URINARY TRACT INFECTIONS IN PRIMARY HEALTH CARE IN NORTHERN SWEDEN
Epidemiological, bacteriological and clinical aspects

by

Sven Ferry
ERRATA

Page 14, line 14  the line should be as follows: "reduce urinary nitrate to nitrite, which is detected ...."

Page 30, line 7  the line should be as follows: "leukocytes, only or together as compulsory requirement, were"

Page 34, line 9  the word "improves" should be improved

Page 51, line 22 the line should be as follows: "(about 20 million US dollars). Probably, posttherapy controls in"

Page 54, line 6  the word "seems" should be seem
URINARY TRACT INFECTIONS IN PRIMARY HEALTH CARE IN NORTHERN SWEDEN
Epidemiological, bacteriological and clinical aspects

Sven Ferry
1. ABSTRACT

The epidemiology of urinary tract infection (UTI) in the population of Vännäs (8,000 inhabitants) was studied during one year. The annual incidence increased from 0.5% in the first decade of life to more than 10% in the age group 90-100 years. Male UTI comprised only 13% of the episodes, increased after middle age and contributed 40% by ≥ 80 years of age. At 17 PHC centres (PHCCs) a prevalence study (McPHC) of mainly uncomplicated UTI was performed. Most episodes were acutely symptomatic (lower 75%, upper 5%).

Microscopy of wet-stained urinary sediment with a minimum of moderate amount of bacteria and/or 5 leukocytes per high power field (400 x) as breakpoint resulted in a desired high sensitivity (97%) and 86% efficacy in acutely symptomatic patients. Diagnosis of bacteriuria using Uricult® dipslides yielded acceptable results with an overall efficacy of 88%. Nitrite test and UrigloX® showed an unacceptable low mean sensitivity of 56 and 69%, respectively. A positive nitrite, sediment or Uricult®, when used in combination, was optimal in diagnosing UTI with a sensitivity of 98% in acutely symptomatic patients during their office visits.

The average risk of drug resistance was 17% in the Vännäs study. Sensicult® satisfactorily predicted drug sensitivity (93%) but not bacterial drug resistance (50%). Using Uricult® with classification of bacteriuria by Gram-grouping, lactose and catalase reactions for targeting UTI therapy, according to local guidelines, resulted in a similar low risk (6%) of prescribing drugs to which the organisms were resistant as when using Sensicult® (7%). This development of the Uricult® method is simple and can be recommended for office practice in PHC.

The spectrum of bacteria causing UTI and their drug resistance was more associated with the selection of patients, sex and age than with symptoms. The pattern of drug resistance was little influenced by UTI history and the mean pretherapy resistance for the seven drugs tested in McPHC was low (7%). Drug resistance was increased in failure (mean 24%) but not in early or repeated recurrence. In McPHC therapy resulted in 8% bacteriological failure and 12% early recurrence, irrespective of whether the bacteria were classified as sensitive or resistant in vitro to the drug given. Thus, in order to be of prognostic value for therapy of uncomplicated UTI, high-level breakpoints focusing more on peak urinary drug concentrations need to be studied.

UTI symptoms in McPHC were eradicated in only 2/3 of the bacteriologically cured episodes and in 1/3 of the failures at control 1-3 days posttherapy showing that symptoms are an unreliable indicator of UTI.

From current literature, it seems unlikely that asymptomatic bacteriuria (ABU) plays a major role in the development of uremia due to chronic pyelonephritis. With the exception of ABU in pregnancy, therapy seems to yield no benefit. Omitting posttherapy bacteriuria controls in patients with symptoms eradicated, at least in women with uncomplicated UTI, would lead to considerable savings both for patients and the health care system.

Key words: Urinary tract infection (UTI), primary health care (PHC), epidemiology, clinical presentation, bacteriuria diagnosis, bacteriology, drug resistance, therapy.
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Epidemiological, bacteriological and clinical aspects

by

Sven Ferry

University of Umeå
Umeå 1988
From the Departments of Family Medicine and Clinical Bacteriology, University of Umeå, S-901 87 Umeå, Sweden.

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Epidemiological, bacteriological and clinical aspects

by
Sven Ferry

Umeå University 1988
"Doktorn jätt hjälp me!
Hä schwir
å
hä bränn,
igänn!"

Äldre dam i Vännäs med recidivierande symtomgivande urinvägsinfektioner.

"Doctor, please help me!
It's itching
and
burning
again!"

Elderly woman in Vännäs with recurrent symptomatic urinary tract infections.
To my patients and my patience!
1. ABSTRACT

During 12 months the epidemiology of urinary tract infection (UTI) in the population of Vännäs (8,000 inhabitants) was studied. The annual incidence increased from 0.5% in the first decade of life to more than 10% in the age group 90-100 years. Male UTI comprised only 13% of the episodes, increased after middle age and contributed 40% by ≥ 80 years of age. At 17 PHC centres (PHCCs) a prevalence study (McPHC) of mainly uncomplicated UTI was performed. Most episodes were acutely symptomatic (lower 75%, upper 5%).

Microscopy of wet stained urinary sediment with a minimum of moderate amount of bacteria and/or 5 leukocytes per high power field (400 x) as breakpoint resulted in a desired high sensitivity (97%) and 86% efficacy in acutely symptomatic patients. Diagnosis of bacteriuria using Uricult dipslides yielded acceptable results with an overall efficacy of 88%. Nitrite test and Uriglox® showed an unacceptable low mean sensitivity of 56 and 69%, respectively. A positive nitrite, sediment or Uricult®, when used in combination, was optimal in diagnosing UTI with a sensitivity of 98% in acutely symptomatic patients during their office visits.

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From current literature it seems unlikely that asymptomatic bacteriuria (ABU) plays a major role in the development of uremia due to chronic pyelonephritis. With the exception of ABU in pregnancy therapy seems to yield no benefit. Omitting posttherapy bacteriuria controls in patients with symptoms eradicated, at least in women with uncomplicated UTI, would lead to considerable savings both for patients and the health care system.

Key words: Urinary tract infection (UTI), primary health care (PHC), epidemiology, clinical presentation, bacteriuria diagnosis, bacteriology, drug resistance, therapy.
2. PREFACE

This thesis is based on the following original papers, referred to in the text by their Roman numerals:


3. ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABU</td>
<td>Asymptomatic bacteriuria</td>
</tr>
<tr>
<td>CAT</td>
<td>Indwelling urethral catheter</td>
</tr>
<tr>
<td>CFU</td>
<td>Colony forming unit</td>
</tr>
<tr>
<td>C+</td>
<td>Catalase positive</td>
</tr>
<tr>
<td>C-</td>
<td>Catalase negative</td>
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<tr>
<td>G+</td>
<td>Gram positive</td>
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<tr>
<td>G-</td>
<td>Gram negative</td>
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<tr>
<td>L+</td>
<td>Lactose positive</td>
</tr>
<tr>
<td>L-</td>
<td>Lactose negative</td>
</tr>
<tr>
<td>GLC</td>
<td>Gram, lactose, catalase (used for classification of bacteria)</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>HPF</td>
<td>High power field (used for microscopy)</td>
</tr>
<tr>
<td>INC</td>
<td>Urinary incontinence requiring other aids than CAT (e.g. uridome or diapers).</td>
</tr>
<tr>
<td>McPHC</td>
<td>Multicentre primary health care study</td>
</tr>
<tr>
<td>OIF</td>
<td>Oil-immersion field (used for microscopy)</td>
</tr>
<tr>
<td>PHC</td>
<td>Primary health care</td>
</tr>
<tr>
<td>PHCC</td>
<td>Primary health care centre</td>
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<tr>
<td>SBU</td>
<td>Symptomatic bacteriuria</td>
</tr>
<tr>
<td>UTI</td>
<td>Urinary tract infection</td>
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</table>
| UUA          | Use understandable abbreviations!
4. DEFINITIONS

4.1. Significant bacteriuria.
Bacteriuria was defined as $\geq 10^5$ G- or $\geq 10^4$ G+ bacteria/ml urine, using Uricip in McPHC and $\geq 10^5$/ml in urine culture, for all isolates in Vännäs, except $\geq 10^4$ bacteria/ml for Staphylococcus saprophyticus.

4.2. Patient categories.
The patients were classified in the following categories:

I Lower symptomatic UTI (cystitis or urethritis)

II Upper symptomatic UTI (pyelonephritis): fever $\geq 38.5^\circ$C or tenderness (by bimanual palpation or throbbing) over one or both kidneys, or specific urinary sediment findings.

III Posttreatment control.

IV Miscellaneous UTI (ABU, foul smelling urine only, vague or uncharacteristic abdominal symptoms, systemic symptoms like unexplained fever etc.).

4.3. Statistical analysis.
Differences were tested for significance using the Chi-square method, sometimes with Yates's correction for continuity (1).

In evaluation of diagnostic methods, the outcome of urine culture at a bacteriological laboratory was used as reference.

The following statistical criteria were used (2):

- **Sensitivity**
  - \text{true positive tests for bacteriuria}
  - all episodes with bacteriuria

- **Specificity**
  - \text{true negative tests for bacteriuria}
  - all episodes without bacteriuria

- **Positive predictive value**
  - \text{true positive tests for bacteriuria}
  - true positive plus false positive tests
Cross breakdown was used in evaluating the outcome of different combinations of tests (3).

5. INTRODUCTION AND BACKGROUND

5.1. Epidemiology of UTI in PHC.

Urinary tract infections (UTI), i.e. bacteriuria associated with symptoms (SBU) or without symptoms (ABU), are second in frequency among bacterial infections only to those of the respiratory tract (4). Screening populations for ABU has been useful in defining the pathogenesis of UTI. In general, the information obtained from these studies is similar to that obtained from clinical observations of SBU (5). However, most studies of UTI are of selected patient groups, either patients from hospitals or primary health care (PHC) patients with SBU collected in connection with drug trials, with subsequent discrepancies between the study populations and unselected PHC patients.

Patients seeking PHC for presumed UTI or control after therapy constitute a large group contributing 4-7% of PHC visits or an estimated one million visits per year in Sweden (population 8.3 million, reference 6). In 1970 a study of UTI in a female population in southern Sweden was reported with a prevalence of 1% among schoolgirls, increasing with about 1% unit per decade to 6% at the age of 60 (7). The same year, another prevalence study of a population in southwest Sweden was published and male UTI was found only in occasional cases below the age of 65 years and increased to 4% above 75 years (8). A third study of a population sample of women aged 38-60, also in southwestern Sweden showed a similar prevalence of bacteriuria in 5% (9). The prevalence increased in the initial bacteriuric group to 23% when reexamened six years later.
An adequate epidemiological description of UTI in PHC should preferably be based on unselected cases occurring in a defined population during a certain period of time, e.g. one year, yielding an annual incidence of UTI. However, no comprehensive Swedish epidemiological study of UTI in PHC has so far been reported.

5.2. Clinical presentation of UTI in PHC.

Studies of UTI often are focused on bacteriology, drug resistance and the bacteriological efficacy of therapy whereas clinical factors and their influence are seldom reported in detail. For example, although patients seeking medical care for presumed UTI primarily want relief of symptoms, these are, in most studies, mentioned only briefly, if at all.

