

Recurrent urethritis in women

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Summary: The bacterial flora of the vestibule, urethra and vagina of a group of patients with recurrent urethritis, and of control subjects without symptoms, was investigated. Organisms regarded as pathogenic, such as enterobacteria and *Streptococcus faecalis*, were recovered significantly more frequently from patients than from controls, whereas the reverse was found for non-pathogenic organisms. The bacterial flora was similar in the three areas, suggesting that a specimen taken from one region only would give adequate bacteriological information. The vestibule is suggested as a suitable site. The incidence of vestibular pathogens was higher in postmenopausal patients. Perineal length and vestibular pH were very similar in patient and control groups. There was some evidence that in most subjects the bacterial flora of the areas investigated remains fairly constant over a period of several weeks. Although bacterial species commonly responsible for urinary tract infection may often cause recurrent urethritis, the absence of these pathogens from some patients suggests that the etiology of this condition is not yet fully understood.

Résumé: L'urétrite récidivante chez la femme

L'auteur a étudié la flore bactérienne du vestibule, de l'urètre et du cagion chez un groupe de femmes souffrant d'urétrite récidivante et une chez un groupe de sujets-témoins asymptomatiques. Des micro-organismes considérés comme pathogènes, notamment des entérobactéries et *Streptococcus faecalis* ont été isolés plus souvent chez les malades que chez les témoins, tandis que la situation inverse prévalait en ce qui concerne des microbes non pathogènes. La flore bactérienne était similaire dans les trois régions, ce qui permet de croire qu'un spécimen prélevé dans une région seulement donnerait des renseignements bactériologiques suffisants. Le vestibule est considéré comme une région convenable. La fréquence des germes pathogènes du vestibule était plus considérable chez les femmes déjà ménopausées. La longueur du périnée et le pH vestibulaire étaient très voisins dans les deux groupes. Certains signes indiquaient que, chez la majorité des sujets, la flore bactérienne de la région intéressée demeure à peu près constante pendant plusieurs semaines. Bien que les espèces bactériennes le plus souvent incriminées dans l'infection des voies urinaires puissent souvent causer une urétrite récidivante, l'absence de ces germes pathogènes chez certaines malades démontre que l'étiologie de cette pathologie n'est pas encore complètement élucidée.

Gallagher and his associates¹ have shown that about one half of the women seen in general practice with symptoms of urinary tract infection have sterile urine and these authors have coined the term "urethral syndrome" to describe this symptom complex. Moore and Hira² have drawn attention to the embryological similarity between the female urethra and the prostatic urethra and along with Huffman^{3,4} have shown in the female the presence of periurethral glands similar to those of the prostate. Moore and Hira² have suggested that organisms may settle and multiply in these glands and be a source of recurrent urinary tract infection. Cox, Lacy and Hinman,⁵ Cox,⁶ Fair *et al.*,⁷ O'Grady *et al.*,⁸ and Marsh, Murray and Panchamia⁹ have studied the bacteriological flora of the lower urinary tract in women with recurrent urethritis and also in controls with no history of urinary symptoms or infection. Considerable disagreement exists between these authors concerning the actual numbers and types of organisms isolated and their significance.

We wish to report the bacteriological aspects of our study of 105 female patients being investigated for recurrent lower urinary tract infection and 60 control patients attending for gynecological consultation. None of this latter group had any previous urinary tract symptomatology and no women in either group were receiving antibiotic therapy.

Methodology

Prior to cystoscopy or pelvic examination the patients were placed in the lithotomy position. Specimens were collected as follows:

1. Vestibular swab: the labia were separated and a swab was taken from the area of the hymenal ring, covering all quadrants.
2. Urethral swab 1: with the labia separated a swab was introduced 1 cm. into the urethra, rotated and withdrawn.

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3. Vaginal swab: a deep vaginal swab was taken with a speculum in place.
4. Urethral swab 2: the periurethral glands were massaged vigorously and then a urethral swab was taken as already described.
5. After cleansing with povidone-iodine and appropriate draping, the urethral meatus was washed with sterile water and a cystoscopic specimen of bladder urine was collected. From the control subjects a clean-catch midstream specimen was obtained.

All specimens were sent immediately to the microbiology laboratory. Vestibular, urethral and vaginal swabs were plated on blood, MacConkey, azide and Sabouraud agar for aerobic incubation, and on blood agar for anaerobic incubation. All organisms growing from these specimens were recorded. Enterobacteria and enterococci were identified to species level; staphylococci were characterized by their coagulase reaction; corynebacteria and lactobacilli were identified to generic level only. Urine specimens were cultured quantitatively by inoculation of three serial tenfold dilutions onto tryptose, MacConkey and azide agar.

