Host-parasite interaction in men with febrile urinary tract infection

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HOST-PARASITE INTERACTION IN MEN WITH FEBRILE URINARY TRACT INFECTION

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I. Ulleryd P, Lincoln K, Scheutz F, Sandberg T.
Virulence characteristics of *Escherichia coli* in relation to host response in men with symptomatic urinary tract infection.
Clin Infect Dis 1994;18:579-84.

II. Ulleryd P, Zackrisson B, Aus G, Bergdahl S, Hugosson J, Sandberg T.
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IV. Ulleryd P, Sandberg T.
Ciprofloxacin for two or four weeks in the treatment of febrile urinary tract infection in men. A randomised trial with a 1-year follow-up.
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ABSTRACT

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Different clinical aspects of febrile UTI were prospectively studied in 86 men. Although only nine (12%) of 76 patients had a tender prostate on digital rectal examination, the initial serum prostate-specific antigen (PSA) was elevated in 58 (83%) men. Among 55 men who had PSA analysed twice, 51 (93%) showed a reduction of PSA by > 25 % after three months. The median prostate volume was reduced from 49 mL to 35 mL. The results indicate that the prostate is frequently engaged by the infection in men with febrile UTI. The slow decline of PSA levels in some patients after treatment should be considered when PSA is used for the detection of prostate cancer.

Radiological examination of the upper urinary tract in 83 patients revealed abnormal findings in 19 (23%) patients. Lower urinary tract investigation disclosed abnormal findings in 35 men. Surgically correctable disorders were found in 20 patients, 15 of whom had previously unrecognised abnormalities. All patients requiring surgery were identified either by a history of voiding difficulties, acute urinary retention, the presence of microscopic haematuria at short-term follow-up, or early recurrent symptomatic UTI. Accordingly, routine imaging of the upper urinary tract seems dispensable in men with febrile UTI.

Seventy-two patients were randomised to treatment with ciprofloxacin 500 mg b.i.d. for 2 or 4 weeks, respectively. The outcome was excellent in both groups. There was no significant difference in short-term bacteriological cure rate between the groups (89% vs 97%), nor in cumulative bacteriological cure rate after 1-year´s follow-up (59% vs 76%). The cumulative clinical cure rate after one year was 72% and 82%, respectively. A 2-week course of ciprofloxacin 500 mg b.i.d. seems adequate for treatment of men with febrile UTI.

Key words: urinary tract infection, fever, male, *Escherichia coli*, serotype, virulence, PSA, prostate, prostatitis, TRUS, urography, cystoscopy, treatment, ciprofloxacin

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2001

To Edgar,

the most sensible and wise man I have ever met

ABSTRACT

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CONTENTS

ABBREVIATIONS

ABU	asymptomatic bacteriuria
BPH	benign prostatic hyperplasia
CFU	colony-forming units
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
H antigen	flagellar antigen
K antigen	capsular antigen
MSU	midstream urine
O antigen	lipopolysaccharide somatic antigen
PSA	prostate-specific antigen
TRUS	transrectal ultrasound of the prostate
TURP	transurethral resection of the prostate
UTI	urinary tract infection(s)
WBC	white blood cell count

INTRODUCTION

Urinary tract infections (UTI) are one of the most common infectious diseases encountered in primary care practice, hospitals and extended care facilities [1]. The incidence of UTI varies with sex, age and predisposing conditions. UTI more frequently afflict women than men at all ages, except in the first year of life [2, 3]. Although the prevalence of bacteriuria and incidence of symptomatic infections increase in elderly men because of urological abnormalities and instrumentation, UTI is very uncommon in otherwise healthy young and middle-aged men [1]. An estimated annual incidence of 6-8 UTI per 10000 men aged 21 to 50 was reported in a study from Norway [4].

UTI is the result of interactions between bacterial virulence and host defence mechanisms at several levels [5]. In individuals with normal urinary tracts, to cause infection, bacteria have to be equipped with certain properties, i.e. virulence factors, making it possible to overcome host defences [6]. Such infections are designated as uncomplicated and typically occur in young, healthy, non-pregnant females.

The term complicated UTI is used for patients who have underlying functional or structural abnormalities of the urinary tract which predispose to infection by impeding urine flow [7, 8]. Patients with complicated UTI tend to be infected with a broader spectrum of less virulent bacteria, run a high risk of bacteraemia, have antibiotic treatment failures, and are prone to recurrent infections [1, 9].

The natural history of UTI, pathogenetic mechanisms, risk factors, as well as the need for urinary tract investigation and follow-up have been extensively studied in women and children [1]. Also, numerous, controlled treatment trials have provided information about the proper choice of antimicrobial agents and duration of treatment of symptomatic UTI in women [10, 11].

In men, however, these issues have received little attention. There is an apparent lack of studies of well-defined groups of men with specified types of UTI [12-14]. One obvious reason for this is that UTI is uncommon in adult men.

Escherichia coli is the most common cause of UTI in women and children, accounting for more than 80 per cent of the episodes, especially in those with uncomplicated infections [15]. Other bacterial species have been proposed to play a more important role in men but patients studied have often been compromised by urological abnormalities [16, 17]. As in young women, however, symptomatic UTI in young healthy men with normal urinary tracts seem to be caused primarily by *E. coli* [18].

The faecal flora constitutes a reservoir for potential uropathogens. Successful invasion of the lower urinary tract in women is preceded by colonisation of the periurethral area and is determined by bacterial virulence and the integrity of host defence mechanisms. Uropathogenic *E. coli* possess an array of virulence properties that participate at different stages of the infectious process. Adhesins mediating attachment to epithelial cells seem to play an important role in colonisation of mucosal surfaces and the ascent of bacteria into the urinary tract [5].

E. coli isolated from women with uncomplicated acute pyelonephritis more often belong to certain O:K:H serotypes and more frequently express virulence properties like P fimbriae, haemolysin and aerobactin than *E. coli* strains in the faecal flora or those isolated from patients with asymptomatic bacteriuria (ABU) or acute cystitis [19]. However, when host defences are compromised, as in patients with functional or structural abnormalities of the urinary tract, infections are often caused by a diversity of less virulent *E. coli* strains [20].

Only a small number of *E. coli* strains from men with various types of UTI have been characterised as regards serotype and virulence properties [21, 22]. As in women and children, bacteria causing UTI in men are thought to reach the urinary tract by the ascending route. The relatively long distance between the urethral meatus and the perianal region, the length of the male urethra and the bactericidal activity of prostatic fluid make it difficult for microorganisms to gain access to the urinary tract in men.

Residual urine secondary to infravesical obstruction due to prostatic enlargement has often been suggested as an important factor for the increased incidence of symptomatic UTI in elderly men but compelling evidence is lacking [23, 24].

