Asymptomatic Bacteriuria in the Elderly

Nils Rodhe
Dissertation presented at Uppsala University to be publicly examined in Föreläsningssalen, Falu lasarett, Falun, Saturday, October 25, 2008 at 13:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract

The aim of this thesis was to explore the features of asymptomatic bacteriuria (ASB) in elderly people living in the community, and to seek diagnostic tools to discriminate between ASB and symptomatic urinary tract infection (UTI).

All men and women aged 80 and over living in an urban district of Falun, Sweden, were invited to participate. Urine samples were obtained together with information on symptoms and on health indicators. The same cohort was surveyed again after 6 and 18 months. Urinary cytokines were analysed in 16 patients with UTI, in 24 subjects with ASB and in 20 negative controls.

ASB occurred at baseline in 19.0% of women and 9.4% of men, and was found at least once in 36.9% of women and in 20.2% of men. ASB in women was associated with reduced mobility and urge urinary incontinence. Of those with ASB at baseline, 60% still had bacteriuria at 6 and 18 months, but among those with repeated findings of ASB with E. coli, only 40% had the same bacterial strain after 18 months. In women, the risk of developing a UTI within 24 months was higher among those with ASB at baseline than in those without. Urinary levels of cytokines (CXCL1, CXCL8 and IL-6) and leukocyte esterase were higher in patients with UTI than in patients with ASB.

There is convincing evidence that ASB is harmless and should not be treated with antibiotics. However, such treatment is still often given, thereby unnecessarily contributing to the increased number of bacteria resistant to common antibiotics. This study confirms the high prevalence of ASB in elderly people living in the community. In order not to be misled by a urinary test showing bacteria, it is important to restrict urinary testing for bacteria to patients where there is a suspicion of UTI. In elderly patients with diffuse symptoms or in patients who are unable to communicate their symptoms, further diagnostic help could possibly be obtained by evaluating the urinary levels of leukocyte esterase and/or IL-6.

Keywords: family practice, aged 80 and over, E. coli, bacteriuria, urinary tract infections, urinary incontinence, leukocyte esterase, cytokines

Nils Rodhe, Department of Public Health and Caring Sciences, Uppsala Science Park, Uppsala University, SE-75183 Uppsala, Sweden

© Nils Rodhe 2008

ISSN 1651-6206
ISBN 978-91-554-7285-6
urn:nbn:se:uu:diva-9288 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-9288)
List of papers

This thesis is based upon the following papers:


II  Rodhe N, Englund L, Mölstad S, Samuelsson E. Bacteriuria is associated with urge urinary incontinence in older women. **Scand J Prim Health Care.** 2008 Mar;26:35-9.**


IV  Rodhe N, Löfgren S, Strindhall J, Matussek A, Mölstad S. Cytokines in urine in elderly subjects with symptomatic and asymptomatic urinary tract infections. (Submitted)

Reproduced with permission from the publishers.

* Oxford University Press
** Taylor & Francis Group
Cover photo taken by Leonore Wide
Contents

Introduction.....................................................................................................9
  Antibiotic treatment and antibiotic resistance ............................................9
  Urinary tract infection ..............................................................................10
    Historical remarks ................................................................................10
    Diagnosis, Kass’ criteria .......................................................................12
    Epidemiology .......................................................................................13
    Clinical presentations ..........................................................................13
Asymptomatic bacteriuria ........................................................................14
  Definition .............................................................................................14
  Prevalence ............................................................................................14
  Clinical importance ..............................................................................15
  Bacteriology .........................................................................................18
Symptomatic or asymptomatic bacteriuria? .............................................19
  Current knowledge ...............................................................................19
  Diagnostic tools ...................................................................................21
  Towards better diagnostics ..................................................................21
Aims ..............................................................................................................22

Subjects and methods....................................................................................23
  Design ......................................................................................................23
  Setting ......................................................................................................23
  Subjects ....................................................................................................23
  Methods ....................................................................................................26
    Research procedures ............................................................................26
    Questionnaire (Papers I-III) .................................................................26
    Laboratory methods (Papers I-IV) ............................................................27
Statistics ...................................................................................................29
Ethics ..........................................................................................................29

Results...........................................................................................................31
  Characteristics of the study population (Papers I-III) .........................31
  Prevalence of asymptomatic bacteriuria (Papers I-III)............................31
  Microbiology (Paper I) .........................................................................33
  Factors associated to asymptomatic bacteriuria (Paper I) ....................33
  Urinary incontinence and asymptomatic bacteriuria (Paper II) ............35
  Incidence of symptomatic urinary tract infection (Paper III) ...............37
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary diagnostics (Paper IV)</td>
<td>38</td>
</tr>
<tr>
<td>Discussion</td>
<td>42</td>
</tr>
<tr>
<td>Methodological considerations</td>
<td>42</td>
</tr>
<tr>
<td>Prevalence</td>
<td>44</td>
</tr>
<tr>
<td>How to define asymptomatic bacteriuria?</td>
<td>45</td>
</tr>
<tr>
<td>Associated factors</td>
<td>45</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>46</td>
</tr>
<tr>
<td>Incidence of symptomatic urinary tract infection</td>
<td>47</td>
</tr>
<tr>
<td>Urinary diagnostics in asymptomatic bacteriuria and acute cystitis</td>
<td>48</td>
</tr>
<tr>
<td>Clinical implications</td>
<td>51</td>
</tr>
<tr>
<td>Conclusions</td>
<td>53</td>
</tr>
<tr>
<td>Sammanfattning (in Swedish)</td>
<td>54</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>59</td>
</tr>
<tr>
<td>References</td>
<td>61</td>
</tr>
</tbody>
</table>
Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADL</td>
<td>Activities of daily living</td>
</tr>
<tr>
<td>ASB</td>
<td>Asymptomatic bacteriuria</td>
</tr>
<tr>
<td>CCL</td>
<td>- A group of cytokines</td>
</tr>
<tr>
<td>cfu</td>
<td>Colony-forming unit</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CXCL</td>
<td>- A group of cytokines</td>
</tr>
<tr>
<td>E. coli</td>
<td>Escherichia coli</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>ESBL</td>
<td>Extended-spectrum beta-lactamase</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin- a group of cytokines</td>
</tr>
<tr>
<td>LUTI</td>
<td>Lower urinary tract infection</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-mental state examination</td>
</tr>
<tr>
<td>ns</td>
<td>Not statistically significant</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>ROC curve</td>
<td>Receiver operating characteristic curve</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumor necrosis factor- a cytokine</td>
</tr>
<tr>
<td>UPEC</td>
<td>Uropathogenic Escherichia coli</td>
</tr>
<tr>
<td>UTI</td>
<td>Urinary tract infection</td>
</tr>
</tbody>
</table>
Definitions

*Bacteriuria:* Bacteria are found in the urine, irrespective if there are symptoms of urinary tract infection or not.

*Asymptomatic bacteriuria:* Bacteria are found in the urine in a subject without symptoms of urinary tract infection.

*Urinary tract infection:* An infection localised somewhere in the urinary tract. May include asymptomatic bacteriuria but mostly only symptomatic infections.

*Symptomatic urinary tract infection:* In the text sometimes used to stress the presence of symptoms caused by the infection, as opposed to asymptomatic bacteriuria.

*Acute cystitis (lower urinary tract infection):* A symptomatic infection localised to the lower urinary tract, i.e. urethra and urinary bladder.

*Pyelonephritis:* An infection localised to the kidney and the upper part of the urinary tract.

*Leukocyturia:* Leukocytes (white blood cells) are found in the urine.
Introduction

Antibiotic treatment and antibiotic resistance

Increasing rates of antibiotic resistance all over the world, owing to over-use of antibiotics, is recognised as a great threat to our future capacity to treat infections. In most European countries there are increasing rates of E. coli resistant to fluoroquinolones, a type of antibiotics frequently used for treatment of urinary tract infections. In Sweden the rates are still low compared with many other countries, but they are increasing. One type of antibiotic resistance of special interest is that found in extended-spectrum beta-lactamase (ESBL)-producing bacteria. These bacteria, mostly E. coli and Klebsiella, are resistant to most beta-lactam antibiotics, including penicillin and cephalosporins. In addition, ESBL-producing bacteria are often, through other mechanisms, resistant to many other classes of antibiotics such as fluoroquinolones, trimetoprim and nitrofurantoin. There is an association between high antibiotic use, especially cephalosporins, and the development of ESBL resistance (1). Patients infected with these bacteria may be difficult to treat with common antibiotics; a simple urinary tract infection may require hospitalisation for parenteral antibiotic treatment.

There are remarkable differences in antibiotic prescription patterns between different parts of Sweden. These marked differences, almost 50%, are seen repeatedly in annual statistics (2). There are also considerable variations in antibiotic prescription patterns between different health care centres and among individual physicians (3). These differences are probably more attributable to “cultural” differences among prescribing physicians and different health care seeking-behaviours in the general population than differences in morbidity (4). These facts imply that there is probably a potential for a reduction of antibiotic use without a risk of increased morbidity.

The use of antibiotics has a peak in early infancy, and then there is a decrease from adolescence through middle age. From about 60 years of age the use again increases and more and more of the antibiotics are then prescribed for urinary tract infections. Half of the antibiotics prescribed for patients ages 80 and over, in Sweden, consists of antibiotics commonly used to treat urinary tract infections (nitrofurantoin, pivmecillinam, trimethoprim, trimethoprim with sulphonamides and fluoroquinolones) (2) (Figure1).
Figure 1. Number of antibiotic prescriptions per 1,000 inhabitants per year in different age groups, Sweden 2007 (2).

In elderly people living in institutions, antibiotics for urinary tract infections account for more than half of all antibiotics prescribed (5).

The link between high use of antibiotics, especially in the elderly, and increasing rates of antibiotic resistance, stresses the importance of limiting this use to those occasions when a clear benefit for the patient can be expected.

Urinary tract infection

Historical remarks

Curtis Nickel made an historical review of urinary tract infections in 2005; (6, 7) some key points are presented below: From ancient China (3000-2000 B.C.) there are texts discussing the inspection of urine as an important diagnostic tool. In classical Greece, Hippocrates gave detailed descriptions of medical conditions in the kidneys and urinary tracts, and in ancient Rome Celcius provided a detailed explanation of urinary catheterisation using bronze catheters. Aetius from Amida (Middle East, 500 A.D.) described urine examination (uroscopy) for clarity, colour, smell, cloudiness and presence of sand and/or blood. It was then practiced in Europe for hundreds
of years, until the time of the Renaissance. Avicenna (Middle East, 1000 A.D.) described, in Canon Medicæ, many kidney disorders as well as disorders of the bladder such as abscesses, dysuria, retention and incontinence.

In the Renaissance (approximately 1500 to 1750), there were advances in anatomy and surgery but it was not until the 19th century that an understanding of disease aetiology emerged. As for infectious diseases, Dutch microscopist Antony van Leeuwenhoek in the 17th century had managed to see small microorganisms, bacteria, but it was not until the mid-19th century that the aetiology of infectious disease began to be clarified.

Ignaz Semmelweiss from Hungary then showed that childbed fever was caused by a contagium and that the outbreak of this disease could be prevented by hygienic measures. English surgeon Joseph Lister successfully introduced chemical antisepsis prior to surgery and, in the same period, Louis Pasteur showed that microorganisms caused fermentative and putridity processes.