The incidence of UTI symptoms in a general population has rarely been studied. A prevalence study of a female population of 20-64 years in South Wales based on interviews showed that at any time in life about half of the women had within the previous year suffered from dysuria, one third from frequency and dysuria and one fifth from dysuria only without any significant association with bacteriuria (10). Only about half of these women, but a significantly higher proportion in the younger age groups, had consulted a doctor for their urinary problems during that year. Another prevalence study of dysuria in London women aged 20-54 years was based upon a postal questionnaire (11). Twenty per cent of all respondents reported dysuria during the previous year with a declining incidence with increasing age. Fifty per cent had suffered from at least one episode of dysuria, 27 and 6% had experienced at least three episodes during their lifetime and the previous year, respectively. A comparison with the practice records showed that only 6% of the females studied had visited their doctors for dysuria during the previous year and, thus, responding by a questionnaire showed about a threefold higher incidence of UTI symptoms than found by studying PHC visits.
In a 18-month prospective survey of Glasgow female patients more than 15 years of age, the most common urinary symptoms were frequency in 77% per year followed by nocturia (58%) and dysuria (57%, reference 12). Only 35% were bacteriuric and there was no significant correlation between any particular symptom and bacteriuria.

Apparently, both the symptoms and the patient's delay in seeking medical care are regarded as trivial in UTI and, therefore, remain poorly described in the literature, including reports from PHC. Available data indicate that ABU may be rather permanent while lower SBU tends to heal spontaneously (7,8,13,14). Moreover, prolonged patient's delay may lead to disappearance of UTI symptoms and an increased probability of self-healing. Thus, clinical presentation of UTI in PHC needs to be further studied.

5.3. Management of UTI patients in PHC.
As a large number of patients with UTI related problems are seeking PHC, it is important to organize the management of this patient group at the PHC centre (PHCC) in a rational manner, and assistance by highly motivated PHCC staff is essential. In 1979 a group of general practitioners prepared guidelines for the management of UTI in PHC in the county of Västerbotten in northern Sweden (15). The guidelines concern schoolchildren and adults and were introduced to the staffs at all PHCCs in the county in 1981.

In bacteriuric patients, water diuresis and frequent micturition lower the urinary bacterial concentration, especially in patients with normal upper urinary tracts, but the concentration rises again during the night (16). Thus, for any bacteruria to achieve significance, it is important to emphasize long bladder incubation time and preferably morning urine (17). Many authors prescribe different methods of prewashing of the periurethral region despite that periurethral cleansing has been shown to be unnecessary (18,19,20). Moreover, many women with recurrent symptoms of UTI or true infections also exaggerate washing of the vulva with different kinds of soap. In a study of women with recurrent UTI who stopped this habit of repeatedly cleansing with soap, the
recurrencies of SBU stopped (20). On the other hand, the clean voided procedure is important to apply in order to collect non-contaminated urine. To improve the collection of specimens, both verbal information by the staff and written instructions handed to the patients and posted on the wall in the surgery toilet are recommended in the guidelines (15).

As symptoms of UTI may be a poor indicator for bacteriuria, it is important to establish the diagnosis by simple and accurate methods at the PHCC, in most patients preferably during their visit. Laboratory facilities need to be used only in certain risk groups of patients.

At many PHCCs in the county of Västerbotten the guidelines are practiced and much of the management of these patients is mainly handled by the staff. To improve the patient’s history a questionnaire was introduced in the county guidelines (15) to be used by the staff before presenting the answers to the doctor, often together with the results of the diagnostic methods used. This model, with assistance of the staff in the management of the patients, was postulated to provide the doctor with a proper basis for the further care of the patient. Parts of the management of patients were evaluated in the MCPHC study (7.2.).

5.4. Diagnosis of UTI.
5.4.1. Criteria for significant bacteriuria.

The diagnosis of UTI is usually based on the concept significant bacteriuria - $\geq 10^5$ bacteria/ml - as originally established by urine culture in females with ABU or acute pyelonephritis (4). However, this traditional diagnostic criterion reportedly identifies only half of the patients with symptoms of UTI as bacteriuric (21,22). Therefore, lowering of the breakpoint to $\geq 10^2$ or $\geq 10^3$ bacteria/ml urine for patients of both sexes with acute UTI symptoms has recently been suggested (23,24,25,26). However, this would lead to a loss of specificity (27) and the use of different threshold values for significant bacteriuria in different patient groups would probably also create practical problems. Therefore, $\geq 10^5$
bacteria/ml remains an acceptable criterion for significant bacteriuria (28).

5.4.2. Urine culture at the bacteriological laboratory.
It is important to avoid growth of contaminating bacteria by keeping the urine specimen cold between sampling and culturing, preferably refrigerated, unless the urine culture can be performed within 1-2 h after collection.

Semiquantitative urine culture is performed in most Swedish laboratories by a streak plate method. A calibrated loop, usually delivering 10 μl, is dipped into the urine and streaked on the surface of each of two different agar plates. The colony count is estimated as the nearest tenth power and converted to bacteria/ml urine.

The classification of bacteria at the local bacteriological laboratory in Umeå is based on the identification system of Cowan and Steel (29) with a simplified modification by Burman and Östensson (30).

Most Swedish laboratories carry out in vitro drug sensitivity testing by the agar diffusion method, using antibiotic discs placed on the agar surface. After incubation overnight, the diameter of the zone of inhibition of bacterial growth is used as a measure of sensitivity (5).

At the local laboratory the more accurate agar dilution method was used. Different dilutions of antibiotic solutions were added to molten agar and allowed to gelify in Petri dishes. Using a steel pin applicator, up to 25 bacterial isolates were tested on each agar plate. The plates were incubated overnight at 37°C and read for growth or inhibition. The break points used were as recommended by the Swedish reference group for antibiotics (31).

5.4.3. Diagnostic methods in PHC.
As reportedly only half of patients with symptoms of UTI have true bacteriuria, it is important to establish the diagnosis with
simple but accurate methods at the PHCC. Urine culture at the bacteriological laboratory is used as reference method and should be reserved for patients belonging to certain risk groups. For office practice, two groups of methods are available, namely, rapid tests yielding the results during the office visit and simplified culture methods requiring incubation overnight before reading.

**Rapid methods.**
Microscopy of urine has been practiced for several decades and is performed in many different ways (32). The most common method in Swedish PHC is microscopy of stained or unstained urinary sediment.

The nitrite test is based on the ability of most bacteria to reduce urinary nitrate, which is detected using a paper strip containing sulphanilamide/quinoline. A pink reaction indicates bacteriuria (28).

The hypoglucosuria test uses a paper strip containing hexokinase and glucose-6-phosphate dehydrogenase response to the low amounts of glucose normally present in the urine. Subnormal levels of urine glucose (< 2.0 mg/100 ml urine) is often associated with bacteriuria (33). Bacterial consumption of urinary glucose leads to an absence of the green colour reaction which thus represents a positive test (bacteriuria).

**Simplified culture methods.**
Displides represent a simplified culture method for office practice requiring overnight incubation. Uricult\(^R\) is the type most commonly used in the Nordic countries and offers not only colony quantitation of bacteriuria but also information on the type of flora (34). Sensicult\(^R\) is a dipslide on which antibiotic discs are placed after inoculation with urine, enabling prediction of bacterial drug resistance (35).
Recently developed methods
After the start of our clinical studies of diagnostic methods reported in this thesis, new methods have been introduced. Most of them are more complicated and expensive than the methods mentioned above, and require special equipment and education. Therefore, only two new methods are briefly mentioned here.

Urinary granulocyte esterase can be demonstrated by the Cytur\textsuperscript{R} test (Boehringer Mannheim Scandinavia AB, Bromma, Sweden) which thus indicates pyuria. Leukocytes are considered indirect markers of an inflammatory process, most often caused by bacteriuria. However, the clinical value of this test is doubtful and lower specificity and sensitivity has been reported than counting of leukocytes in urinary sediment (28). Apparently, leukocyturia occurs in women with and without UTI and thus, measuring leukocyte esterase activity is neither sensitive nor specific enough as a screening test for significant bacteriuria in midstream urine from women (36).

Detection of bacteriuria by luciferase assay of bacterial adenosine triphosphate (ATP-test, LKB-Wallac, Turku, Finland) is another more sophisticated method of diagnosing bacteriuria. The procedure can be summarized as follows: non-bacterial ATP is eliminated and bacterial ATP extracted and assayed by luminometric analyses with the use of special instruments and reagents. The test is rapid and provides an objective and numerical result. However, its outcome in PHC practice appears to be modest (sensitivity only 70\%, specificity 89\% and efficacy 86\%, reference 28).

In my view, further studies are needed before the clinical value of these tests can be firmly established.

5.5 Bacteriology and drug resistance.
Current knowledge of UTI bacteriology in PHC is mainly based on studies of selected patient groups. Out-patient data routinely collected at bacteriological laboratories may represent individuals with recurrent and/or complicated UTI, which probably influence bacteriology and overestimates the risk of bacterial
drug resistance in PHC (37). On the other hand, the numerous drug trials published mainly concern uncomplicated UTI in women in whom resistant organisms are relatively uncommon (38,39). Further, the infecting bacterial species in such studies are often reported without information on their drug resistance (40,41).

Only few studies of unselected UTI in PHC have been published (42,43). They usually contain scarce information about clinical data that may influence the spectrum of infecting bacteria and the risk of drug resistance. Therefore, the relation between epidemiological and clinical factors and UTI bacteriology in PHC needs to be further studied.

5.6 Therapy and therapeutic outcome.
According to a current textbook of medicine, therapy of UTI should be given for 7-10 days (5). A prolonged treatment is needed to eradicate infection in the upper urinary tract. In the local guidelines for the county of Västerbotten from 1981, 7 days' of therapy is proposed for lower, and 10-14 days for upper UTI. Occasionally, recurrent UTI ought to be treated for longer periods and sometimes long-term prophylaxis is recommended (15). The outcome of therapy has often been reported with initial successful rates of 80-90% and eradication of bacteriuria within one month posttherapy of 70-80%, irrespective of the choice of drug (40,44). The Drug Information Committee of the Swedish National Board of Health and Welfare reported in 1986 that therapy for 3-5 days seems to give the same good results as 1 week's therapy of cystitis (45). Even shorter courses, e.g. single dose therapy, have been studied and appear promising (46). Further assessment of single dose therapy in unselected populations has to be performed to firmly establish the efficacy of therapy in lower infections in women with either initial drug resistant infections or with multiple previous infections. Further, this therapy is not accurate in upper or otherwise complicated infections.

A common experience in PHC is that eradication of both symptoms and bacteriuria may occur despite in vitro resistance of the
infecting organism to the drug given. This question is, however, seldom addressed in the drug trials published and needs to be further analyzed.

5.7. Asymptomatic bacteriuria.
The natural history of ABU is still obscure and it is unknown whether complications will eventually lead to renal failure in the end. After stopping the usage of phenacetin, the incidence of uremia due to chronic pyelonephritis was dramatically decreased in Sweden (47). However, a more aggressive UTI therapy and improved follow-up could also be reasons why the incidence has declined. During the last ten years a mean of 20 uremia patients per million inhabitants and year resulting from chronic pyelonephritis and requiring dialysis or kidney transplantation were discovered in the north health region of Sweden (48). However, the role of persisting bacteriuria for the development of chronic pyelonephritis is dubious and, according to Kass, it is unlikely that bacteriuria is a major contributor to the problem of renal failure (49).

