturing any number of Gram-negative organisms. In the event of between 10^7 and 10^8 CFU/l being cultured from an MSU specimen, the possibility of infection was recognised, but considered "doubtful". Controls were considered not to be infected if their urine contained $< 10^7$ CFU/l. The presence of *E coli* in low vagina, superficial urethra and deep urethra was not quantified.

"Abacterial" cystitis was defined as painful micturition or unaccustomed frequency, in the absence of significant bacteriuria, in a patient who had not taken an antibiotic for at least one week.

SPECIMENS

Six hundred and forty-three MSU and LVS culture pairs and 168 SUS and DUS culture pairs were made from patients. One hundred MSU and LVS culture pairs were made from the control women. Cultures made at a time of significant bacilluria or doubtful urine infection, within one week of antibacterial therapy, in subjects with vulval pruritus, or on the 15 occasions when symptoms or therapy were incompletely documented, were excluded. There remained for analysis 414 MSU and LVS cultures, and 68 SUS and DUS cultures from 92 patients aged 34 ± 1.4 yr (mean $\pm$ SEM). Three hundred and twenty-seven of the LVS cultures came from 44 patients who had no evidence of significant bacteriuria during follow-up; these were called non-bacteriuric (NB) patients. Eighty-seven were taken

Table 1 Relation between symptoms of abacterial cystitis and *E coli* in swabs from low vagina, superficial urethra and deep urethra

Specimen (No)	Growth of <i>E coli</i>	Symptoms of abacterial cystitis	
		Present	Absent
LVS (n = 414)	+	28	141
	-	44	201
SUS (n = 68)	+	12	33
	-	6	17
DUS (n = 68)	+	4	14
	-	14	36

The relation between symptoms and bacteriology at individual patient visits is shown.

from 48 patients who had significant bacteriuria at some time during follow-up, but at visits when their urine was not infected; these were called intermittently bacteriuric (IB) patients. After exclusions as above there remained MSU and LVS cultures from 82 controls aged 34 ± 1.1 yr. Statistical analysis was done using the χ^2 test and Student's paired *t* tests, significance being defined as $p < 0.05$.

Results

RELATIONS BETWEEN SYMPTOMS OF ABACTERIAL CYSTITIS AND *E COLI* IN SWABS FROM LOW VAGINA, SUPERFICIAL URETHRA AND DEEP URETHRA

Escherichia coli were grown from low vaginal swabs at 41% of patient visits, from the superficial urethra at 66%, and from the deep urethra at 26% of visits. Overall they were not significantly more often cultured from symptomatic patients (Table 1) and were cultured from IB and NB patients' swabs with a similar frequency. In NB patients the proportion of positive LVS taken at symptomatic visits (11/40 swabs) was less than that of swabs taken at asymptomatic visits (121/287 swabs), but the difference was not significant (Table 2). Although in IB patients a greater proportion of LVS was positive when patients were symptomatic (17/32 swabs) than when they were not (20/55 swabs) the difference

Table 2 Relation between symptoms of abacterial cystitis and *E coli* in swabs from the low vagina in non-bacteriuric and intermittently bacteriuric patients

Growth of <i>E coli</i> in low vaginal swabs	Symptoms in non-bacteriuric patients		Symptoms in intermittently bacteriuric patients	
	+	-	+	-
+	11* (27)	121 (42)	17* (53)	20 (36)
-	29	166	15	35
Total No of swabs	40	287	32	55

Figures in parentheses refer to the percentage of LVS swabs from which *E coli* could be cultured in each group of patients.

* $p < 0.05$.

was not significant. However the proportion of positive LVS in symptomatic IB patients (17/32 swabs) was greater at a significant level ($0.05 > p > 0.025$) than that proportion in symptomatic (but not asymptomatic) NB patients (11/40 swabs). The number of superficial and deep urethral swabs taken from IB patients was too few to enable similar comparisons to be made.

RECOVERY OF *E. COLI* FROM THE LOW VAGINAL SWABS OF CONTROL SUBJECTS

Escherichia coli were grown from the LVS of 18 of the 82 control women (22%). This is significantly less than the proportion of positive swabs from the patients, whether all of these were considered (Table 2), or only the first LVS taken from each patient ($0.01 > p > 0.001$). Of the latter group 43 of 92 were positive. The proportion of positive swabs in the controls was less than that in each of the patient sub-divisions; significantly so when compared with the symptomatic IB ($p < 0.005$) and asymptomatic NB ($p < 0.005$) patients.

ISOLATION OF *E. COLI* SEROTYPES FROM SWABS IN PATIENTS WITH AND WITHOUT SYMPTOMS

Seventy to 82% of *E. coli* from the different areas could be typed with the available antisera. Twelve different serotypes were isolated. The heterogeneity of serotypes was greatest in *E. coli* derived from rectal swabs, least in those from urine, and intermediate in those cultured from the introitus and urethra. Serotype O6 was by far the commonest isolate; O2 was the only serotype which was more often than not associated with symptoms of "abacterial" cystitis; however this was because it was only cultured from one patient who was frequently symptomatic yet persistently abacteriuric.