Further steps towards an understanding of infectious diseases were taken in Germany by Robert Koch in the 1870s, who discovered the bacteria causing anthrax, cholera and tuberculosis. Koch developed methods to refine individual bacterial species, and formulated the famous Koch’s postulates, four criteria designed to establish a causal relationship between a microbe and a disease: The microbe must be found in all subjects suffering from the disease, the microbe must be isolated from a diseased subject and grown in pure culture, the cultured microorganism must cause disease when introduced into a healthy subject and the microbe must be reisolated from the now diseased subject and identified as identical to the original specific causative agent. These postulates were important in the development of an understanding of infectious diseases, although they are now considered an insufficient model. It was early recognised that the occurrence of asymptomatic carriernship of bacteria necessitated a revision of the postulates, and modern understanding of genetics and cell biology reveals the cause of infections to be too complex to be explained by Koch’s postulates (8).

The intestinal bacterium Escherichia coli (E. coli), the most common and important bacterial species in urinary tract infections, was discovered in 1885 by German paediatrician Theodor Escherich, and later named after him.

Despite the discovery of bacteria as the cause of infectious diseases, it took many years for it to be understood that bacteria could cause diseases in the urinary tract. Around the turn of the twentieth century antiseptics were coming into use for urinary tract infections, but more successful treatments were not available until the introduction of sulphanilamide in 1937. Sulphanilamide was effective for treatment of infections in the urinary tract but was unfortunately associated with serious side effects, substantially
reducing its therapeutic usefulness. Nitrofurantoin, still in first line use today, was introduced as early as 1953 as a safe and effective treatment for uncomplicated urinary tract infections. In 1962, nalidixic acid, a prototype to the fluoroquinolones, was introduced. Trimetoprim and β-lactams (ampicillin, mecillinam and cephalosporins), effective for treatment of urinary tract infections, came in to use in the 1970s (6, 7).

Some decades ago there was widespread conviction concerning the danger of urinary tract infections. A finding of bacteria in the urine was always regarded as abnormal, even in the absence of symptoms. There was believed to be a substantial risk for the development of a subsequent urinary tract infection of a more severe degree, culminating in chronic pyelonephritis and uraemia. This concept of gradual worsening has now been largely disproved, but it was also supported at the time by drug companies marketing newly developed antibiotics (9), and this concept is probably still an important reason for the misuse of antibiotics.

Diagnosis, Kass’ criteria

In the 1950s, American microbiologist Edward Kass carried out classical studies on the interpretation of quantitative urinary cultures in relation to the diagnosing of urinary tract infections in an attempt to sort out those cultures that were not truly positive but only contaminations. Kass studied women with pyelonephritis and women without symptoms of urinary tract infection. In women with pyelonephritis, 95% had a urinary bacterial count of \( \geq 1 \times 10^8 \) colony forming units/litre (cfu/L) \( (\geq 1 \times 10^5 \) cfu/ml) while most asymptomatic women had no bacterial growth or a bacterial count of \(< 1 \times 10^6 \) cfu/L even in repeated cultures, giving a dividing line between the true bacteriuria in pyelonephritis and contaminated samples in asymptomatic subjects. Kass’ findings resulted in the concept of significant bacteriuria \( (\geq 1 \times 10^8 \) cfu/L), as a diagnostic indication of urinary tract infection; smaller bacterial counts were regarded as contaminations (Kass’ criteria). However, some of the asymptomatic women were also found to have a urinary bacterial count of \( \geq 1 \times 10^8 \) cfu/L, and this result was verified in repeated, consecutive samples from the same individuals, confirming the presence of asymptomatic bacteriuria (10, 11).

A major problem with these criteria was that they were based only on findings in patients with pyelonephritis and asymptomatic subjects, while patients with cystitis, the most common type of urinary tract infection, were not included. In the 1970s it was found that staphylococcus saprophyticus could cause acute cystitis despite lower bacterial counts (12), and it has later been shown that lower bacterial counts are a common finding in acute cystitis, mostly in those infections caused by primary pathogenic bacteria (bacteria with the capacity to infect normal urinary tracts, mostly E. coli and Staphylococcus saprophyticus) (13).
Epidemiology

Urinary tract infections are one of the most common bacterial infections in humans. They are common among sexually active women and, except in the first months of life, more common in women than in men (14). In adult women the incidence of urinary tract infection in 12 months is 10.8-13.3% and the lifetime risk of urinary tract infection in women is estimated at 50-60% (15, 16). The highest incidence rate is seen in women aged about 20, after which there is a slow decrease toward middle age and then a gradual increase from about 65 years of age (15). In young men the 12-month incidence of urinary tract infection is only about 1%, but increases from about 65 years of age to 7-8% above 80 years (17). However, in old age the population of women is markedly larger than that of men. Consequently, women account for a proportionally larger proportion of the urinary tract infections treated in the health care system. This fact also in part explains studies on women being more common than on men, resulting in inferior knowledge about men and urinary tract infections.

Incidence figures are mostly based on diagnoses from the health care system and/or number of antibiotic prescriptions. As urinary tract infections are often transient and self-healing, the real incidence in younger populations is probably higher. In contrast, the high occurrence of asymptomatic bacteriuria (see below) may result in over-estimation of the real incidence of symptomatic urinary tract infections in the elderly.

Recurrent urinary tract infections are common, and the majority of people having urinary tract infections have a history of two or more such infections in their lifetimes (16). There are subpopulations that are more prone to developing urinary tract infections, such as pregnant women (18), patients with catheters (19), and patients with spinal cord injuries (20), diabetes (21), multiple sclerosis (22) or HIV-infection (23).

Among non-institutionalised elderly people, genitourinary infections are the second most common infections (after respiratory tract infections), accounting for nearly 25% of all infections (24).

Clinical presentations

The most common presentation of symptomatic urinary tract infection is acute cystitis, which constitutes approximately 90% of the episodes of urinary tract infections (25). Acute cystitis is an infection engaging the lower urinary tract, resulting in an inflammatory response in the bladder and urethra, causing leukocyturia and focal symptoms such as dysuria (painful urination), urgency (sudden compelling desire to urinate) and frequency (frequent urination). Generalised symptoms of feeling out of sorts are also common in acute cystitis (26). The diagnosis in women is based primarily on typical symptoms, and a urinary test is in most cases unnecessary (27).
Although the symptoms of acute cystitis can be very troublesome, it is generally innocuous and self-healing, and the primary reason for antibiotic treatment is to shorten the time with symptoms. Untreated acute cystitis only occasionally progresses to pyelonephritis (28, 29).

In *acute pyelonephritis* the infection involves the kidneys and causes focal symptoms such as flank pain and signs of systemic inflammation with fever and general malaise. In pyelonephritis there are sometimes, but not always, concomitant symptoms from the lower urinary tract. Focal symptoms from the upper urinary tract are sometimes absent, especially among elderly patients, and the only symptom may be fever and general malaise. Bacteraemia (occurrence of bacteria in the blood) is found in 20-30% of patients with febrile urinary tract infections (30).

Signs and symptoms of urinary tract infection in men are similar to those in women. Major predisposing factors are genitourinary instrumentation and urinary obstruction due to prostatic hypertrophy. There is often presumed to be an infectious focus in the prostate, which can make the infection more complicated to treat (31).

In addition to these clinical presentations of symptomatic urinary tract infections, there is, as mentioned above, sometimes bacteriuria (bacteria in the urine) in a subject with no symptoms of a urinary tract infection; *asymptomatic bacteriuria*.

Asymptomatic bacteriuria

**Definition**

According to the most common definition, asymptomatic bacteriuria occurs in a woman when, without symptoms of urinary tract infection, in two voided consecutive urine samples, she shows growth of the same bacterial strain with a count of $\geq 10^8$ cfu/L (32).

In men, there is support for the use of a definition of only one voided sample with growth of $\geq 10^8$ cfu/L to confirm asymptomatic bacteriuria (33, 34). This applies even for men using a freshly applied condom catheter (35, 36).

A urine sample obtained by urethral catheterisation showing one bacterial species with a count $\geq 10^5$ cfu/L identifies asymptomatic bacteriuria in both women and men (37).

**Prevalence**

The prevalence of asymptomatic bacteriuria in schoolgirls is about 1%, in women up to 50 years, including pregnant women, 1-5%. From about 50
years of age the prevalence increases from 3 to 9% to around 20% in women aged 80 and over (38, 39). Asymptomatic bacteriuria, like symptomatic urinary tract infections, is more prevalent among sexually active women (40, 41).

Asymptomatic bacteriuria is uncommon in young men (<1%) but the prevalence increases from the age of 60 up to 5-10% in men aged 80 and over (31, 39).

In the elderly living in institutions asymptomatic bacteriuria is very common. In women, the prevalence is found to be 25-50% and in men 15-40% (42, 43). These figures vary depending on differences in populations studied, and whether one or two cultures were required for diagnosing asymptomatic bacteriuria. In women and men who have chronic indwelling urinary catheters, the prevalence of bacteriuria is almost 100% (44).

In women with diabetes the prevalence of asymptomatic bacteriuria is higher than in age-matched non-diabetic women, while diabetic and non-diabetic men seems to have asymptomatic bacteriuria to the same extent (45, 46).

Although asymptomatic bacteriuria is often transient in young and middle-aged women (40), as in elderly women and men (47-49), a considerable proportion of individuals have bacteriuria repeatedly. In diabetic women almost 20% of women with asymptomatic bacteriuria at baseline remained bacteriuric with the same infecting species throughout an observation period of three years (50). In young girls, persistent asymptomatic bacteriuria (E. coli) was mostly attributable to infection with the same bacterial strain, and a change of strain was often a result of antibiotic treatment (51).

Clinical importance

Children
Asymptomatic bacteriuria in children is well investigated. It may persist for many years without evidence of any adverse outcomes (52). In children there are in fact indications that asymptomatic bacteriuria may prevent infections with more virulent bacterial strains, and that antibiotic treatment may increase the risk of symptomatic urinary tract infections (52). Therefore, screening for, and treatment of asymptomatic bacteriuria in children is not recommended.

Young and middle-aged women
The prevalence of asymptomatic bacteriuria in young and middle-aged women increases with age. Known risk factors are, like for symptomatic urinary tract infections, sexual intercourse and use of diaphragm or spermicides as birth control (40, 53). The prevalence of asymptomatic
bacteriuria in sexually active women is 3-5 times higher than in women in the same age groups who are not sexually active (41). In these age groups, women who where found to have asymptomatic bacteriuria had an increased risk of developing a symptomatic urinary tract infection within one week (40). There was also, in long-term follow-up (15 years), an increased risk of developing symptomatic urinary tract infections as compared with women without bacteriuria (54).

In a Swedish study, 1,462 women aged 38-60 at entrance were followed for 24 years. Those with initial bacteriuria (4%) were more likely to have bacteriuria at 6 and 12 year follow-up. Mortality and rate of kidney disease were similar for those with and without bacteriuria after 24 years (38).

Antimicrobial treatment of women with asymptomatic bacteriuria (20-65 years, randomised placebo-controlled study) resulted in temporary cure in the treatment group but after one year the prevalence of bacteriuria was the same in the antibiotic and placebo groups, and equal proportions of the two groups were identified with symptomatic urinary tract infections during the year of follow-up (55).

