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.
Submitted.

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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.

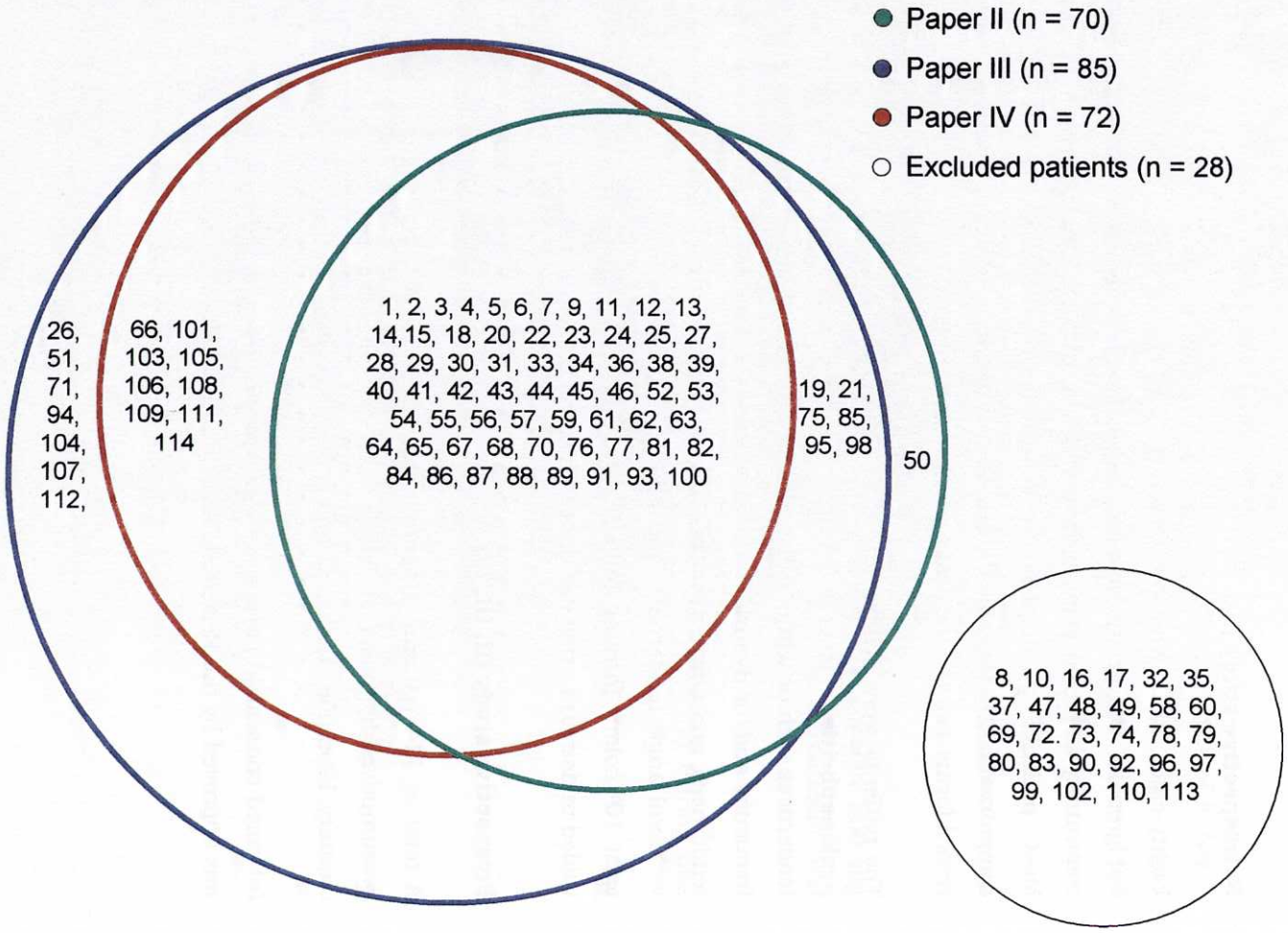
The patients were divided into three diagnostic groups by clinical criteria: **Acute pyelonephritis** – fever ≥ 38.0°C and flank pain and/or costo-vertebral angle tenderness with or without disturbed micturition; **febrile UTI** - fever ≥ 38.0°C and frequency and/or dysuria in the absence of flank pain 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).

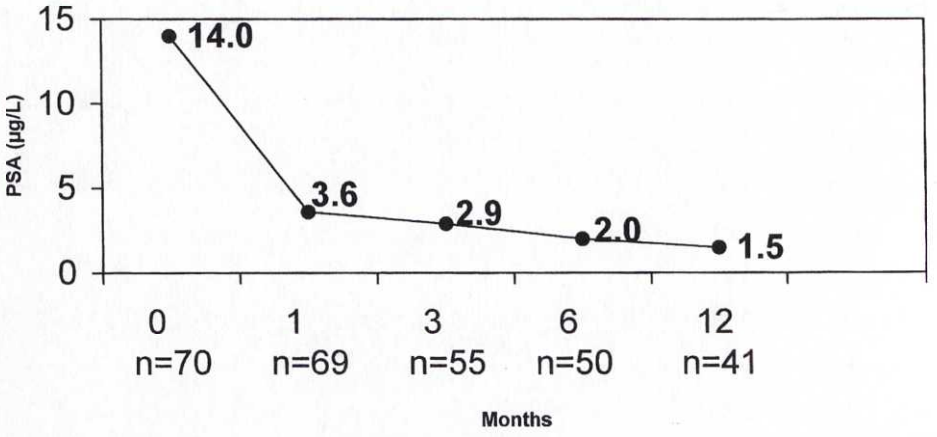
Table 7. Median serum PSA after an episode of febrile UTI.

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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Table 1. Host response to infection according to clinical diagnosis.

	CRP concentration (mg/L)	
	Printed	**Correct**
Acute pyelonephritis	77 (40-224)	84 (40-224)
Febrile UTI	55 (6-280)	80 (6-280)
Acute cystitis	9 (<5-75)	9 (2-75)

Virulence Characteristics of *Escherichia coli* in Relation to Host Response in Men with Symptomatic Urinary Tract Infection

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To assess virulence properties in uropathogenic *Escherichia coli* isolates from men with symptomatic urinary tract infection (UTI), we analyzed 88 urinary isolates from men with acute pyelonephritis (n = 41), febrile UTI without clinical signs of renal infection (n = 33), or acute cystitis (n = 14) for O:K:H serotype, P fimbriae, and production of hemolysin and aerobactin. In the three diagnostic groups, 88%, 67%, and 79% of the strains, respectively, were represented by 10 O antigen groups commonly associated with acute pyelonephritis in women and children. Fifty-eight different O:K:H serotypes could be identified, of which O18ac:K5:H− predominated (n = 8). There was a higher frequency of hemolytic strains among patients with pyelonephritis (73%) and febrile UTI (76%) and a lower frequency of P-fimbriated strains (56% and 45%, respectively) and aerobactin-positive strains (51% and 39%, respectively) among these patients than was previously encountered in women and children with uncomplicated acute pyelonephritis. The distribution of bacterial properties was unrelated to patient age and underlying complicating factors. The findings suggest differences in host-parasite relationships between men and women with symptomatic UTI caused by *E. coli*.

Virulence characteristics of uropathogenic *Escherichia coli* have been thoroughly studied in women and children with various forms of urinary tract infection (UTI). It is well recognized that certain O:K:H serotypes of *E. coli* [1–4], which commonly express P fimbriae [2–5] or aerobactin [6, 7], are isolated from the urine of patients with uncomplicated acute pyelonephritis but are less often isolated from those with acute cystitis or asymptomatic bacteriuria. Although hemolysin production and resistance to the bactericidal effect of serum seem to be more common among urinary isolates than among strains from the fecal flora of healthy carriers [3, 6, 8, 9], these properties have shown no clear-cut association with the pyelonephritogenic potential of *E. coli* [4, 8, 9].

Bacterial virulence is multifactorial. P fimbriae are thought to facilitate the ascent of bacteria to the upper urinary tract by specific binding to receptors on uroepithelial cells [10]. Aerobactin-mediated uptake of iron may promote bacterial growth and persistence in tissues [6, 9], while hemolysin, besides lysing erythrocytes, may contribute to tissue injury by cytotoxic effects [9, 11].

Whether the same serotypes and virulence properties of *E. coli* are typical of strains causing UTI in men is largely unknown. Therefore, we decided to characterize a large number of *E. coli* strains from men with various types of symptomatic UTI and to assess the relationship between bacterial virulence properties and the host response to infection.

Patients and Methods

Patient Selection

Eighty-eight men who presented at the Department of Infectious Diseases (Östra Hospital, Göteborg, Sweden) between 1983 and 1992 with community-acquired symptomatic UTI due to *E. coli* were enrolled in this retrospective study. The availability of stored urinary isolates of *E. coli* was a prerequisite for inclusion in the study. Most strains were collected in connection with controlled, comparative treatment trials of symptomatic UTI [12–14]. Pertinent clinical and laboratory data were obtained from case-record forms and the medical records of the patients.

Diagnostic Criteria

All patients had at least 10^5 cfu of *E. coli* in pure growth per milliliter of freshly voided midstream urine (n = 86) or indwelling bladder catheter urine (n = 2).

On the basis of clinical criteria, the patients could be divided into three diagnostic groups: acute pyelonephritis—fever (temperature, ≥38.0°C) and flank pain and/or tenderness of the costovertebral angle with or without disturbed micturition; febrile UTI—fever (temperature, ≥38.0°C) and

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frequency and/or dysuria in the absence of flank pain or tenderness of the costovertebral angle; and acute cystitis—frequency and/or dysuria, no flank pain or renal tenderness, and a body temperature <38.0°C.