It is unknown to what extent the prostate is coinfected in men with UTI. Recurrent UTI, however, is often caused by the same bacterial strain as the previous infections, indicating a chronic focus of infection within the urinary tract. In the absence of concretions, exacerbation of chronic bacterial prostatitis has been suggested as a cause of such recurrences [25-27]. Retrograde transport of bacteria from the urethra into the prostate, facilitated by reflux of urine into the prostatic ducts, has been proposed as a possible mechanism by which bacteria reach the prostate gland [28].

It is generally agreed that men with UTI warrant a thorough urological evaluation to identify predisposing structural or functional abnormalities [29-31]. This recommendation is based on the assumption that such disorders are common in male UTI, but most studies were carried out in highly selected patients in various clinical settings. It has recently been suggested, however, that imaging studies of the upper urinary tract should primarily be reserved for men with febrile UTI, those who fail to respond to appropriate antibiotic treatment and those prone to recurrent infections [32].

Few studies have focused on appropriate treatment of UTI in men. Published studies have included patients with a history of recurrent UTI and ABU [33, 34] or miscellaneous types of infections [27, 35]. Treatment courses of 6-12 weeks have resulted in higher bacteriological cure rates than short-term treatment for 10-14 days but the follow-up periods have usually been short.

This study was initiated to investigate various aspects of the host-parasite relationship in men with febrile UTI. It has been a multidisciplinary project performed in close collaboration between bacteriologists, urologists and infectious disease specialists.

AIMS OF THE STUDY

- To characterise O:K:H serotypes and phenotypic virulence properties of *E. coli* in relation to the host response in men with symptomatic UTI.

- To study the frequency of prostatic involvement in men with febrile UTI.

- To investigate the occurrence and clinical relevance of urological abnormalities in men with febrile UTI.

- To compare the bacteriological and clinical efficacy of ciprofloxacin 500 mg twice daily for two and four weeks in a prospective, randomised treatment trial of men with febrile UTI.

- To determine the frequency and characteristics of recurrent UTI during one year´s follow-up after treatment of men with febrile UTI.

PATIENTS

Retrospective study (I)

Eighty-eight men who presented at the Department of Infectious Diseases, Sahlgrenska University Hospital/Östra, Göteborg between 1983 and 1992 with community-acquired symptomatic UTI due to *E. coli* were enrolled in the study. Most patients participated in controlled, comparative treatment trials of symptomatic UTI [36-38]. Clinical and laboratory data were obtained from case-record forms and the medical records of the patients.

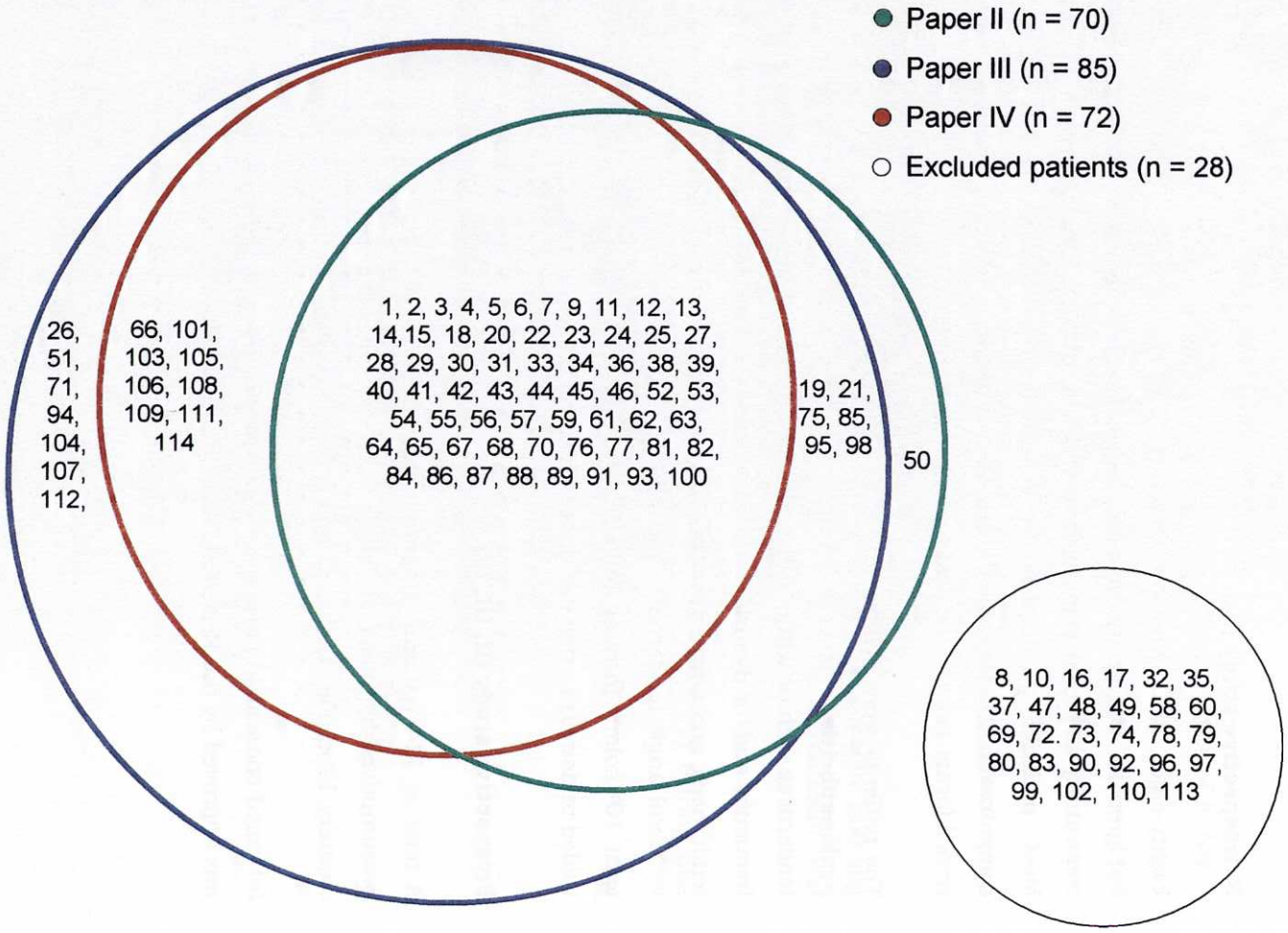
The patients were divided into three diagnostic groups by clinical criteria: **Acute pyelonephritis** – fever ≥ 38.0°C and flank pain and/or costo-vertebral angle tenderness with or without disturbed micturition; **febrile UTI** - fever ≥ 38.0°C and frequency and/or dysuria in the absence of flank pain and/or costo-vertebral angle tenderness, and **acute cystitis** - frequency and/or dysuria, no flank pain or costo-vertebral angle tenderness, and a body temperature < 38.0°C. All patients had at least 10^5 colony-forming units (CFU) of *E. coli* in pure growth per mL of freshly voided midstream urine (MSU) or indwelling bladder catheter urine (n=2).