In conclusion, young and middle-aged women with asymptomatic bacteriuria more often experienced symptomatic urinary tract infections and recurrent episodes of asymptomatic bacteriuria. However, antimicrobial treatment did not decrease the number of symptomatic infections, and asymptomatic bacteriuria was not associated with any negative long-term side effects. Thus, asymptomatic bacteriuria in young and middle-aged women need not be screened for or treated with antibiotics.

**Pregnant women**

Pregnant women with untreated asymptomatic bacteriuria are at 20-30 times higher risk of developing pyelonephritis later in pregnancy than women without bacteriuria (18, 32). These women also may have an increased risk for premature delivery and of having babies with low birthweight. Whether this is an independent risk or associated with the development of pyelonephritis is controversial (56). Antibiotic treatment is effective in reducing the high rate of pyelonephritis in pregnancy (56) and thus screening for and treatment of asymptomatic bacteriuria in pregnancy is warranted.

**Elderly living in the community**

There are several long-term studies including elderly people where the effects of asymptomatic bacteriuria on morbidity and mortality have been evaluated without finding any adverse outcomes (57, 58) (men and women), (38) (women).

A randomised placebo-controlled clinical trial including ambulatory elderly women reported a lower prevalence of bacteriuria after six months but there was no significant difference in the number of symptomatic urinary tract infections in the same period (59). Thus, screening for and treatment of
asymptomatic bacteriuria in elderly people living in the community is not warranted.

**Institutionalised elderly**

Asymptomatic bacteriuria is very common among the institutionalised elderly. The occurrence of asymptomatic bacteriuria in this population has been shown to be associated with dementia and impaired functional status, including incontinence of urine and bowel (60, 61).

An important cause of bacteriuria in this group is thought to be impaired bladder voiding owing to degenerative or vascular diseases, and in men urinary obstruction secondary to prostatic hypertrophy and even chronic infective prostatitis (39). However, the causality is not fully clarified; in one study no association was found between residual urine volume and bacteriuria in elderly institutionalised men and women (62) while in another study on younger, non-institutionalised men referred for prostate evaluation but without symptoms of urinary tract infection, there was an increased risk of bacteriuria when post-void residual volume exceeded 180 ml (63).

In one study on institutionalised elderly women, higher mortality was found in subjects with bacteriuria than in those without (64). However, later studies have failed to reveal any association between bacteriuria and mortality in men (61) or women (60). In the latter study, the most important predictors for mortality were age and self-rated health.

Antibiotic treatment for asymptomatic bacteriuria in this population did not affect mortality in women (60) or men (65), did not decrease the numbers of symptomatic urinary tract infections (66), did not reduce chronic urogenital symptoms (66-68), and did not positively affect physical and mental functioning (69). On the contrary, antibiotic treatment gave adverse effects and an increase in the number of bacteria resistant to antibiotics (66).

Most studies on treatment of asymptomatic bacteriuria in elderly populations refer to women alone (59, 60, 66, 68) or to women and men, but not separated (59, 60, 66-70). There is only one study of men only (65), and it gives support to the same non-treatment approach in men as in women. Judging by the above-mentioned studies, it is obvious that treatment of asymptomatic bacteriuria in the elderly living in institutions is of no benefit.

**Diabetes**

Women with diabetes have an increased risk of developing both asymptomatic bacteriuria and symptomatic urinary tract infections, and the symptomatic infections tend to be more severe than in non-diabetic subjects (71). In a 14-year follow-up comparing 53 diabetic women with and 54 without bacteriuria, mortality and the rate of pyelonephritis was the same in the two groups and there were no significant differences in the progress of creatinine elevations or increase in blood pressure (72). Similar results were found in a prospective study on 644 women with diabetes followed for 6
years (73). Adjusted for age and diabetes duration there were no detectable differences in the decline in renal function or the development of hypertension, either in type 1 or in type 2 diabetes. Furthermore, no differences in secondary diabetic complications between diabetic patients with and without bacteriuria were demonstrated (74).

This was confirmed in a randomised trial comparing antibiotic treatment with no treatment for asymptomatic bacteriuria in women with diabetes, followed for up to 3 years (75). Antibiotics did not reduce the frequency of symptomatic urinary tract infections or the progression of diabetic complications such as nephropathy compared to patients where the bacteriuria was left without antibiotic treatment. These findings indicate that there is no benefit in treating asymptomatic bacteriuria in patients with diabetes.

Patients with spinal cord injuries
The prevalence of bacteriuria in patients with spinal cord injuries is high (76), and there is nothing to be gained by antibiotic treatment in asymptomatic subjects (77).

In connection with urologic interventions
Men with bacteriuria exposed to urological interventions with bleeding of the mucosa have a higher risk of developing bacteraemia and sepsis. Antibiotic treatment before the intervention can have preventive effects (78).

Patients with long-term indwelling urethral catheters
Almost 100% of patients with long-term indwelling urethral catheters develop bacteriuria, which is asymptomatic in most cases (44). Antibiotic treatment of this bacteriuria is of no benefit and increases the risk of reinfection with resistant organisms (79).

Bacteriology
E. coli are found in both asymptomatic bacteriuria, and in symptomatic urinary tract infections. They are the most commonly isolated species (38), and thereby the most investigated. In asymptomatic bacteriuria they seem to harbour or express fewer virulence factors than in symptomatic infections (80, 81). The bacteria in asymptomatic bacteriuria surviving in the urinary tract have to resist removal by the urinary flow without causing any substantial local host response, in contrast to the bacteria causing symptomatic urinary tract infections. Several studies have been conducted to determine the properties characterising those E. coli occurring in asymptomatic bacteriuria. Some strains of E. coli occurring in asymptomatic bacteriuria had a higher growth rate in urine (82) and were better biofilm formers than strains causing symptomatic urinary tract infections (83).
Actually, E. coli causing asymptomatic bacteriuria may help to prevent infections with more virulent bacteria, so deliberate colonisation with such strains is proposed as a non-antibiotic treatment alternative in recurrent urinary tract infections (84).

In elderly women, E. coli still accounts for 60-80% (85, 86) of isolates in asymptomatic bacteriuria. Other bacterial species occurring are Klebsiella pneumoniae, coagualase-negative staphylococci, Streptococcus group B and enterococci. In institutionalised women, the proportion of E. coli is only 50-60% (66) and Klebsiella pneumoniae, enterococci and Proteus mirabilis occurs more frequently (42). In institutionalised men with asymptomatic bacteriuria Proteus mirabilis is even more frequent than E. coli (65). The bacterial flora in the institutionalised elderly is often polymicrobial, and bacteria with antibiotic resistance are more common owing to repeated courses of antibiotics and transfer of organisms between patients (42). In women and men with long-term indwelling catheters there is usually polymicrobial urinary growth including Pseudomonas aeruginosa (42).

Symptomatic or asymptomatic bacteriuria?

Current knowledge

In spite of existing evidence that asymptomatic bacteriuria should not be treated with antibiotics other than in pregnant women and in men prior to urological interventions (32, 87), antibiotics are frequently prescribed in the elderly without symptoms of urinary tract infections or with only vague symptoms (88, 89). This may in part be due to the difficulty in interpreting a finding of bacteriuria in a patient with a diffuse symptomatology or who is not capable of communicating her/his subjective concerns, owing to cognitive impairment or a weak state of health.

Elderly patients with pyelonephritis may have fever, confusion and even chest symptoms with or without dysuria or other focal symptoms from the urinary tract (90, 91). Women with cystitis also often have general symptoms of being “out of sorts”, such as feeling unwell, weak and tired (26). However, the links between general, vague symptoms, symptomatic urinary tract infection and asymptomatic bacteriuria in the elderly are very unclear.

A Canadian study from an emergency department identified 100 elderly patients with general symptoms (acute confusion, weakness or fever) but no apparent urinary or other focal symptoms, and 100 elderly patient controls with non-infectious complaints. The aim was to evaluate a urinary reagent strip testing for nitrite and leukocyte esterase and compare it with urinary cultures, diagnosing urinary tract infection. The reagent strip proved to be a poor instrument for identifying patients with a positive urinary culture, and
the rate of positive urinary cultures was only slightly higher in patients with
general but no focal symptoms than in patient controls “suggesting that
many positive cultures in elderly patients with non-focal systemic symptoms
are false-positive tests reflecting asymptomatic bacteriuria and no urinary
tract infections” (92).

In another study from Canada, episodes of fever in 187 residents of two
long-term care institutions were identified prospectively. Bacteriuria was
found in 40% (cases without indwelling catheter). Of the 372 episodes, 7%
satisfied the clinical criteria for urinary tract infections and 8% satisfied the
serological criteria for urinary tract infections. Out of 132 episodes of fever
of unknown origin, 11% satisfied serological criteria for urinary tract
infection. The positive predictive value of bacteriuria for febrile urinary tract
infection identified by clinical criteria was 11%, and when identified by
serological criteria 12%. If only episodes identified clinically as urinary tract
infection or fever of unknown origin were considered, the positive predictive
value of bacteriuria for serologically identified febrile urinary tract infection
was 19% (93). In conclusion, urinary tract infections contributed to less than
10% of episodes of fever in this population, and bacteriuria was a poor
predictor of urinary tract infection.

Occurrence of general and local urinary symptoms was investigated in 72
ambulatory elderly subjects who were followed with repeated urinary
cultures. Symptoms were registered in the same individual on one occasion
when bacteriuria was present and on one occasion when there was no
bacteriuria. No differences in focal urinary symptoms (incontinence,
frequency, urgency, suprapubic pain) or general symptoms (eating or sleep
disturbances, fatigue, malaise, weakness) were found when bacteriuric
subjects were compared with their own status when they were not
bacteriuric. The authors concluded that bacteriuria without dysuria in the
elderly seems to be asymptomatic (94).

These studies illustrate the difficulties in differentiating between
asymptomatic bacteriuria and symptomatic urinary tract infection in the
elderly with vague symptoms. Bacteriuria in a patient with fever, as an
isolated symptom, was a poor predictor of urinary tract infection. Other
general symptoms, such as eating disturbances, fatigue, malaise and
weakness, without focal urogenital symptoms are often regarded in clinical
practice as possible expressions of urinary tract infections when there is also
a finding of bacteriuria, and they are consequently treated with antibiotics.
However, there is no evidence supporting this, and given the high prevalence
of asymptomatic bacteriuria in elderly populations there is an obvious risk
that the finding of bacteriuria is just an insignificant coincidence (89).
Diagnostic tools

How can we differentiate between symptomatic urinary tract infection and asymptomatic bacteriuria? The first and most important step is the clinical evaluation. Is there a previous history of urinary tract infection? Is there new onset of symptoms typical of a urinary tract infection such as dysuria, urgency and frequent voiding? However, as mentioned above, it is often difficult to interpret clinical symptoms and signs in the elderly.

Urinary culture is of no use as it shows bacterial growth in both asymptomatic bacteriuria and symptomatic urinary tract infection. The same applies for urinary nitrite, which is a chemical marker for bacteriuria.

Urinary leukocytes are widely used as markers for urinary tract infection. Urine samples are traditionally evaluated for leukocytes using microscopy, although this method is increasingly being replaced by chemical testing (reagent strip) measuring leukocyte esterase. Urinary leukocytes are reported to be common in the elderly both with and without bacteriuria (42, 95)

In urinary tract infections, immune cells and various other cell types such as endothelial and uro-epithelial cells, participate in the host response. Cytokines and chemokines are small proteins that play an important role in the regulation of the local inflammatory response to infections (96-107). Measurements of urinary cytokines/chemokines are performed in studies to explore the host response in urinary tract infection and to evaluate the use of such measurements in diagnostics, but are not yet in use in clinical practice.