Patient Characteristics

There were 41 men with a diagnosis of acute pyelonephritis (median age, 57 years; range, 24–86 years), 33 men with febrile UTI (median age, 67 years; range, 23–83 years), and 14 men who had acute cystitis (median age, 72 years; range, 22–81 years). Twenty-eight patients had a history of previous episodes of UTI, while 55 had no history of UTI; these data were not available for five patients. Excretory urography was performed for 56 patients, while four patients were examined with ultrasonography of the kidneys. Complicating factors that might have contributed to increased susceptibility to UTI were recognized in 25 patients; these factors included diabetes mellitus (n = 10), recent instrumentation of the urinary tract (n = 1), neurogenic bladder dysfunction (n = 1), bladder diverticulum (n = 1), a renal cyst (n = 1), an indwelling urinary catheter (n = 2), duplication of the collecting system (n = 2), a scarred atrophic kidney (n = 2), renal stones (n = 3), and urethral stricture (n = 3). One patient had more than one complicating factor (bladder diverticulum and a renal stone). The occurrence of infravesical obstruction could not be assessed since cystoscopy or measurement of residual urine was not routinely performed.

Laboratory Procedures

Urine samples were semiquantitatively cultured by the calibrated loop technique. Blood specimens for culture were obtained from 26 patients (63%) with acute pyelonephritis and 17 patients (52%) with febrile UTI. Species identification was performed by standard methods. Urinary and blood isolates of *E. coli* were stored in deep nutrient agar stabs at room temperature until analyzed for O:K:H serotype and virulence properties.

Serotyping. The somatic (O), capsular (K), and flagellar (H) antigens were determined by previously described methods [15]. Antisera to 171 O, 74 K, and 53 H antigens were used. Capsular polysaccharides K1 and K5 were identified by specific phages [15]. Nontypeable strains were defined as ON, KN, and HN, respectively. Strains that agglutinated in saline were designated spontaneously agglutinating or rough. Strains with no demonstrable capsule were denoted K−. Nonmotile strains were denoted H−.

P fimbriae. The occurrence of P fimbriae was assayed by a P-specific agglutination test (PF-test; Orion Diagnostica, Espoo, Finland) [16].

Hemolysin. Hemolysin production was assessed in nutrient agar with 5% washed sheep erythrocytes. A hemolytic zone larger than the overlying colony after overnight incubation was considered positive [17].

Aerobactin. Aerobactin secretion was determined in a bioassay in which aerobactin-producing test strains promoted growth of the aerobactin-requiring *E. coli* strain LG1522 [7].

Acute-phase response. Pretreatment blood samples were analyzed for C-reactive protein (CRP), total white blood cell (WBC) count, and erythrocyte sedimentation rate (ESR).

Statistics. Proportions were compared by the χ^2 test with Yates' correction, and distribution of data was compared between groups by the Mann-Whitney U-test. Two-tailed tests were used, and a P value of $< .05$ was considered statistically significant.

Results

Host Response

Patients with a clinical diagnosis of acute pyelonephritis or febrile UTI demonstrated a systemic inflammatory response to infection by elevated CRP concentration, ESR, and WBC count (table 1). There were no significant differences in these parameters between the two patient groups, regardless of the presence of complicating factors (data not shown).

O:K:H Serotypes

Seventy-six *E. coli* strains (86%) had a typeable somatic antigen, with 18 different O groups represented. Spontaneously agglutinating *E. coli* occurred in three strains (7%) from men with acute pyelonephritis, six strains (18%) from men with febrile UTI, and two strains (14%) from men with acute cystitis. Sixty-nine strains (78%) expressed somatic antigens belonging to 10 common O antigen groups associated with acute pyelonephritis (O1, O2, O4, O6, O7, O8, O15, O16, O18ac, and O75; table 2). These O antigen groups were represented by 88%, 67%, and 79% of the strains from patients with acute pyelonephritis, febrile UTI, and acute cystitis, respectively. A large proportion of the *E. coli* strains (26%) belonged to serogroup O6, but the serotypes within this group varied considerably (table 2).

A capsular polysaccharide was found in 72 strains (82%), 11 (15%) of which were nontypeable. UTI-related types of K antigen (K1, K2, K3, K5, K12, K13, and K53) were expressed by 63%, 58%, and 57% of the strains from patients with acute pyelonephritis, febrile UTI, and acute cystitis, respectively. 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 noncapsulated. Twenty-nine (39%) of these strains were nonmotile.

In all diagnostic groups, the O:K:H serotypes showed great diversity. Fifty-eight different serotypes were represented among the 88 strains. Except for serotype O18ac:K5:H−

Table 1. Host response to infection according to clinical diagnosis.

Diagnosis	Median value (range) for indicated measurement, no. of patients*			
	Temperature (°C)	CRP concentration (mg/L)	ESR (mm/h)	WBC count (× 10^9/L)
Acute pyelonephritis	39.2 (38.1–40.4), $n = 41$	77 (40–224), $n = 40$	43 (10–105), $n = 38$	13.7 (5.5–26.4), $n = 14$
Febrile UTI†	38.6 (38.0–40.8), $n = 33$	55 (6–280), $n = 28$	29 (2–90), $n = 28$	13.7 (3.9–24.3), $n = 24$
Acute cystitis	37.2 (36.3–37.8), $n = 14$	9 (<5–75), $n = 13$	16 (2–81), $n = 14$	8.1 (4.9–12.7), $n = 13$

NOTE. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; WBC = white blood cell.
* Number of patients for whom measurement was determined.
† Without flank pain or tenderness of the costovertebral angle.

(eight strains), no other serotype was represented by more than three strains.

Virulence Properties of *E. coli*

Regardless of the presence of complicating factors, there were no significant differences in the distribution of P fimbriae, hemolysin, or aerobactin between strains from patients with acute pyelonephritis or febrile UTI (table 3). P fimbriae were expressed by 56% and 45% of the strains, respectively. A large proportion of the isolates showed hemolytic activity (73% and 76%, respectively), while aerobactin production was found in 51% and 39% of the strains, respectively. P fimbriae, hemolysin, and aerobactin were coexpressed by 28% of the strains, while 8% of isolates did not show any of these properties ($P < .01$). Hemolysin and aerobactin production coappeared in 31% of the strains, while 89% had one or both of these phenotypic attributes.

There were also no significant differences when strains from patients with acute pyelonephritis and febrile UTI were compared with those from patients with acute cystitis. The distribution of virulence properties was similar among isolates from men older or younger than 50 years of age (data not shown).

P fimbriae were primarily associated with O2, O4, O16, and O18ac serogroups compared with all other O antigen groups (81% vs. 35%; $P < .001$). Hemolysin production was commonly associated with O4, O6, O16, and O18ac serogroups but was less often associated with other O antigen groups (87% vs. 60%; $P < .01$).

Virulence Properties in Relation to the Host Response

Among patients with acute pyelonephritis and febrile UTI, there were no significant differences in inflammatory activity, as measured by the temperature, the levels of CRP, and the ESR, whether or not the infection was caused by P-fimbriated *E. coli* (table 4). There were also no differences in this respect whether or not the strains produced hemolysin or aerobactin (data not shown).

Blood Isolates of *E. coli*

Among patients who provided blood for cultures, bacteremia was found in 4 (15%) of 26 with acute pyelonephritis and in 4 (24%) of 17 with febrile UTI (not significant). Five of eight patients with positive blood cultures had underlying complicating factors (three were diabetics and two had urinary tract abnormalities). Three blood isolates of *E. coli* had been lost during subculture; however, for five patients, the identities of concurrent blood and urinary isolates were shown by P fimbriation, production of hemolysin and aerobactin, and O:K:H serotype, except for one case in which the urinary isolate had lost its O antigen (O2:K1:H7 vs. OR:K1:H7). Six (75%) of eight urinary isolates were both P-fimbriated and aerobactin-positive, while four strains (50%) showed hemolytic activity. There was no significant difference in P fimbriation between urinary isolates from patients with or without positive blood cultures (75% vs. 57%; not significant).

Discussion

Most *E. coli* strains examined in this study were obtained from men participating in prospective, controlled treatment trials of community-acquired symptomatic UTI. The patients were thus not typical of those seen in a urologic surgery clinic, possibly explaining the rather low prevalence of underlying complicating factors. Although the level of infection among patients with fever who did not have clinical signs and symptoms of pyelonephritis is hard to pinpoint, the systemic inflammatory response in the absence of instrumentation of the lower urinary tract is highly suggestive of renal involvement. The host response to infection was of the same magnitude in men with acute pyelonephritis and febrile UTI and corresponded to the findings for women with acute pyelonephritis [18]. Furthermore, in the elderly, the presentation of acute renal infection is often atypical (without flank pain or renal tenderness) [19]. Indeed, the patients with febrile UTI were 10 years (median age) older than those who had pyelonephritis.

Table 2. Distribution of O:K:H serotypes of *E. coli* according to type of UTI.

Serotype*	Acute pyelonephritis (n = 41)	Febrile UTI† (n = 33)	Acute cystitis (n = 14)
O1:K1:H−	0	1	0
O2:K1:H6	0	0	1
O2:K1:H7‡	0	1	0
O2:K5:H4	1	0	0
O2:K7:H−	2	0	0
O2:KN:H−	0	1	0
O4:K5:H5	1	0	0
O4:K12:H1	1	1	0
O4:K−:H1	1	0	0
O4:K−:H−	2	0	0
O6:K2:H−	0	0	1
O6:K5:H1	2	0	1
O6:K5:H−	1	0	0
O6:K13:H1	1	1	1
O6:K14:H−	1	1	0
O6:K23:H1	1	0	0
O6:K53:H1	1	1	0
O6:K53:H7	0	1	0
O6:K53:H−	1	0	0
O6:KN:H5	0	0	1
O6:KN:H31	1	0	0
O6:KN:H−	0	0	1
O6:K−:H1	0	2	0
O6:K−:H31	1	1	0
O6:K−:H−	1	0	0
O7:K1:H−	1	0	0
O8:KN:H41	0	1	0
O8:K−:H5	0	0	1
O15:K2:H5	1	0	0
O15:K2:H−	0	1	0
O15:K3:H5	1	0	0
O15:K52:H1	0	2	0
O15:KN:H5	1	0	0
O15:KN:H45	0	1	0
O15:K−:H5	0	1	0
O16:K1:H6	2	1	0
O16:K1:H−	1	0	0
O18ac:K1:H7	1	1	0
O18ac:K5:H5	1	0	0
O18ac:K5:H−	6	1	1
O18ac:KN:H1	1	0	0
O75:K1:H7	0	1	1
O75:K1:H−	0	0	1
O75:K5:H−	1	1	1
Subtotal (%)	36 (88)	22 (67)	11 (79)
Other serotypes	5	11	3

* KN denotes a nontypeable capsular antigen and K- denotes lack of a capsular antigen. H- means a nonmotile strain.