There are many studies of bacteria causing UTI that concern different virulence factors such as O- and K-antigens (50), pili or P-fimbrie (51) and bacterial adherence (52). Overall, there are differences in these virulence factors between bacteria causing pyelonephritis, cystitis or ABU with most factors in the first group and least in the last group (50,51,52). Also, there are so far no studies showing discrepancies in virulence factors or clinical prognosis in ABU found primarily in screening of a population or secondarily at posttherapy control of SBU. The long-term natural course of ABU in adults is difficult to study. Perhaps 40 years are required to finally develop uremia. Follow-up studies for such a long time is probably difficult to perform without interference with misleading factors and the initial study group would have to be extremely large in order to make confident conclusions. In some patient groups, such as pregnant women, children and the elderly, as well as patients with known renal failure, it is easier to study complications associated with ABU because of the need of shorter follow-up times in these groups.
Patients with known renal insufficiency are usually not managed in PHC and thus not dealt with further in this study. The former dominant opinion of the long-term adverse effects of ABU thus ought to be reconsidered.

5.8. Posttherapy control.
The aim of UTI therapy is traditionally to achieve eradication of both bacteriuria and symptoms. Most studies of UTI therapy are focused on eradication of bacteriuria, but full relief of symptoms despite ineffective therapy has previously been described (13,38 53,54). Further, remaining UTI symptoms, despite elimination of bacteriuria, have previously been reported (38,41,54,55,56). In the literature there are divergent reports concerning the proportions of posttherapy UTI ranging from 6% ABU in females in recurrent UTI to 39% in uncomplicated UTI in non-pregnant women (13,57). Therefore, the importance of ABU and the long-term history and complications strongly influence the need of posttherapy controls in patients whose symptoms are eradicated.

In Dalby, in southern Sweden posttherapy follow-up studies showed that patients with recurrent and difficult to treat UTI were usually identified as bacteriuric within three weeks posttherapy (7). How important then is posttherapy control of patients not belonging to any risk group and with symptoms eradicated? In 1983 this subject was discussed at a symposium on UTI in PHC in Sweden (6). The symposium was sent by television to eight different places throughout Sweden. A majority of the participating general practitioners and specially invited bacteriologists and infectious disease specialists expressed the opinion that also a sporadic episode of cystitis should be controlled for bacteriuria after therapy. However, the routines of posttherapy control needs to be reconsidered.
6. AIMS

The overall purpose of this thesis was to seek the optimal management of UTI patients in PHC. This was achieved by using two different patient materials hypothesized to represent unselected and mainly uncomplicated UTI in PHC, respectively. The following aspects were studied:

- the epidemiology of UTI in unselected PHC with respect to demographic data including sex, age and patient category (I)

- the clinical presentation of patients with uncomplicated UTI, with particular emphasis on symptoms and patient delay (II)

- the bacteriology and drug resistance compared to data routinely collected at a county bacteriological laboratory (III)

- the influence of clinical and epidemiological factors on bacteriology (III)

- the influence of therapy on the ecology of UTI bacteria (IV)

- the bacteriological and clinical outcome of therapy in relation to the \textit{in vitro} drug sensitivity of the infecting strains (IV)

- the diagnostic efficacy of urinary sediment microscopy, nitrite, Uriglox$^R$ and Uricult$^R$ when used singly (V, VI) and the outcome of various combinations of these tests

- the prediction of bacterial drug resistance by two simplified culture methods, Sensicult$^R$ and further developed Uricult$^R$ dipslides (VI).
7. MATERIAL AND METHODS

7.1. The Vännäs PHC study.
Vännäs is a community in the county of Västerbotten in northern Sweden with about 8 000 inhabitants in the catchment area (Figures 1 and 2). The age and sex distribution of the population is similar to the national average (58).

Figure 1. VÄSTERBOTTEN COUNTY in northern SWEDEN.

Figure 2. VÄSTERBOTTEN COUNTY, catchment area of VÄNNÄS PHCC and city of UMEÅ
During the course of this study three general practitioners and three deputies served at the Vännäs PHCC which was the only medical service available in the community during office hours (weekdays 8.00 am - 5.00 pm). After 5.00 pm and during weekends the patients, if necessary, turned to the Emergency Clinic at the regional hospital of Umeå, 30 km away. The PHCC also served two homes for elderly and a nursing home with 30 beds used mainly for long-term care.

During 12 months (1980-1981) consecutive consultations at the Vännäs PHCC because of suspected UTI or control after UTI therapy were recorded. The patients were asked to bring a clean voided midstream sample of morning urine (minimum six hours bladder incubation, if possible) collected without pre-washing of the vulva or glans penis. Patients with dominating symptoms from the prostate or testicles (prostatitis) or vagina (gynaecological disorders) were excluded.

Patients with indwelling urethral catheter (CAT) or urinary incontinence (INC) requiring other aids such as uridome and diapers were presented separately (CAT + INC, group B), as they differed from other UTI patients (group A) with regard to symptoms, infecting bacterial species and their drug resistance. The episodes were classified in one out of four patient categories, as previously described (4.2.). Posttreatment controls were routinely performed at 1-3 weeks after therapy. A patient who returned earlier than initially planned because of persistent or recurring UTI symptoms was again recorded as an episode of SBU (category I or II, see below) and not as a control visit (category III).

A portion of the urine specimen was transported at +4°C to the county bacteriological laboratory in Umeå, where semiquantitative culturing and identification of microorganisms was performed as previously described (5.4.2).
At the PHCC the following diagnostic methods of UTI were performed according to the instructions of the manufacturers and as previously described (5.4.3.): nitrite test (Niture-Test\textsuperscript{R}, Boehringer Mannheim Scandinavia AB, Bromma, Sweden), hypoglucosuria test (Uriglox\textsuperscript{R}, Kabi Diagnostika AB, Stockholm, Sweden), urinary sediment microscopy of bacteria and leukocytes as described in paper V, and quantitation of bacteriuria using dipslides (Uricult\textsuperscript{R} and Sensicult\textsuperscript{R}, Orion Diagnostica AB, Trosa, Sweden).

Prediction of drug resistance was also performed using Sensicult\textsuperscript{R} and Uricult\textsuperscript{R}. With Uricult\textsuperscript{R}, this was achieved by classification of the bacteriuria by Gram grouping, lactose and catalase reactions, as described in detail in paper VI. Briefly, Uricult\textsuperscript{R} dipslide has MacConkey agar selective for Gram negative (G-) bacteria on one side and CLED agar on the other. Thus, G- bacteria should grow on both sides and Gram positive (G+) bacteria only on the CLED agar. G- bacteria can be divided into lactose positive (L+) or negative (L-) and G+ bacteria in catalase positive (C+) or negative (C-), respectively.

The definition of significant bacteriuria and the statistical analysis were as previously described (4.1. and 4.3, respectively).

A total of 632 visits by 265 patients resulted in 279 bacteriologically verified episodes of UTI in 185 individuals (Figure 3). Patients without CAT or INC contributed 254 episodes with bacteriuria (by 165 patients, group A1), 180 episodes without bacteriuria (group A2) and 156 visits without urine culture performed (group A3). Twenty patients with CAT or INC contributed 25 episodes with bacteriuria (group B1), 11 without bacteriuria (group B2) and 6 visits without urine culture performed (group B3). Groups A2 and A3 were contributed by 80 individuals.
Figure 3. Distribution of UTI episodes in patient groups studied in Vännäs. A total of 632 episodes were contributed by 265 patients. In 80 patients neither urine culture was performed nor bacteriuria was found (group A2 and A3).

Group A1 (40%): 254 episodes of bacteriuria in 165 patients without CAT or INC.

Group A2 (28%): 180 episodes without bacteriuria in patients without CAT or INC.

Group A3 (25%): 156 episodes without urine culture performed in patients without CAT or INC.

Group B1 (4%): 25 episodes of bacteriuria in 20 patients with CAT or INC.

Group B2 (2%): 11 episodes without bacteriuria in patients with CAT or INC.

Group B3 (1%): 6 episodes without urine culture performed in patients with CAT or INC.
In most of the episodes in groups A3 and B3 urine culture was excluded deliberately. As the study was going on for a whole year, in order to record the yearly incidence of UTI, it consumed considerable time and resources. After the first half year preliminary results of the outcome of various diagnostic methods were calculated and later discussed with the participating doctors and assistant nurses. In order to reduce the extra work we decided after nine months' study that the doctor could choose to exclude urine culture if the outcome of physical examination, nitrite and Uriglox R test was negative and the urinary sediment was blank. Urine culture in those episodes is reported as missing. However, in groups A3 and B3 also some visits with urine culture not deliberately excluded were recorded as a missing urine culture.

We postulated that the exclusion of urine culture would have only a little influence on the outcome of the diagnostic methods tested. Though, for practical reasons, we had to accept this slight impairment in the quality of the study.

7.2 The multicentre PHC study.
In 1981, local guidelines for the management of PHC patients with UTI were established for the county of Västerbotten (15). During one month (September-October 1982) 17 PHCCs distributed throughout the county participated in an evaluation of the UTI management programme (the McPHC study, Figure 4). Most consultations, because of suspected UTI or control after UTI therapy, were included in the study and classified in patient categories, as earlier described (4.2).

Patients with dominating symptoms from prostata or testicles (prostatitis) or vagina (gynaecological disorders) were excluded as also patients with CAT or INC and earlier institutional care within one month lead to exclusion of the patient.

Using a questionnaire to the patients, the spectrum of symptoms and their duration, the history of urinary tract problems and patient's delay were recorded. The instructions to patients concerning collection of specimens was as in the Vännäs study
(7.1). The definition of significant bacteriuria and statistical analysis were as previously described (4.1. and 4.3., respectively).

Dipslide urine cultures (UricultR), were inoculated, incubated and inspected at each participating PHCC. Those judged to yield significant growth (5.4.1.) were mailed to the county bacteriological laboratory in Umeå for control reading, identification and drug resistance testing of organisms by standard methods (5.4.2.). Bacteriuria was classified by Gram grouping, lactose and catalase reactions, as later described in detail in paper VI.

Category I, III and IV episodes were treated for 7 days and category II episodes for 10-14 days using ampicillin, mecillinam, trimetoprim or trimetoprim-sulfametoxazole, as later described in detail (IV). Posttreatment controls were routinely performed 1-3 days and 3-4 weeks after therapy. A total of 355 episodes contributed by 302 patients were studied.

![Figure 4. Distribution of 17 participating primary health care centres in the county of Västerbotten.](image)

- In city of Umeå the following five primary health care centres participated: Backen, Mariehem, Teg, Umeå and Ålidhem.
8. RESULTS

8.1.1. Epidemiology.
The incidence of unselected UTI in the Vännäs population increased markedly among women in the second decade of life, showed a minor peak in the third decade and reached a high level in the seventh and eighth decades (I). Male UTI was always in the minority and comprised only 13% of all episodes in patients without CAT or INC (group A). UTI in men increased after middle age and peaked at ≥80 years of age (about 40% of UTI episodes).