Towards better diagnostics

The facts:

- Asymptomatic bacteriuria is common in the elderly.
- Urinary testing is often used in screening; the result is often a finding of bacteriuria.
- There is high use of antibiotics in the elderly.
- A large proportion of these antibiotics are prescribed for suspected or confirmed urinary tract infections.
- High use of antibiotics causes increased rates of bacteria resistant to common antibiotics.

These facts imply the importance of exploring the occurrence and the characteristic features of asymptomatic bacteriuria in the elderly, and of looking for associations between asymptomatic bacteriuria and health related factors. This will help to improve our knowledge of when to order urinary tests for bacteriuria and how to interpret the results. Further, there is a need for better urinary tests when the diagnosis is uncertain. In the light of increasing rates of bacteria resistant to common antibiotics, we need to improve our diagnostic abilities in order to limit antibiotic use only to patients who can benefit from such treatment.
Aims

The overall aim of this thesis was to study characteristics of asymptomatic bacteriuria in elderly people living in the community.

Specific aims were:

- To study the prevalence of asymptomatic bacteriuria and associated health factors in a population of elderly people, aged 80 and over, living in the community.
- To follow the occurrence of asymptomatic bacteriuria in the same population during 18 months.
- To investigate the association between bacteriuria and frequency and type of urinary incontinence in the same population.
- To investigate the extent to which an individual with persistent asymptomatic bacteriuria carried the same E. coli strain after 6 and 18 months.
- To determine whether elderly women with asymptomatic bacteriuria, compared with those without, more often developed symptomatic urinary tract infections.
- To investigate the levels of cytokines/chemokines and leukocyte esterase in the urine of elderly patients with acute cystitis as compared with subjects with asymptomatic bacteriuria and subjects without bacteriuria.
Subjects and methods

Design
The methodological designs used in this thesis were:
- Cross-sectional population-based survey (Papers I and II).
- Repeated cross-sectional, closed cohort, survey (Paper III).
- Comparative laboratory study (Paper IV).

Setting
The study was performed in the geographical catchment area of Britsarvets primary health care centre in the municipality of Falun, located in central Sweden in the county of Dalarna. The number of inhabitants in Falun was, at the time of data collection, 55,000, 16.8% of whom were 65 or older. Socio-economic factors such as mean income from work, proportion of population employed, and costs per capita for the elderly in Falun were close to the average in Sweden (108).

The catchment area included a total of 12,000 inhabitants residing in both areas with one-family houses and apartment buildings. There were also three blocks of service apartments for the elderly and the disabled. In these blocks there was a nurse available during the daytime, but the residents lived in their own apartments with the possibility of having their meals in a common dining room.

Outpatient medical care in the catchment area was primarily performed at Britsarvets primary health care centre, as there were almost no alternative medical services available in this area.

Data were collected in March to June 2003 (Papers I and II), March 2003 to June 2005 (Paper III) and September 2004 to September 2005 (Paper IV).

Subjects

Papers I, II and III
All registered residents in the catchment area, not living in an institution, age 80 and over (642 subjects) were identified. Before the investigation was
carried out 48 had moved out and 17 had died, making the eligible number of subjects 577. Of these, 30 (5.2%) were excluded as unable to provide a sample owing to dementia and/or incontinence. In addition, 9 (2%, all of them men) who had an indwelling catheter and one woman who was diagnosed as having a symptomatic urinary tract infection at the time of the investigation were also excluded. Of the remaining 537 elderly individuals invited to participate, 105 (19.6%) declined the invitation to participate (Table 1). The number of participants thus ended up at 432 (294 women and 138 men) (Paper I). Participation rate was 80.4% (432/537) of possible participants or 74.9% (432/577) of all subjects age 80 and over outside institutional care living in the area. In Paper II the number of participants was 431, owing to lacking information on urinary incontinence in one subject.

The medical records at the health care centre were monitored to compare individuals who declined to participate with the participants. No differences in the number of registered contacts were found, indicating similar levels of morbidity in the two groups. The only factor that distinguished those who declined to participate from the others was that fewer of them lived in the service apartments (Table 1).

Table 1. Study population (n=432) versus individuals who declined to participate (n=105).

<table>
<thead>
<tr>
<th></th>
<th>Study population</th>
<th>Not consenting</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (years)</td>
<td>84</td>
<td>84</td>
<td>ns</td>
</tr>
<tr>
<td>Women (%)</td>
<td>68.1</td>
<td>67.6</td>
<td>ns</td>
</tr>
<tr>
<td>Living in service apartments (%)</td>
<td>14.4</td>
<td>3.8</td>
<td>0.005</td>
</tr>
<tr>
<td>Medical care contact* (%)</td>
<td>93.2</td>
<td>89.5</td>
<td>ns</td>
</tr>
<tr>
<td>Number of contacts (if any)</td>
<td>18.9</td>
<td>17.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

* At least one contact noted in the medical record of the health care centre in the year before the study.
ns=no significant difference

In Paper III this population was followed in repeated surveys. Of the 432 participants at the baseline survey, 76.4% (330/432, 236 women and 94 men) completed the 6 and 18-month surveys (Figure 2).

As compared with those who participated in all three surveys (n=330), the participants who were lost to follow-up (n=102) were at baseline older, 86 years vs. 84 years (p=0.002), and more often had reduced cognitive capacity (MMSE-score<24), 27% vs. 12% (p=0.0004). The prevalence of asymptomatic bacteriuria at baseline among those who were later lost to follow-up was 24.1% for women and 9.1% for men.
Figure 2. Participants in the surveys at baseline and after six and eighteen months.

**Paper IV**

*Patients with acute cystitis*

Sixteen consecutive patients ≥80 years old (15 women and 1 man, median age 85 years), diagnosed with acute cystitis at Britsarvets primary health care centre in Falun, Sweden, were included. The diagnosis required recent onset of dysuria, frequency and/or urgency and bacterial growth in the urine (in two subjects the urine was not cultured but tested positive for nitrite).

*Subjects with asymptomatic bacteriuria*

Twenty-four individuals with asymptomatic bacteriuria (22 women and 2 men, median age 86 years) were recruited from the third 18-month survey (Paper III). They all had growth of ≥10⁵ cfu/L of E. coli in two consecutive urine samples, obtained within 1-2 weeks, without recent onset of dysuria, frequency and/or urgency.

*Negative controls*

Twenty controls (15 women and 5 men, median age 84 years) with a negative urinary culture and no symptoms of urinary tract infection were selected from the third 18-month survey described above.
Methods

Research procedures

A letter of enquiry was sent to all individuals age 80 or over in the catchment area, and about one week later a specially trained study nurse contacted the prospective participants, usually by telephone. If (s)he agreed to participate, the study nurse arranged a home visit where she interviewed the participant and registered the data in a questionnaire. Some of the participants were frail and cognitively impaired and therefore, if necessary, close relatives and nursing staff were also used as informants. Supplementary information was obtained from medical records when needed.

The nurse also collected a urine sample. Participants were instructed to pass urine, preferably midstream, into a clean plastic mug. Bladder incubation time was more than 2 hours in 80% of the cases. The urine was immediately poured into a clean sampling tube, cooled and transported to the microbiology laboratory of Falun.

Data from the questionnaire and results from the urinary cultures were used solely for research purposes and not entered into the medical records.

Twenty-four months after the baseline survey, the medical records at the health centre were examined to determine whether the participants had experienced any symptomatic urinary tract infections. Only episodes with a distinct symptomatology of infection were included.

Questionnaire (Papers I-III)

In Paper I the questionnaire gave data about accommodation, diabetes mellitus, stroke, prostatic disease, oestrogen and diuretic treatment, cognitive status, functional independence, mobility, urinary incontinence, symptoms from the urinary tract and whether antibiotic treatment had been given in the previous three months. Urinary incontinence was defined (Paper I) as complaints of involuntary leakage at least once a week. Diabetes was defined as having medication or insulin treatment for diabetes, and prostatic disease as being on medication for prostatic disease or having a history of prostatic surgery. Oestrogen treatment included local and/or systemic treatment. Cognitive status was evaluated using the Mini-Mental State Examination (MMSE) (109) and reduced cognitive status was defined as having a MMSE score less than 24. Functional status was measured using the Katz index of activities of daily living (ADL), and reduced functional status was defined as need of assistance in at least one activity (bathing, dressing, toileting, transfer, continence or feeding, Katz index A+B). Reduced mobility was defined as not being able to walk indoors without support (other than a stick).

At the 6 and 18-month surveys there was a shorter questionnaire.
Urinary incontinence (Paper II)
The opening question regarding urinary incontinence was: “Do you suffer from involuntary urine leakage?” Giving an affirmative answer, the incontinence was then classified according to frequency (seldom, at least once a month, at least once a week or daily) and in two questions according to type. Stress urinary incontinence was defined as a positive answer to the question: “Do you have urinary leakage during exertion (e.g. coughing or sneezing)?” Urge urinary incontinence was defined as answering yes to the question: “Do you have urinary leakage associated with a sudden desire to pass urine?” This is in accordance with the accepted definition of urge urinary incontinence: “The complaint of involuntary leakage (of urine) accompanied by or immediately proceeded by urgency” (110). Subjects who answered yes to both questions regarding type were classified as having mixed urinary incontinence and subjects who answered yes to the opening question but gave no answer to the subsequent questions as having unclassified urinary incontinence.

By putting “seldom” together with “at least once a month” the number of categories was reduced when incontinence was related to bacteriuria. Very good reproducibility of the question defining urinary incontinence was found in a previous study (111), and the definitions are close to those used by Hannestad (112).

Laboratory methods (Papers I-IV)

Urinary cultures (Papers I-III)
Quantification, identification and susceptibility testing of organisms were performed at the microbiology laboratory of Falun on CLED-agar according to Swedish standards (113). If this first culture was positive a second, confirming, sample was obtained within 1-2 weeks. A positive culture was defined as growth of $\geq 10^8$ cfu/L. Cultures with a mixed flora or a growth of $<10^8$ bacteria per litre were regarded as negative.

In women, asymptomatic bacteriuria was defined as growth of $\geq 10^8$ cfu/L of the same bacterial species, in two consecutive urine samples in the absence of new, obvious symptoms from the urinary tract. In men, asymptomatic bacteriuria was defined as growth of $\geq 10^8$ cfu/L of one bacterial species in one sample (32). However, in Paper I the definition of asymptomatic bacteriuria in men is based on two consecutive positive cultures.

Typing of E. coli (Paper III)
Bacterial samples for phenotyping (Paper III) were stored at -80°C until testing, which were done at the microbiology laboratory of the County Hospital Ryhov, Jönköping. The isolated E. coli strains were subtyped using
a system for biochemical fingerprinting (PhP-EC, PhPlate Microplate Techniques, Sweden, www.phplate.se) (114). In brief, a loopful of a pure bacterial culture was added to a suspension medium. Aliquots (150 µl) of the suspensions were then inoculated into a 24 well microtiter plate containing four sets of 24 different substrates. The plates were incubated at 37°C and after 7, 24, and 48 hours, light emission (A620) of each well was measured using a microplate reader. The mean value of all readings was then calculated, resulting in 24 different numerical values for each tested isolate (the biochemical fingerprint]. Isolates yielding PhP patterns with correlation coefficients of ≥0.95 after pairwise comparisons were defined as belonging to the same type.