† Without flank pain or tenderness of the costovertebral angle.

‡ The urinary strain was typed as OR:K1:H7, while the blood isolate from the same patient was typed as O2:K1:H7.

The *E. coli* strains were collected during a 10-year period, thus minimizing the risk of selecting serotypes that predominate because of variations in occurrence with time [20]. The large number of O:K:H serotypes isolated actually reflects the fact that this goal was achieved. Despite this heterogeneity, it was striking that a majority of strains contained somatic O antigens commonly associated with acute pyelonephritis in women [4] and children [2, 3, 5, 6] and/or capsular K antigens commonly related to various forms of UTI [1, 3, 4, 20, 21].

It has been proposed that acidic capsular polysaccharides increase the virulence of *E. coli* in the urinary tract by preventing opsonization and phagocytosis [22, 23]. Nevertheless, 16% of the strains causing acute pyelonephritis or febrile UTI were noncapsulated, thereby confirming the findings in previous studies [4, 24]. The K1 and K5 antigens were found in 42% of these isolates compared with 63% of isolates from women with acute pyelonephritis [4]. These capsular antigens are thought to enhance *E. coli* virulence because of close structural resemblance to certain host structures [25, 26], with resultant low immunogenicity [25]. Obviously, such strains may have a selective advantage by escaping host defenses.

The proportion of spontaneously agglutinating *E. coli* was 12%, which is similar to the findings for women with acute pyelonephritis [4]. Such strains may have undergone adaptive changes in their envelope structures in response to host defense [20, 27]. However, loss of the O side chain may as well have occurred during storage in deep agar. P fimbriae and hemolysin are stable properties that are chromosomally encoded, while aerobactin genes are located either on plasmids or on the chromosome. It is thus possible that some strains may have lost aerobactin-encoding plasmids during storage, thereby resulting in an underestimation of aerobactin-producing strains.

E. coli strains expressing P fimbriae are regarded as especially virulent since they are overrepresented (75%–90%) among urinary isolates from women [4, 28] and children [2, 5, 8] with uncomplicated acute pyelonephritis as compared with isolates from those with acute cystitis [2–5, 29] or asymptomatic bacteriuria [5, 8]. By contrast, in the presence of predisposing factors, the frequency of P fimbriation among isolates from individuals with pyelonephritis is reduced to 50% [4]. In this study, 56% and 45% of *E. coli* strains

Table 3. Distribution of virulence properties of *E. coli* according to diagnosis for men with symptomatic UTI.

Diagnosis	Total no. of patients	No. (%) of patients with indicated virulence property: P fimbriae	Hemolytic activity	Aerobactin production
Acute pyelonephritis	41	23 (56)	30 (73)	21 (51)
Febrile UTI*	33	15 (45)	25 (76)	13 (39)
Acute cystitis	14	5 (36)	7 (50)	6 (43)

* Without flank pain or tenderness of the costovertebral angle.

Table 4. Host response to infection by *E. coli* with or without P fimbriae according to clinical diagnosis.

Diagnosis, P fimbriae	Median value (range) for indicated measurement, no. of patients*		
	Temperature (°C)	CRP concentration (mg/L)	ESR (mm/h)
Acute pyelonephritis			
Positive	39.2 (38.1–40.0), $n = 23$	73 (40–224), $n = 23$	44 (11–86), $n = 20$
Negative	39.3 (38.2–40.4), $n = 18$	96 (43–165), $n = 17$	35 (10–105), $n = 18$
Febrile UTI†			
Positive	38.9 (38.0–40.8), $n = 15$	100 (6–238), $n = 15$	28 (2–80), $n = 15$
Negative	38.5 (38.0–39.9), $n = 18$	61 (11–280), $n = 13$	35 (6–90), $n = 13$
Acute cystitis			
Positive	37.4 (37.2–37.8), $n = 5$	11 (2–11), $n = 5$	31 (6–54), $n = 5$
Negative	37.0 (36.3–37.5), $n = 9$	9 (9–75), $n = 8$	10 (2–81), $n = 9$

NOTE. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
* Number of patients for whom measurement was determined.
† Without flank pain or tenderness of the costovertebral angle.

from men with acute pyelonephritis and febrile UTI, respectively, were P-fimbriated.

Furthermore, aerobactin production by *E. coli* isolates from men with acute pyelonephritis and febrile UTI was lower than that by isolates from women [7] and children [6, 7] with pyelonephritis. The remarkably high proportion of hemolytic strains (74%) could be ascribed to the frequent occurrence of serogroups O4, O6, and O18ac, which are known to be associated with hemolysin production [9, 30].

It has been proposed that P-fimbriated *E. coli*, in children, elicit a stronger systemic and local inflammatory response to UTI than do strains lacking this property [31]. This could not be confirmed in the present study, nor in a previous study of women with acute pyelonephritis [18]. Once bacteria have invaded the renal parenchyma, the inflammatory response seems to be independent of the adhesive properties of the infecting strain.

Only limited data are available regarding virulence properties of *E. coli* in male UTI. Of 30 urinary isolates of *E. coli* from boys younger than 3 years of age who had acute pyelonephritis, the frequency of P fimbriation, hemolysin production, and aerobactin production was 83%, 60%, and 77%, respectively [24]. In addition, the frequency of hemolysin production among 25 isolates from individuals with cystitis was 60%.

Of 14 urinary isolates of *E. coli* from young adult men with symptomatic lower UTI [32], 43% expressed P fimbriae, and 71% were hemolytic; 57% had genes coding for aerobactin. Among homosexual men with various forms of UTI [33], 11 *E. coli* strains were isolated, and 73% possessed P fimbriae; 91% were hemolytic.

Pathogenic mechanisms and risk factors for UTI in men have not been fully elucidated. The long distance between the urethral meatus and the fecal reservoir of uropathogens, the length of the male urethra, and the bactericidal activity of prostatic secretions [34, 35] act in concert, thus making it difficult for microorganisms to gain access to the male urinary tract via the ascending route. Instead, extrinsic factors like genitourinary instrumentation and bladder catheterization may be of importance for bacterial entry into the urinary tract. Lack of circumcision has been identified as a possible risk factor for UTI [32], and in some cases the acquisition of bacteriuria may occur via the heterosexual mode of transmission [36–38]. Furthermore, in men with UTI the prostate gland may become infected, sometimes resulting in a persisting focus of infection [34] that later on may exacerbate a bacteriologic relapse, not necessarily with the same clinical picture as the index infection. Accordingly, most UTIs in men may be regarded as complicated.

Taken together, our findings and those of other investigators [32, 33] suggest different host-parasite relationships in the male and female urinary tracts. In men with acute pyelonephritis or febrile UTI, there was an overrepresentation of hemolytic strains of *E. coli* that were less often P-fimbriated or aerobactin-positive compared with *E. coli* strains that cause pyelonephritis in women and children with normal urinary tracts. In fact, the virulence properties were more similar to those associated with complicated acute pyelonephritis [4, 5]. The high frequency of hemolysin-producing strains suggests that this property is important for the virulence of uropathogenic *E. coli* in men.

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II

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Prostatic involvement in men with febrile urinary tract infection as measured by serum prostate-specific antigen and transrectal ultrasonography

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Objective To determine the frequency of prostatic involvement in men with community-acquired febrile urinary tract infection.

Patients and methods This prospective study included 70 men (18–85 years old) who had a fever of ≥ 38.0 °C, symptoms or signs of urinary tract infection and a positive urine culture. Serum prostate-specific antigen (PSA) was measured and transrectal ultrasonography of the prostate and seminal vesicles performed during the acute phase of the disease and during a 1-year follow-up.

Results Although only six patients had a tender prostate on digital rectal examination, the initial serum PSA level was elevated in 58 (83%) patients (median 14 ng/mL, range 0.54–140). There was no correlation between PSA levels, patient age, inflammatory response to infection or presence of positive blood cultures. Despite a rapid decline in PSA level after one month, there was a protracted decrease in some patients. After 3 months the median prostate volume was reduced by 31% (range 11–54; $P<0.001$) in 46 of 55 patients examined, and the width of the right and left seminal vesicle was reduced by 14% and 22%, respectively. The reductions in PSA and prostate volume were significantly correlated ($r=0.36$, 95% confidence interval 0.09–0.58; $P=0.01$).

Conclusion These results show that the prostate and seminal vesicles are frequently involved in men with febrile urinary tract infection and that PSA may be a useful marker of prostatic infection. The slow decline of PSA levels in some patients after appropriate antibiotic treatment indicates a protracted healing process and should be considered when PSA is used to detect prostate cancer.

Keywords Urinary tract infection, male, PSA, TRUS, prostate gland, seminal vesicles

Introduction

Urinary tract infections more frequently afflict women than men at all ages, except in the first year of life [1,2]. Although the prevalence of UTI increases in elderly men, mainly through prostatic enlargement and instrumentation of the lower urinary tract, it still is a rare disease among those < 50 years old [1]. The natural history and evolution of UTI in men is less well investigated than in children and women. Risk factors that have been implicated are the presence of a foreskin, [3], homosexuality [4], and having a female sexual partner whose vaginal microflora is colonized by uropathogens [5–7]. Recurrent infections in men are often caused by the same bacterial strain, indicating a chronic focus of infection within the urinary tract [1,8,9]. In the absence of concretions, exacerbation of chronic bacterial prostatitis have been suggested as a cause of such recurrences [1,8,9]. In this prospective study of community-acquired febrile UTI in men, we assessed the prostatic involvement of infection by serial measurements of serum PSA and by TRUS of the prostate.