The total annual incidence of UTI was 2.3%, (2.1% in group A and 0.2% in patients with CAT or INC). In group A the annual risk of contracting one episode of UTI or more increased from 0.5% in the first decade of life to 1.5% in decades 3-5 and then successively to 9% in decade 10. The age and sex distribution of individuals with UTI and UTI episodes was largely the same.

Except in the first two decades of life when recurrences were rare, the average number of episodes per UTI patient in group A was 1.4-2.3 in each age group with a mean value of 1.5 episodes per patient and year. Thus, in adult patients the risk of recurrence of UTI was relatively independent of sex and age. In group A, 67% of the patients had experienced one episode, 18% two and 15% at least three episodes during the year studied.

The episodes of UTI diagnosed in group A were distributed relatively evenly over the year with a dominance of Escherichia coli (70%). In contrast, the second common species, Staphylococcus saprophyticus (10%), occurred mainly during the summer months, showed a peak in August (28%) and was the single cause of the minor peak of the total episodes recorded during this month. This organism was found only in women aged 15-64 years, particularly in the age group 15-44 years (21% of all episodes and 50% in August).

In the McPHC study of mainly uncomplicated UTI there was a peak of UTI episodes among patients aged 20-29 years and again in decades
 Male UTI seldom occurred before the age of 60 years and comprised overall only 7% of all episodes. About 70% of the patients had not suffered from UTI during the previous year while 20% had experienced at least three episodes of UTI. Fifteen percent of the episodes represented early recurrence (within one month posttherapy). E.coli was the dominating causative organism (77%) followed by S.saprophytics (7%).

8.1.2. Clinical presentation.
In the Vännäs study among group A patients lower SBU was more frequent (56%) than upper SBU (12%) and 25% of episodes of bacteriuria were diagnosed at posttreatment controls. On the other hand, in selecting patients with CAT or INC, symptoms were rarely low (8%), more often high (16%) but in most cases vague or absent (76%). The opposite was found in the selection of uncomplicated UTI in the McPHC study, where lower SBU comprised 75%, upper SBU 5%, posttreatment control 16% and miscellaneous UTI 4%. The discrepancies between patient categories in the different patient materials were highly significant (p <0.001). Thus, bacteriuria was accompanied by symptoms more often among younger patients (with uncomplicated UTI) than among elderly.

The male proportion of Vännäs group A patients was 12-13% in categories I, II and III but higher in category IV (22%). In the McPHC study male episodes were more common in posttreatment controls (19%) than in the other categories (5-8%). The differences between men and women in the distribution of patient categories were highly significant in both studies.

By definition, all episodes in patient categories I and II were symptomatic. In contrast, 79% of episodes in category III and only 20% in category IV were associated with symptoms. Nevertheless, the vast majority of UTI episodes were symptomatic (92%), with urgency (77%) and dysuria (70%) being the most common symptoms. Urinary incontinence was reported in 35%. Loin pain was the symptom showing the highest sensitivity for upper SBU (88%) but was surprisingly reported also in 23% of lower SBU episodes.
Patient delay differed between PHCCs and patient categories and was surprisingly long, four weeks in 9% of episodes and on average 8.4 days. The delay tended to be shorter in young and very old UTI patients than in the age group 40-69 years. The mean delay was only slightly shorter in upper than in lower SBU (6.4 vs. 8.7 days) but surprisingly short in patients with miscellaneous UTI (3.6 days).

8.1.3. Bacteriology.
The spectrum of bacteria causing UTI and their patterns of drug resistance were found to be more associated with the process of selecting the patients and their sex and age than with the symptoms of the patient (lower, upper or asymptomatic UTI). E.coli always dominated as causative organism, particularly in McPCHC (77% of episodes). This organism was found in the Vännäs study in 70% among group A patients and 58% of patients with CAT or INC as compared to 64% of out-patient and in 50% of in-patient episodes analysed at the bacteriological laboratory.

S.saprophyticus was the second most common species in PHC (10% in Vännäs group A and 7% in McPHC) but rarely occurred among in- and out-patients (1-2%). This organism was seen mainly in female patients with a peak in August (28%) and was particularly found in women 15-44 years (21% of all episodes and 50% in August). S.saprophyticus was rarely complicated by therapeutic failures or recurrences.

G- bacteria other than E.coli (e.g. Klebsiella, Enterobacter, Citrobacter, Proteus and Pseudomonas) were seldom encountered in uncomplicated UTI in PHC (3% in McPHC and 6% in Vännäs group A). Such organisms were found in 14% of out-patients, 23% of in-patients and 34% of patients with CAT or INC in Vännäs. Enterococcal UTI was generally rare and found in only one episode in the McPHC study.

The average risk of resistance of the infecting strain to the seven drugs tested increased from 8% for the uncomplicated to 17% for the average PHC patient and 36% among patients with CAT or
INC, whereas recurrences of UTI were associated with a surprisingly small increase of drug resistance. In all UTI patient groups studied, the lowest incidences of bacterial drug resistance were recorded for trimethoprim and co-trimoxazole (0-17%).

A comparison of laboratory data from 1973, 1976, 1983 and 1986 showed similar distributions of causative organisms but somewhat changing patterns of drug resistance. In general, the risk of resistance was greatest in 1976 and had by 1983 declined to lower levels than 1973 but tended to increase again in 1986.

8.1.4. Therapy.
The influence of UTI history (previous therapy) on current UTI bacteriology and drug resistance was studied in McPHC. In patients belonging to potential risk groups indicating therapeutic problems, namely those with repeated recurrence (≥3 episodes during the preceding year) or early recurrence (within one month), Klebsiella was more common than among patients with sporadic episodes in whom Klebsiella was not found. In contrast, S. saprophyticus infected 10% of patients with sporadic episodes but never those with early or repeated recurrence. In therapeutic failure G-bacteria other than E.coli showed an increased prevalence whereas S. saprophyticus was not found. The general pattern of drug resistance was little influenced by UTI history and the mean pretherapy prevalence of resistance to the seven antibacterial agents studied was low (7%). Drug resistance was increased in failure (mean 24%) even for agents not used for therapy (sulphonamide and nitrofurantoin) but not in early or repeated recurrence.

UTI symptoms were eradicated in only 2/3 bacteriologically cured episodes but in as many as 1/3 failures recorded at the posttreatment control. On average, therapy resulted in 8% bacteriological failure and 12% early recurrence, with no significant difference between the various agents used. The failure rate tended to be lower in patients with SBU (9%) than among asymptomatic patients (18%). The bacteriological cure rate was the same irrespective of
whether the infecting bacteria were classified as sensitive or resistant \textit{in vitro} to the drug given. (7 and 10\% failures, respectively).

8.1.5. Urinary sediment microscopy.
Microscopy of wet-stained urinary sediment as an indicator of bacteriuria was evaluated in the Vännäs study. Bacteria or leukocytes, only or together, as compulsory requirement were suboptimal criteria, whereas a minimum of moderate amounts of bacteria and/or 5 leukocytes/HPF (400x) as breakpoint yielded the best diagnostic accuracy. Sediment microscopy thus optimized resulted in a desired high sensitivity (97\%) and 86\% efficacy in acutely symptomatic patients (11\% false positive, 3\% false negative results). In mainly asymptomatic episodes, higher specificity (84\%) but moderate sensitivity (70\%) was obtained resulting in 79\% efficacy. The sensitivity of sediment microscopy was little influenced by bladder incubation time.

8.1.6. Uricult$^R$ and Sensicult$^R$ dipslides.
In the Vännäs study, Uricult$^R$ dipslide as an indicator of bacteriuria yielded better results in symptomatic patients (sensitivity 94\%, positive predictive value 94\%, efficacy 90\%) than in asymptomatic patients (76, 87 and 77\%, respectively). Its efficacy in the total material was 88\%. In McPHC the local quantitations of Uricult$^R$ were similar to those performed by trained laboratory technicians, with clinically important discrepancies in only 3\%. This indicated that most differences between Uricult$^R$ and semi-quantitative urine culture were due to problems inherent to the two methods compared.

Sensicult$^R$ dipslide showed an ability to detect bacteriuria similar to that of Uricult$^R$ but was moderately accurate in sensitivity testings. Its ability to predict bacterial drug resistance was low (50\%) whereas its predictive value for bacterial drug sensitivity was satisfactory (93\%). The use of Sensicult$^R$ in targeting therapy resulted in a similar risk of prescribing drugs to which the bacteria were resistant (7\%) as using Uricult$^R$ if the local guidelines for therapy were followed.
and classification of bacteria was done using Gram grouping, lactose and catalase reactions (6%). The results of GLC classification of bacteria at the 17 PHCCs agreed with laboratory data in 93% for coliform bacteria and 80% for staphylococci, and the results were very similar when read by trained laboratory technicians. Thus, GLC classification of bacteriuria using Uricult offers qualitative and thus prognostic information about bacteriuria.

8.2. Other diagnostic methods (nitrite and Uriglox) and combinations tested.

8.2.1. Outcome of nitrite test and Uriglox compared to urinary sediment and Uricult.

In the Vännäs study all urines were subject also to nitrite and Uriglox tests. The diagnostic outcome was calculated as for urinary sediment and Uricult, i.e. for patient categories I+II, III+IV and the total material (4.2., 4.3.). The outcome of all methods tested is summarized in Table I. In symptomatic patients (categories I+II), urinary sediment microscopy showed a considerably higher sensitivity (97%) than the chemical tests (nitrite and Uriglox, 64 and 75%, respectively) but the specificity of sediment was low (39%). The efficacy of sediment was higher (86%) than of the chemical tests (67 and 77%, respectively). Uricult and sediment were equal in sensitivity and efficacy.

In mainly asymptomatic patients (category III+IV) the sensitivity was generally lower but the specificity higher than in symptomatic patients (category I+II). This applied especially to chemical tests. The efficacy was about 80% for all methods except for Uricult (87%).

In the total material the sensitivity was unsatisfactorily low for the chemical tests (especially nitrite 56%), whereas their specificity was higher than for urinary sediment microscopy. The efficacy was lowest for nitrite (72%) and highest for Uricult (88%).
8.2.2. The influence of bladder incubation time on outcome of diagnostic methods.

Another important factor for diagnosis of UTI is the bladder incubation time. Many diagnostic methods are claimed to give more accurate results in morning urine and it is also easier for the patient to bladder incubate during the night than during daytime.

The influence of bladder incubation time on the sensitivity of diagnostic methods in symptomatic patients is shown in Figure 5.

Figure 5. Influence of bladder incubation time on sensitivity of diagnostic tests in symptomatic patients (category I+II, n=165) as compared to urine culture. Patients with CAT or INC excluded.
The urine culture positivity rate was little influenced by bladder incubation. Both in the Vännäs and McPHC studies more than 3/4 of the patients could bladder incubate for at least 4 h. Using urine culture as reference, no obvious influence of bladder incubation time on the sensitivity of urinary sediment or Uricult\textsuperscript{R} was seen, whereas the chemical tests seemed to give a somewhat improved outcome after \( \geq 3 \) h. However, these results may not be interpreted as though bladder incubation does not matter but so that sediment microscopy and dipslide show the same, and chemical tests a greater, dependence on incubation than culture. Thus, as long bladder incubation time as possible is desirable, preferably morning urine or at least 3 h. But if the patient has not been able to bladder incubate it can still be worth analysing the urine, above all by sediment microscopy and Uricult\textsuperscript{R}.