**Urinary leukocyte esterase (Paper IV)**

Urinary leukocyte esterase was analysed semi-quantitatively using Clinitek 50 (Bayer) on a urinary dipstick (Multistix® 5, Bayer), showing the leukocyte esterase concentration on a scale from 0 to 4.

**Urinary cytokine (Paper IV)**

Urine for cytokine analyses (Paper IV) was stored at -20°C until testing, which was done at the microbiology laboratory of the County Hospital Ryhov, Jönköping. All urine samples were centrifuged at 3000 rpm for 10 min at 4°C before quantitative determinations of IL-1β, TNF-α, IL-12, CXCL8, IL-6 and IL-10 concentrations were performed using the human Cytometric Bead Array Inflammation kit (CBA; Becton Dickinson Biosciences, Stockholm, Sweden), with flow cytometry (FACS Canto, Becton Dickinson), according to the manufacturer’s instructions. The levels of CXCL1 and CCL2 were analysed using human Quantikine® ELISA (R&D Systems, Abingdon, UK), with an automatic plate reader (Reader 530 TC, Organon Teknika, Stockholm, Sweden). CCL2 was analysed according to the manufacturer’s instructions. There was no protocol available for CXCL1 in urine samples. Spike, recovery, and linearity experiments were therefore performed to validate this assay, as recommended by the manufacturer.

**Urinary creatinine (Paper IV)**

Urinary creatinine concentration was measured using a modified Jaffé reaction (ADVIA 1650, Bayer, Stockholm, Sweden), and the ratios of cytokine/creatinine (pg/mg) were calculated to normalise sample results for dilution.
Statistics

Software used was JMP® 4.0.2 of the SAS System for Windows (Paper I) and SPSS for Windows, Rel. 14.0.0, (Paper II-IV). Statistical tests used were two-tailed, and p-values <0.05 were regarded as significant.

Missing data was 0.5% for variables used in the models evaluating factors associated with bacteriuria (Papers I and II); the highest values were for frequency (2.1%) and dysuria (1.9%).

*Chi-square test* was used to compare proportions on categorical data and was applied when comparing characteristics between participants and individuals who declined to participate, and between men and women, except for comparisons of median age, where *Mann-Whitney U-test* was used (Paper I). The chi-square test was also used when comparing occurrence of bacteriuria in groups with increasing frequencies of incontinence (Paper II), and when comparing characteristics of participants and those who were lost to follow-up (Paper III).

Associations between asymptomatic bacteriuria and characteristics (Paper I) were expressed as relative risks, and 95% confidence intervals were calculated. *Logistic regression analysis* was used to determine the independent factors associated with asymptomatic bacteriuria, expressed as odds ratios and their 95% confidence intervals, and to create the regression surface in Figure 4 (Paper I). This method was also used when relating frequency and type of urinary incontinence to occurrence of asymptomatic bacteriuria (Paper II). As frequency and type of incontinence in some respects measure the same thing, the R-value between them being 0.74, we carried out the multivariate analyses separately for these two different classifications of incontinence.

*Cox regression* analysis was used to compare the cumulative incidence of symptomatic urinary tract infection in participants with and without asymptomatic bacteriuria (Paper III).

Urinary cytokine concentrations in urinary tract infection, asymptomatic bacteriuria and negative controls were compared using the *Mann-Whitney U-test* (Paper IV).

Ethics

This was an epidemiological and observational study. No clinical interventions were carried out. In the studied age group, 80 years and over, there is high use of antibiotics as well as of other types of medication, especially in individuals with impaired health status. Therefore, it is particularly important to include this group, in order to improve the clinical basis for decisions on antibiotic treatment and thereby reduce unnecessary use of antibiotics. Informed consent was sought and obtained directly from...
most participants. However, in some cases this was not possible owing to impaired health status and reduced cognitive capacity, in which case informed consent was obtained from close relatives.

Giving a urine sample today is considered a routine measure in medical care and is probably not experienced as worrisome by most people.

Previous studies have consistently shown that asymptomatic bacteriuria in this age group is harmless and should not be treated. Therefore, the fact that the results of the urine culture were not automatically returned to the individual or his/her doctor was judged as ethically correct, as this could have resulted in anxiety in the participants and also increased the risk of unnecessary courses of antibiotics.

The studies were approved by the Ethics Committee of Uppsala University, Sweden, Dnr 02-547, 03-581 (Papers I-III), and the Regional Ethical Review Board of Uppsala, Sweden, Dnr 2005:177 (Paper IV).
Results

Characteristics of the study population (Papers I-III)

The characteristics of the study population (Paper I and II) are presented in Table 2. These are also the baseline characteristics in Paper III.

Table 2. Characteristics of the study population (n=432)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n=138)</th>
<th>Women (n=294)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (years)</td>
<td>83</td>
<td>84</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>10.9</td>
<td>9.5</td>
<td>ns</td>
</tr>
<tr>
<td>History of stroke (%)</td>
<td>10.2</td>
<td>14.3</td>
<td>ns</td>
</tr>
<tr>
<td>Prostatic disease (%)</td>
<td>39.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oestrogen treatment (%)</td>
<td></td>
<td>19.1</td>
<td></td>
</tr>
<tr>
<td>Diuretic treatment</td>
<td>27.5</td>
<td>38.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Reduced cognitive capacity, MMSE &lt;24 (%)</td>
<td>16.4</td>
<td>14.7</td>
<td>ns</td>
</tr>
<tr>
<td>Reduced functional status, ADL ≥5 (%)</td>
<td>16.1</td>
<td>16.2</td>
<td>ns</td>
</tr>
<tr>
<td>Reduced mobility (%)</td>
<td>13.9</td>
<td>30.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary incontinence once a week or more (%)</td>
<td>20.3</td>
<td>34.0</td>
<td>0.003</td>
</tr>
<tr>
<td>Faecal incontinence (%)</td>
<td>1.5</td>
<td>7.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Dysuria (%)</td>
<td>5.9</td>
<td>5.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns=no significant difference

Prevalence of asymptomatic bacteriuria (Papers I-III)

Occurrence of bacteriuria in the initial and in the second, confirmational, urine sample at baseline (Paper I) and at the 6 and 18-month surveys is presented in Table 3, where figures for asymptomatic bacteriuria according to the different definitions for women and men are also given. Asymptomatic bacteriuria was found at least once in 26.9% (72/268) of women and 15.7% (18/115) of men who participated in the first and second surveys (p=0.018), and at least once in 36.9% (87/236) of women and 20.2% (19/94) of men who participated in all three surveys (p=0.004) (Paper III).

Mortality rate within 2 years was 17% in both those with and without asymptomatic bacteriuria at baseline.
Table 3. Prevalence of bacteriuria in initial sample and in a second, confirmational sample within two weeks. Figures for asymptomatic bacteriuria, according to definition, in bold type.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
<th>18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>n=294</td>
<td>n=138</td>
<td>n=268</td>
<td>n=115</td>
</tr>
<tr>
<td>Initial sample</td>
<td>66 (22.4%)</td>
<td>13 (9.4%)</td>
<td>60 (22.4%)</td>
</tr>
<tr>
<td>Second sample</td>
<td>56 (19.0%)</td>
<td>8 (5.8%)</td>
<td>52 (19.4%)</td>
</tr>
</tbody>
</table>

a A second sample was obtained only from those with bacteriuria in the initial sample.

The occurrence of asymptomatic bacteriuria and the changes between baseline, 6 and 18 months for the 330 individuals who participated in all three surveys are presented in Figure 3.

Figure 3. Occurrence of asymptomatic bacteriuria (ASB) among individuals participating in all three surveys. N=330 (of which women in brackets).

There were 27 women and 4 men with asymptomatic bacteriuria on all three occasions, constituting 60% (31/52) of those with asymptomatic bacteriuria at baseline. In these 31 individuals, 24 (21 women and 3 men) had E. coli, two had Klebsiella pneumoniae and one had Proteus mirabilis at all three surveys, while the remaining four had different species at the different surveys.
Conversion from positive to negative status of asymptomatic bacteriuria was preceded by treatment with antibiotics (for any indication) in 52% (17/33), while of the participants with persistent asymptomatic bacteriuria in all three surveys, 23% (7/31) had been treated with antibiotics between the surveys (p=0.02) (Paper III).

**Phenotyping**

Phenotyping showed that the majority of the individuals carried their own, unique, type of E. coli. There were 29 subjects who had asymptomatic bacteriuria with E. coli at baseline and also at the 6-month survey. Isolates from 25 of these subjects were available for phenotyping, revealing the same type at baseline and at 6 months in 19 cases (76%). Furthermore, there were 24 subjects who had asymptomatic bacteriuria with E. coli at all three surveys, and isolates from 20 of these subjects were available for phenotyping, revealing the same type at all three surveys in 8 cases (40%). None of the 8 subjects with identical E. coli types at all three surveys had received antibiotics in between. At the third survey the E. coli isolates from the two-week follow-up culture were also typed and compared with the isolate from the initial third survey sample. Eighteen of the 20 individuals (90%) carried the same type on both occasions (Paper III).

**Microbiology (Paper I)**

E. coli occurred at the baseline survey in 68.8% (44/64) of the subjects with asymptomatic bacteriuria, in 50% (4/8) of the men and in 71.4% (40/56) of the women. Klebsiella pneumoniae occurred in 9.4% (6/64), all of whom were women. Of the remaining species found, each constituted <5% of the positive cultures. E. coli were trimetoprim-resistant in 14.3% and mecillinam-resistant in 2.1% (one case). No E. coli resistant to nitrofurantoin, norfloxacin or cephadroxil was found in the baseline survey.

**Factors associated to asymptomatic bacteriuria (Paper I)**

Associations with health factors are shown in Table 4.

When adjusted in a logistic regression model for the studied indicators (including age), the remaining significant factors for women were reduced mobility, urinary incontinence and oestrogen treatment (Table 5).
### Table 4. Associations of asymptomatic bacteriuria (ASB) versus no ASB with health factors in men (n=138) and women (n=294). Relative risks (RR) with 95% confidence intervals (CI).

<table>
<thead>
<tr>
<th>Health Factor</th>
<th>Men ASB (RR 95% CI)</th>
<th>Women ASB (RR 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living in blocks of service apartments</td>
<td>5.31 (1.42-19.90)</td>
<td>0.85 (0.43-1.69)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.14 (0.54-2.42)</td>
<td>0.72 (0.33-1.57)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>5.27 (1.41-19.74)</td>
<td>0.72 (0.33-1.57)</td>
</tr>
<tr>
<td>Prostatic disease</td>
<td>10.63 (1.35-83.98)</td>
<td></td>
</tr>
<tr>
<td>Oestrogen treatment</td>
<td>2.01 (1.24-3.24)</td>
<td></td>
</tr>
<tr>
<td>Diuretic treatment</td>
<td>1.58 (0.40-6.29)</td>
<td>1.95 (1.22-3.12)</td>
</tr>
<tr>
<td>Reduced cognitive capacity</td>
<td>3.06 (0.79-11.86)</td>
<td>0.97 (0.49-1.90)</td>
</tr>
<tr>
<td>Reduced functional status</td>
<td>3.14 (0.81-12.18)</td>
<td>1.90 (1.15-3.14)</td>
</tr>
<tr>
<td>Reduced mobility</td>
<td>6.21 (1.70-22.75)</td>
<td>2.30 (1.45-3.65)</td>
</tr>
<tr>
<td>Urinary incontinence ≥ once a week</td>
<td>6.55 (1.66-25.77)</td>
<td>2.70 (1.67-4.35)</td>
</tr>
<tr>
<td>Faecal incontinence</td>
<td>2.41 (1.37-4.25)</td>
<td></td>
</tr>
<tr>
<td>Dysuria</td>
<td>2.29 (0.32-16.39)</td>
<td>2.13 (1.07-4.21)</td>
</tr>
<tr>
<td>Frequency</td>
<td>1.26 (0.32-16.39)</td>
<td>1.28 (0.52-3.11)</td>
</tr>
<tr>
<td>Antibiotic treatment previous 3 months</td>
<td>3.58 (0.51-25.25)</td>
<td>1.05 (0.42-2.61)</td>
</tr>
</tbody>
</table>

*RR could not be calculated because there were no men with asymptomatic bacteriuria and diabetes, faecal incontinence or frequency.