Patients and methods

A total of 70 men were enrolled in the study, recruited at the Department of Infectious Diseases, Sahlgrenska University Hospital, Göteborg, Sweden, which serves as a referral centre for adults with community-acquired febrile UTI. To be included in the study, patients had to have a fever of ≥ 38.0 °C and at least one symptom or sign referable to the urinary tract (frequency, dysuria, flank pain or costovertebral angle tenderness), as well as a positive urine culture. Patients with a chronic indwelling urinary catheter and those who had been treated with antibiotics during the preceding 3 days were not eligible for enrolment. There were otherwise no obvious selection factors for the recruitment of patients for the study. Informed consent to participate was obtained from all patients. The study protocol was

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approved by the Research Ethics Committee at the University of Göteborg.

Clinical procedures

A detailed clinical history was obtained and a physical examination performed on admission. Signs and symptoms, and a history of previous UTI and genitourinary disorders were recorded. A MSU sample for culture and urine analysis, and blood specimens for culture and measurements of serum PSA and C-reactive protein, were obtained before antibiotic treatment. As part of a controlled treatment trial, the patients were randomly assigned to receive oral ciprofloxacin 500 mg twice daily for 2 or 4 weeks.

The patients underwent TRUS and a DRE of the prostate during the acute phase of their illness and again 3 months later. TRUS was conducted using Bruel and Kjaer 3535 equipment with a 7 MHz 8551 multiplane probe. The prostate volume was calculated as the height × width × length × $\pi/6$ [10]. The width of the seminal vesicles was measured as the maximum anteroposterior diameter.

The patients were scheduled for follow-up at 1, 3, 6 and 12 months after inclusion in the study. At each visit, a MSU sample was obtained for urine analysis and culture, and a blood sample taken for the measurement of serum PSA. The urine was cultured semiquantitatively using the calibrated-loop technique. Significant growth was defined as $\geqslant 10^4$ c.f.u./mL urine [11]; all isolates were identified by standard methods. PSA was analysed using a monoclonal fluoroimmunoassay (Delfia®, Wallac Oy, Turku, Finland) and C-reactive protein in serum measured using a fluorescence-polarization immunoassay (TDX® system, Abbott Laboratories, Irving, Texas).

For the purpose of the study, recurrent symptomatic UTI with fever was considered an end-point for the further evaluation of serum PSA and prostate volume. However, patients who had asymptomatic bacteriuria or recurrent lower UTI with no fever continued to be assessed according to the protocol, as were those who were bacteriologically cured. Patients who underwent TURP during the study period were excluded from further analyses.

Fisher's test for pair-wise comparisons [12] was used to compare serum PSA levels, prostate volume and width of seminal vesicles during the acute phase of illness, and after 3 months. Pitman's test [12] or Fisher's permutation test [12] was used to compare differences in the distribution of data between groups. Correlations among the variables were tested using Pitman's test. Two-tailed significance tests were used and $P<0.05$ was considered to indicate statistical significance; 95% CI were calculated according to standard methods.

Results

The characteristics of the 70 patients are shown in Table 1; 19 were < 50 years old, 32 (46%) patients had experienced previous episodes of symptomatic UTI and two men were circumcised. Most patients sought medical attention shortly after the onset of disease (the median duration of fever before enrolment was one day). Twenty-six (37%) patients had clinical symptoms or signs of acute pyelonephritis, while the remainder had fever in conjunction with symptoms from the lower urinary tract. In six patients the prostate was tender on DRE. There was a strong systemic inflammatory response to infection, as measured by the temperature and serum C-reactive protein.

Escherichia coli was the predominant urinary pathogen isolated from 56 (80%) patients. Among other urinary isolates there were five cases of *Klebsiella pneumoniae*, four enterococci, two Group B streptococci, and one each of *Enterobacter aerogenes*, *E. agglomerans* and *Staphylococcus epidermidis*. Blood samples for culture were obtained from 69 of the 70 patients and yielded bacterial growth in 10 (14%) cases.

PSA levels

The initial serum PSA was elevated in 58 of 70 (83%) patients (median 14 ng/mL, range 0.54–140; Table 2). There was no correlation between PSA concentrations, patient age, the magnitude of the systemic inflammatory response as measured by C-reactive protein, or the occurrence of positive blood cultures (data not shown). Data were incomplete for 29 patients who did not comply with all scheduled visits (10), who underwent TURP (nine), had recurrent febrile UTI (six) or biopsy-verified prostate cancer (two), or died (two) during the follow-up.

Despite a rapid decline in PSA level after 1 month ($P<0.001$; Table 2), 43% of the patients still had raised PSA levels; PSA decreased further after 3, 6 and 12 months (Table 2). The time before PSA levels became normal varied considerably between patients and was not related to the initial PSA level. Among 12 patients whose initial serum PSA was < 4.0 ng/mL, nine had lower levels after 1 month (median reduction 50%, range 14–79), compared with 54 of 57 (95%) patients with initial PSA levels $\geqslant$4.0 ng/mL (median reduction 72%, range 41–96). In 52 of 55 patients, the initial PSA value was higher than that obtained after 3 months, while in three patients the levels remained unchanged.

Six patients had a recurrent febrile UTI during follow-up, five of whom could be analysed for PSA. After treatment for the initial infection, the PSA levels decreased in all but one patient, followed by a transient increase associated with the recurrence (Table 3). No

Table 1 Clinical characteristics of 70 men with febrile UTI

Characteristic	*No. (%) of patients*	*Median (range)*
Age (years)	70	62.5 (18–85)
History of UTI	32 (46)	
History of febrile UTI	20 (29)	
Previous urinary tract instrumentation	33 (47)	
Recent urinary tract instrumentation*	9 (13)	
Previous TURP	7 (10)	
Days of fever before enrolment		1.0 (1–10)
Flank pain and/or costovertebral angle tenderness	26 (37)	
Prostate tenderness	6 (9)	
Temperature (°C)†		39.5 (38.0–41.4)
C-reactive protein (mg/L)		130.0 (9–420)

*Within 2 weeks before entry. †Maximum temperature measured at home or in hospital before treatment.

Table 2 Serum PSA after an episode of febrile UTI

*Months**	*No. of patients†*	*Median (range) serum PSA (ng/mL)*	*No (%) of patients with serum PSA > 4 ng/mL*
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)

*Time after an episode of febrile UTI. †Incomplete data from 29 patients (see text).

patient who recurred with asymptomatic bacteriuria (nine) or LUTS with no fever (five) showed an increase in PSA level.

TRUS findings

During the acute phase of the infection, 67 patients underwent TRUS; the prostate was commonly enlarged, containing intraglandular calcifications and hypoechogenic areas in the peripheral zone. Among 55 patients who had two TRUS examinations, at entry and after 3 months, there was a significant decrease in the median (range) prostate volume, from 49 (14–104) mL to 35 (15–91) mL ($P<0.001$). The prostate volume increased slightly in one patient, and was unchanged in three, while of the remaining 51 patients, 46 had a reduction of > 10% (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

After 3 months, among the 49 patients who had complete data from both examinations, the reductions of serum PSA and prostate volume were correlated significantly ($r=0.36$, 95% CI 0.09–0.58; $P=0.01$). A reduction of serum PSA by > 25%, irrespective of the initial PSA level, and/or a decrease in prostate volume by > 10% between the acute phase and follow-up after 3 months was taken as evidence of prostatic involvement in the infection. With these assumptions, 46 of 49 patients (94%) who completed both examinations had a concomitant infection of the prostate. Of the 55 patients who had two PSA measurements, 51 (93%) showed a reduction of PSA level 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 with patient age, the magnitude of initial C-reactive protein levels, the presence of bacteraemia, whether the infection was first-time or recurrent, or caused by Gram-negative or Gram-positive bacteria (data not shown). Nor were the results influenced by

Table 3 Serum PSA levels in five men with recurrent episodes of febrile UTI

Patient no.	*Months after the initial episode of febrile UTI*							
	0	*1*	*2*	*3*	*6*	*7*	*11*	*12*
1	5.8	7.2*		1.2	1.6			1.0
2	4.6	2.7			23.0*	3.8		3.5
3	33.0	3.9			1.8			11.0*
4	1.4	1.2	9.6*	0.80	7.4*	0.86		1.1
5	19.0	1.3		2.1	1.5		35.0*	2.2

*Recurrent febrile UTI.

previous TURP. However, patients treated with ciprofloxacin for 4 weeks had a significantly larger reduction in prostate volume than those who received a 2-week course, with a mean (SD) reduction of 30.0 (14.3)% vs 20.4 (16.3)% ($P=0.024$).

After the acute infection resolved a possible association between prostate volume and serum PSA was examined. Among the 43 patients investigated, the prostate volume after 3 months (median 33 mL, range 15–78) showed a positive correlation with the serum PSA levels after 6 months (median 2.0 ng/mL, range 0.37–13; $r=0.56$, 95% CI 0.31–0.74; $P<0.001$).

Biopsy and TURP

Five patients underwent TRUS-guided needle biopsies, because of findings suspicious for cancer on DRE or TRUS after 3 months, as did nine of 15 patients who had a persistently elevated serum PSA level (> 4.0 ng/mL) 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 ng/mL and 74, 20, 19, 20 ng/mL, 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.

Discussion

The present study provides evidence that the prostate gland and seminal vesicles are frequently co-infected in men with acute febrile UTI. Although no attempt was made to isolate bacteria by culture of expressed prostatic fluid, these findings strongly support prostatic involvement by the infection. First, as measured by TRUS, the prostate and seminal vesicles were frequently transiently enlarged, indicating an acute localized inflammatory process which after appropriate antibacterial treatment subsided within a couple of months. Such changes in prostate volume, although less pronounced, have previously been shown in patients with bacterial prostatitis who clinically improved in response to antibiotic treatment [13]. Second, during the acute phase of the infection most patients had increased serum PSA concentrations which after varying periods returned to baseline levels. A second rise in PSA occurred in patients who experienced recurrent attacks of febrile UTI but not among those who had recurrences with no fever.

For practical reasons TRUS was performed by four urologists, implying a risk of inter-observer bias. However, it has recently been shown that the mean difference in prostate volume estimates between investigators was < 10% [14]. Accordingly, we defined a reduction of volume between examinations by > 10% as clinically significant.

