Bacteriuria and primary biliary cirrhosis

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SUMMARY Significant bacteriuria was found in 19% of 87 women with primary biliary cirrhosis, whereas in 89 women with other types of chronic liver disease bacteriuria was present in only 7%. In 74 women with rheumatoid arthritis 8% were bacteriuric. Midstream urine specimens obtained from 144 consecutive women with primary biliary cirrhosis attending hospital over a two year period showed that 50 (35%) developed bacteriuria during 12 months of follow up. Bacteriuria was unrelated to age, raised serum bilirubin, drug therapy or urinary pH but was more common in patients with late stage (fibrotic) disease as judged by histological criteria. Fifty seven per cent of bacteriuric primary biliary cirrhosis patients suffered more than one urinary infection. Fifty nine per cent of the 156 bacteriuric episodes were asymptomatic. The types of organism isolated, the antibiotic sensitivity patterns and cure rate were similar to those reported in bacteriuric women without other underlying disease. The reinfection rate (34%), however, was double that reported for bacteriuric episodes in 'problem' women with recurrent bacteriuria, indicating a special susceptibility to urinary infection. The most common isolates were *E coli* (70%), which did not show abnormal adhesiveness to uroepithelial or buccal cells of normal women, or to those of primary biliary cirrhosis patients. Patients with primary biliary cirrhosis have not been reported to be more susceptible to infection in general. Bacteriuria, however, was common throughout all clinical stages of primary biliary cirrhosis. Thus there may be a unique association between bacteriuria and primary biliary cirrhosis.

Patients with primary biliary cirrhosis have marked disturbances of humoral and cellular immunity, but an increased susceptibility to infection has not been described previously. We have observed, however, that patients with primary biliary cirrhosis have a high incidence of bacteriuria. This increased susceptibility to urinary infection has been studied and our findings are reported.

Methods

PATIENTS

Patients with primary biliary cirrhosis were diagnosed by the usual criteria,¹ and classified into prefibrotic (stage 1 and 2) and fibrotic disease (stage 3 and 4). Women with other forms of chronic liver disease (non-primary biliary cirrhosis) confirmed by liver biopsy, and women with rheumatoid arthritis,

served as controls in three separate studies: (I) During a six month period, single midstream urine specimens were obtained from each consecutive primary biliary cirrhosis and non-primary biliary cirrhosis patient admitted to hospital. (II) A retrospective study on the results of midstream urine specimens recorded in the hospital notes of the patients in study I. (III) Three months after study I, single midstream urine specimens were obtained prospectively from each consecutive primary biliary cirrhosis and non-primary biliary cirrhosis patient attending weekly outpatient clinics over a period of three months. Consecutive outpatients with rheumatoid arthritis (not confined to a wheelchair) were studied in a similar fashion at a later date.

Three months after completing these comparative studies, a prospective survey (study IV) of bacteriuria was carried out to investigate the natural history and type of organisms involved. Midstream urine specimens were obtained from 158 consecutive primary biliary cirrhosis patients (144 women and 14 men) and 24 women with other forms of chronic

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cholestasis, whenever they attended hospital. Previous bacteriuric episodes in these patients were also analysed. One hundred and three of the female primary biliary cirrhosis patients had been surveyed either in study I or III.

Midstream urines were collected,² examined immediately or stored at 4°C and quantitative cultures made within two hours. Significant bacteriuria was defined as the growth of 10⁵ or more organisms/millilitre in pure culture.²⁻⁴ Infecting organisms were identified and their antibiotic sensitivity determined.⁵ Extended biotyping⁶ and O serotyping was carried out on all strains of *E coli* to differentiate between re-infection (different strain) or relapse (same strain).

Urines were tested with standard reagent strips (Labstix, Ames Division, Miles Laboratories Ltd.). Patients with significant bacteriuria were treated for seven days with oral co-trimoxazole (two tablets 12 hourly), unless contraindicated by patient hypersensitivity or antibiotic resistance. Response to treatment was assessed at two and six weeks after starting therapy by repeating the midstream urine examination.⁵ Some specimens were obtained using dip-slides⁵ (Uricult, Orion), which were mailed to us by the patient. Bacterial adhesion was studied using methods modified from those of other workers.^{7,8} Several strains of *E coli* isolated from primary biliary cirrhosis patients' urine, were mixed with buccal and uroepithelial cells (in separate experiments) from primary biliary cirrhosis patients and compared with a healthy control with no history of urinary infection.^{7,8} The mean number of bacteria adhering to 40 cells in a stained preparation was counted. The χ^2 test was used to analyse discontinuous data.

Results

In study I, 21% of 89 primary biliary cirrhosis and 8% of 90 non-primary biliary cirrhosis inpatients had significant bacteriuria ($p < 0.05$). In study II, significant bacteriuria was documented previously in hospital records of 42% of 72 primary biliary cirrhosis and 13% of 60 non-primary biliary cirrhosis patients in study I ($p < 0.01$).