### Table 5. Remaining, independent, significant associations of asymptomatic bacteriuria (ASB) versus no ASB with health factors in a logistic regression model (women, n=294). Odds ratios (OR) with 95% confidence intervals (CI).

<table>
<thead>
<tr>
<th>Health Factor</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary incontinence ≥ once a week</td>
<td>2.99 (1.60-5.60)</td>
</tr>
<tr>
<td>Reduced mobility</td>
<td>2.68 (1.42-5.03)</td>
</tr>
<tr>
<td>Oestrogen treatment</td>
<td>2.20 (1.09-4.45)</td>
</tr>
</tbody>
</table>

Estimated prevalences of asymptomatic bacteriuria in relation to the occurrence of reduced mobility and urinary incontinence are illustrated in Figure 4. This estimated prevalence would be 46% if these factors coincided.

It was not meaningful to apply this logistic regression model in men, as the number of men with asymptomatic bacteriuria was low.
Table 6 shows the frequencies and types of urinary incontinence and their relation to bacteriuria (positive initial urinary culture) in women and men. Some level of involuntary leakage of urine was reported by 64.5% of the women and 46.4% of the men. Less frequent incontinence was mostly of stress type in women and of urge type in men. When incontinence occurred at least weekly, mixed urinary incontinence was the most common type for both men and women. The prevalence of bacteriuria increased from 14% among continent women to 39% among those who were incontinent daily, while the corresponding figures for men were 7% and 25% respectively. More than one third of women with urge or mixed incontinence had bacteriuria.

**Figure 4.** Estimated occurrence of asymptomatic bacteriuria (ASB) in women related to urinary incontinence and reduced mobility.

**Urinary incontinence and asymptomatic bacteriuria (Paper II)**

Table 6 shows the frequencies and types of urinary incontinence and their relation to bacteriuria (positive initial urinary culture) in women and men. Some level of involuntary leakage of urine was reported by 64.5% of the women and 46.4% of the men. Less frequent incontinence was mostly of stress type in women and of urge type in men. When incontinence occurred at least weekly, mixed urinary incontinence was the most common type for both men and women. The prevalence of bacteriuria increased from 14% among continent women to 39% among those who were incontinent daily, while the corresponding figures for men were 7% and 25% respectively. More than one third of women with urge or mixed incontinence had bacteriuria.
Table 6. Frequency and type of urinary incontinence and occurrence of bacteriuria (positive initial culture) in women (n=293) and men (n=138).

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bacteriuria within group</td>
<td></td>
<td>Bacteriuria within group</td>
</tr>
<tr>
<td></td>
<td>n (% of all)</td>
<td>n (%)</td>
<td>n (% of all)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Frequency:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No leakage</td>
<td>104 (35.5)</td>
<td>15 (14.4)</td>
<td>74 (53.6)</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td>Leakage seldom</td>
<td>77 (26.3)</td>
<td>14 (18.2)</td>
<td>33 (23.9)</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>Leakage monthly</td>
<td>11 (3.8)</td>
<td>0 (0)</td>
<td>3 (2.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Leakage weekly</td>
<td>23 (7.8)</td>
<td>7 (30.4)</td>
<td>4 (2.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Leakage daily</td>
<td>78 (26.6)</td>
<td>30 (38.5)</td>
<td>24 (17.4)</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td><strong>Type:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some urinary leakage:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress incontinence</td>
<td>50 (17.1)</td>
<td>7 (14.0)</td>
<td>4 (2.9)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Mixed incontinence</td>
<td>65 (22.2)</td>
<td>19 (29.2)</td>
<td>17 (12.3)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Urge incontinence</td>
<td>52 (17.7)</td>
<td>21 (40.4)</td>
<td>33 (23.9)</td>
<td>3 (9.1)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>22 (7.5)</td>
<td>4 (18.2)</td>
<td>10 (7.2)</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Leakage at least weekly:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress incontinence</td>
<td>16 (5.5)</td>
<td>5 (31.3)</td>
<td>3 (2.2)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Mixed incontinence</td>
<td>47 (16.0)</td>
<td>15 (31.9)</td>
<td>14 (10.1)</td>
<td>3 (21.4)</td>
</tr>
<tr>
<td>Urge incontinence</td>
<td>30 (10.2)</td>
<td>14 (46.7)</td>
<td>9 (6.5)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>8 (2.7)</td>
<td>3 (37.5)</td>
<td>2 (1.4)</td>
<td>1 (50.0)</td>
</tr>
</tbody>
</table>

The odds ratio for having bacteriuria was 3.7 for women with leakage daily as compared with continent women (Table 7), and there was a trend towards higher odds with increasing frequency of incontinence (p<0.001). The odds ratios were similar after adjustment for reduced mobility and use of oestrogen. The associations with frequency and type of urinary incontinence remained even when the stricter definition of asymptomatic bacteriuria (two positive cultures) was used.
Table 7. Associations of bacteriuria and asymptomatic bacteriuria (ASB) (two positive cultures) with frequency and type of urinary incontinence in women (n=293). Odds ratios (OR) with 95% confidence intervals (CI).

<table>
<thead>
<tr>
<th></th>
<th>Bacteriuria</th>
<th>Bacteriuria</th>
<th>ASB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Adjusted for mobility and oestrogen use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Frequency:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No leakage</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Leakage seldom</td>
<td>1.12 (0.51-2.48)</td>
<td>0.92 (0.41-2.09)</td>
<td>1.14 (0.47-2.78)</td>
</tr>
<tr>
<td>Leakage weekly but not daily</td>
<td>2.60 (0.92-7.37)</td>
<td>2.09 (0.68-6.39)</td>
<td>2.45 (0.75-7.96)</td>
</tr>
<tr>
<td>Leakage daily</td>
<td><strong>3.71 (1.82-7.56)</strong></td>
<td><strong>2.83 (1.35-5.94)</strong></td>
<td><strong>3.52 (1.58-7.87)</strong></td>
</tr>
<tr>
<td><strong>Type:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No leakage</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Stress incontinence</td>
<td>0.97 (0.37-2.54)</td>
<td>0.82 (0.30-2.26)</td>
<td>1.21 (0.42-3.45)</td>
</tr>
<tr>
<td>Mixed incontinence</td>
<td><strong>2.45 (1.14-5.27)</strong></td>
<td>1.86 (0.83-4.16)</td>
<td>2.16 (0.90-5.17)</td>
</tr>
<tr>
<td>Urge incontinence</td>
<td><strong>4.02 (1.85-8.76)</strong></td>
<td><strong>3.36 (1.49-7.58)</strong></td>
<td><strong>4.15 (1.74-9.88)</strong></td>
</tr>
<tr>
<td>Unclassified</td>
<td>1.32 (0.39-4.44)</td>
<td>0.75 (0.20-2.76)</td>
<td>0.81 (0.19-3.45)</td>
</tr>
</tbody>
</table>

The prevalence of bacteriuria among men was too low to make any meaningful estimations of the association between bacteriuria and frequency and type of incontinence.

**Incidence of symptomatic urinary tract infection (Paper III)**

The cumulative incidence of symptomatic urinary tract infection during 24 months in women with and without asymptomatic bacteriuria at baseline is presented in Figure 5. The risk of developing a symptomatic infection within 24 months was higher among women with asymptomatic bacteriuria at baseline (p=0.019, adjusted for age).
Figure 5. Cumulative incidence of symptomatic urinary tract infection (time to first infection) in women with and without asymptomatic bacteriuria (ASB) at baseline.

Urinary diagnostics (Paper IV)

Cytokines/chemokines/leukocyte esterase
Urinary levels of tested cytokines and chemokines, corrected for urinary creatinine, are presented in Table 8, comparing the levels in patients with acute cystitis, asymptomatic bacteriuria and negative controls. There were significantly higher levels of urinary CXCL1, CXCL8 and IL-6 in subjects with asymptomatic bacteriuria than in negative controls, and even higher levels in acute cystitis. In CXCL1 there were non-detectable levels in most negative controls and occasionally in the groups with asymptomatic bacteriuria and acute cystitis, while there were detectable levels of CXCL8 and IL-6 in all subjects.

Comparisons without correction for urinary creatinine revealed similar significant differences among the three groups regarding CXCL1 and CXCL8. For IL-6 there were higher levels in acute cystitis than in asymptomatic bacteriuria, while there was no difference when asymptomatic bacteriuria was compared with negative controls.
Table 8. Urinary levels of tested cytokines/chemokines in patients with acute cystitis, asymptomatic bacteriuria and negative controls. Concentrations are in pg/mg creatinine.

<table>
<thead>
<tr>
<th></th>
<th>Acute cystitis (n=16)</th>
<th>Asymptomatic bacteriuria (n=24)</th>
<th>Negative controls (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
<td>p</td>
</tr>
<tr>
<td>IL-1β</td>
<td>97.1</td>
<td>0-11 500</td>
<td>ns</td>
</tr>
<tr>
<td>TNF-α</td>
<td>5.8</td>
<td>0-33.9</td>
<td>ns</td>
</tr>
<tr>
<td>IL-12</td>
<td>17.8</td>
<td>0-53.2</td>
<td>ns</td>
</tr>
<tr>
<td>IL-18</td>
<td>4.1</td>
<td>1.1-16.8</td>
<td>ns</td>
</tr>
<tr>
<td>CXCL1</td>
<td>222</td>
<td>0-&gt;6000</td>
<td>0.011</td>
</tr>
<tr>
<td>CXCL8</td>
<td>313</td>
<td>137-550</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCL2</td>
<td>340</td>
<td>144-621</td>
<td>ns</td>
</tr>
<tr>
<td>IL-6</td>
<td>54.7</td>
<td>10.7-443</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-10</td>
<td>12.5</td>
<td>1.4-31.3</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns=no significant difference

The ROC curve in Figure 6 presents the paired values for sensitivity and (1−specificity) according to different cut-off levels of CXCL1, CXCL8 and IL-6, comparing samples from patients with acute cystitis and asymptomatic bacteriuria.

Figure 6. ROC plot for urinary CXCL1, CXCL8 and IL-6 (corrected for urinary creatinine) when distinguishing between asymptomatic bacteriuria (n=24) and acute cystitis (n=16).
Table 9 shows values for sensitivity and specificity in discriminating between acute cystitis and asymptomatic bacteriuria. Cut-off values for cytokines were chosen as the most optimal according to the ROC plot.