Regardless of the clinical presentation, it is well recognized that recurrent UTI in men is predominantly caused by the same bacterial strain, even though many years might have elapsed between the episodes [1,8]. This has been taken as evidence of a chronic bacterial focus within the urinary tract, which in the absence of concretions is probably localized to the prostate [1,8,9]. In the present study, less than half the patients had a previous history of symptomatic UTI, suggesting the possibility of underlying chronic bacterial prostatitis.

Elevated serum PSA concentrations have been detected in patients with acute bacterial prostatitis [15]. The pathophysiological mechanisms involved are unclear, but it has been suggested that the release of PSA into the blood might be caused by increased vascular permeability associated with the inflammatory process [16,17]. Most of the present patients had a transiently enlarged prostate, indicating an acute inflammation of the gland, thus explaining the increased serum PSA level.

After an initial rapid decline in serum PSA concentration, there was a protracted decrease up to one year after the acute infection in some patients, indicating a slow healing process. Two patients with persistently high PSA levels 6 months after treatment and who underwent biopsy of the prostate had microscopic evidence of cancer. Among those who had normal biopsy findings, BPH

might have contributed to the raised serum PSA level. This was suggested by a positive correlation between PSA and prostate volume after the acute infection had resolved. Furthermore, there are reports showing an association between elevations in PSA and BPH [18,19].

The clinical implications of these results are two-fold: first, as the prostate is often co-infected in men with UTI the choice of antibiotic for treatment should be based on its ability to penetrate prostatic tissue. This criterion is fulfilled by fluoroquinolones and trimethoprim, both of which achieve high concentrations in the gland, as opposed to e.g. beta-lactam antibiotics [20]. The goal is not only to eliminate bacteria from the urine but also, in cases of first-time infection, to prevent the establishment of a chronic infection in the prostate or to eradicate a pre-existing prostatic focus of infection. The larger reduction in the prostate volume seen after a 4-week than a 2-week course of ciprofloxacin suggests that the longer treatment regimen might be superior. Second, the transient but prolonged increase in serum PSA after successful antibiotic treatment of febrile UTI should be considered when PSA is used in the detection of prostate cancer.

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III

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Selective urological evaluation in men with febrile urinary tract infection

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Objective To investigate the prevalence and clinical importance of urological abnormalities in men with community-acquired febrile urinary tract infection (UTI).

Patients and methods In this prospective study, 85 men (median age 63 years, range 18–86) were followed for 1 year after an episode of febrile UTI. They were investigated by excretory urography, cysto-urethroscopy, uroflowmetry, digital rectal examination and measurement of postvoid residual urine volume by abdominal ultrasonography.

Results The radiological examination of the upper urinary tract in 83 patients revealed 22 abnormal findings in 19 men. Relevant clinical abnormalities leading to surgical intervention were found in only one patient who had renal calyceal stones. The lower urinary tract investigation disclosed 46 findings in 35 men. In all, surgically correctable disorders were found in 20 patients, of whom 15 had previously unrecognized abnormalities. All patients who required surgery were identified either by a history of voiding difficulties, acute urinary retention at the time of infection, the presence of microscopic haematuria at follow-up after one month, or early recurrent symptomatic UTI.

Conclusion Routine imaging studies of the upper urinary tract seem dispensable in men with febrile UTI. To reveal abnormalities of clinical importance, any urological evaluation should primarily be focused on the lower urinary tract.

Keywords urinary tract infection, fever, male, urography, cystoscopy, urodynamics.

Introduction

UTI is one of the most common bacterial infections encountered. Most UTIs are uncomplicated, i.e. they occur in otherwise healthy individuals with normal urinary tracts, and predominantly afflict women, except in the first year of life [1,2]. The general view is that a symptomatic UTI in a man of any age should be considered as a complicated infection that demands a thorough evaluation of the urinary tract, to exclude structural or functional abnormalities of clinical importance [1,3,4]. This recommendation is based on the assumption that such disorders are common in men with UTI, but most studies were carried out in highly selected patients in various clinical settings [5–7].

Some risk factors for UTI in men have been identified, e.g. lack of circumcision [8], homosexuality [9], heterosexual transmission of uropathogens [10–12], or instrumentation of the urinary tract [1,3]. Furthermore, the prostate gland may harbour microorganisms, which have been suggested to be the main cause of recurrent UTI [3,13,14]. Recently, a study of febrile UTI in men showed a transient increase in prostate volume and serum PSA during the acute stage of disease, lending support to a concurrent infection of the prostate [15].

The aim of this study was to evaluate the anatomy and function of the urinary tract in men with community-acquired febrile UTI, and to attempt to identify those patients most likely to have abnormalities amenable to surgical correction.

Patients and methods

Eighty-five men who were referred to the Department of Infectious Diseases, Sahlgrenska University Hospital, Göteborg, Sweden with community-acquired febrile UTI were prospectively recruited to the study. The diagnosis was based on fever of $\geq 38.0^{\circ}C$ and at least one symptom or sign referable to the urinary tract (frequency, dysuria, flank pain or costovertebral angle tenderness), and a positive urine culture. Patients with a chronic indwelling urinary catheter and those who had been treated with antibiotics during the preceding 3 days were excluded from enrolment. Informed consent to participate was obtained from all patients. The study protocol was approved by the Research Ethics Committee at the University of Göteborg

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A detailed clinical history was obtained and the men examined physically on admission. Signs and symptoms, a history of previous UTI and genitourinary disorders, and concomitant diseases were recorded. A MSU sample for culture and urine analysis, and blood specimens for culture and measurement of C-reactive protein, ESR and a white blood cell count were obtained before antibiotic treatment. As part of a treatment trial, the patients were randomly assigned to receive oral ciprofloxacin 500 mg twice daily for 2 or 4 weeks.

The patients were scheduled for follow-up at 1, 3, 6 and 12 months after inclusion in the study. At each visit a MSU sample was obtained for urine analysis and culture. Uroflowmetry, a DRE and measurement of postvoid residual urine (PVR) by abdominal ultrasonography (transducer 8542, B&K Medical, Naerum, Denmark) were undertaken at entry and after 3 months. A peak urinary flow rate (Q_{max}) of <10 mL/s (voided volume >100 mL) was regarded as abnormal, as was a PVR of $\geqslant 50$ mL [16,17]. Cysto-urethroscopy was undertaken ≈ 3 months after enrolment, as were imaging studies of the upper urinary tract, unless carried out within the last 5 years (seven men).

After collection, MSU specimens were kept at 4°C until examined. The urine was cultured semiquantitatively using the calibrated-loop technique. The threshold value for significant growth was defined as $\geqslant 10^4$ c.f.u./mL urine [18]. Urine samples containing more than two bacterial species were considered to be contaminated. Two sets of blood cultures were obtained from each patient. All isolates were identified by standard methods. The Ames Multistix® test strip (Bayer Diagnostics) was used to assess pyuria and haematuria; any reaction of trace or greater was considered positive. C-reactive protein in serum was measured by a fluorescence-polarization immunoassay (TDX® system, Abbott Laboratories, Irving, TX). Creatinine clearance was estimated by the Cockcroft-Gault formula [19].

Proportions were compared using Fisher's exact test; Pitman's test [20] was used to compare differences in the distribution of data between groups and the Wilcoxon signed-rank test to compare paired data. Two-tailed significance tests were used, with $P<0.05$ considered to indicate statistical significance.

Results

Of the 85 patients, 25 (29%) were aged $\leqslant 50$ years; 48 (56%) patients had never experienced an episode of symptomatic UTI (Table 1). A history of previous UTI was no more common among men over than under 50 years of age, 27/60 (45%) vs 10/25 (40%). Nine men had undergone previous prostatic surgery, four were circumcised, two were using CISC because of bladder dysfunction after spinal cord injury, and one had an orthotopic ileal bladder. Five patients had diabetes mellitus and four were treated with low-dose corticosteroids. Thirteen patients had an estimated creatinine clearance of <50 mL/min (median 40, range 22–49) at follow-up. The median (range) age of these patients was 82 (62–86) years; four had scarred kidneys and two were diabetics.

Table 1 Clinical characteristics of 85 men with febrile urinary tract infection

Characteristic	*No. (%) of patients*
Median (range) age (years)	63 (18–86)
History of UTI	37 (44)
History of febrile UTI	24 (28)
Previous prostatic operation	9 (11)
Recent urinary tract instrumentation*	13 (15)
Flank pain and/or costovertebral angle tenderness	31 (36)
Prostatic tenderness	9/76 (12)
Temperature (°C)†	85
Median (range)	39.5 (38.0–41.4)
C-reactive protein (mg/L)	85
Median (range)	130 (9–420)
ESR (mm/h)	81
Median (range)	30 (4–100)
White blood cell count ($\times 10^9$/L)	84
Median (range)	13.2 (4.0–29)
Pyuria	68/81 (84)
Haematuria	80 (94)
Positive blood cultures	14/83 (17)

*Within 2 weeks before entry; †maximum temperature measured at home or in hospital before treatment.

Most patients presented shortly after the onset of disease; the median duration of fever before enrolment was 2 days. Thirty-one (36%) patients had clinical symptoms or signs suggestive of acute pyelonephritis, while the remainder had fever in conjunction with LUTS. There was a strong systemic inflammatory response to infection, as measured by the temperature and serum C-reactive protein (Table 1).

Escherichia coli comprised 66 (78%) of the urinary isolates, in one case together with *Serratia marcescens*. Other bacteria isolated from the urine included seven *Klebsiella pneumoniae*, four enterococci, three *Staphylococcus epidermidis*, two Group B streptococci and one each of *Enterobacter aerogenes*, *En. agglomerans* and *Proteus mirabilis*. Blood samples for culture were obtained from 83 patients and yielded bacterial growth in 14 (17%) cases. There were 10 *E. coli* and one each of *S. epidermidis*, *En. aerogenes*, *En. agglomerans*, and *P. mirabilis*. Bacteria of the same species, or the same O:K:H serotype in case of *E. coli*, were recovered from concurrent blood and urine samples.