Prospective study (II, III, IV)

A total of 114 patients attending the Department of Infectious Diseases with a presumptive diagnosis of febrile UTI were enrolled between March 1993 and January 1996 (Fig. 1).

Informed consent to participate was obtained from all patients. The study protocol was approved by the Research Ethics Committee at Göteborg University.

Fig. 1. Patients (randomisation number) recruited to the prospective study.



Inclusion criteria

The patients were required to be 18 years of age or older, have fever ≥ 38.0°C and at least one symptom or sign referable to the urinary tract (frequency, dysuria, flank pain or costo-vertebral angle tenderness).

Non-inclusion criteria

Indwelling urinary catheters, treatment with antibiotics during the preceding three days, known hypersensitivity to ciprofloxacin, renal impairment (estimated creatinine clearance < 20 mL/min or serum creatinine > 240 μmol/L), concomitant treatment with drugs that might interact with ciprofloxacin, such as theophylline and warfarin, or earlier inclusion in this study.

A computer-generated randomisation list was used to allocate patients to either of the two treatment groups (IV).

Definition of febrile UTI

The patients had to fulfill the inclusion criteria and have a positive urine culture defined as ≥ 10^4 CFU per mL urine [39]. Among 114 patients randomised to the treatment trial (IV), 42 (37%) were withdrawn from efficacy analyses since they did not meet the criteria for evaluation (Table 1). However, 14 of these patients fulfilled the definition of febrile UTI and could thus participate in the other two studies (II, III).

Patient characteristics

Characteristics of study patients are shown in Table 2.

Patients in the retrospective study (I) who were assigned a diagnosis of acute pyelonephritis or febrile UTI are here given a diagnosis of febrile UTI.

Table 1. Reasons for non-evaluation after randomisation (IV).

	Ciprofloxacin 500 mg b.i.d. 2 weeks (n=19)	4 weeks (n=23)
Not fulfilling inclusion criteria[a]	6	8
Other diagnosis than febrile UTI[b]	3	3
Negative initial urine culture	4	7
Isolated pathogen resistant to ciprofloxacin	1	0
No follow-up	2	3
Premature discontinuation of treatment because of adverse event	0	1
Insertion of a permanent urinary catheter during treatment	3	1

[a] Treatment with other antibiotics (n=7) or with drugs that might interact with ciprofloxacin (n=4), hypersensitivity to ciprofloxacin (n=1), previous inclusion in the study (n=1) and inability to comply with the study protocol (n=1).
[b] All with negative urine cultures.

Table 2. Characteristics of patients with febrile UTI.

	Retrospective study		Prospective study	
	No. (%)	**Median (range)**	**No. (%)**	**Median (range)**
No. of patients	74		86	
Age (years)		61 (23-86)		63 (18-86)
History of UTI	21/69 (30)		38 (44)	
History of febrile UTI			24 (28)	
Recent urinary tract instrumentation			13 (15)	
Indwelling urinary catheter	2 (3)		0	
Previous prostatic surgery			9 (10)	
Diabetes mellitus	10 (14)		6 (7)	
Dysuria	44 (59)		66/83 (80)	
Frequency	54 (73)		73/83 (88)	
Flank pain and/or costo-vertebral angle tenderness	41 (55)		31 (36)	
Prostatic tenderness			9/76 (12)	
Circumcision			4/82 (5)	
Temperature (°C)	74	39.0 (38.0-40.8)	86	39.5 (38.0-41.4)
CRP (mg/L)	68	83 (6-280)	86	130 (9-420)
ESR (mm/h)	66	38 (2-105)	82	30 (4-100)
WBC ($x10^9$/L)	38	13.7 (3.9-26.4)	85	13.2 (4.0-29.0)
Pyuria			69/82 (84)	
Haematuria			81 (94)	
Positive nitrite test			45 (52)	
Positive blood cultures	8/43 (19)		14/84 (17)	

METHODS

Retrospective study (I)

Bacteriological procedures

The *E. coli* strains had been stored in deep agar nutrient stabs at room temperature until analysed.

The somatic (O), capsular (K) and flagellar (H) antigens were determined with antisera to 171 O, 74 K and 53 H antigens [40]. Capsular polysaccharides K1 and K5 were identified by specific phages [40]. Non-typeable strains were defined as ON, KN and HN, respectively. Strains that agglutinated in saline were designated spontaneously agglutinating (OR). Strains with no demonstrable capsule were denoted K-. Non-motile cultures were denoted H-.

The occurrence of P fimbriae was assayed by a P-specific latex agglutination test (PF-test; Orion Diagnostica, Espoo, Finland) [41].

Alpha haemolysin production was assessed in nutrient agar with 5% washed sheep erythrocytes. A haemolytic zone larger than the overlying colony after overnight incubation was considered positive [42].

Aerobactin secretion was determined in a bioassay in which aerobactin-producing test strains promoted growth of the aerobactin-requiring *E. coli* strain LG1522 [43].

Prospective study (II, III, IV)

Bacteriological procedures

After collection, urine specimens were kept at 4°C until examined. The urine was cultured semiquantitatively on blood agar and Cysteine-Lactose-Electrolyte-Deficient (CLED) agar plates under aerobic and also under anaerobic conditions using the calibrated loop technique [44]. Urine samples containing more than two bacterial species were considered contaminated.

Two sets of blood cultures obtained before treatment were incubated both aerobically and anaerobically.

All isolates were identified by standard methods [44]. Antimicrobial susceptibility testing was done using the disk diffusion method [45]. *E. coli* strains were stored in deep agar nutrient stabs at room temperature before O:K:H serotyping and determination of virulence properties were done.

Biochemical analyses

C-reactive protein in serum (CRP), erythrocyte sedimentation rate (ESR), white blood cell count (WBC) and creatinine in serum were measured by standard methods.

Ames Multistix®5 test strip (Bayer Diagnostics) was used for assessment of urinary nitrite, pyuria and haematuria. A reaction of trace or greater was considered positive.

Prostate-specific antigen (PSA) was analysed using a monoclonal fluoro-immunoassay (Delfia®, Wallac Oy, Turku, Finland).

Creatinine clearance was estimated by the Cockcroft-Gault formula [46].

Urological investigations

Transrectal ultrasound of the prostate (TRUS) was conducted using Bruel and Kjaer 3535 equipment with a 7 MHz 8551 multiplane probe. The prostate volume was calculated as the height x width x length x $\pi/6$ [47]. The width of the seminal vesicles was measured as the maximum antero-posterior diameter.