Table 9. Sensitivity and specificity for selected cut-off values of urinary cytokines (pg/mg creatinine) and leukocyte esterase when discriminating between acute cystitis and asymptomatic bacteriuria.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXCL1 (&gt;150pg/mg)</td>
<td>69</td>
<td>79</td>
</tr>
<tr>
<td>CXCL8 (&gt;285 pg/mg)</td>
<td>63</td>
<td>96</td>
</tr>
<tr>
<td>CXCL8 (&gt;135 pg/mg)</td>
<td>100</td>
<td>71</td>
</tr>
<tr>
<td>IL-6 (&gt;30 pg/mg)</td>
<td>81</td>
<td>96</td>
</tr>
<tr>
<td>Leukocyte esterase (&gt;2)</td>
<td>88</td>
<td>79</td>
</tr>
</tbody>
</table>

Values for leukocyte esterase in acute cystitis and asymptomatic bacteriuria are presented in Figure 7, where they are plotted together with IL-6. Among the negative controls (n=20), 16 had no urinary leukocyte esterase, 3 had level 1, and 1 had level 2. None of the controls had a level higher than 2.

Figure 7. Urinary IL-6 (pg/mg creatinine) plotted against urinary leukocyte esterase in subjects with acute cystitis and asymptomatic bacteriuria. Cut-off values (leukocyte esterase >2; IL-6 >30pg/mg) indicated as bold lines.
Diagnostic possibilities are illustrated in Figure 7. Combined test with leukocyte esterase >2 and IL-6 >30 pg/mg gives a specificity of 100% and a sensitivity of 69% in discriminating between acute cystitis and asymptomatic bacteriuria.

**Leukocyte esterase (additional unpublished data)**

The distribution of urinary leukocyte esterase in the 432 individuals (294 women and 138 men) who participated in the baseline survey is presented in Figure 8. No leukocyte esterase was found in 19% (13/69) of subjects with asymptomatic bacteriuria and in 60% (219/363) of those without. Leukocyte esterase >2 was found in 35% (24/69) of subjects with asymptomatic bacteriuria and in 8% (29/363) of those without.

*Figure 8. Distribution of leukocyte esterase in subjects with asymptomatic bacteriuria (ASB) (n=69), and in those without (n=363).*
Discussion

Methodological considerations

Subjects and setting
This study (Papers I-III) provides information concerning 432 elderly residents living in the community; the participant rate was 74.9% (432/577) of all subjects age 80 and over outside institutional care, living in the geographical catchment area. Including only possible participants (excluding those who were unable to provide a urine sample or who had an indwelling catheter) gives a participant rate of 80.4% (432/537). This participation rate, plus the facts that the non-participants did not differ in terms of age, sex or rate of care consulting from the participants, and that socio-economic factors in Falun were close to the average in Sweden support the possibility of generalising the results to Swedish elderly people living in the community at large. However, the possibility of obtaining fully correct and complete information from each individual in an elderly population is limited by the presence of dementia and other disorders common in the elderly. In some cases, second-hand information had to be gathered from close relatives or from medical records alone.

Small subgroups, especially men with asymptomatic bacteriuria, resulted in low power and wide confidence intervals. For instance, the population was too small to make any detailed estimates of the association between asymptomatic bacteriuria and urinary incontinence in men.

It is important to note that this was a cross-sectional study, which does not give evidence of causal relationships.

In order to make the results more reliable regarding the comparison between acute cystitis, asymptomatic bacteriuria and negative controls (Paper IV), we tried to clearly define the groups, making sure that only those subjects with distinct symptoms of infection from the lower urinary tract were included in the acute cystitis group. However, this was a small, explorative, study and the results need to be confirmed.
Laboratory methods

**Urinary cultures**

Measures performed to reduce the risk of including contaminated samples:

- Specially trained study nurses handled the urine samples.
- Midstream urine samples were requested.
- The strict criterion of two consecutive positive urinary cultures for asymptomatic bacteriuria in women was used.
- Cultures with growth of mixed flora were excluded.
- Cultures with growth of $<10^8$ cfu/L were excluded.

To minimise the risk of obtaining false negative urinary cultures it is desirable for the subject to keep the urine in the bladder as long as possible before giving a sample. In our study, this bladder incubation time was more than 2 hours in 80% of the cases, which can be considered as an acceptable figure.

The use of the strict criterion for asymptomatic bacteriuria, two consecutive positive urinary cultures in women, may exclude some cases of true, transient bacteriuria, and excluding those with growth of mixed flora and growth of $<10^8$ cfu/L may exclude some cases of true bacteriuria.

In summary, these problems associated with performing urinary cultures and interpreting the results are well known and occur both in scientific studies and in clinical practice. We do not think they affect the generalisability of our results either more or less than in other similar studies.

**Phenotyping (Paper III)**

The PhP System for biochemical phenotyping has been used in many studies for more than twenty years. The reproducibility in typing E. coli has been documented to be as good as with other biochemical typing systems (115), while the ability to discriminate has been shown to be even better.

**Correction for urinary creatinine (Paper IV)**

Correction for urinary creatinine was carried out to diminish the influence of differences in diuresis, in order to create a more accurate image of real cytokine exudation into the urine. Such corrections were also performed in some of the previous studies on urinary cytokines and bacteriuria/urinary tract infection (100, 107, 116-118) but not in others (96, 98, 101, 103-106, 119, 120). From a clinical perspective, when using measurement of urinary cytokines for diagnostic purposes, measurement without creatinine correction would be more appropriate.
Prevalence

The first cross-sectional survey (Paper I) presents prevalence figures for asymptomatic bacteriuria in men and women in a community living non-institutionalised population aged 80 and over. Asymptomatic bacteriuria according to the accepted definition (2 positive urinary cultures in women and 1 positive culture in men), was identified in 19.0% of women and 9.4% of men (Paper I), corresponding well with previous findings among the elderly in other non-institutional populations (85, 86). However, these prevalences are markedly lower than figures found for institutional populations (42, 43).

We found that 27% (14/52) of the elderly with asymptomatic bacteriuria at baseline were culture negative at 6 months, and that 6% (16/278) of the elderly with a negative culture at baseline had developed asymptomatic bacteriuria at 6 months (Paper III). This is in agreement with the results from studies performed on the elderly in institutional living (48, 49).

Of all individuals with persistent asymptomatic bacteriuria, 87% (27/31) carried the same species (24 E. coli, two Klebsiella pneumoniae and one Proteus mirabilis) at each survey (Paper III), supporting data from other studies based on typing to species level (48, 86). We wanted to investigate to what extent this reflects persistence of the same bacterial strain over time, and therefore E. coli typing using the PhenePlate method was performed. Our finding that 76% of those with asymptomatic bacteriuria with E. coli carried the same type after 6 months is in concordance with the findings of LiPuma et al. (121), where 79% of elderly women with untreated asymptomatic bacteriuria after 6 months remained colonised with the same type of E. coli. Moreover, we also extended the observation period to 18 months and then found that 40% of those with E. coli at all three surveys carried the same type (Paper III). In most cases this is probably attributable to the persistence of bacteria in the urinary tract, but in some cases it may represent a reinfection of the same strain of E. coli from the faecal flora, as this flora may be stable for long periods of time (122, 123).

Another possible explanation could be the presence of several different E. coli strains in the bladder simultaneously, but that owing to culture limitations we only found one of the present strains. This was indicated in our data because some patients were found to carry two strains observed through different morphologies. To further address this issue, a large number of different colonies in each sample should be typed, possibly by developing new more powerful DNA based typing methods for a mixture of bacteria.

One cause of changing E. coli type may be antibiotic treatment. Among subjects with persistent E. coli bacteriuria, we identified six individuals who had a course of antibiotics between the surveys. Subsequently, there was a change of strain in three of these individuals and negative urinary cultures in the other three on the next culture occasion. In contrast, none of the 8
individuals with an identical type at all three surveys had received antibiotics between the culture occasions. However, in ten cases there was a shift in bacterial strain between 2 culture occasions without any antibiotics in between (Paper III).

There is probably a mix of bacterial and host properties influencing the acquisition of asymptomatic bacteriuria, and when asymptomatic bacteriuria occurs if it is persistent or transient, and if, when persistent, it persists with the same or different bacterial strains.

**How to define asymptomatic bacteriuria?**

Asymptomatic bacteriuria in men is defined as the occurrence of one urinary culture with growth of $\geq 10^8$ cfu/L, and in women as two consecutive urinary cultures with growth of $\geq 10^8$ cfu/L of the same species, in an individual without symptoms of urinary tract infection (32).

We present figures for both an initial and a confirmational culture in women and men (Paper III). When the figures from the three sampling occasions were combined, we found that in 17% of women and in 25% of men, the second, confirmational sample did not yield bacterial growth.

The definitions of asymptomatic bacteriuria are based on the studies by Kass and others from the 1950s, which showed that lower bacterial counts in an asymptomatic woman usually do not represent true bacteriuria but contamination, and that bacteriuria in an initial urine sample was confirmed in women by a second urine sample in only 80% of the cases (10, 124). However, since asymptomatic bacteriuria, at least among younger women, is often transient (40) the demand for a second confirmational urinary culture may underestimate the true occurrence of bacteriuria. In some studies there has been a demand for three consecutive cultures with the same bacterial species (41, 125) for the ascertainment of asymptomatic bacteriuria, while others are satisfied with just one urinary culture yielding growth of $\geq 10^8$ cfu/L, consequently giving a somewhat higher prevalence (40, 73).

In our opinion, the results of this thesis do not support a different definition of asymptomatic bacteriuria for women than men in this age group. We suggest that when proper sampling routines and laboratory criteria are used, asymptomatic bacteriuria in women can also be based on a single sample. This is probably already the routine in clinical practice.

**Associated factors**

Host factors associated with asymptomatic bacteriuria in the elderly can be factors facilitating bacterial ascent into and growth in the urinary tract. Such factors are thought, for example, to be loss of oestrogen effects on the female
genital mucosa, neurological diseases leading to impaired voiding, increased residual volumes, reflux and urinary incontinence. In men they are thought to be prostatic diseases with obstruction, decrease in bactericidal activity of prostate secretions, and infectious foci in the prostate (42). The importance and relative impact of these different host factors are largely unknown and it may be difficult to judge whether there is a causative connection or just a shared underlying cause.

In Paper I, we found asymptomatic bacteriuria in women to be associated with impaired mobility (OR:2.68, CI:1.42-5.03), oestrogen treatment (OR:2.20, CI:1.09-4.45) and urinary incontinence (OR:2.99, CI:1.60-5.60).

**Impaired mobility** in our study was defined as not being able to walk indoors without support (other than a stick). One previous report on nursing home residents (n=195) did not show an association with impaired mobility (126) while another (n=865, women) had findings in accordance with ours (48). The explanation of this association may be that impaired mobility is just a marker of general functional impairment, associated with higher prevalence of bacteriuria (48, 61, 85, 127). Another explanation may be that impaired mobility more directly affects bladder voiding.

The **oestrogen treatment** in our study was topical and/or systemic. The WHI study revealed a strong association between urinary incontinence and the use of conjugated equine oestrogen in postmenopausal women (128). In Sweden it is uncommon to use this kind of oestrogen for women aged 80 or over, and the oestrogen used in the present study was probably exclusively oestriol or topical low dose oestrogen. The association between the use of oestrogen and bacteriuria could possibly be explained by the fact that older people with bacteriuria seem to have an increased risk of being diagnosed with recurrent symptomatic urinary tract infections (42), and oestrogen is often used to prevent these infections.