Urinary tract investigation

The upper urinary tract was investigated radiologically by excretory urography in 76, ultrasonography in four or CT in three men; there were 64 (77%) investigations showing no abnormality. Abnormalities were disclosed in 19 patients, of whom nine had previously unrecognized lesions (Table 2). The findings had clinical implications in only one patient who eventually underwent surgical intervention because of renal calyceal stones.

The findings from the lower urinary tract investigation are shown in Table 3. Incomplete data were obtained from many patients because of refusal to participate, the presence of an indwelling urinary catheter, early surgical treatment of the lower urinary tract, or un-assessable uroflowmetry. Of the 85 men, 12 (14%) had no cysto-urethroscopy and among these all eight of those assessed had a Q_{max} of ≥ 10 mL/s and a PVR of <50 mL.

Twenty-three patients underwent two uroflow measurements that were evaluable, and the Q_{max} was significantly higher after 3 months than at study entry, with a median (range) of 15 (3–48) vs 13 (4–32) mL/s ($P=0.03$). In 51 men examined, the PVR was significantly higher at the acute stage of infection than at the follow-up after 3 months, with a median (range) of 44 (0–514) vs 30 (0–250) mL ($P=0.02$). In the acute phase, 11 of 45 (24%) patients had a Q_{max} of <10 mL/s compared with eight of 35 (23%) at the follow-up (not significant). The PVR was ≥ 50 mL in 33 of 69 (48%) and 19 of 54 (35%), respectively (not significant).

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 on voiding difficulties, which were diagnosed and dilated or incised at cysto-urethroscopy after 3 months.

Table 2 Radiological abnormalities of the upper urinary tract in 83 men with febrile UTI

Abnormality	*Previously unknown**	*Total†*
Renal cortical scarring with or with no calyceal deformity	4	12
Renal cyst	4	5
Unilateral duplication of collecting system	2	2
Renal calyceal stones	1	1
Bilateral ureteric dilatation‡	0	1
Single kidney	0	1

*Eleven findings in nine patients; †22 findings in 19 patients; ‡associated with an orthotopic ileal bladder.

Table 3 Lower urinary tract abnormalities in 83 men with febrile UTI (diagnosed by cysto-urethroscopy in 73, ultrasonographic measurement of PVR in 60 and uroflowmetry in 52 at the follow-up after 3 months)

Abnormality	*No. (%) of findings**
Infravesical obstruction from BPH requiring TURP	10
Urethral stricture	5
Bladder diverticulum	5
Bladder stones	3
Bladder cancer	1
Phimosis	1
PVR ≥ 50 mL†	13 (22)
Q_{max} <10 mL/s†	8 (15)

*Forty-six abnormal findings in 35 patients; †based on the best performance during the acute stage or at follow-up.

Urological abnormalities, bacteriological findings, the inflammatory response and the outcome of treatment

During the 1-year follow-up, 20 patients underwent surgical intervention because of urinary tract abnormalities. In five men with voiding difficulties from BPH and who underwent TURP, the findings were known before study entry. The characteristics of the remaining 15 patients who had lesions that were previously unrecognized are shown in Table 4. Four of these men were under 50 years of age, of whom three had urethral strictures and one renal calyceal stones.

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. *E. coli* was isolated from the patient who had renal calyceal stones and among those with bladder stones the infection was caused by *E. coli* in one and *S. epidermidis* in two. One of the latter also had bacteraemia caused by *S. epidermidis*. The three patients with bladder stones had infravesical obstruction from BPH and eventually underwent both TURP and lithotripsy. Positive blood cultures were found in five (25%) of 20 patients who underwent surgery, compared with nine (14%) of 63 who did not (not significant). The initial serum levels of C-reactive protein in these groups were similar, with a median (range) of 135 (9–230) and 130 (15–420) mg/L.

Fifteen (22%) of 67 patients tested had haematuria as measured by dipstick analysis at the follow-up after 1 month. Three of four patients with stone disease and the man with bladder cancer had haematuria at the first post-treatment visit (Table 4). During the 1-year follow-up, 26 patients had 37 episodes of culture-confirmed recurrent UTI, 16 of which were symptomatic.

Table 4 Characteristics of 15 men with febrile UTI who had surgically correctable lesions that were previously unrecognized

Abnormality	*No. of patients*	*History of voiding difficulties*	*Acute urinary retention*	*Haematuria**	*Recurrent symptomatic UTI†*
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

*As measured by dipstick analysis at follow-up after 1 month; †within 1 month after the end of antibiotic treatment.

Three of five patients with early recurrent symptomatic UTI within a month after the end of antibiotic treatment had an abnormality leading to surgery (Table 4).

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 assessment after treatment. Thus, in this study only 20 (24%) of 85 men would have demanded both upper and lower urinary tract investigation to reveal such abnormalities.

Discussion

The present study shows that routine radiological examination of the upper urinary tract is dispensable in men with febrile UTI. These results challenge current recommendations which advocate radiological studies of all men with UTI, to exclude the possibility of underlying urological complications [1,3,4], but corroborate the findings in women with acute pyelonephritis [21]. That study showed that women who needed imaging studies to reveal surgically correctable lesions could be identified by early recurrence of UTI, particularly if it was caused by the same strain as that originally isolated. As UTI occurs less frequently in men than in women, urinary tract abnormalities have been thought to be more important in the pathogenesis of UTI among the former [1,3]. However, the frequency of structural disorders disclosed by radiological examination in the present study was comparable with that previously found in women [21]. Furthermore, we recently showed, using TRUS and serial measurements of serum PSA, that the prostate is involved in most men with febrile UTI [15]. The findings suggested that an underlying chronic bacterial prostatitis is probably the most common cause of UTI in men. The present study lends further support to this assumption, as structural abnormalities of the urinary tract that might predispose to infection were infrequent. However, two patients used CISC and another 11 had undergone lower urinary tract instrumentation within 2 weeks before infection; thus external factors well known to elicit UTI were present in 15% of the patients.

E. coli was the predominant pathogen and accounted for 78% of the episodes, which is comparable with findings in women with community-acquired symptomatic UTI [22,23]. A higher isolation rate of other bacterial species would have indicated the occurrence of more severely compromised urinary tracts [24].

The transient increase in PVR and the lower Q_{max} apparent during the acute stage of the disease should be attributed to impaired bladder emptying elicited by the acute infection. Nevertheless, 52% of the patients had an initial PVR of < 50 mL and 76% a Q_{max} of ≥ 10 mL/s.

This is the first study to prospectively investigate many men with community-acquired febrile UTI over a long-term follow-up of 1 year, making it possible to ascertain the type and frequency of recurrent UTI. Another strength of this study is that patients were recruited with no selection, and 98% of them underwent imaging studies of the upper urinary tract. Previous studies have mainly focused on highly selected patients in urological settings [5–7], i.e. those with an expected high frequency of urinary tract abnormalities, or young male students [25]. The latter study comprised 38 patients and the authors suggested that at least young men with symptomatic UTI have normal urinary tracts, and routine urological evaluation therefore seems unnecessary. However, the conclusions were based on only 11 (29%) investigated patients and the follow-up after antibiotic treatment was short.

Nonetheless, the present study has some limitations, as the lower urinary tract investigation was incomplete for the urodynamic evaluation and cysto-urethroscopy. The low recurrence rate during the 1-year follow-up and normal urodynamic studies among those who had not undergone cysto-urethroscopy suggests that major

abnormalities were probably infrequent among those not fully investigated.

Altogether, 15 patients had newly detected 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. Renal imaging studies only revealed one patient with an abnormality, i.e. renal calculi, that lead to surgical intervention. This patient had no history of previous UTI or renal stone disease and the clinical importance of this finding might thus be questioned.

To conclude, routine radiological examination of the upper urinary tract seems unnecessary in men with febrile UTI. Imaging studies should mainly be reserved for those who experience clinical treatment failure, have early recurrent symptomatic UTI or persisting microscopic haematuria, indicating major urological abnormalities. Cysto-urethroscopy and urodynamic measurements should also be offered to these patients, and to those with a history of voiding problems or acute urinary retention. Although not documented in the present study, it seems reasonable to initiate a urological evaluation when the infection is caused by urea-splitting bacteria or non-lactose-fermenting Gram-negative organisms, indicating a high probability of underlying lesions of clinical importance [24].

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Abbreviations: **PVR**, postvoid residual urine volume; Q_{max}, peak urinary flow rate.

IV

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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Running head: ciprofloxacin for treatment of UTI in men

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ABSTRACT

In an open, prospective, single-centre study, 114 men with a presumptive diagnosis of febrile urinary tract infection (UTI) were randomised to oral treatment with ciprofloxacin 500 mg twice daily for two or four weeks. Seventy-two patients were assessable for efficacy according to the protocol, all of whom responded successfully with resolution of fever and symptoms during treatment. There was no significant difference in short-term bacteriological cure rate between the two treatment regimens (89% vs 97%; 95% CI for difference in proportions, -4% to 19%), nor in cumulative bacteriological cure rate after 1-year's follow-up (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%). Among 21 recurrences there were eight bacteriological relapses. The recurrence pattern comprised 10 cases with asymptomatic bacteriuria, five with symptomatic lower UTI, and six with another episode of febrile UTI. Neither a history of previous UTI, nor the presence of urinary tract abnormalities were associated with increased risk of recurrent UTI. Adverse events were reported by 23 (24%) of 95 patients, were usually mild and occurred early during the course even among those assigned to the 4-week treatment. The results suggest that a 2-week course of ciprofloxacin is adequate for febrile UTI in men.

INTRODUCTION

The natural history of urinary tract infection (UTI) in women has been well studied and numerous prospective, controlled treatment trials have provided information about proper choice of antimicrobial agents and optimal duration of treatment of various types of UTI (1, 2). In men, however, these issues have received little attention. There is an apparent lack of large, randomised, controlled studies of well-defined groups of patients. Those published have mainly focused on men with a history of recurrent UTI and asymptomatic bacteriuria (3) or mixed infections (4, 5). Short treatment courses of 10-14 days were compared with longer courses of 6-12 weeks and the latter resulted in higher bacteriological cure rates (3, 4). The follow-up period was relatively short and relapse was the most common type of recurrence demonstrated in 68% and 93% of cases, respectively (3, 4). The high relapse rate after treatment has been attributed to the failure to eradicate bacteria from an underlying chronic focus of infection in the prostate (6-8). In fact, chronic bacterial prostatitis is generally considered to be the main cause of recurrent UTI (6-8).