Postvoid residual urine volume was measured by abdominal ultrasonography (transducer 8542, Bruel and Kjaer Medical, Naerum, Denmark).

Uroflowmetry, cysto-urethroscopy and imaging studies were performed by standard methods.

Assessment of treatment efficacy (IV)

The clinical response was considered satisfactory if all symptoms related to the infection resolved during treatment. Persistent or worsened symptoms were designated as **clinical failure**.

Bacteriological cure: eradication of the infecting strain with no recurrence of bacteriuria ($<10^4$ CFU/mL) during follow-up.

Relapse: post-treatment bacteriuria with the same strain as that originally isolated.

Reinfection: post-treatment bacteriuria with a strain different from that originally isolated.

In case of *E. coli* infection, serotyping made it possible to differentiate between relapse and reinfection.

In asymptomatic recurrences, bacteriuria was defined as $\geq 10^5$ CFU/mL of a single strain in two consecutive urine samples or $\geq 10^5$ CFU/mL in one sample together with a positive nitrite test.

Statistical methods

Papers I-IV

Pitman´s test [48] , Fisher´s permutation test [48], or the Mann-Whitney U-test was used to compare differences in the distribution of data between groups. Proportions were compared by the chi-square test with Yates´ correction or Fisher´s exact test. Fisher´s test for pair-wise comparisons [48] or Wilcoxon´s signed-rank test was used for paired data. Correlations among variables were tested using Pitman´s test.

Two-tailed significance tests were used and $P < 0.05$ was considered to indicate statistical significance. 95% confidence intervals (CI) were calculated according to standard methods.

Paper IV

To detect a 20% unit difference in bacteriological cure rate between the two treatment regimens, and assuming a cure rate of 95% at short-term follow-up of patients treated for 4 weeks, it was calculated that approximately 100 evaluable patients had to be enrolled in the trial. This was based on a 2-tailed chi-square test with a type I (α) error of 0.05 and a type II (β) error of 0.2.

Scheduled investigations (II, III, IV)

At study entry

- Detailed clinical history
- Physical examination
- Blood specimens for
  - Two sets of cultures
  - Analyses of PSA, CRP, ESR, WBC and creatinine
- MSU sample for
  - Dipstick urine analyses
  - Culture
- Digital rectal examination
- Uroflowmetry
- Measurement of postvoid residual urine volume
- TRUS

At 1, 3, 6 and 12 months

- Detailed clinical history
- Physical examination
- Blood specimens for analyses of
  - PSA, CRP, ESR, WBC and creatinine
- MSU sample for
  - Dipstick urine analyses
  - Culture

At 3 months

- Excretory urography
- Cysto-urethroscopy
- Digital rectal examination
- Uroflowmetry
- Measurement of postvoid residual urine volume
- TRUS

RESULTS

Serotypes and virulence properties of *E. coli* isolated from men with symptomatic UTI (I)

O:K:H serotypes

The *E. coli* serotypes showed great diversity in all diagnostic groups. Fifty-eight different serotypes could be identified among the 88 strains examined. Eight strains belonged to serotype O18ac:K5:H-, while no other serotype was represented by more than three strains.

Seventy-six strains (86%) had a typeable somatic antigen, representing 18 different O groups. Sixty-nine strains (78%) expressed somatic antigens belonging to 10 common O antigen groups associated with acute pyelonephritis in women and children (O1, O2, O4, O6, O7, O8, O15, O16, O18ac, and O75). A large proportion of the strains (26%) belonged to serogroup O6.

UTI-related types of K antigen (K1, K2, K3, K5, K12, K13, and K53) were expressed by 60% of the strains. Among isolates from patients with acute pyelonephritis and febrile UTI, 15 (20%) and 16 (22%) possessed K1 and K5 antigens, respectively, while 12 (16%) were non-encapsulated.

Virulence properties

There were no significant differences in the distribution of P fimbriae, haemolysin, or aerobactin between strains from patients with acute pyelonephritis and those with febrile UTI (Table 3). P fimbriae were expressed by 51% of the strains, while haemolytic activity and production of aerobactin could be demonstrated in 74% and 46%, respectively. The distribution of virulence properties was similar among isolates from men older and younger than 50 years of age.

P fimbriae were primarily associated with O2, O4, O16 and O18ac compared with all other O antigen groups (81% vs 35%; $P<0.001$). Haemolytic activity was commonly associated with O4, O6, O16 and O18ac but was less often associated with other O antigen groups (87% vs 60%; $P<0.01$).

Table 3. Distribution of virulence properties of *E. coli* according to diagnosis in men with symptomatic UTI (%).

Diagnosis	No. of patients	P fimbriae	Haemolytic activity	Aerobactin production
Acute pyelonephritis	41	23 (56)	30 (73)	21 (51)
Febrile UTI[a]	33	15 (45)	25 (76)	13 (39)
Acute cystitis	14	5 (36)	7 (50)	6 (43)

[a]Without flank pain or costo-vertebral angle tenderness.

Virulence versus host response

In patients with acute pyelonephritis or febrile UTI, there were no significant differences in inflammatory activity whether the infection was caused by P fimbriated *E. coli* or not (Table 4). Nor were there any differences in this respect whether or not the strains produced haemolysin or aerobactin.

Table 4. Host response to infection by *E. coli* with or without P fimbriae in patients with acute pyelonephritis or febrile UTI. Median (range).

P fimbriae	Temperature (°C)	CRP (mg/L)	ESR (mm/h)
Pos	39.0 (38.0-40.8) n=38	93 (6-238) n=38	42 (2-86) n=35
Neg	39.0 (38.0-40.4) n=36	84 (11-280) n=30	35 (6-105) n=31

Bacteriological findings in the prospective study (II, III, IV)

E. coli was the predominant pathogen and accounted for 78% of the urinary isolates (Table 5). Gram-positive bacteria which often occur as commensals in the urethral flora were isolated in 10% of cases, but not among those who were under 57 years of age (n=30). Indeed, non-*E. coli* strains were only isolated from patients ≥ 57 years old (n=56). *E. coli* of the same O:K:H serotype were recovered from concurrent blood and urine samples. Patients with positive blood cultures were older than those with negative blood cultures (median age 72 years, range 48-84 vs 61 years, range 18-86;P=0.02).

Table 5. Bacteriological findings in 86 patients with febrile UTI.

	Urinary isolates	**Blood isolates[a]**
Escherichia coli[b]	67 (78 %)	10
Klebsiella pneumoniae	7	
Enterobacter aerogenes	1	1
Enterobacter agglomerans	1	1
Proteus mirabilis	1	1
Enterococci	4	
Staphylococcus epidermidis	3	1
Group B streptococci	2	

[a]Blood cultures were obtained from 84 patients.
[b]In one case together with Serratia marcescens.