In addition the pH of the vestibule was estimated using nitrazine indicator paper and the distance between the anal margin and the fourchette was measured. Urethral calibration and cystoscopy were then carried out.

In a special group of eight patients (seven from the infected group, chosen at random, and one from the control group), weekly cultures and pH studies were repeated through a full menstrual cycle.

Results

The quantitative urine cultures showed that none of the patients or control subjects had significant bacteriuria. Fig. 1 shows for both groups of women the relative incidence of pathogenic organisms in the vestibular, urethral and vaginal specimens, and also the incidence of pathogens in any of the four areas. We have regarded as pathogenic organisms any members of the family Enterobacteriaceae and also *Streptococcus faecalis*. The figures for percentage incidence are based on the presence of any degree of growth of the organisms concerned. The following significant points emerge:

1. There was a marked similarity of findings, in both patients and controls, in the cultures of specimens taken from these four areas.
2. For each specimen the incidence of pathogens in the patients was considerably higher than in the controls. When all four specimens were considered together, the incidence was 53% for the patients and 20% for the controls. This percentage difference is statistically significant at the 0.001 level, based on the normal curve test of the difference between percentages in two independent samples.

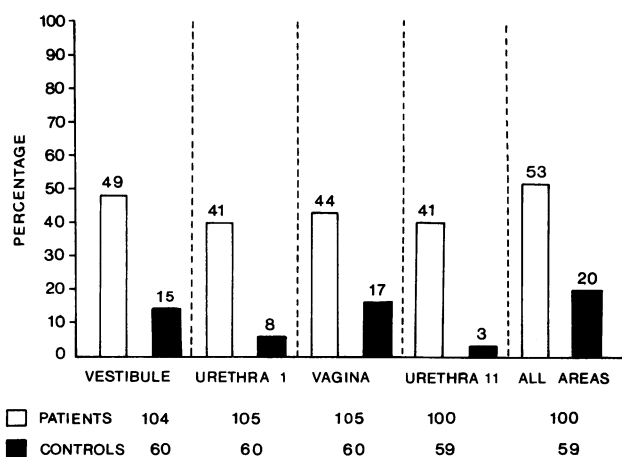


FIG. 1—Relative incidence of pathogenic organisms in different areas found in patients and control subjects.

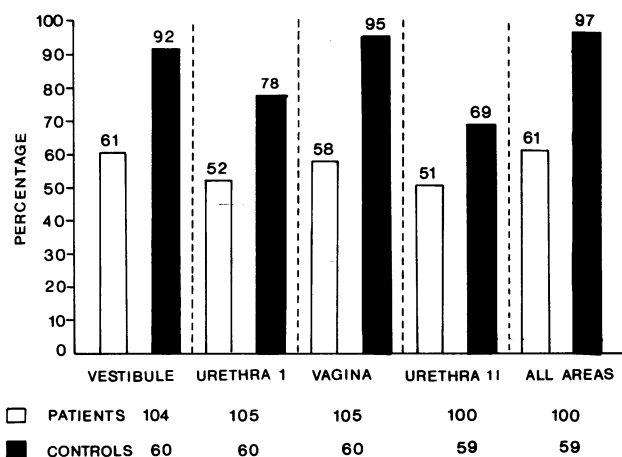


FIG. 2—Relative incidence of nonpathogenic organisms in different areas found in patients and control subjects.

Table I
Collective incidence of various pathogenic and nonpathogenic organisms in specimens taken from vestibular, urethral and vaginal areas of patients and controls

Organisms	Incidence in 100 patients Number	Incidence in 100 patients Percentage	Incidence in 59 controls Number	Incidence in 59 controls Percentage	Significance level (P) of percentage difference
<i>Escherichia coli</i>	30	30	7	12	0.01
<i>Streptococcus faecalis</i>	35	35	7	12	0.01
Staphylococcus (coagulase-negative)	49	49	49	83	0.0001
Corynebacterium	46	46	46	78	0.0001
Lactobacillus	43	43	19	32	0.05
Enterobacteria* and <i>Strep. faecalis</i>	53	53	12	20	0.001
Staphylococcus (coagulase-negative), Corynebacterium and Lactobacillus	61	61	57	97	0.0001

*Including *E. coli*, *Klebsiella aerogenes*, *Enterobacter aerogenes*, *Citrobacter freundii*, and members of the *Proteus* group

Fig. 2 shows the incidence of nonpathogenic organisms, consisting almost entirely of coagulase-negative staphylococci, corynebacteria and lactobacilli, in the two groups of women. For each specimen individually and for all specimens together, the incidence of nonpathogens was consistently lower in the patients than in the controls. The percentage difference for all specimens together is significant at the 0.0001 level. The pattern was therefore the reverse of that shown for the pathogens.