We have recently shown that more than 90% of men with febrile UTI had evidence for prostate infection, as measured by a transient increase in serum prostate-specific antigen (PSA) and prostate volume during the acute stage of infection (9). Antimicrobials reaching free drug concentrations in prostatic tissue and prostatic fluid that exceed the minimum inhibitory concentrations of most of the causative bacteria should therefore primarily be chosen for treatment of UTI in men. The fluoroquinolones, like ciprofloxacin, have such favourable antibacterial spectra and pharmacokinetic properties (10, 11).

The objective of this study was to compare the efficacy of orally administered ciprofloxacin 500 mg twice daily for two and four weeks in the treatment of

febrile UTI in men and to determine the type and number of recurrent episodes of UTI during 1 -year´s follow-up.

MATERIAL AND METHODS

Study design

This was a prospective, randomised, controlled, open trial conducted between March 1993 and January 1996. Men attending the Department of Infectious Diseases, Sahlgrenska University Hospital, Göteborg, Sweden with a diagnosis suggestive of febrile UTI were eligible for inclusion into the study. Informed consent to participate was obtained from all patients. The study protocol was approved by the Research Ethics Committee at Göteborg University

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 four weeks, it was calculated that approximately 100 evaluable patients had to be enrolled in the trial. This was based on a 2-tailed χ^2 test with a type I (α) error of 0.05 and a type II (β) error of 0.2.

Patients

To be included in the study, 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 were: presence of a chronic indwelling urinary catheter, known hypersensitivity to ciprofloxacin, treatment with antibiotics during the preceding 72 hours, earlier inclusion in this trial, renal impairment (estimated creatinine clearance <20 ml/min or serum creatinine >240 µmol/l) or concomitant treatment with drugs that might interact with ciprofloxacin, such as theophylline and warfarin.

Clinical procedures

A detailed medical history was elicited and physical examination performed on admission. Signs and symptoms, a history of previous UTI and genitourinary disorders and concomitant diseases were recorded. A voided midstream urine sample for culture and screening for the presence of nitrite and granulocytesterase as an indicator of pyuria, and blood specimens for culture and measurement of C-reactive protein (CRP), a total white blood cell (WBC) count, PSA and creatinine were obtained prior to antibiotic treatment. In two patients with spinal cord injuries urine was collected by clean intermittent catheterisation.

The patients were initially hospitalised and randomly assigned to oral treatment with ciprofloxacin 500 mg twice daily for two or four weeks. Computer-generated randomisation lists were used. Compliance was ascertained by inquiry and by counting the amount of unused trial drug at the first post-treatment visit. Treatment was initiated with ciprofloxacin 200 mg intravenously in patients who were vomiting or severely ill (n=10). The temperature was recorded twice daily until normalised.

Follow-up was scheduled two weeks post-treatment and after 3, 6 and 12 months. Clinical assessment and inquiry of further episodes of antibiotic treatment was done at each visit. Repeat urine and blood samples for the same analyses as before the start of treatment were also obtained. Patients were encouraged to consult the outpatient clinic at the department in case of recurrent symptoms of UTI during follow-up.

Imaging studies by excretory urography (n=69) or renal ultrasonography (n=2) and cystoscopy (n=61) were done to reveal urinary tract abnormalities of

clinical importance. The prostate volume was measured by transrectal ultrasonography in the acute phase of disease and after three months.

Prostatic involvement by the infection was defined as a reduction of serum PSA by more than 25% and/or a decrease in prostate volume by more than 10% between the acute phase of infection and follow-up after three months (9).

Laboratory 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 anaerobic conditions using the calibrated loop technique. Significant growth was defined as $\geq 10^4$ colony-forming units (CFU) per ml urine (12). Urine samples containing more than two bacterial species were considered contaminated. Antimicrobial susceptibility testing was done using the disk diffusion method (13). Two sets of blood cultures obtained before treatment were incubated both aerobically and anaerobically. Urinary and blood isolates of *Escherichia coli* were stored in deep nutrient agar stabs at room temperature until analysed for O:K:H serotype (14).

Assessment of efficacy

Evaluation according to the protocol required that patients had met the inclusion criteria, demonstrated bacteriuria ($\geq 10^4$ CFU/ml) with a pathogen not resistant to ciprofloxacin, taken the trial drug for a minimum of 12 and 24 days, respectively, and delivered at least one follow-up urine culture. Concomitant treatment with other antimicrobials was not allowed. Clinical response was considered satisfactory if all symptoms related to the infection resolved during treatment. Persistent or worsened symptoms were designated as clinical failure. Recurrence of symptoms of UTI during follow-up was considered as a definite endpoint for assessment of clinical efficacy.

Recurrence of bacteriuria after treatment was considered to be a definitive end-point for assessment of bacteriological efficacy. Cure was defined as eradication of the infecting strain with no recurrence of bacteriuria ($<10^4$ CFU/ml) during follow-up. Recurrences were designated as relapse (the same strain as that initially isolated) or reinfection (a new strain compared to that originally isolated). Serotyping of *E. coli* strains made it possible to differentiate between relapse and reinfection. In patients with 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.

Assessment of adverse events

Patients who fulfilled the entry criteria, received at least one dose of the study drug and appeared at follow-up were included in the safety analysis. Adverse events were reported spontaneously and were also recorded by asking the patient a non-leading question.

Statistics

Fischer's exact test was used to compare categorical data and the Mann-Whitney U- test to compare distributional data. Two-tailed tests were used, and $P < 0.05$ was considered to indicate statistical significance. 95% confidence intervals (CIs) were calculated according to standard methods.

RESULTS

Study population

A total of 114 patients were randomised to the study, 72 of whom could be evaluated for efficacy according to the protocol. Among these, 24 (33%) were $\leq$ 50 years of age. The two treatment groups were comparable as regards the systemic inflammatory response to infection, as measured by the temperature,

CRP and WBC, though positive blood cultures were somewhat more common among those allocated to the 2-week regimen (Table I). Prostatic engagement by the infection, as measured by transient increases in serum PSA and prostate volume, was a frequent finding and occurred in 90% of the patients. Five patients had diabetes mellitus and two in the 2-week group were using clean intermittent catheterisation because of bladder dysfunction. Seven patients did not complete the scheduled follow-up period for one year (six in the 2-week group and one in the 4-week group).

Structural abnormalities of the urinary tract leading to surgical intervention during follow-up were present in 14 patients [infravesical obstruction due to benign prostatic hyperplasia (n=7), urethral stricture (n=5), bladder cancer (n=1) and renal calyceal stones (n=1)], 10 of whom were randomised to the 2-week regimen.

Forty-two (37%) randomised patients were withdrawn from the efficacy analysis since they did not meet the criteria for evaluation (Table II). Of six patients who did not have febrile UTI, three were considered to suffer from a viral disease, two had pneumonia, and one pancreatitis. Because of a large post-void residual urine volume secondary to prostatic hyperplasia, four men received an indwelling urinary catheter which was kept in place until transurethral resection of the prostate was performed.

Microbiological findings

E. coli was the most common urinary pathogen, isolated in 59 (82%) of 72 cases (Table III). All 28 patients who were < 57 years old were infected by *E. coli*, while non-*E. coli* species were recovered only from those who were older. Positive blood cultures were found in 10 (14%) patients. Paired urine and blood isolates of *E. coli* (n=8) were of the same O:K:H serotype. Patients who had positive

blood cultures were older than those with negative blood cultures [median age 72 years, range (48-83) vs 61 years, range (18-85); P = 0.05].

Outcome of treatment

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

There was no significant difference in short-term bacteriological cure rate two weeks post-treatment between patients treated for two or 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%).

Recurrent UTI during follow-up

Of the 21 (32%) culture-verified recurrences after one year, there were eight relapses, 12 reinfections, and one unspecified (Table IV). The relapses consisted of six *E. coli* strains of the same O:K:H serotype as the index isolates and one each of enterococci and Group B streptococci with the same antibiogram. There were 10 episodes of asymptomatic bacteriuria. The clinical recurrence pattern comprised symptomatic lower UTI (n=5) and another episode of febrile UTI (n=6). Furthermore, four patients recurred with culture-negative lower UTI (Table V). Most bacteriological and clinical recurrences occurred within three months after discontinuation of treatment: 9/13 (69%) and 6/9 (67%), respectively in the 2-week group, and 5/8 (62%) and 4/6 (67%), respectively in the 4-week group. The presence of urinary tract abnormalities did not influence the outcome, but two of four patients with early symptomatic recurrences within one month after the end of treatment had major disorders requiring surgery (severe urethral stricture with phimosis and bladder cancer).

Although recurrent UTI was an endpoint for evaluation of efficacy, all patients were closely monitored during the rest of the follow-up period. In all, 13 (38%) of 34 patients with a history of UTI had at least one bacteriological recurrence during follow-up, compared with eight (21%) of 38 patients without previous UTI. The difference was not significant. After one year, five patients had contracted a total of 14 episodes of UTI, one of whom using clean intermittent catheterisation had experienced three recurrent febrile episodes caused by different bacterial strains (reinfections). One patient had two symptomatic recurrences, while asymptomatic bacteriuria was diagnosed on three occasions in one patient and twice in two patients. A history of UTI was present in four (80%) of the patients with multiple recurrences. Otherwise, these patients did not differ from those who were cured from the infection as regards age, the presence of structural abnormalities of the urinary tract, type of bacteria causing the index infection or virulence properties of isolated *E. coli* (data not shown).

Antibiotic treatment during follow-up

Twenty-three patients received other antibiotics than the study drug on 27 occasions before reaching the end-point in the study (16 courses in the 2-week group and 11 in the 4-week group). The reasons for prescribing antibiotics were prophylaxis in association with prostatic biopsy or transurethral resection of the prostate, and respiratory tract and soft-tissue infections.