Characteristics of *E. coli* strains

A total of 55 of 67 *E. coli* strains have so far been examined for O:K:H serotype, and production of haemolysin and aerobactin (unpublished data). The findings were comparable to those obtained in the retrospective study (I). Thus, 42 (76%) strains belonged to the 10 common O antigen groups and 14 (27%) strains belonged to serogroup O6. Among 40 (73%) encapsulated strains, 10 (25%) and eight (20%) possessed K1 and K5 antigens, respectively. Production of haemolysin and aerobactin was found in 39 (71%) and 19 (35%) of the isolates, respectively.

Involvement of the prostate gland in men with febrile UTI (II)

PSA levels

The PSA levels peaked early during the acute infection (Table 6). The initial serum PSA was elevated (> 4 μg/L) in 58 (83%) of 70 patients (Table 7). Despite a rapid decline in PSA after one month ($P<0.001$), 43% of the patients still had raised PSA levels (Fig 2). A further decrease in PSA could be demonstrated after 3, 6 and 12 months. Interestingly, one patient (No. 51; Table 6) with disseminated prostate cancer who had raised baseline levels of PSA responded to the infection with a further increase in serum PSA.

Table 6. PSA levels (μg/L) in repeat serum samples during the first week of treatment.

Patient No.	Days after study entry 0	1	2	3	4	5	6	7
3	7.2				3.1			
12	11	14	9					
36	43	26	17	11	8.2	7.8		
51	130	280	230					130
76	23	13	19	11			8.4	7.8
77	23	11	9					
82	4.3	25						
95	3.2	2.6						
98	18	24						
101	58	51	47					
107	17	15	16	13				

The median time of fever before entry was 1 day (range 1-4 days).

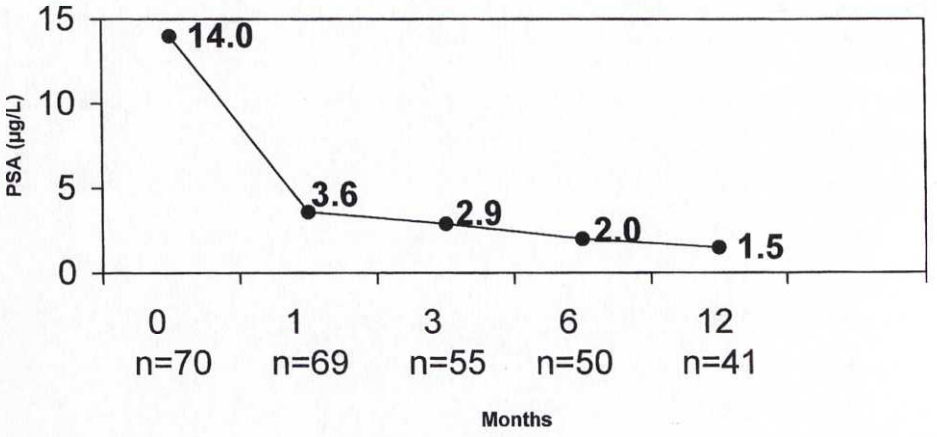
Table 7. Median serum PSA after an episode of febrile UTI.

Months[a]	No. of patients[b]	Serum PSA (μg/L) Median	Range	No. (%) of patients with serum PSA > 4 μg/L
0	70	14.0	0.54-140	58 (83)
1	69	3.6	0.43-21	30 (43)
3	55	2.9	0.38-19	23 (42)
6	50	2.0	0.37-20	16 (32)
12	41	1.5	0.36-16	10 (24)

[a] Time after an episode of febrile UTI.

[b] Incomplete data from 29 patients who did not comply with all scheduled visits (n=10), underwent TURP (n=9), had recurrent febrile UTI (n=6) or biopsy-verified prostate cancer (n=2), or died (n=2) during follow-up.

Fig 2. Median serum PSA after an episode of febrile UTI.



Six patients had a recurrent febrile UTI during follow-up, five of whom could be analysed for PSA. After treatment of the initial infection, the PSA levels decreased in all but one patient, followed by a transient increase associated with the recurrence (Table 8). No patient with recurrent ABU (n=9) or lower urinary tract symptoms without fever (n=5) showed an increase in PSA.

Table 8. Serum PSA levels (µg/L) in men with recurrent episodes of febrile UTI.

Patient	**Months after the initial episode of febrile UTI.**							
No.	**0**	**1**	**2**	**3**	**6**	**7**	**11**	**12**
1	4.6	2.7			23.0 [a]	3.8		3.5
3	5.8	7.2 [a]		1.2	1.6			1.0
12	33.0	3.9			1.8			11.0 [a]
43[b]	1.4	1.2	9.6 [a]	0.80	7.4 [a]	0.86		1.1
55	19.0	1.3		2.1	1.5		35.0 [a]	2.2

[a] Recurrent febrile UTI.
[b] Patient using clean intermittent self catheterisation.

PSA levels in patients with other febrile infectious diseases

Sixteen men (median age 49 years, range 22-90) who were admitted with a temperature ≥ 38.0° C, no clinical signs of UTI and a negative urine culture were included as controls. None had been treated with antibiotics during the preceding three days. The final diagnoses at discharge were pneumonia (n=5), influenza (n=4), other viral diseases (n=2), salmonellosis (n=2) and one each of endocarditis, malaria and streptococcal pharyngitis. The median PSA level at entry was 0.99 µg/L (range 0.40 – 2.7).

Prostate volume

Among 55 patients who had two ultrasound examinations of the prostate, at entry and after three months, a significant decrease in prostate volume was found [median (range) mL, 49 (14-104) vs 35 (15-91); P<0.001]. The prostate volume increased slightly in one patient, was unchanged in three patients, while 51 patients had a reduction, which exceeded 10% in 46 cases (median 31%, range 11-54).

The seminal vesicles were measured twice in 40 patients.

On the right side the maximum width was reduced by 14%, from a median (range) of 11.0 (3.0-20.0) mm to 9.4 (4.2-16.0) mm (P<0.001), and on the left side by 22 %, from 11.5 (4.0-18.0) mm to 9.0 (4.6-17.0) mm (P<0.001), at follow-up.

Serum PSA and prostate volume

A reduction of serum PSA by more than 25%, irrespective of the initial PSA level, and/or a decrease in prostate volume by more than 10% between the acute phase and follow-up after three months was taken as evidence of prostatic involvement of the infection. With these assumptions, 46 (94%) of 49 patients who completed both examinations had a concomitant infection of the prostate (Table 9). Of the 55 patients who had two PSA measurements performed, 51 (93%) showed a reduction of PSA by > 25%, suggesting that serum PSA alone could be used as a marker of prostatic involvement.