8.2.3. Combination of methods tested.
The outcome of different combinations of diagnostic methods tested is shown in a simplified form in Table II. Various combinations showed no better outcome than Uricult\textsuperscript{R} alone. A major disadvantage with Uricult\textsuperscript{R} is that the result is not available until the following day, and this is why Uricult\textsuperscript{R} is not acceptable as the only diagnostic method. As Uricult\textsuperscript{R} also yields qualitative information, as previously described (8.1.6.) it should, in my opinion, always be used in diagnosis of UTI in PHC.

The sensitivity was, in general, highest in patient categories I+II, which is essential in order to find bacteriuria in as many symptomatic patients as possible. However, the specificity was highest in patient category III + IV, which also is desirable in order not to falsely classify healthy patients as bacteriuric at control.

The use of chemical tests only showed unsatisfactorily low sensitivity as compared to urinary sediment, but an improved accuracy was seen on the following day upon combination with Uricult\textsuperscript{R}. In all combinations including sediment the specificity and thus the efficacy was lower than in combinations including chemical test. However, the qualitative information obtained with
urinary sediment microscopy, as previously described (8.1.5.), and its high sensitivity in symptomatic patients (category I+II) represent advantages not offered by chemical tests. In patient categories III+IV the sensitivity was improved by adding nitrite to sediment + Uricult\(^R\) (from 73 to 81%, data not shown).

In my opinion, Uricult\(^R\) with GLC-classification of bacteria (VI) and urinary sediment (model B) should always be used in diagnosis of UTI in PHC. Because of its high specificity, nitrite test can be added, which also somewhat improves the sensitivity at post-therapy control (see above). If this combination of tests is used, an addition of Uriglox\(^R\) would not contribute anything of value. For those who are uncertain in reading urinary sediment a combination of nitrite, Uriglox\(^R\) and Uricult\(^R\) can be an acceptable alternative (model E in Table II).

9. DISCUSSION

Studies of patients seeking PHC for symptoms of UTI reflect only half to one third of the true incidence of these problems in a population (10,11). Using a questionnaire, 2.8% of a sample of the Vännäs population aged 15-70 years reported such problems during the previous three months (59). Only half of these individuals had consulted a doctor for their symptoms, suggesting that self-care and self-healing contributes to an underestimation of the true incidence of UTI in the population when UTI is studied by patients at a PHCC. Before the present Vännäs study was initiated a project was conducted at the Vännäs PHCC with the intention to improve accessibility, continuity and utilization of care (58). Therefore, visits by UTI patients from Vännäs at the regional hospital in Umeå during or after office hours were rare. One newborn and three other Vännäs children aged <10 years with UTI had been managed at the Department of Paediatrics in Umeå. Thus, the annual incidence of UTI in children was somewhat lower in Vännäs than reported from Gothenburg, Sweden. (60).
Other factors influencing the recorded incidence of UTI in PHC are, in particular, the diagnostic procedures used, e.g. bladder incubation time, collection of urine, definition and demonstration of bacteriuria. In the Vännäs study a bladder incubation time of $\geq 6$ h and preferably morning urine was encouraged. However, in most studies four hours are recommended and this was achieved by $>3/4$ of SBU patients. Also clean voided midstream urine was emphasized. These routines for management of UTI patients probably contributed to the high incidence of bacteriuria recorded among patients with typical UTI symptoms (82% culture positives). Nevertheless, the number of UTI episodes recorded in Vännäs probably represents a minimum estimate in view of the recent suggestions of lowering the breakpoint for significant bacteriuria to $\geq 10^2$ or $\geq 10^3$ bacteria/ml urine for patients of both sexes with acute UTI symptoms (23,24,25,26). As our culture positivity rate in acute episodes was high, the scope of further UTI diagnoses by a lowering of the break point was limited. Taken together, accessibility of care, prolonged bladder incubation time and the large set of diagnostic methods used probably kept the loss of UTI episodes in the Vännäs study at a minimum.

A factor with possible negative influence on the incidence of UTI in the Vännäs study was that urine culture was not performed or missing in 162 visits (156 in group A3 and 6 in group B3, together 26%). In most of these visits, urine culture was deliberately excluded, especially during the last three months of study. After the first half year preliminary results of the outcome of diagnostic methods showed a high specificity for the nitrite and Uriglox$^R$ combination (97%) and when these tests were negative and the urinary sediment was blank, the doctor could choose to exclude urine culture in order to reduce the extra work caused by the study. Our hypothesis was that excluding these cultures would have only a minor influence on the outcome of the diagnostic methods tested and the incidence of episodes of bacteriuriia studied.

In general, it is difficult to evaluate the importance of missing observations. One way of analysing this can be to postulate that the missing episodes without urine culture did not differ from
those episodes included. As the possibility of a negative urine culture was high in patients with negative nitrite and Uriglox tests (97%) we can consider the extreme situation that all these episodes would have resulted in negative urine culture. Let us hypothetically apply the most accurate diagnostic office method, Uricult, to our group of patients with missing but probably true negative culture results. If so, then 139 negative and 13 positive Uricult results among the 156 missing episodes in group A patients would have occurred (specificity of Uricult 89%). The outcome of Uricult in our study was: sensitivity 88%, specificity 89%, positive predictive value 92%, negative predictive value 85% and efficacy 88% in all group A episodes. After inclusion of missing episodes, sensitivity and specificity would not have been influenced, the positive predictive value declined (from 92 to 85%), the negative predictive value increased (from 85 to 91%) as did efficacy (from 88 to 89%). The same tendency (no influence on sensitivity and specificity and little influence on predictive values and efficacy) would have occurred for the other methods tested. If instead, a few positive urine cultures were registered in the missing group, this would have resulted in an even smaller influence on the outcome of the diagnostic methods tested. Therefore, the hypothesis that the exclusion of missing cultures only marginally would have influenced the outcome of diagnostic methods tested seem to be valid.

All deliveries were carried out at the hospital in Umeå and UTI in newborns was therefore managed at the paediatric clinic. An annual UTI morbidity of 1.7% in the age group <10 years (excluding newborns) was recorded in Gothenburg (60). Including the four preschool children with UTI managed by paediatricians during the year of study, the corresponding morbidity in Vännäs was 0.9%. This was again a somewhat higher incidence than reported from PHC in England (61,62). With the limitations given, it seems that the Vännäs study is representative for unselected UTI in PHC.

In the McPHC study, patients were included according to the Uricult readings by the staffs at different PHCCs and only episodes with dipslides yielding significant bacteriuria were
included. As compared to results of semiquantitative urine culture, the Uricult\textsuperscript{R} readings at the Vännäs PHCC tended to underestimate the colony counts with possible clinical consequences in 11\% (7\% false negative and 4\% false positive results). In the McPHC study the rate of discrepant Uricult\textsuperscript{R} readings between PHCC staffs and laboratory technicians potentially leading to changed management of patients was only 3\%. However, according to the Vännäs study, up to 7\% of UTI episodes at the PHCCs could have been missed in the McPHC study.

In McPHC, patients with CAT or INC were excluded as well as patients with earlier institutional care within one month and patients with dominating symptoms from the prostate, testicles or vagina. However, we have no information on how many patients that were actually excluded. The proportion male episodes was only 5\% in the McPHC study compared to 13\% in Vännäs. In McPHC 20\% of the patients had experienced at least 3 episodes of UTI during the previous year and 15\% of the episodes represented early recurrence. However, these two latter patient groups did not differ in bacteriology and drug resistance patterns from those with sporadic episodes of UTI. To summarize, the hypothesis that the McPHC study would represent mainly uncomplicated UTI in PHC seems to be valid.

9.2.1 Epidemiology.
In most published studies of community acquired UTI it is not stated whether episodes or invididuals are reported as patients. In the Vännäs study, 165 individuals in group A contracted 254 episodes of UTI during the year studied. The yearly incidence of UTI increased by age, most markedly after the age of 60. Presumably, sexual activity of women in the child-bearing age group and also increasingly compromised urinary tracts in the elderly contributed to the higher incidence of UTI recorded among adults than among children. Similar annual rates of UTI in PHC, although with a less striking increase with age, were recently reported from Norway (63).
About one third of the group A patients in Vännäs had one recurrence or more during the study period. The overall risk of recurrence of UTI was similar to that found in other studies (7,13,14). A somewhat unexpected finding was that the risk of recurrence was roughly the same in all age groups (average 50%) except in the first two decades of life, where recurrences of UTI were relatively rare. In McPHC about 70% of the patients had not suffered from UTI during the previous year while 20% had experienced at least three episodes. Fifteen per cent of the episodes represented early recurrence (within one month posttherapy). In Vännäs 25% of the UTI episodes were diagnosed at posttreatment control compared to 16% in McPHC. Of the latter, 79% were associated with symptoms. In McPHC 4/5 of episodes were abacteriuric at control 3-4 weeks after therapy, which corresponds to an average outcome in drug trials. Thus, 16% of the posttherapy controls in McPHC concerned symptomatic bacteriuria. If this result is representative, the vast majority of posttherapy controls may not need to be performed.

In another recent Swedish study of UTI in PHC (64), men contributed on average 13%, as in group A episodes in the Vännäs study. Typically, the percentage male UTI cases rose sharply after middle age, peaking in decades nine and ten. The exclusion criteria used in McPHC resulted in younger patients than in the Vännäs study and thus male UTI episodes represented only 7% in McPHC.

Probably, the differences between results of the rare epidemiological studies of UTI in PHC depend on the numerous methodological difficulties involved rather than on bacterial or host factors.

9.2.2. Clinical presentation.

Among group A patients in the Vännäs study, 56% of bacteriuric episodes were associated with lower and 12% with upper UTI symptoms. The latter figure was lower than that reported from PHC in Denmark (17-18%, references 13,40) but higher than that in another Swedish study (2%, reference 42). These differences may be due to methodological factors such as selection of patients and
the well-known problem in definition of upper UTI. Despite that bacteriuric patients with CAT or INC usually had no classical UTI symptoms but often fever >38.5°C, they were classified as upper UTI in 16%. Probably due to the selection of patients, a low incidence of upper UTI was recorded in McPHC (5%).

In McPHC the classical symptoms urgency or frequency were most common (in 77%) followed by dysuria (70%). As many as 35% of the episodes were associated with urinary incontinence. The spectrum and incidences of symptoms were similar in a Glasgow PHC study (12). However, in the latter study, 42% of patients complained of loin pain compared to 25% in McPHC, where it was most common in upper UTI (88%) but surprisingly also reported in 23% in lower SBU. In our study the definition of high UTI was based on tenderness by palpation or throbbing over the kidneys and not on the patients' report of loin pain only. Thus, the overall incidence of loin pain recorded was five-fold that of high SBU diagnosed (25 vs 5%). This illustrates that the incidence of clinical pyelonephritis depends on its definition and the use of loin pain as the sole indicator may lead to overdiagnosis. In a Danish study of UTI in PHC (40), loin pain plus fever was defined as upper UTI and resulted in 18% pyelonephritis whereas in our study of unselected PHC patients fever and/or tenderness over the kidney(s) was required, resulting in only 12% pyelonephritis. It is thus possible that loin pain often reflects referred bladder pain only rather than true upper UTI.