Table I presents the relative incidence of individual pathogenic and nonpathogenic organisms, in the four specimens collectively, for patients and controls. The total numbers of patients and controls are only 100 and 59 respectively, since a few individuals were not subjected to the second urethral swab. The differences in percentage incidence, except for lactobacilli, were all statistically significant.

The patients and controls were further subdivided into premenopausal and postmenopausal subgroups, and the incidences of pathogenic and nonpathogenic organisms in the vestibule were compared. Fig. 3 shows the greater frequency of vestibular pathogens in both pre- and postmenopausal patients as compared to the controls, and also demonstrates that the incidence of vestibular pathogens was higher in the post- than in the premenopausal patients. The differences are statistically significant at P values ranging from 0.05 to 0.0001, with the exception of the percentage difference between pre- and postmenopausal controls. Fig. 4

Table II
Ranges and means of anovestibular lengths in premenopausal and postmenopausal patients and controls

	Premenopausal (97)		Postmenopausal (67)	
	Patients (56)	Controls (41)	Patients (48)	Controls (19)
Range (cms.)	2.9—4.0	1.9—3.6	2.2—4.0	1.9—3.3
Mean (cms.)	3.2	2.8	3.0	2.4

Table III
Ranges and means of vestibular pH measurements in all subjects

	Premenopausal (97)		Postmenopausal (67)	
	Patients (56)	Controls (41)	Patients (48)	Controls (19)
Range	4.5—7.5	4.5—7.0	4.5—7.5	4.5—7.5
Mean	5.8	6.2	6.0	5.6

Table IV
Ranges and means of vestibular pH measurements in subjects with vestibular pathogens

	Premenopausal (26)		Postmenopausal (34)	
	Patients (21)	Controls (5)	Patients (30)	Controls (4)
Range	4.5—7.5	5.5—6.5	4.5—7.5	4.5—6.0
Mean	5.7	6.0	6.3	5.2

FIGURE 3

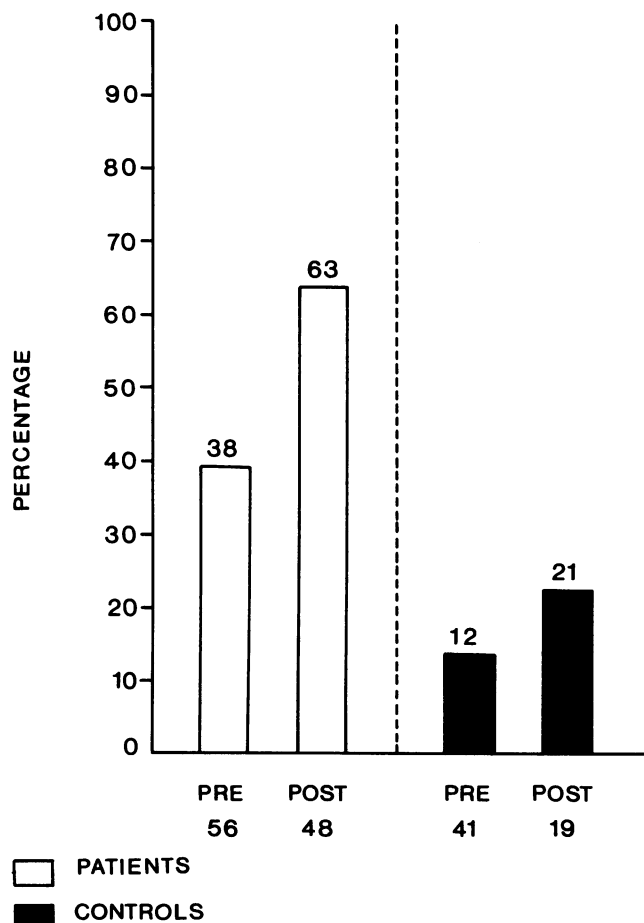


FIG. 3—Incidence of vestibular pathogens in pre- and postmenopausal subgroups of patients and controls.