The reductions of PSA and prostate volume were not significantly correlated to patient age, the magnitude of initial C-reactive protein levels, the presence of bacteraemia, whether the infection was first-time or recurrent, or whether it was caused by Gram-negative or Gram-positive bacteria. Nor were the results influenced by previous transurethral resection of the prostate (TURP).

Table 9. Changes in serum PSA and prostate volume between the acute stage of infection and 3 months later in 49 men with febrile UTI.

Reduction in serum PSA	**Reduction in prostate volume**	
	>10%	**≤10%**
>25%	40	4
≤25%	2	3

Prostate biopsy and TURP

Five patients underwent TRUS-guided prostate needle biopsy, because of findings suggesting cancer on digital rectal examination or TRUS after 3 months, as did 9 of 15 patients who had persistently elevated serum PSA (> 4.0 mg/L) after 6 months. The reasons for not performing a biopsy were patient refusal in five cases, three of whom had normal PSA levels at 12 months, and TURP in one case. Microscopic evidence of prostate cancer was found in two patients with increased PSA levels (27, 21, 11, 11 µg/L and 74, 20, 19, 20 µg/L at entry and after 1, 3 and 6 months, respectively). None of the nine patients who underwent TURP had evidence of cancer in the resected tissue.

Urinary tract investigation (III)

Upper urinary tract

Imaging studies were carried out by excretory urography (n=76), ultrasonography (n=4) or computed tomography (n=3). Abnormalities were disclosed in 19 patients, nine of whom had previously unrecognised lesions. The findings had clinical implications in only one patient, who eventually underwent surgical intervention because of renal calyceal stones.

Lower urinary tract

In five of 10 men with voiding difficulties from benign prostatic hyperplasia (BPH) and who subsequently underwent TURP, the findings were known before study entry (Table 10). A young man with a urethral stricture also had phimosis and a history of voiding difficulties. He experienced an early recurrence of febrile UTI caused by the same *E. coli* strain as that originally isolated. The stricture was diagnosed by cysto-urethroscopy and surgically corrected. Four patients had mild urethral strictures with no voiding difficulties, which were diagnosed and dilated or incised at cysto-urethroscopy after three months.

Table 10. Lower urinary tract abnormalities in 83 men with febrile UTI[a].

Abnormality	**No. (%) of findings[b]**
Infravesical obstruction from BPH requiring TURP	10
Urethral stricture	5
Bladder diverticulum	5
Bladder stones	3
Bladder cancer	1
Phimosis	1
Postvoid residual urine ≥ 50 mL[c]	13 (22)
Peak urinary flow rate < 10 mL/s[c]	8 (15)

[a] Diagnosed by cysto-urethroscopy (n=73), ultrasonographic measurement of postvoid residual (n=60) and uroflowmetry (n=52) at the follow-up after 3 months.
[b] Forty-six abnormal findings in 35 patients.
[c] Based on the best performance during the acute stage or at follow-up.

Urological abnormalities in relation to bacteriological findings, host response and recurrent UTI

There was no association between the bacteriological aetiology, the occurrence of positive blood cultures or the magnitude of fever and inflammatory response to infection and urological abnormalities leading to surgery. Fifteen (22%) of 67 patients tested had haematuria as measured by dipstick analysis at follow-up

after one month. Three of four patients with stone disease and the one with bladder cancer had haematuria at short-term follow-up (Table 11).

During the 1-year follow-up, 26 patients had 37 episodes of culture-confirmed recurrent UTI, 16 of which were symptomatic. Three of five patients with early recurrent symptomatic UTI within one month after the end of antibiotic treatment had an abnormality leading to surgery. All patients who had urological disorders that warranted surgical intervention were identified among those with a history of voiding difficulties, acute urinary retention, early recurrent symptomatic UTI or microscopic haematuria at the first post-treatment control. Thus, in this study only 20 (24%) of 85 men would have required both upper and lower urinary tract investigation to reveal such abnormalities.

Table 11. Characteristics of 15 men with febrile UTI who had surgically correctable lesions that were previously unrecognised.

	No. of patients	**History of voiding difficulties**	**Acute urinary retention**	**Haematuria[a]**	**Recurrent symptomatic UTI[b]**
Infravesical obstruction from BPH requiring TURP	5	5	2	1	
Urethral stricture	5	1		1	1
Bladder stones	3	3		2	1
Renal calyceal stones	1			1	
Bladder cancer	1			1	1

[a] As measured by dipstick analysis at follow-up after 1 month.
[b] Within 1 month after the end of antibiotic treatment.

Renal function in patients with scarred kidneys

Twelve patients with a median (range) age of 73 (29-86) years had radiological signs of renal scars. They had an estimated creatinine clearance [median (range)] of 56 (22-125) mL/min at follow-up. Four of these patients, aged 73 – 86 years, had an estimated creatinine clearance of < 50 mL/min.

Ciprofloxacin for two or four weeks in men with febrile UTI (IV)

A total of 72 patients randomly allocated to oral treatment with ciprofloxacin 500 mg twice daily for two or four weeks were assessable for bacteriological and clinical efficacy.

Signs and symptoms cleared in all patients during treatment. The median time to resolution of fever was 2 days (range 1 – 9). The cumulative bacteriological and clinical cure rates during the 1-year follow-up are shown in table 12.

There was no significant difference in short-term bacteriological cure rate two weeks post-treatment between patients treated for two and four weeks (89% vs 97%; 95% CI for difference in proportions, -4% to 19%), nor after one year (59% vs 76%; 95% CI, -5% to 39%). The cumulative clinical cure rate after one year was 72% and 82%, respectively (95% CI, -10% to 30%).

The presence of urinary tract abnormalities did not influence the outcome, but two of four patients with early symptomatic recurrence had major disorders requiring surgery (severe urethral stricture with phimosis and bladder cancer). The results suggest that a 2-week course of ciprofloxacin 500 mg twice daily is adequate treatment for febrile UTI in men.

Adverse events were seen in one of four patients, were usually mild and occurred early during the course even among those assigned to the 4-week treatment.

Table 12. Cumulative cure rate (%).

	Ciprofloxacin 500 mg b.i.d.	
	2 weeks (n=38)	**4 weeks (n=34)**
2 weeks post-treatment:	n=38	n=34
Bacteriological cure	34 (89)	33 (97)
Clinical cure	35 (92)	33 (97)
After 12 months:	n=32	n=33
Bacteriological cure	19 (59)	25 (76)
Clinical cure	23 (72)	27 (82)

Recurrent UTI during follow-up

Among 21 (32%) culture-verified recurrences after one year, there were eight relapses and 12 reinfections. The clinical recurrence pattern comprised ABU (n=10), lower urinary tract symptoms with bacteriuria (n=5) and another episode of febrile UTI (n=6).