Safety assessments

109/114 randomised patients received at least one dose of ciprofloxacin. Fourteen of these could not be assessed for safety. Significantly more patients in the 4-week group reported adverse events than in the 2-week group [17/46 (37 %) vs 6/49 (12 %); P=0.008]. However, fourteen events among the former started during the first two weeks of treatment. The symptoms were usually

mild and only two patients in the 4-week group discontinued treatment because of diarrhoea, which occurred on day 11 and 24, respectively.

DISCUSSION

This study is the first to compare varying lengths of antimicrobial treatment of febrile UTI in men with a long follow-up period for one year, allowing analyses of the number and types of recurrent UTI and associated risk factors. Previous studies have mainly focused on men with a history of recurrent UTI and asymptomatic bacteriuria (3) or various types of infections (4, 5), but the follow-up period was rather short. There are some randomised, controlled treatment trials of acute pyelonephritis which included both women and men (15, 16), but firm conclusions regarding efficacy among the latter is hard to draw because quite few men were recruited to the studies.

Our study population was most probably representative of unselected patients with community-acquired febrile UTI. This is supported by the recovery of *E. coli* as causative pathogen in 82% of initial urine cultures and the occurrence of few major structural abnormalities of the urinary tract leading to surgery (17). Another strength of this study is the long-term follow-up of one year and the good patient compliance with few drop-outs. The results suggest that for the treatment of febrile UTI in men, a 2-week course of ciprofloxacin yields bacteriological and clinical cure rates at short-term follow-up comparable with those obtained with a 4-week regimen. There was a tendency towards more bacteriological recurrences in the 2-week group which possibly might be attributed to a somewhat larger proportion of men with previous UTI (53% vs 41%) and urological lesions requiring surgical intervention (26% vs 12%) in that group. The outcome of both regimens was excellent since no clinical failures were recorded. However, the wide confidence interval for differences in cure

rates between study groups will reduce the power of the trial. The results should therefore be interpreted with some caution.

Interestingly, *E. coli* caused all infections in men under 57 years of age, while non-*E. coli* species only were recovered from those who were older. This may be explained by the fact that earlier prostatic surgery or instrumentation of the urinary tract was more common among the elderly (data not shown). It is well-known that such procedures enhance colonisation and subsequent infection with less virulent bacteria (18).

For various reasons, during a long follow-up period, there is an obvious risk that many older patients will receive further courses of antibiotics, which may contribute to the eradication of a concomitant asymptomatic bacteriuria. Thus, the episodes of recurrent UTI recorded might have been underestimated to some extent. Furthermore, the fact that half (53%) the patients had no history of previous UTI may also have contributed to a low recurrence rate.

Most infections recurred within three months, as compared to four weeks following completion of treatment in women with acute pyelonephritis (19) and men with recurrent UTI (4). Relapses constituted 40% of the bacteriological recurrences after one year, indicating an underlying chronic infection of the prostate. In fact, as many as 90% of the patients had evidence for prostate infection, as measured by transient increases in serum PSA and prostate volume in the acute phase of disease (9). However, 60% of recurrent episodes were reinfections with a new bacterial strain compared to that causing the index infection. This may be due to extrinsic factors, e.g. instrumentation of the lower urinary tract and in patients using clean intermittent catheterisation of the bladder. New strains are easily introduced into the bladder in conjunction with such procedures (7). Reinfections in men might also be caused by intrinsic

factors, i.e. reactivation of a chronic bacterial focus in the prostate gland that harbours more than one bacterial species (6).

The proportion of men who had at least one bacteriological recurrence after one year is comparable to that observed in women with acute pyelonephritis (20) followed for the same period (32% vs 40%). There was a tendency towards an increased risk of recurrences among men who had experienced previous UTI than among those who had not, which agrees with the findings in women (20).

The question why exacerbations of chronic bacterial prostatitis frequently result in various clinical manifestations of UTI with the same bacterial strain is unknown. Furthermore, on an individual basis the natural history of UTI is quite unpredictable. In some patients many years may elapse between episodes of UTI, while others experience frequent relapses within a relatively short time. To minimise the risk of recurrence, however, antimicrobials that penetrate prostatic tissue and secretions should be used for treatment, preferably a fluoroquinolone or trimethoprim (11). In contrast, the use of beta-lactam antibiotics should be discouraged since they seem to result in lower cure rates (15, 16), most probably attributed to the low concentrations attained by these drugs in the prostate (11, 21).

Bacteria may be hidden in biofilms adjacent to calculi in prostatic tissue or the epithelial lining of ducts and acini, as well as in focal areas of scarring (22, 23). The biofilm serves as a penetration barrier for many antibiotics, and bacteria localised deeply within biofilms are quiescent with low metabolic activity and slow growth which alter the susceptibility to various antimicrobial drugs. Apparently, under these circumstances, it is difficult to eradicate bacteria in the prostate even with appropriate antimicrobial treatment. What is achieved is rather an eradication of the planktonic bacteria but not of bacteria persisting

within biofilms (23). Regardless of courses with ciprofloxacin for two or four weeks in the present study, some patients had multiple recurrences during the 1-year follow-up period, particularly those who had a history of UTI. Taken together, longer treatment courses do not seem to be of any benefit as antimicrobials rarely cure chronic bacterial prostatitis.

The cumulative bacteriological cure rates in this study are consistent with those obtained in men with chronic bacterial prostatitis who received a 4-week course with oral ciprofloxacin 500 mg twice daily and were followed-up for nine months (24). The bacteriological response was based on cultures of urine and prostatic secretion, and the cure rates after three, six, and nine months were 82%, 76%, and 59%, respectively (24).

In conclusion, this study demonstrates that a 2-week course of ciprofloxacin is adequate for men with febrile UTI. Prostatic involvement by the infection was present in a majority of patients, suggesting an underlying chronic bacterial prostatitis. Longer treatment courses seem unnecessary since all patients responded with clinical success. It is unlikely that antimicrobials, regardless of duration of treatment, will completely eradicate bacteria in the prostate gland. The recurrence pattern of UTI in individual cases appears to be highly variable and unpredictable.

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Table I. Characteristics of study patients.

	Ciprofloxacin 500 mg b.i.d.	
	2 weeks	**4 weeks**
Patients randomised	57	57
Patients valid for efficacy analysis	38	34
Median age in years (range)	61 (18-85)	62.5 (30-77)
History of UTI (%)	20 (53)	14 (41)
Median initial temp °C (range)[a]	39.3 (38.0-40.7)	39.6 (38.0-41.4)
Median initial CRP mg/L (range)	135 (15-420)	130 (9-370)
Median initial WBC x10 ^{9}/L (range)	13.2 (4.0-25.6)	13.6 (5.1-29.8)
Pyuria (%)	28/35 (80)	28/33 (85)
Positive blood culture (%)	7 (18)	3 (9)
Flank pain and/or costo-vertebral angle tenderness (%)	12 (32)	15 (44)
Signs of prostatic involvement (%)[b]	34 (89)	31 (91)

[a]Maximum temperature measured at home or in hospital before treatment.

[b]Based on a reduction of serum PSA by more than 25% and/or a decrease in prostate volume by more than 10% between the acute phase and follow-up after 3 months (9).

Table II. Reasons for non-evaluation after randomisation.

	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 an adverse event	0	1
Insertion of a permanent indwelling 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 III. Bacteria isolated from pre-treatment urine cultures.

Organism	Ciprofloxacin 500 mg b.i.d.	
	2 weeks (n = 38)	**4 weeks (n = 34)**
E. coli[a]	32 (5)	27 (3)
Klebsiella spp.	1	3
Enterobacter spp.[a]	2 (2)	0
Enterococci	0	3
Gr. B streptococci	2	0
S. epidermidis	1	1

[a] Within parenthesis number of patients with positive blood cultures.

Table IV. Cumulative bacteriological 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)
Relapse	2	1
Reinfection	2	0
After 3 months:	n = 36	n = 34
Bacteriological cure	27 (75)	29 (85)
Relapse	3	4
Reinfection	6	1
After 6 months:	n = 33	n = 33
Bacteriological cure	21 (64)	27 (82)
Relapse	4	4
Reinfection	7	2
Unspecified recurrence	1	0
After 12 months:	n = 32	n = 33
Bacteriological cure	19 (59)	25 (76)
Relapse	4	4
Reinfection	8	4
Unspecified recurrence	1	0

Table V. Cumulative clinical cure rate (%) and type of recurrent UTI.

	Ciprofloxacin 500 mg b.i.d.	
	2 weeks (n = 38)	**4 weeks (n = 34)**
2 weeks post-treatment:	n = 38	n = 34
Cure	35 (92)	33 (97)
Lower urinary tract symptoms with bacteriuria	2	0
Febrile UTI with bacteriuria	1	0
Lower urinary tract symptoms without bacteriuria	0	1
After 3 months:	n = 36	n = 34
Cure	30 (83)	30 (88)
Lower urinary tract symptoms with bacteriuria	3	2
Febrile UTI with bacteriuria	2	0
Lower urinary tract symptoms without bacteriuria	1	2
After 6 months:	n = 33	n = 33
Cure	25 (76)	29 (88)
Lower urinary tract symptoms with bacteriuria	3	2
Febrile UTI with bacteriuria	4	0
Lower urinary tract symptoms without bacteriuria	1	2
After 12 months:	n = 32	n = 33
Cure	23 (72)	27 (82)
Lower urinary tract symptoms with bacteriuria	3	2
Febrile UTI with bacteriuria	5	1
Lower urinary tract symptoms without bacteriuria	1	3

Table VI. Adverse events (%).

	Ciprofloxacin 500 mg b.i.d	
	2 weeks (n = 49)	**4 weeks[a] (n = 46)**
No. reporting adverse events	6 (12)	17 (37)
No. discontinuing treatment	0	2
Type of adverse event		
Gastrointestinal disorders	4	8
Exanthema and/or pruritus	0	3
Weakness and/or dizziness	1	7
Balanitis	1	0

[a]One patient reported two adverse events.

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