In study III (outpatients) 19% of 87 primary biliary cirrhosis and 7% of 89 non-primary biliary cirrhosis patients had significant bacteriuria ($p < 0.05$) (Table 1). Approximately half of the patients in the primary biliary cirrhosis and non-primary biliary cirrhosis groups were the same as those in study I. Only a third of the primary biliary cirrhosis patients infected as inpatients were also infected as outpatients. In the outpatient non-primary biliary cirrhosis group bacteriuria was found

Table 1 Bacteriuric patients in studies comparing primary biliary cirrhosis and non-primary biliary cirrhosis patients

	Female primary biliary cirrhosis patients		Women with other types of chronic liver disease	
	Total no	Bacteriuric (%)	Total no	Bacteriuric (%)
Inpatient study*	89	19 (21%)‡	90	7 (8%)
Outpatient study*	87	17 (19%)‡	89	6 (7%)
Retrospective study†	72	30 (42%)§	60	8 (13%)

* Prevalence at first hospital attendance during study period.

† Summation of bacteriuric episodes documented in hospital notes in patients in the inpatient study.

‡ $p < 0.05$. § $p < 0.01$.

in 8% of 51 patients with autoimmune chronic liver disease ($p < 0.05$), 5% of 20 with alcoholic liver disease and 11% of 9 with other forms of chronic cholestasis. Bacteriuria was not found in the remaining nine patients with cryptogenic cirrhosis, chronic non-A, non-B hepatitis or Wilson's disease. In the rheumatoid arthritis group, 8% of 74 women had significant bacteriuria ($p < 0.05$).

The mean age in outpatients was 52.9 years (range 30–72 years) in the primary biliary cirrhosis, 46.2 years (range 22–69 years) in the non-primary biliary cirrhosis, and 52.1 years (range 25–81 years) in the rheumatoid group.

In study IV (prospective survey), 890 midstream urine specimens from 144 female primary biliary cirrhosis patients were examined in a period of one to 24 months. In their first urine 28 patients (19%) had significant bacteriuria and in 51 patients (35%) bacteriuria was found during one year. These findings were not confined to any particular age group (Table 2). Forty one per cent of 156 episodes of bacteriuria were symptomatic and 65% of urines showed pyuria (>10 WBC/ μ l). *E coli* was cultured in 109 (70%) of the specimens (Table 3). At six weeks, the cure rate (clearance of the infecting

Table 2 Survey of significant bacteriuria in women with primary biliary cirrhosis

Years	Patients (no)	Significant bacteriuria	
		First urine	Follow up period one year or less
30–39	10	0	3 (30%)
40–49	28	7 (25%)	10 (36%)
50–59	58	11 (19%)	23 (40%)
60–69	39	8 (21%)	13 (33%)
70+	9	2 (22%)	2 (22%)
Total	144	23 (19%)	51 (35%)

Table 3 Urinary organisms found in the survey of primary biliary cirrhosis patients

Organisms	Episodes of significant bacteriuria
<i>E coli</i>	109 (70%)
<i>Klebsiella spp</i>	11
<i>Streptococcus faecalis</i>	7
<i>Citrobacter freundii</i>	4
<i>Proteus mirabilis</i>	3
<i>Streptococcus spp</i>	3
<i>Pseudomonas spp</i>	3
<i>Staphylococcus epidermidis</i>	2
<i>Staphylococcus aureus</i>	1
<i>Enterobacter aerogenes</i>	1
<i>E coli/S faecalis</i>	4
<i>E coli/Klebsiella spp</i>	3
<i>E coli/Streptococcus spp</i>	2
<i>E coli/Serratia spp</i>	1
<i>E coli/Proteus</i>	1
<i>Bacteroides spp/Peptococcus</i>	1
Infections - total	156

organism) was 92% and the reinfection rate due to a different organism was 34%.

Over the two year study period, 57% of the 58 bacteriuric patients had more than one bacteriuric episode and 26% had three episodes or more in less than one year. The latter group had normal intravenous urograms and micturating urethrocytograms. Two patients developed acute pyelonephritis (one with septicaemia) but both recovered. Otherwise there was no obvious change in clinical status such as precipitation of hepatic encephalopathy. No patient had biochemical evidence of chronic renal failure.

Biotypes of *E coli*⁶ were similar to those causing bacteriuria in other groups of women outside hospital. Eighty three per cent of *E coli* strains isolated were sensitive to ampicillin, 69% to sulphonamides and 94% to trimethoprim. Bacterial adhesion studies in 10 primary biliary cirrhosis patients showed no difference in the ability of *E coli* strains to adhere to buccal or uroepithelial cells from primary biliary cirrhosis patients when compared with similar cells from a healthy control. Urinary pH was 6 or less in 86% of urines and dipstick testing for glucose, ketones, and blood was normal in all but two urines. Urine pH did not correlate with bacteriuria.

In the survey, bacteriuric and non-bacteriuric primary biliary cirrhosis groups did not differ as regards drug therapy (cholestyramine, penicillamine, diuretics, and lactulose) and 28 (50%) bacteriuric patients were taking no drugs. Bacteriuria was present in 35% of 57 patients with normal and 44% of those with raised serum bilirubin concentrations. This difference was not significant.