Most recurrences (67%) occurred within three months after the end of antibiotic treatment, with no significant differences between the 2- and 4-week ciprofloxacin regimens.

Recurrent UTI tended to be more common among patients with a past history of UTI than in those without [13 (38%) of 34 vs 8 (21%) of 38; ns]. However, four of five patients who experienced multiple recurrences during follow-up had a history of previous episodes of UTI.

DISCUSSION

Study populations

In the retrospective study (I), the *E. coli* strains were mainly obtained from patients participating in controlled treatment trials of community-acquired symptomatic UTI. Accordingly, these patients were well-characterised. The strains studied were collected during a 10-year period, minimising the risk of selecting serotypes that predominate because of variations in occurrence with time.

The prospectively studied patients (II, III, IV) were probably representative of men with community-acquired febrile UTI. Some of them had known urological abnormalities, such as prostatic hyperplasia, and recent instrumentation of the urinary tract predisposing to infection, while others had never experienced a previous UTI.

The medical records of all males admitted to the Department of Infectious Diseases during the prospective part of the study and discharged with a final diagnosis of acute pyelonephritis or febrile UTI were reviewed. Twenty-five patients met the inclusion criteria but had for various reasons not been included in the study. They were comparable to study patients as regards age, severity of infection and bacteriological aetiology.

Virulence of *E. coli* causing male UTI (I)

The vast majority of symptomatic infections in men were caused by O:K:H serotypes of *E. coli* commonly associated with acute pyelonephritis in women [20].

Most strains were encapsulated (84%), which is consistent with the findings in women with acute pyelonephritis [20]. The capsule has been proposed to increase virulence by preventing opsonisation and phagocytosis [49]. The K1 and K5 antigens were found in 42 % of the isolates, compared with 63% of isolates from women. These capsular antigens are thought to enhance *E. coli* virulence because of close structural resemblance to certain host structures [50, 51], thereby having a selective advantage by escaping host defences.

The proportion of P fimbriated *E. coli* was lower (51%) than that in women with uncomplicated acute pyelonephritis (80%), but comparable to that in women with complicated infections (50%) [20]. P fimbriae are considered to be an important virulence property since P fimbriated *E. coli* become resident and persist longer in the faecal flora than other *E. coli* strains [52]. Furthermore, P fimbriae facilitate the spread of *E. coli* to the urinary tract by adhesion to mucosal surfaces and seem to be important for ascent of bacteria to the kidneys and invasion of the renal parenchyma in patients with normal urinary tracts [53].

There was an unexpectedly high proportion of strains that showed haemolytic activity (74%), which could also be confirmed in the prospective part of this study (71%). The finding could be ascribed to the frequent occurrence of *E. coli* strains of serogroup 06 (26% and 27%, respectively), which is known to be associated with haemolysin production [19, 54]. A similar high proportion of haemolytic strains (91% and 71%) was reported in two earlier small studies of men with symptomatic UTI comprising 11 and 14 *E. coli* strains, respectively [21, 22]. In contrast, expression of haemolysin was found in approximately 50% of strains from women with uncomplicated pyelonephritis [19, 20].

Furthermore, in a study of 30 men with acute or chronic bacterial prostatitis, 22 (73%) *E. coli* strains showed haemolytic activity and 16 (53%) possessed P fimbriae [55]. Similarly, in a study from Japan, 107 (69%) *E. coli* strains from men with acute prostatitis were haemolytic [56].

Haemolysin may contribute to mucosal damage and tissue injury by its cytotoxic effects (57), thereby facilitating invasion by bacteria. Since 94% of the men with febrile UTI in the prospective part of this study had signs of prostatic involvement by the infection, it is tempting to speculate that haemolysin production offers bacteria a selective advantage to infect and/or persist in the prostate tissue.

Aerobactin, a siderophore which has the ability to compete with iron-binding proteins in the host, has been regarded as a virulence factor of uropathogenic *E. coli* since it occurrs in a large proportion of strains (73%) associated with pyelonephritis in women [19]. Again, in men with febrile UTI, aerobactin was expressed by *E. coli* strains in a lower frequency (46%).

To conclude, *E. coli* strains from men with febrile UTI belonged to a variety of O:K:H serotypes commonly encountered in women with acute pyelonephritis. The distribution of virulence properties, however, suggests different host-parasite relationships in the male and female urinary tracts, which may possibly be attributed to the role of the prostate gland in male UTI.

Prostatic involvement in men with febrile UTI (II)

At enrolment, nine (12%) of 76 patients with febrile UTI had a tender prostate on digital rectal examination, indicating a concomitant infection of the prostate gland. PSA is a serine protease which is produced by epithelial cells of the prostate gland and is secreted into the seminal fluid, where it liquefies the ejaculate [58]. Under normal conditions, only small amounts of PSA leak into the bloodstream. Increased serum concentrations of PSA are found in patients with prostate cancer [59]. The tissue-specific property has made PSA a useful marker for the detection of prostate cancer but raised serum levels have also been demonstrated in men with benign prostatic hyperplasia [60, 61] or acute prostatitis [62]. It has been suggested that the release of PSA into the blood might be enhanced by increased vascular permeability associated with an inflammatory process in the prostate [63, 64].

Among the prospectively studied men with febrile UTI, 83 % had increased serum PSA (>4 μg/L) in the acute stage of the infection, suggesting prostatic involvement. Indeed, the serum concentrations were comparable to those found in patients with prostate cancer [65], in some cases exceeding 100 μg/L. After an intitial rapid decline in serum PSA, there was a protracted decrease which in some patients lasted for several months. Sixteen (32%) of 50 patients still had raised serum PSA after six months. The possibility of a prolonged increase in serum PSA after successful antibiotic treatment of febrile UTI should therefore be considered when PSA is used for the detection of prostate cancer. However, only two of nine patients

with a sustained increase in serum PSA had microscopic evidence of prostate cancer at biopsy. It may thus be suggested that prostate biopsy should not be performed earlier than six months after an episode of febrile UTI, unless digital rectal examination or TRUS arouses strong suspicion of cancer.

Furthermore, a second rise in serum PSA occurred in five patients who experienced recurrent episodes of febrile UTI during follow-up, but not among those who had recurrences without fever.

Among patients who underwent TRUS, the prostate was commonly enlarged, containing intraglandular calcifications and hypoechogenic areas in the peripheral zone. Those who underwent two TRUS examinations, at study entry and after three months, showed a significant decrease in the prostate volume as well as in the width of the seminal vesicles. These findings strongly suggest the presence of an acute inflammatory process in the prostate which subsided after appropriate antimicrobial treatment. Such changes in prostate volume, although less pronounced, have previously been shown in patients treated for bacterial prostatitis [66].