Discussion

There is indirect evidence to suggest that the symptoms in bacterial and at least some forms of "abacterial" cystitis are due to similar causes. Thus the symptoms in each are qualitatively identical, although usually less severe when bacteriuria is not found, and often respond to treatment in the same way.⁵⁻⁷ In a general practice survey 40% of women presenting with bacterial cystitis developed "abacterial" cystitis during follow-up, only 29% developing a recurrence of bacterial cystitis; many developed both.² O'Grady *et al.*⁸ also noted the occurrence of episodic "abacterial" cystitis in patients with recurrent bacterial cystitis; at such times their urine tended to contain leucocytes more often and in greater numbers than the urine of

patients with similar symptoms but persistently uninfected urine. They considered that unrecognised bacterial infection might cause the symptoms in the first group of patients. Such an explanation is supported by the work of Stamm *et al.*⁹ who demonstrated *E. coli* and less often *Staphylococcus saprophyticus* in concentrations less than $3.4 \times 10^7/l$ in the suprapubic bladder aspirate of nearly half their patients with "urethral syndrome" whose mid-stream urine cultures showed no evidence of significant bacteriuria. They did not study asymptomatic control women in the same way, but patients without pyuria were rarely so infected. Chronic inflammation in the lamina propria of the bladder is found in patients with recurrent bacterial and "abacterial" cystitis, but is less severe in the latter.¹⁰

Therefore, there is a possibility that unrecognised coliform infection of the lower urinary tract often causes "abacterial" cystitis, unrecognised because of its transience, or because of failure of the bacteria to achieve high concentration in urine. We have tested the hypothesis that coliform infection of the urethra may cause symptoms of "abacterial" cystitis by relating our ability to culture *E. coli* from the vestibule and urethra of women with a history of frequent cystitis to the patients' symptoms at the same clinic visits. We did not quantify the *E. coli* from these areas, having found this unhelpful in predicting the development of urinary infection;³ the advantages of qualitative over quantitative analysis of introital swabs have been emphasised by others.¹¹ Overall, we were unable to relate symptoms to the growth of *E. coli* from swabs of vaginal introitus, external urethral meatus or proximal urethra. Our finding that *E. coli* were more likely to be isolated from LVS of symptomatic IB than symptomatic NB patients may have been due to chance, for the difference was only weakly significant and *E. coli* were often isolated from such swabs taken from asymptomatic NB patients. However it is compatible with previous suggestions that apparently "abacterial" cystitis in intermittently bacteriuric patients is due to coliform infection. Stamm *et al.*⁹ were usually able to isolate *E. coli* from the urethra and vagina of women with the "urethral syndrome" whose bladder urine contained low concentrations of bacteria, but did not often find them in similar women with sterile bladder urine or in asymptomatic women. Cattell *et al.*¹² noted no difference in periurethral *E. coli* carriage rate between persistently symptomatic abacteriuric patients, asymptomatic abacteriuric patients with a history of cystitis and patients with recurrent bacteriuric cystitis studied between attacks of infection; they did not make cultures from the proximal urethra. In contrast, the same group had previously been able to

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relate symptoms of cystitis to the introital carriage of enterobacteria.¹³

We isolated *E coli* twice as often from the introitus of our non-bacteriuric and intermittently bacteriuric patients as from control women, although their age distributions were similar. This differs from the findings of O'Grady¹³ and Cattell¹² but agrees with those of others in patients with less well defined urinary infections.^{14 15} The similar overall isolation rate in IB and NB patients suggests that although the presence of *E coli* at the introitus is not associated with symptoms of cystitis it may denote lack of resistance to vulval and perhaps urethral bacterial colonisation in both groups, or more specifically may predispose to *E coli* urine infection in both. It supports the possibility that the symptoms of apparent "abacterial" cystitis in both IB and NB patients may most often be due to occult coliform infection of the urinary tract, despite the differences claimed between them.

We detected *E coli* much less often in the proximal urethra than at the urethral meatus. This implies that the urethra is inhospitable to bacteria in women as in men, or that it is difficult to culture bacteria from it. The former is suggested by the results of Mortimer *et al*,¹⁶ whose method of making cultures from the proximal urethra was similar to ours. They found bacteria in the proximal urethra only half as often as at the urethral meatus in abacteriuric antenatal patients. There was no reduction when bacteriuric antenatal patients were studied, implying that a urethral defence mechanism has been overcome in them.

We have also examined the possibility that some *E coli* serotypes may be more likely than others to cause symptoms of "abacterial" cystitis, but found no evidence for this. The distribution of serotypes in urethra and introitus reflected that in the faeces, although it was less heterogeneous.¹⁷

Slow-growing microaerophilic organisms have been suggested to cause "abacterial" cystitis¹⁸ as have chlamydia.⁹ However, the former may often be isolated from the vestibule, urethra and urine of normal women, and were no more often cultured from the urine of symptomatic patients.^{19 20} In many patients the cause remains unknown. Our results do not support the hypothesis that unrecognised colonisation of the urethra by *E coli* is an important cause. They are compatible with the hypothesis that symptoms of "abacterial" cystitis in intermittently bacteriuric, and possibly in persistently "non-bacteriuric", women are often due to unrecognised coliform infection of the urine.

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