Both the general length of the UTI patient’s delay (>4 weeks in 9% and on average 8 days) and the difference in delay between patient categories, age groups and PHCCs were surprising. Presumably, patient’s delay depended on symptoms, patient habits as well as on local routines for management of patients with urinary tract problems. The major causes of patient delay and its possible positive and negative clinical consequences remain to be elucidated.
9.2.3. Bacteriology.
UTI bacteriology in PHC varied markedly with sex, age and clinical history and thus, depends on the process by which the patients are selected. In the unselected patient group A in the Vännäs study, E.coli was the causative agent in 70% of the episodes of UTI. Different ways of selecting the patients lead to either higher (100% in children, 77% in McPHC) or lower (50% in in-patients) percentages of E.coli episodes. A low proportion of E.coli was balanced by an increase of other G- bacteria, such as Klebsiella, Proteus, Pseudomonas, and by enterococci and staphylococci other than S.saprophyticus. These latter bacteria are usually indicators of therapeutic problems and are more common in men than in women and frequent also in laboratory out- and in-patients and particularly in patients with CAT or INC. This group of organisms was generally less sensitive to antibiotics and its relative proportion in different patient materials seemed to explain most of the differences between these with regard to drug resistance. Thus, the present study showed that out-patient data routinely collected at bacteriological laboratories do not represent the average PHC UTI patient but rather patients with recurring or persistent infection.

S.saprophyticus was virtually absent in patients with recurring UTI and in in-patients. It was rare also in our out-patients specimens. Apparently, S.saprophyticus UTI seldom caused therapeutic problems necessitating analysis of urine specimens at a bacteriological laboratory. In fact, both we and others (65) have recorded very high initial cure rates in UTI due to this organism (90-100%).

Because of the rareness of S.saprophyticus in repeatedly recurrent UTI, such patients had fewer mecillinam or nalidixic acid resistant infecting bacteria than the average. For other antibiotics recurrent UTI was associated with a suprisingly small increased risk of drug resistance. Both in single episodes and recurrences of UTI, trimethoprim and co-trimoxazole were the agents least associated with bacterial drug resistance in PHC.
The occurrence of drug resistance among UTI isolates from out-patients and in-patients was lower in 1983 than in 1976. This is probably due to the recent efforts to minimize antibiotic usage in UTI and the increasing number of therapeutic alternatives available. The marked decline of nitrofurantoin and sulphonamide resistance corresponded in time with the introduction in 1981 of the new county guidelines for management of UTI in PHC advising against the use of these agents as first choices of therapy (15). Furthermore, the differences recorded in drug resistance between PHCCs suggested an influence of local variations in drug prescribing habits. Apparently, drug resistance in UTI is a changing phenomenon. Since therapy traditions differ between PHCCs and with time result in variable patterns of drug resistance, monitoring of drug resistance of UTI bacteria should preferably be performed at regular intervals at the local level.

9.2.4. Therapy.
The two most common UTI species, E.coli, and in particular, S.saprophyticus, caused little therapeutic problems whereas Klebsiella and other G- bacteria were associated with failure and recurrence. This may be due to their disposition to drug resistance and represents an ecological effect of previous UTI therapy, although a contribution by virulence or host factors cannot be excluded. The overall prevalence of in vitro resistance to the antibacterial agents tested was low and similar to that in other studies of UTI in PHC (38,64). Resistance was most common and found against the two major drugs used, mecillinam and nalidixic acid, and was generally increased only in therapeutic failure. In early recurrence, drug resistance had returned almost to pre-therapy values, except for sulphonamide and nitrofurantoin, despite none of the patients having been given these agents. Thus, antibiotic therapy of UTI selected multiresistant organisms, including E.coli, with moderately lasting resistance also to drugs that were not given. It seems likely that the chromosomal nature of nitrofurantoin resistance and part of the sulphonamide resistance helped to maintain these resistant traits longer than average in the multiresistant bacteria selected.
Despite that relief of UTI symptoms is important to the patient, this aspect is usually not addressed and rarely analysed in detail in drug trials (38,41,56). Full relief of symptoms despite ineffective therapy has previously been described (13,38,53). In a Danish study, 21 out of 23 patients with bacteriological failure had become asymptomatic during therapy (13) as compared to 9 out of 26 episodes with failure in our study (IV). Furthermore, 39 % of the recurrences were reported to be ABU in the Danish study, which differed from an US report of 94% symptomatic episodes in women with recurrent UTI (57). Again, in another US study of women with uncomplicated lower SBU 90% of recurrences were symptomatic and nearly 100 follow-up cultures were needed to find one case of ABU (66). However, in our MCPHC study, 16% of the controls at 3-4 weeks after therapy concerned SBU. Since dysuria and frequency tend to decrease by time despite persisting bacteriuria, the variable correlation between symptoms and bacteriuria observed in recurrent UTI may partly be due to differences in patients' delay, which was relatively long in the MCPH study (mean 8 days).

Persistence of UTI symptoms despite elimination of bacteriuria has previously been reported (38,41,53,56). In McPHC, symptoms had disappeared posttherapy in only 2/3 bacteriologically cured episodes as compared to in 1/3 failures. In as many as 17% of finally bacteriologically cured episodes at control 3-4 weeks after therapy, symptoms still persisted. Available data thus indicate that symptoms cannot be used to monitor the bacteriological result of UTI therapy.

The low overall rates of bacteriological failure (8%) and early recurrence (12%) were similar to those reported in many drug trials (38,41,53,56). Surprisingly, we observed no difference in outcome whether the infecting bacteria were classified as sensitive or resistant in vitro to the drug given. Similar results have occasionally been reported previously (40,53,54).

Only few studies have critically evaluated the outcome of UTI therapy related to results of in vitro sensitivity tests (67,68). Such studies have demonstrated that achievement of antibacterial
drug concentrations in the urine, exceeding the in vitro sensitivity level of the infecting organism, is a prerequisite for, but does not insure, effective elimination of bacteriuria. On the other hand, inhibitory serum levels of drugs have not been shown to enhance eradication of bacteriemia of urinary tract origin.

The McPHC study indicated that the cure rate in patients with uncomplicated UTI depends more on other factors than the antibiotic sensitivity of the infecting strains. Thus, serum levels and the low-level bacterial resistance studied in the laboratory may need to be considered only in nephropathy and otherwise compromised urinary tracts, in tissue engagement, and when UTI has progressed to septicemia. Our data indicate that the present breakpoints are too conservative and of limited relevance for the treatment of sporadic or recurrent episodes of UTI in PHC. Apart from too low breakpoints in relation to urinary drug levels, an effect of sub-MIC concentrations of drugs on bacterial virulence and host defence including urine flow and frequent micturitions may have contributed to the favourable therapeutic results with strains classified as drug resistant in vitro. Evidently, in order to become of prognostic value in uncomplicated UTI in PHC high-level breakpoints focusing more on peak urinary drug concentrations need to be studied.

9.2.5. Urinary sediment microscopy.
In a recent comprehensive review of microscopy for bacteriuria, differences in outcome between methods but also large discrepancies between investigators were noted (32). High power field (HPF) analyses of unstained, uncentrifuged urine using various breakpoints yielded on average lower sensitivity (46-88%) and specificity (65-94%) than HPF analyses of unstained, centrifuged urine and ≥10 bacteria/HPF as breakpoint (85-95 and 78-99%, respectively). Microscopy of stained centrifuged urine and ≥1 organism/oil-immersion field (OIF) as breakpoint appeared to be the most satisfactory method resulting in 95-100% sensitivity and 74-97% specificity.
The most widely used indicator of pyuria, >5 leukocytes/HPF in sediment, yielded sensitivities of only 63% (69) to 80% in patients with acute UTI in the Vännäs study and 33% (14) to 63% in asymptomatic episodes in our study. Enumerating leukocytes in uncentrifuged urine using a counting chamber with >10^6 ul as breakpoint improved sensitivity in symptomatic patients (95-100%, references 25,70) with moderate specificity (72%, reference 25) and opposite results in asymptomatic patients (sensitivity 49%, specificity 98%, reference 70). Thus, microscopic pyuria appeared to be less accurate as indicator of bacteriuria than microscopic bacteriuria.

There are relatively few studies of urinary sediment analysing bacteria and leukocytes in combination. This combination yields increased sensitivity but decreased specificity. We found that an optional presence of these components offered the best overall correlation with results of urinary culture and that microscopy depend on bladder incubation time no more than did culture. Sediment analysis was particularly useful in acute patients with a desired high sensitivity (97%) and only a moderate risk of false positive results (11%) and, thus, 86% efficacy. In patients with little or no symptoms, sediment analysis showed a rather low sensitivity, moderate specificity and, thus, a somewhat lower total efficacy (79%). This microscopy method using centrifugation offers qualitative advantages as other elements of diagnostic importance than leukocytes and bacteria are concentrated and thus easier to detect. Staining also simplifies distinction between cocci and different rod-shaped bacteria and amorphous debris. Optimized sediment microscopy was found to be particularly useful in patients with acute symptoms of UTI, i.e. where the need for rapid diagnosis is greatest.

9.2.6. Uricult\textsuperscript{R} and Sensicult\textsuperscript{R} dipslides.
Uricult\textsuperscript{R} read by assistant nurses at one PHCC was satisfactory for diagnosis of bacteriuria, especially in acute symptomatic patients (overall efficacy 90%). At the laboratory 8% were considered contaminated but only 4% at the PHCCs in the McPHC study. In 4% of episodes the colony counts were not registered neither at the
PHCCs nor at the laboratory, probably due to difficulties with readings. These contaminated dipslides were excluded in the following comparative study. In this study, quantitation of bacteria was performed by staffs without laboratory training at 17 PHCCs and by two specially trained laboratory technicians.

Discrepancies between the two groups potentially altering patient management were noted in only 3% of episodes of bacteriuria. Difficulties in reading Uricult\textsuperscript{R} for PHCC staffs appeared to be a less important cause of discrepant results than to those related to the method, e.g. the ability of the dipslide to support growth of certain bacteria.

The \textit{in vitro} drug resistance varied considerably between the different groups of bacteria according to GLC classification when using Uricult\textsuperscript{R} (7.1). The PHC UTI management program used in our county recommends pivmecillinam or nalidixic acid as the first choice for therapy of G- and ampicillin for G+ bacteria (15). Nitrofurantoin and sulphonamide are no longer recommended as first choice drugs, because of the serious adverse reactions reported (71,72), and co-trimoxazole is a second choice therapy reserved e.g. for presumed difficult to treat (non-coliform) or otherwise complicated UTIs. In the Vännäs study, the use of GLC classification of bacteriuria and these therapy recommendations would have resulted in 6% of episodes being treated with drugs to which the bacteria were resistant \textit{in vitro}. This method of selecting antibiotics in UTI would have diminished the risk of prescribing potential inactive drugs by about three-fold (from 17 to 6%).