Bacteriuria was found in 49 of 104 (47%) patients with late stage (fibrotic or cirrhotic) liver histology and nine of 40 (23%) with early stage (prefibrotic) primary biliary cirrhosis¹ ($p < 0.02$). The mean age of these groups were similar (57 and 54.7 years respectively). Five of nine patients with early stage disease and 28 of 49 patients with late stage disease became reinfected.

Retrospective survey of patients in study IV showed that similar numbers of late and early stage patients had documented bacteriuric episodes. Repeated episodes were more frequent in late stage patients. Three patients had had acute pyelonephritis.

One of the 14 male primary biliary cirrhosis patients showed significant bacteriuria. This patient was taking cotrimoxazole prophylactically for recurrent bacteriuria persisting after transurethral prostatectomy. Four other male patients had previously documented significant bacteriuria (one with acute pyelonephritis), unassociated with prostatic or renal pathology.

Only one of 24 jaundiced women with other forms of chronic cholestasis had significant bacteriuria. This patient had primary sclerosing cholangitis.

Discussion

The association of significant bacteriuria in women with primary biliary cirrhosis as compared with women with rheumatoid arthritis or women with other forms of chronic liver disease, including other types of chronic cholestasis, has not been described previously.

The prevalence of bacteriuria in 19% of women with primary biliary cirrhosis contrasted with the five to six per cent found in aged matched (50-69 years) populations of normal women,⁹ female patients seen in general practice,¹⁰ or those attending medical outpatients.² Scrutiny of hospital records showed that bacteriuria had been well documented previously, showing that primary biliary cirrhosis patients studied had not recently become more susceptible to urinary infection.

Factors predisposing primary biliary cirrhosis patients to bacteriuria are unknown. Age is not a factor as bacteriuria was as frequent in younger as in older patients, with an incidence of 35% per year (Table 2). Although no primary biliary cirrhosis patient was pregnant, a high proportion of patients had no symptoms, a finding similar to that in otherwise healthy bacteriuric women, in early pregnancy. None of the patients with pyelonephritis or recurrent bacteriuria had evidence of structural renal tract damage, ureteric reflux or detrusor dysfunction. The low incidence of bacteriuria in

jaundiced women with other forms of chronic cholestasis and high incidence in primary biliary cirrhosis patients with normal serum bilirubin concentrations shows that raised urinary bilirubin and bile salt concentrations are not important aetiological factors. Renal tubular acidosis is common in patients with primary biliary cirrhosis but is usually a 'latent' phenomenon. Urinary pH is usually acidic unless acid loading is used to establish the diagnosis. Urinary pH was acid in the majority of patients and did not correlate with bacteriuria. Thus pH is unlikely to be a predisposing factor.

Varieties of organisms, the biotypes and serotypes of *E coli*, antibiotic sensitivity patterns and cure rates were similar to those causing bacteriuria in the community.^{10 11} This suggests that infection was related to the normal prevalence of bacterial species in faeces rather than being due to bacteria with unusual pathogenicity.¹² It also shows that infection was not acquired in hospital.¹² Although cure rates were similar to those found in otherwise normal general practice patients, treated for urinary infection, the reinfection rate (34%) in primary biliary cirrhosis patients was double that found in 'problem' women with recurrent bacteriuria, who were otherwise healthy.⁵ This again shows a particular susceptibility of primary biliary cirrhosis patients to bacteriuria. An abnormal epithelium increasing adhesion and colonisation of the introitus may be important in recurrent bacteriuria of otherwise normal women.¹³ Preliminary studies, however, suggest this was not so in primary biliary cirrhosis patients studied by us.

Although bacteriuria correlated significantly with histologically late stage disease as compared with early stage disease, this difference was not apparent in a retrospective analysis of bacteriuric episodes in the same patients. Moreover, bacteriuria did not correlate with severity of liver disease as assessed by serum bilirubin concentrations.¹⁴ The incidence of bacteriuria was common throughout all clinical stages of primary biliary cirrhosis.

Despite not overtly affecting clinical status in the majority of primary biliary cirrhosis patients, bacteriuria may reflect a generalised disturbance of humoral and cellular immunity. Other infections, however, have not been found to be more common in primary biliary cirrhosis, so that bacteriuria may have a unique association with primary biliary cirrhosis.

A cross reaction has been observed between *E coli* lipopolysaccharide and HLA antigens.¹⁵ Such antigens have been invoked in the pathogenesis of primary biliary cirrhosis.¹⁶ Moreover the immunological phenomena of primary biliary cirrhosis are consistent with a microbial agent in their patho-

genesis.¹⁷ Particularly interesting is the mitochondrial antibody M2, associated specifically with primary biliary cirrhosis.¹⁸ This is directed against part of the ATPase complex of the inner mitochondrial membrane which has been shown to have structural similarity with the cell membranes of certain micro-organisms.¹⁹ On theoretical grounds it is possible that urinary organisms could be involved in the pathogenesis or progression of primary biliary cirrhosis, and this merits further investigation.

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