FIGURE 4

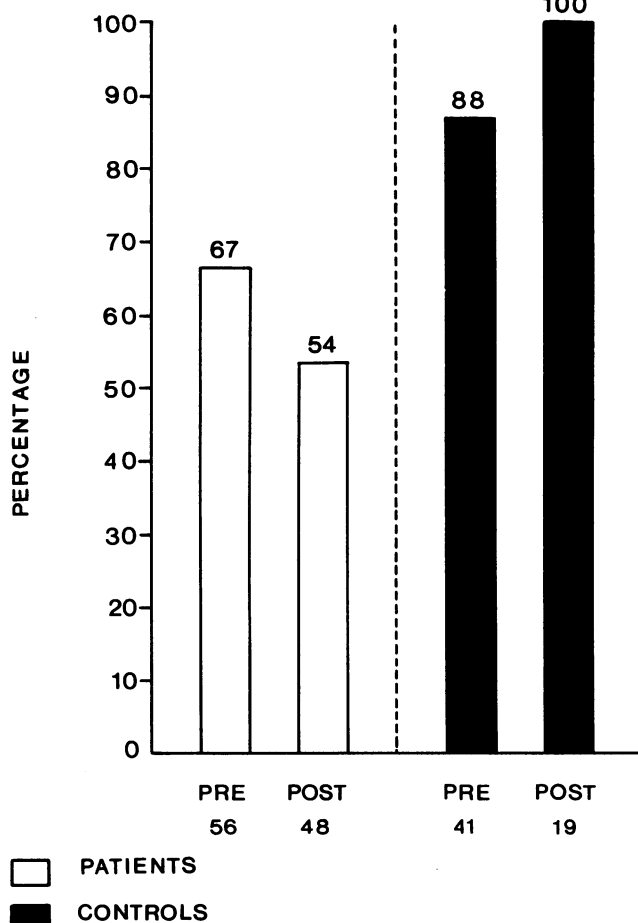


FIG. 4—Incidence of vestibular nonpathogens in pre- and postmenopausal subgroups of patients and controls.

shows that vestibular nonpathogens occurred more frequently in controls than patients in both pre- and postmenopausal subgroups (differences significant at 0.05 and 0.001 levels, respectively), and also that these organisms were isolated more frequently from the premenopausal individuals of the patient group and the postmenopausal subjects of the control group. These last two differences were also significant ($P=0.05$).

Table II sets forth the ranges and means of perineal lengths in the two groups of patients and the two groups of controls. Ranges and means were similar in all groups. It would appear that perineal length is of no etiological significance in recurrent urethritis.

The ranges and means of vestibular pH readings for all subjects are set forth in Table III and for those individuals with vestibular pathogens in Table IV. There were no appreciable differences in vestibular pH between the different groups.

In the eight patients subjected to repeated cultures there were two interesting findings:

1. Only minimal increases in vestibular pH were noted throughout the menstrual cycle, and these were always noted prior to menstruation.
2. In seven patients the bacterial flora was similar in the weekly samples taken during the menstrual cycle. In the eighth patient there was more variation between samples, particularly in the vestibular cultures.

Discussion

We would like to emphasize the close similarity between the cultural findings in the distal urethra, vagina and vestibule. This is not surprising in view of the anatomical proximity, common developmental origin and endocrine control of these areas. It follows that in the investigation of any female patient with lower urinary tract symptoms it is mandatory to obtain a culture representative of this area. From our studies and those of others⁵⁻⁹ we would suggest that the vestibule be used since pathogenic organisms are most frequently cultured from this readily accessible site.

There has been much criticism of the method of urethral sampling used in this study. Fair *et al*⁷ have advocated that culture of the first 5 ml. of urine would serve to identify the urethral flora. Our results suggest that vestibular cultures probably provide equally accurate and useful information. The percentages of patients and controls showing pathogenic organisms in the vestibular area are virtually identical in our series and in those of Cox^{5,6} and O'Grady *et al.*⁸ they differ substantially from those reported by Fair *et al.*⁷ In contrast to these groups of workers, we found that the important pathogen *Streptococcus faecalis* was cultured as frequently as *E. coli* (Table I). Fair *et al*⁷ have also emphasized the significance of a pH below 5.0 in reducing growth of pathogenic bacteria in the vestibule; our findings would not support this view. Comparison of the results of urethral cultures before and after massage of the periurethral glands suggests that pathogenic organisms are located super-

ficially, reinforcing the opinion that the vestibule is the primary focus of infection.

We have recently begun a study of the effect of chlorhexidine cream applied to the vestibule in patients with positive vestibular cultures, and preliminary results indicate that this may be of real practical value in preventing reinfection. Hexachlorophene (pHisoHex®) has been advocated by Tein and Smith,¹⁰ who have shown the significance of vagino-urethral reflux in the causation of urinary tract infection. Landes, Melinek and Hoffman¹¹ have demonstrated the usefulness of povidone-iodine ointment applied topically in preventing recurrent cystourethritis. Chlorhexidine cream has the advantage of avoiding staining of undergarments.

We have assumed in this investigation that organisms commonly responsible for urinary tract infection, such as enterobacteria and *Streptococcus faecalis*, are also likely to be causal agents in recurrent urethritis. Failure to culture such organisms from some patients with symptoms of urethritis provides a warning that other causes of urethritis must be looked for. These causes may be infective, e.g. organisms such as *Mycoplasma*, *Candida albicans* or even bacterial species regarded in this investigation as nonpathogenic. Alternatively, parasitic infestations (e.g. *Enterobius vermicularis*), or allergic responses to food, drugs, detergents or inhaled materials may be responsible for this syndrome.¹²

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