Sensicult\textsuperscript{R} disagreed considerably with \textit{in vitro} drug sensitivity testing by agar dilution, particularly for drug resistant bacteria. If Sensicult\textsuperscript{R} had been used for targeting UTI therapy in the Vännäs study, the average risk of prescribing drugs to which the bacteria were resistant \textit{in vitro} would have been 7%, e.g. similar to the risk with GLC classification and current therapy recommendations. As the mean predictive value for resistance using Sensicult\textsuperscript{R} was only 50%, on average half of the patients
with drug resistant bacteria would have been denied therapy to which the isolate was sensitive in vitro.

However, we observed errors in the GLC classification, apparently dependant upon the agar media of the UricultR. Poor growth of enterococci on UricultR has also previously been reported (35,73). Furthermore, staphylococci were growing on the MacConkey agar in 4 out of 38 episodes, as read by the technicians. Moreover, in an earlier study such unexpected growth of S.saprophyticus was seen in 73% (74). In a later pilot study, performed at the bacteriological laboratory, S.saprophyticus was found to grow on MacConkey agar in 40-79%. In addition, the lactose reaction was sometimes weak resulting in wrong GLC classification of the bacteria.

SensicultR offered no advantage over GLC classification as indicator of drug resistance. It also adds to the cost and lacks prognostic information, and for these reasons, it cannot be recommended for PHC practice. Moreover, it is not unlikely that the ability of UricultR to predict drug resistance can be further improved. However, in my opinion, UricultR can be recommended in PHC both for diagnosis of bacteriuria and targeting of UTI therapy in PHC.

9.2.7. Nitrite and UrigloxR and combinations of methods tested. In symptomatic patients, chemical tests (nitrite and UrigloxR) showed lower sensitivity than urinary sediment and UricultR. In mainly asymptomatic patients, the sensitivity was lower, especially for chemical tests, but the specificity higher. In the total material, the sensitivity was unsatisfactorily low for the chemical tests and the lowest efficacy was found for nitrite whereas the highest was showed for UricultR.

No obvious influence of bladder incubation time on the sensitivity of urinary sediment or UricultR was seen as compared to urine culture whereas the chemical tests yielded a somewhat improved outcome at ≥3 h incubation.
Various combinations of the different tests gave no better outcome than Uricult alone. As the result of Uricult is not available until the following day, it is not acceptable as the only diagnostic method. The use of chemical tests showed unsatisfactorily low sensitivity on the day of visit compared to urinary sediment. The qualitative advantages with urinary sediment and the high sensitivity in symptomatic patients are part of the reason why the advantages with sediment outweigh those of chemical tests only. My opinion is that Uricult with GLC classification of bacteria and urinary sediment should be used in diagnosis of UTI, and that the nitrite test can be added, contributing to an optimal combined diagnostic model of UTI in PHC.

9.3. Asymptomatic bacteriuria.
As earlier mentioned, the long-term natural course of ABU and the risk of developing complications ought to be studied in different patient groups. ABU in patients with known renal failure and other serious urinary tract diseases is known to be hazardous, but these patients are seldom managed in PHC and will therefore not be further discussed.

In some patient groups, such as pregnant women, children and the elderly, it is easier to study the complications associated with ABU than in adults in general, because of the need of shorter follow-up times in the former groups.

9.3.1. ABU during pregnancy.
ABU during pregnancy has been thoroughly studied. If left untreated, a high incidence of acute pyelonephritis and kidney damages has been reported as well as premature delivery and perinatal death. The risk of complications is significantly decreased by therapy (75,76). Thus, screening for and therapy of ABU and posttherapy bacteriuria control should be recommended in pregnancy.

9.3.2. ABU in children.
Also UTI in children has been investigated in detail. Recently, long-term follow-up (mean 4 years) of renal function in children
aged 1.5-15 years was reported (77). Functional renal damage after recurrent UTIs seemed to occur only before the age of 3 years. If the patients were adequately treated, no further functional deterioration was observed. However, the number of patients was too small to allow definite conclusion to be drawn regarding this age threshold.

In a 3-year follow-up study of ABU among school girls aged 7-15 years, ABU usually did not lead to symptomatic pyelonephritis. The risk of developing renal damage because of ABU in schoolgirls, with radiologically normal urinary tracts, appeared to be small (78). A 10-year study of bacteriuria in schoolgirls showed that UTI often occurred as ABU, whereas frequently recurring UTI often was symptomatic (51). It was reported in another study of schoolgirls that therapy was not essential for most of the children with ABU, as their renal growth was similar to that in normal children whether therapy was given or not (52). From a 4-year follow-up study of ABU in schoolgirls, treatment was reported to have no effect on the emergence of UTI symptoms, kidney growth or progression of kidney scars. New kidney scars did not develop in previously unscarred kidneys (53). A long-term (9-18 years) case-control study of school girls with ABU showed that ABU was associated with recurrent SBU as well as UTI later during pregnancy (79). However, the risk of reducing renal function measured as serum creatinine, creatinine or inulin-clearance was low.

At a recent pyelonephritis symposium it was reported that girls with renal scarring and ABU, during a 6-year follow-up study, were at high risk of contracting recurrent SBU and also pyelonephritis posttherapy, even during and after long-term antibiotic prophylaxis. In this material (mean age 8 years at the start, of the study, average follow-up time 6 years) ABU never developed into SBU, if antibiotics were not given. Kidney growth was normal whether or not ABU had persisted for more than 3 years (80).
To summarize, ABU in children, even with renal scars, does not appear to negatively affect kidney growth and function, and therapy of UTI seems to be unnecessary, and possibly harmful, unless symptoms are present.

9.3.3. ABU in adults.
Fry et al reported already in 1962 that, up to 6 years after therapy of acute SBU in general practice, patients with recurrent and persistent UTI had not developed signs of chronic pyelonephritis (81). Treatment of ABU in non-pregnant women has again been reported to be initially successful in 80% but therapy failed to prevent later development of symptoms of UTI and SBU (14). In a screening study of a female population in southern Sweden, ABU was found in 4%. Of these women 13% had advanced radiological pyelonephritis changes (82). One year later, screening of the same population was performed and ABU was found in 0.5% of the initially abacteriuric women but without any association with radiological changes. The authors' comments were that perhaps patients with ABU in the initial screening had suffered from bacteriuria during a longer period (from childhood?) than those diagnosed in the second screening and, therefore, renal damages were found only in the first group identified with ABU.

In another screening study bacteriuria was found in 5% of a female population in the agegroup of 38-60 years in western Sweden. Seventeen per cent of these had pathological radiological renal changes. These patients were followed for 10 years without any of them developing progressive renal impairment (9). In a study of a female population aged 21-66 years in southern Sweden, an incidence of 4% of bacteriuria was detected. The group with ABU was followed for 15 years and these individuals contracted SBU at a significantly higher rate compared to a control group, but progressive renal damage was not found (83).

Thus, ABU in adults, even associated with renal damages, does not seem to be of any risk of further progressive kidney lesions as judged by a follow-up period of up to 15 years.
9.3.4. ABU in the elderly.

In a Finnish study of elderly women with ABU a higher rate of death 5 years later was found compared to those not infected (84). In Greece, ABU in the elderly was reported as an important factor associated with a reduction of the survival time in both sexes (85).

The relation of bacteriuria to subsequent mortality was investigated in cohort studies of women in Jamaica and Wales (86). Three surveys of each cohort were done over a 13-year period. Women with \( \geq 10^5 \) G- bacteria/ml in three consecutive cultures were considered bacteriuric. Mortality was determined at the second and third surveys. Bacteriuria was associated with increased mortality both in the crude data and in life-table analysis adjusted for the confounding effect of age and weight. The adjusted risk ratio for death between the first and third surveys was 1.5 for women bacteriuric at the first survey compared with nonbacteriuric women, and 2.0 in women who were bacteriuric at both of the first two surveys. These results suggest a positive association between bacteriuria and mortality in the general population of women. The conclusion of the study was that biological mechanisms may explain the association but studies of other variables, such as serious illness and admission to hospital, are needed to determine the medical importance of this association.

On the other hand, a recent screening study of a 70-year old population in western Sweden showed that fatal diseases associated with bacteriuria (e.g. cancer) may account for the increase of mortality among elderly individuals with bacteriuria (87). Thus, the health risks possibly associated with ABU in this population remain unclear. That screening of the elderly for ABU and subsequent therapy would be of benefit seems to be an even more remote possibility. Therefore, this interesting issue needs further large-scale studies to become definitely clarified.

Summary of ABU.

The natural history of ABU in different age groups and the risk of complications is doubtful, with the exception of ABU during
pregnancy and in early childhood. Whether the prognosis of ABU is affected by preceding or subsequent SBUs or not is also unknown. Furthermore, both in children and adults, (even with renal damage) and in the elderly any benefit of therapy of ABU has not been proved.

9.4. Posttherapy control.
Judging from the available literature, posttherapy bacteriuria controls of UTI in PHC is a routine of unproven and probably of no value and thus often unnecessary, at least in uncomplicated UTI in women. As long as symptoms are eradicated the risk of developing complications appears to be negligible in this large patient group. In Sweden an estimated one million PHC visits per year are due to urinary tract problems. About 600 000 of these visits concern suspected acute UTI of which about 2/3 yield significant bacteriuria. Today most of the episodes treated for bacteriuria are subject to posttherapy bacteriuria control. Women with uncomplicated UTI comprise a dominating group accounting for perhaps 200 000 control visits, in which UTI symptoms have disappeared. As the total cost of a visit to a PHC doctor in Sweden is about 500 Swedish Crowns (SEK), omitting these control visits would result in yearly national savings of 100 million SEK (about 20 million US dollars) Probably, posttherapy controls in other patient groups with abating UTI symptoms after therapy could also be abandoned with even greater savings.

9.5. Management of UTI patients in PHC.
Based on a study of the literature, development work in connection with preparing county UTI guidelines and my own studies, I regard the following management of UTI patients to be optimal in PHC.

9.5.1. Patient history and physical examination.
Diagnosis of UTI is based on three components, namely: patient history, physical examination and diagnosis of bacteriuria. The patient's history is important and as an aid a questionnaire can be used, preferably also by the staff. Besides symptoms and their duration the risk of upper UTI and other complicating factors
ought to be estimated. Patients with presumed uncomplicated lower
SBU need not be closer examined as long as they are instructed to
return in the event of clinical failure. If symptoms persist but
are not dramatically worse, the patient should wait at least five
days after start of therapy before returning for renewed
evaluation. Then palpation of the abdomen ought to be performed
and preferably gynecological examination or palpation of the
prostate to exclude other underlying causes of the failure than
ineffective antibiotics.

9.5.2. Collection of urine specimens.
The collection of urine specimens is important and clean voided
midstream urine without prewashing the periurethral region after
prolonged bladder incubation time, preferably morning urine, is
recommended. To increase the possibility to obtain a
representative urine sample, both verbal information by the staff
or doctor and written instructions should be given. Similar
written instructions should also be posted on the wall in the
surgery toilet.

9.5.3. Laboratory investigation.
In the management of patients with presumed UTI a simple but
accurate indicator of bacteriuria for office use is needed.
Furthermore, an estimation of lower or upper infection and
identification of certain risk groups should be performed.
According to our studies a diagnostic model combining nitrite
test, microscopy of urinary sediment and UricultR dipslide, with
GLC-classification, is satisfactory for diagnosis of bacteriuria
and also offers a proper basis for targeting of therapy. The role
of erythrocyte sedimentation rate, the pitressin test and assay
for C reactive protein in serum in the management of UTI patients
in PHC are not yet established and therefore not further dis-
cussed.