The age-adjusted prostate volume after three months was comparable to that found in a study of healthy Swedish men [67], supporting the conclusion that the inflammation had resolved. The serum half-life of PSA has been estimated to 2.2 days in patients undergoing radical prostatectomy [59]. The slow decline in serum PSA found in some patients after treatment of febrile UTI, despite normalised prostate volume, is therefore hard to explain. Perhaps the epithelial cells of the prostate continue to produce or release PSA for some time after the inflammation has subsided.

Assuming that a reduction in serum PSA by more than 25% and/or a decrease in prostate volume by more than 10% indicates prostatic engagement by the infection, a total of 94% of the patients examined had a concomitant infection of the prostate.

Urinary tract investigation in men with febrile UTI (III)

Since UTI rarely occurs in adult men, it is generally considered that a symptomatic UTI in a man of any age should be regarded as a complicated infection that necessitates a thorough evaluation of the urinary tract, to exclude predisposing factors of clinical importance [1, 68]. In this study of unselected men with community-acquired febrile UTI, radiological examination of the upper urinary tract revealed relevant clinical abnormalities in only one patient, who had renal calyceal stones. This patient had no history of previous UTI or renal stone disease. Renal scars were found in 12 patients, most of whom were elderly. Four of these patients had an estimated creatinine clearance of < 50 mL/min. Assessment of renal function seems more relevant than the disclosure of a renal scar by imaging techniques. In all, 19 (23%) of 83 patients investigated had some abnormality. The findings were similar to those in a previous study of women with community-acquired acute pyelonephritis [69].

In a retrospective study of 50 elderly men with recurrent bacteriuria, 11 (22%) had urological abnormalities detectable by excretory urography [70], which accords with the findings in the present study. In another study of 38 young male students with symptomatic UTI [18], 11 (29%) of those investigated had normal urinary tracts. It was concluded that routine urological evaluation seems unnecessary in young men.

In the present study, lower urinary tract investigation disclosed a variety of abnormalities, some of which had clinical implications. Altogether, 15 of 85 patients with febrile UTI had previously unrecognised lesions that were surgically corrected. They were all identified either by a history of voiding difficulties, acute urinary retention, early recurrent symptomatic UTI or microscopic haematuria at the first follow-up after treatment, except for four men with mild urethral strictures diagnosed at the scheduled cysto-urethroscopy. Only 20 (24%) of the 85 men would have required both upper and lower urinary tract investigation to reveal urological disorders that warranted surgical intervention.

Antibiotic treatment of febrile UTI in men (IV)

This was the first study to compare different lengths of antibiotic treatment of febrile UTI in men. A 2-week course of ciprofloxacin 500 mg twice daily seemed to give similar bacteriological and clinical cure rates as a 4-week course. The cumulative cure rates were comparable during follow-up for one year. The results should be interpreted with some caution, however, since the wide confidence interval for differences in cure rates between the study groups will reduce the power of the trial. The high cure rates at short-term follow-up are consistent with those obtained with a fluoroquinolone in women with acute pyelonephritis [37, 39].

The cumulative bacteriological cure rates were also comparable to those obtained in men with chronic bacterial prostatitis who received a 4-week course of ciprofloxacin 500 mg twice daily and were followed-up for nine months [71].

Since more than 90% of the men had a concomitant infection of the prostate, as measured by transient increases in serum PSA and prostate volume (II), the goal is not only to sterilise the urine but also to eradicate the prostatic infection. Antimicrobials reaching free concentrations in prostatic tissue and prostatic fluid that exceed the minimum inhibitory concentrations of most of the causative bacteria should therefore be chosen for treatment of UTI in men. The fluoroquinolones, like ciprofloxacin, have such favourable pharmacokinetic properties and antibacterial spectra [72, 73]. Trimethoprim also yields good concentrations in the prostate and is an alternative to fluoroquinolones provided the causative bacteria are fully sensitive to the drug. In contrast, the use of beta-lactam antibiotics should be discouraged because of the low concentrations attained by these drugs in the prostate [32, 73]. Actually, beta-lactam antibiotics seem to result in lower cure rates in men with febrile UTI [37, 74].

Chronic bacterial prostatitis is considered to be the main cause of recurrent UTI in men [12, 25]. The high relapse rate after treatment has been attributed to the failure to eradicate bacteria from the prostate [12, 25].

Bacteria may be protected in biofilms adjacent to calculi in prostatic tissue, as well as in areas of scarring [75, 76]. Bacteria embedded in biofilms are quiescent, with low metabolic activity and slow growth, which diminishes their susceptibility to various antimicrobial drugs. Accordingly, it is extremely difficult to eradicate bacteria in the prostate even with appropriate antimicrobial treatment. Long treatment courses do not seem to be of any benefit since antimicrobials rarely cure chronic bacterial prostatitis.

In the present study, relapses constituted 40% of the bacteriological recurrences after one year, suggesting an underlying chronic infection of the prostate. Sixty per cent of the recurrences were reinfections with a new bacterial strain. This may be due to instrumentation of the urinary tract, since new strains are easily introduced in conjunction with such procedures [12]. Neither a history of previous UTI, nor the presence of urological abnormalities was associated with an increased risk of recurrent UTI. On an individual basis, the natural history of UTI in men is quite unpredictable. Why exacerbations of chronic bacterial prostatitis result in various clinical manifestations of UTI with the same bacterial strain is unknown.

CONCLUSIONS

- *E. coli* strains from men with febrile UTI belonged to a variety of serotypes commonly encountered in women with acute pyelonephritis. There was a higher proportion of haemolytic strains but a lower frequency of P fimbriated and aerobactin-producing strains than previously found in women, suggesting different host-parasite relationships in the male and female urinary tract.

- The prostate was coinfected in over 90% of men with febrile UTI, as measured by transient increases in serum PSA and/or the prostate volume.

- Routine radiological examination of the upper urinary tract seems dispensable in men with febrile UTI. Abnormalities of clinical importance were mainly disclosed by lower urinary tract investigation.

- All patients who had lesions that required surgical intervention could be identified either by a history of voiding difficulties, acute urinary retention, microscopic haematuria at short-term follow-up or early recurrent symptomatic UTI.

- There were no significant differences in cure rates between patients treated with ciprofloxacin for two and four weeks. A 2-week course of ciprofloxacin seems to be adequate for febrile UTI in men.

- Most episodes of recurrent UTI occurred within three months after the end of treatment. Neither a history of previous UTI nor the presence of urological abnormalities was associated with an increased risk of recurrent UTI.

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