9.5.4. The need of urine culture.
Urine culture at a bacteriological laboratory should be used for
diagnosis of bacteriuria only in certain groups of patients and
situations, e.g.:
1. Presumed upper infection.
2. CAT and severe symptoms of infection, when washing or change of cathether have not helped, or in presumed urosepsis.
3. Pregnant women.
5. Therapeutic failure.
6. Repeatedly recurring UTI.
7. Known impaired renal function (e.g. chronic pyelonephritis) or kidney stones.
8. Known allergy towards at least two first choice drugs.

9.5.5. Choice of antibiotics.

As most of UTI episodes in PHC are uncomplicated and the risk of bacterial drug resistance is low, there are many antibiotic alternatives with satisfactory therapeutic outcome. Considering that new antibiotics are continuously introduced, and that there is an increasing knowledge of their clinical and ecological side effects, I avoid specifying optimal choices of therapy. In principle, each doctor ought to have at least two or three antibiotics as his first-hand choices of therapy to minimize antibiotic pressure on bacterial ecology. However, for certain bacteriological risk groups, such as non-coliforms which can be identified by Uricult\textsuperscript{R} (G-,L-), or staphylococi which often can be seen in urinary sediment, targeting of therapy is desirable.

In the choice of drugs, their influence on bacterial ecology, adverse reactions and costs need to be considered. Nitrofurantoin and sulphonamide are no longer recommended as first choice drugs and co-trimoxazole is a second choice therapy reserved for e.g. difficult to treat bacteria (non-coliforms) or complicated UTIs.

9.5.6. Duration of therapy.

The duration of therapy has been debated for a long time. Prolonged treatment (10-14 days) is recommended for eradication of infection in the upper urinary tract. In lower SBU good results with antibiotic courses shorter than the usual seven days have repeatedly been reported, including a drug trial of my own with nalidixic acid plus sodium citrate for 3-5 days (88). Even shorter
courses, e.g. single dose therapy, have been studied and appears promising in uncomplicated lower UTI (46). Further, assessment of single dose therapy in unselected populations has to be undertaken to firmly establish the effect of therapy in lower infections in patients with drug resistant bacteria or repeatedly recurrent infections. Moreover, single dose therapy does not seem to be accurate in upper SBU or otherwise complicated infections.

9.5.7. Posttherapy control.
A majority of posttherapy controls are probably unnecessary. At least in women treated for uncomplicated sporadic UTI whose symptoms are eradicated, the posttherapy control should be abandoned. As disappearance of symptoms often requires at least five days, as shown by us, bacteriuria control in suspected failure should be further postponed. In order to find both failures and early recurrent UTI, it is proposed that an optimal time for therapy control, if necessary at all, is three weeks posttherapy. However, this routine is based on the experience from therapy with sulphonamide for two months and perhaps not generally applicable after shorter therapy courses. In most patients ABU should probably not be searched for or be treated if found. Therefore, the question which patients should be controlled and when, needs to be further studied.

10. SUMMARY

A study of unselected and mainly uncomplicated UTI in PHC was performed at the Vännäs PHCC and 17 different PHCCs, respectively, in the county of Västerbotten, northern Sweden. The following results obtained and my conclusions can be summarized as follows:

- An annual UTI incidence of 2.3% was registered with a dominance of women (87%) and an increase with age (>10% in patients >90 years). The risk of recurrence was not correlated to sex and age with an average of 1.5 episodes per patient and year.
The clinical presentation of patients with uncomplicated UTI showed a dominance of acutely lower SBU episodes in 75%. The vast majority of episodes were symptomatic (92%) with urgency (77%) and dysuria (70%) as the most common symptoms. Urinary incontinence in the total patient material was reported in 35%. Loin pain was present in 88% of upper SBU but surprisingly also in 23% of lower SBU episodes. The patient's delay varied between the different PHCCs and patient categories and was surprisingly long with an average of eight days.

The bacteriological findings and patterns of drug resistance were associated more with the process of selecting the patients and their sex and age than with e.g. the patient's symptoms or time. E.coli always dominated as causative organism and contributed 70% of the unselected episodes not associated with CAT or INC and dominated even more in mainly uncomplicated UTI (77% in McPHC). S.saprophyticus was the second most common species in PHC (10% in unselected and 7% in uncomplicated UTI) but rarely occurred among in- and out-patients recorded at the bacteriological laboratory (1-2%). This organism was seen mainly in women patients with a peak in August (28%). S.saprophyticus was rarely complicated with therapeutic failures or recurrences in contrast to non-coliform bacteria. The average risk of drug resistance increased from 8% in uncomplicated to 17% for the average PHC patient and 36% among PHC patients with CAT or INC. Surprisingly, only a small increase of drug resistance was seen in early or repeated recurrence. Laboratory data showed a similar distribution of bacteria between 1973 and 1986 but a slight change in the pattern of drug resistance.

The effect of therapy on ecology in uncomplicated UTI was demonstrated by the tendency of E.coli episodes to be less frequent in failure than pretherapy or in early recurrence. In contrast, G- bacteria other than E.coli (Klebsiella, Proteus, Enterobacter and Citrobacter) tended to be more prevalent in failure and early recurrence than pretherapy.
S. saprophyticus was not seen in failure and rarely in early recurrence.

Eradication of UTI symptoms was reported in 2/3 of the bacteriologically cured episodes but also in 1/3 of failures at control 1-3 days posttherapy. Thus, symptoms only weakly reflect any bacteriological efficacy of UTI therapy. The bacteriological outcome of treatment was in general successful with an average of 8% failure and 12% early recurrence within one month posttherapy. The failure rate tended to be lower in patients with SBU (9%) than among asymptomatic patients (18%). No significant differences were observed between drugs in eradication of bacteriuria. Furthermore, outcome of therapy was the same whether the infecting bacteria were classified as sensitive or resistive *in vitro* to the drug given. Thus, in order to be of prognostic value for therapy in uncomplicated UTI, high-level breakpoints focusing more on peak urinary drug concentrations need to be studied.

Diagnosis by optimized microscopy of wet-stained urinary sediment showed a considerably higher sensitivity (97%) in symptomatic patients than the chemical tests nitrite and Uriglox\textsuperscript{R} (64 and 75%, respectively) but the specificity of sediment was low (39%). The efficacy of sediment diagnosis was higher in SBU compared to the chemical tests but Uricult\textsuperscript{R} and sediment were equal in sensitivity and efficacy. In mainly asymptomatic patients the efficacy was about 80% for all methods except for Uricult\textsuperscript{R} (87%). Overall, the sensitivity was unsatisfactorily low for nitrite and Uriglox\textsuperscript{R}, whereas their specificity was higher than that of urinary sediment. The total efficacy was lowest for nitrite (56%) and highest for Uricult\textsuperscript{R} (88%). The outcome of combinations of different tests in the total material was not better than of that Uricult\textsuperscript{R} alone. As the result of Uricult\textsuperscript{R} is not available until the following day, Uricult\textsuperscript{R} is not acceptable as the only diagnostic method. The combination of nitrite test, urinary sediment and Uricult\textsuperscript{R} dipslide with GLC
classification of bacteria seem to represent the optimal diagnostic model for UTI in PHC.

The prediction of bacterial drug resistance using Sensicult\textsuperscript{R} in unselected UTI was low (50%) whereas its predictive value for drug sensitivity was satisfactory (93%). The use of Sensicult\textsuperscript{R} for targeting of therapy resulted in an average risk of 7% to prescribe drugs to which the organisms were resistant. The corresponding risk using Uricult\textsuperscript{R} and GLC classification of bacteria and local guidelines for therapy of different bacterial groups was only 6%. The latter method is also simple, offers qualitative and thus, prognostic information but can be further improved.

On the basis of the results of this thesis, the following optimal management of UTI patients in PHC can be proposed:

Clean voided midstream urine, without prewashing the periurethral region after prolonged bladder incubation time, preferably morning urine, is recommended for collection of urine specimens. The use of a questionnaire as an aid is valuable to improve the patient's history. The combination of nitrite test, urinary sediment and Uricult\textsuperscript{R} yields the optimal diagnostic outcome. GLC classification of bacteriuria offers a proper basis for targeting of therapy. In choice of antibiotics, the influence on bacterial ecology, adverse reactions and cost benefit are important factors to consider. The duration of therapy of lower SBU is most commonly seven days but shorter courses, e.g. 3-5 days, seem to give a satisfactory outcome. Single dose therapy appears promising but further assessment is needed to firmly establish its efficacy. Probably, many posttherapy controls are unnecessary, at least in women with sporadic uncomplicated UTI with symptoms eradicated, and the abandoning of these controls would lead to large savings. The optimal point of time for posttherapy control, if necessary at all, is proposed to be 3-4 weeks after therapy.
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Table I. Outcome of methods to diagnose bacteriuria.

<table>
<thead>
<tr>
<th>Diagnostic methods</th>
<th>Patient Categorya (%)</th>
<th>I+II (n=209)</th>
<th>III+IV (n=225)</th>
<th>All visits (n=434)</th>
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</thead>
<tbody>
<tr>
<td>Sediment</td>
<td></td>
<td>97</td>
<td>70</td>
<td>88</td>
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<tr>
<td>Nitrite</td>
<td></td>
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<tr>
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<td>UricultR</td>
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<td>90</td>
<td>87</td>
<td>88</td>
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</table>

a I lower symptomatic control, II upper symptomatic UTI, III post-treatment control, IV miscellaneous UTI. Patients with CAT or INC excluded.
Table II. Outcome of combinations of methods to diagnose bacteriuria.

<table>
<thead>
<tr>
<th>Diagnostic model</th>
<th>I+II (n=209)</th>
<th>III+IV (n=225)</th>
<th>All visits (n=434)</th>
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<td>Day</td>
<td>Sens.</td>
<td>Spec.</td>
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<td>2</td>
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<td>93</td>
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<td>97</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>99</td>
<td>79</td>
</tr>
<tr>
<td>C. Nitrite+Sediment + Uricult&lt;sup&gt;R&lt;/sup&gt;</td>
<td>1</td>
<td>98</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>99</td>
<td>79</td>
</tr>
<tr>
<td>D. Nitrite+Uriglox&lt;sup&gt;R&lt;/sup&gt;+Sediment + Uricult&lt;sup&gt;R&lt;/sup&gt;</td>
<td>1</td>
<td>98</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>99</td>
<td>76</td>
</tr>
<tr>
<td>E. Nitrite+Uriglox&lt;sup&gt;R&lt;/sup&gt; + Uricult&lt;sup&gt;R&lt;/sup&gt;</td>
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<td>83</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>96</td>
<td>91</td>
</tr>
</tbody>
</table>

<sup>a</sup> I lower symptomatic UTI, II upper symptomatic UTI, III post-treatment control, IV miscellaneous UTI. Patients with CAT or INC excluded.

<sup>b</sup> Sens. sensitivity

<sup>c</sup> Spec. specificity
13. REFERENCES