The association between asymptomatic bacteriuria and **urinary incontinence** was evaluated more closely, see below.

**Urinary incontinence**

In this study (Paper II), two thirds of the women and almost half of the men reported some level of urinary incontinence. Incontinence weekly or more often was reported by one third of the women and one fifth of the men. Our prevalence figures for frequency and type of urinary incontinence are almost the same as found in corresponding populations in other, larger studies (112, 129-131).

Others have also found an association between urinary incontinence and bacteriuria (43, 126, 132, 133) although those studies focused mainly on people in institutional settings. As far as we know, there are no previous
studies on the presence of bacteriuria in relation to frequency and type of
incontinence.

The causes of the association between urinary incontinence and
bacteriuria are not clear. In this age group, there is probably not an absolute
and distinct boundary between normal variations in mild urogenital
sensations and symptoms caused by urinary tract infections, and some
individuals might in reality suffer from symptomatic cystitis. An alternative
explanation of the association between bacteriuria and incontinence is that
both conditions have a common cause in bladder dysfunction and/or mucosal
atrophy. This hypothesis is supported by the finding that treating bacteriuria
with antibiotics had no effect on the severity of chronic urinary incontinence
among nursing home residents (67).

The finding (Paper II) that urge urinary incontinence but not stress urinary
incontinence was associated with bacteriuria in women may be due to a real
difference between the two types, explained by differences in physiology
and pathogenesis. The finding may also be explained in terms of the strong
association between the frequency of incontinence and bacteriuria, as stress
urinary incontinence was characterised by less frequent urine loss than urge
urinary incontinence. Bacteriuria may stimulate frequent leakage or frequent
leakage may facilitate bacterial ascent.

Incidence of symptomatic urinary tract infection

The finding (Paper III) that symptomatic urinary tract infections occurred
more often in women with asymptomatic bacteriuria than in those without
(Figure 4) is consistent with a similar finding in a younger population (54).
However, antibiotic treatment of asymptomatic bacteriuria did not decrease
the number of symptomatic urinary tract infections either in non-pregnant
women (55) or in older ambulatory women (68). In fact, in both these studies
subsequent symptoms of urinary tract infection were more common in the
groups treated with antibiotics.

Owing to the limited number of participants, it was not possible to control
for other possible influencing factors such as antibiotics given during the
observation period. Could courses of antibiotics given for other reasons than
urinary tract infections affect the incidence of urinary tract infections
through a change to more virulent bacterial strains? Neither was it possible
to control for other background factors. A larger study would be required to
determine whether the increased incidence is caused by the bacteriuria alone
or if there are other commonly associated factors.
Urinary diagnostics in asymptomatic bacteriuria and acute cystitis

Cytokines and chemokines (Paper IV)

Except for higher levels of IL-12 and slightly lower levels of IL-18 in asymptomatic bacteriuria as compared with negative controls, we found no differences between the groups with regard to the pro-inflammatory cytokines IL-1β, TNF-α, IL-12 and IL-18 (Table 8). There are few other reports on urinary levels of these cytokines in relation to urinary tract infections. In children, elevated urinary levels of IL-1β in pyelonephritis as compared with controls without bacteriuria have been found (116), while TNF-α was found in very low levels in symptomatic urinary tract infections as well as in negative controls (119). In another study neither IL-1β nor TNF-α was found to be elevated in the urine of patients (mostly adults) with urinary tract infections (101).

CXC-chemokines play an important role in neutrophil activation (102), and urinary levels of CXCL8 correlate with the level of leukocyturia (100, 101, 104, 134). There is evidence that in urinary tract infections these chemokines are produced locally in the urinary tract (101, 117, 134). We found gradually increasing urinary levels of CXCL1 and CXCL8 going from negative controls to asymptomatic bacteriuria and on to acute cystitis (Table 8). Our findings are in accordance with previous reports on younger populations: The urinary level of CXCL1 and CXCL8 in urinary tract infection is elevated, and the level seems to reflect disease severity (106, 117). Renal transplant patients showed the same pattern of increasing urinary levels of CXCL8 from negative controls to asymptomatic bacteriuria to symptomatic urinary tract infection (135), and there were also higher levels of urinary CXCL8 in children with febrile urinary tract infection than in children with asymptomatic bacteriuria (96). CCL-2 was found in higher urinary levels in individuals with urinary tract infection than in negative controls, especially when the patients were infected with more virulent strains of E. coli (120), and it was found to be significantly correlated to both C-reactive protein (CRP) and temperature (106).

IL-6 is a pro-inflammatory and regulatory cytokine, stimulating the production of acute phase reactants such as CRP, and the development of fever. We found higher urinary levels of IL-6 in acute cystitis than in asymptomatic bacteriuria, and somewhat higher levels again in asymptomatic bacteriuria than in negative controls (Table 8). This difference, comparing urinary tract infection with asymptomatic bacteriuria, has also been found in children (96). Urinary IL-6 was elevated in children and adults with urinary tract infection (101, 106, 119, 136), and urinary levels of IL-6 in urinary tract infection reflected disease severity (105, 107, 118).
With the exception of one previous study by Nicolle (103) this is, to our knowledge, the first study evaluating urinary cytokine response in relation to bacteriuria in an elderly population. Asymptomatic bacteriuria is highly prevalent in the elderly, and the cytokine response found in our study fits into a model where asymptomatic bacteriuria in this population, can be regarded as an infection rather than merely bacterial colonisation. Symptoms in urinary tract infections are caused by the inflammatory response. However, the bacteria in asymptomatic bacteriuria may be less virulent, and result in a milder inflammatory response (80). As cytokines/chemokines are early mediators of this inflammatory response, they are likely to be found in lower levels in subjects with asymptomatic bacteriuria than in patients with symptomatic urinary tract infections.

Cytokines are produced locally in the urinary tract, in addition to leakage of cytokines through the kidneys from the bloodstream, emanating from other inflammatory processes in the body. Ageing has also been shown to be accompanied by increases in plasma/serum levels of inflammatory mediators such as cytokines (137). Therefore, findings of high levels of urinary cytokines in the elderly must be interpreted with caution. Our study was small and ought to be supplemented with studies where urinary cytokines are followed in the same individuals with and without asymptomatic bacteriuria, and if they develop symptomatic urinary infections, also collecting data regarding co morbidity.

**Leukocyte esterase**

When comparing urinary leukocyte esterase in acute cystitis, asymptomatic bacteriuria and negative controls (Paper IV), we found gradually increasing values, with the highest ones in acute cystitis (Table 9). The figures for asymptomatic bacteriuria and negative controls are essentially verified in the baseline population (Figure 6). Most studies on the use of leukocyte esterase in diagnosing urinary tract infections have been performed on younger populations, revealing usefulness in excluding the presence of infection (138). However, there are few studies on elderly populations and even fewer addressing the question of differentiating between asymptomatic bacteriuria and symptomatic urinary tract infections (139, 140). Leukocytes in the urine are common in the elderly. In a Finnish study, the prevalence was 47% in a population aged 85 years or over, 77% in those with bacteriuria and 37% in those without (141). Others have found leukocyturia in 90% of subjects with asymptomatic bacteriuria (42), but these studies do not usually distinguish between different levels of leukocyturia.

**Possible usefulness in practice**

We plotted a ROC curve (Figure 5) showing the paired values of sensitivity and specificity for different cut-off values of CXCL1, CXCL8 and IL-6 in discriminating between symptomatic urinary tract infection and asympto-
matic bacteriuria. Choosing IL-6 and a cut-off value of 30 pg/mg gives a specificity of 96% and a sensitivity of 81%. This sensitivity rate is probably acceptable in the clinical situation for discriminating between symptomatic urinary tract infection and asymptomatic bacteriuria in patients with diffuse symptomatology, as urinary tract infections are usually benign and often self-healing. CXCL8 is also increased in acute cystitis as compared with asymptomatic bacteriuria, but since CXCL8 is involved in recruiting leukocytes to the site of an infection, there is a strong correlation between urinary levels of CXCL8 and the number of leukocytes in urine (134). Therefore, measurement of CXCL8 probably does not contribute more to this diagnostic procedure than measurement of leukocyte esterase. Other researchers have proposed measurement of cytokines for diagnosing febrile urinary tract infection, with cut-off values similar to those found in our study (105-107).

Although previous studies have shown that an increase in the number of leukocytes in the urine is an unspecific finding, our results indicate that with higher cut-off values (>2), measurement of leukocyte esterase could be helpful in distinguishing between symptomatic urinary tract infection and asymptomatic bacteriuria. The combination of a positive test for leukocyte esterase (>2) and for IL-6 (>30 pg/mg) seems to further increase specificity (Figure 7). As our study was small, these results need to be confirmed in a larger study.
Clinical implications

Our study showed a high prevalence of asymptomatic bacteriuria in elderly people living in the community, markedly higher in those with impaired mobility and urinary incontinence (Paper I). There is convincing evidence that asymptomatic bacteriuria in this population should not be treated with antibiotics (59, 60, 65-70). Our finding of a high turnover of strains (Paper III) also supports this non-treatment regimen – the bacteriuria will soon recur, possibly with a more virulent bacterial strain, or with a strain showing a more problematic pattern of antibiotic resistance.

However, as urinary testing is a frequent routine measure in different kinds of medical care, it is common for a doctor to be presented with a urinary test indicating bacteriuria. The result is often course of antibiotics, even for asymptomatic patients (88, 142). It is important to reduce this unnecessary use of antibiotics, which can be done through educational efforts about antibiotic use and asymptomatic bacteriuria, and also, even more importantly, by avoiding routine urinary testing. Urinary testing for bacteriuria should be performed when doctors order it and limited to patients who have signs and symptoms suggestive of urinary tract infections.

Bacteriuria in elderly women was found to be associated with urge but not stress urinary incontinence (Paper II). Consequently, there is no indication for a urinary test for bacteriuria in a woman reporting solely stress incontinence. When bacteriuria is found in a woman with urge urinary incontinence, it is close at hand to try a course of antibiotics. This may be correct when there is recent onset of the urge incontinence, but in longstanding incontinence there is no clear causal connection, and it is important to search for other causes, and to consider other treatment strategies.

One common reason for dubious antibiotic use in the elderly is the “on the safe side” treatment given when bacteriuria is found in a patient with diffuse symptoms. This may be a patient experiencing fatigue, vertigo or general malaise, but without focal signs of a urinary tract infection. Many doctors advocate antibiotic treatment in these cases, but evidence for its utility is lacking (89, 92, 94). This issue ought to be addressed in a randomised placebo controlled trial. There may also be a patient who is unable, owing to cognitive impairment, to state whether (s)he has dysuria or other focal symptoms of urinary tract infection. In these cases there is a need for better diagnostic tools to discriminate between true symptomatic urinary
tract infection and innocuous asymptomatic bacteriuria. Leukocyte esterase, using \( >2 \) as the cut off point for acute cystitis in a patient with bacteriuria, showed reasonable specificity (Paper IV) and could be used in clinical practice today. Our results (Paper IV) also indicate that urinary leukocyte esterase and IL-6 used together could further improve diagnostic specificity. However, this needs to be verified in a prospective study using these urinary diagnostics in a clinical context.
Conclusions

- Bacteriuria without symptom of urinary tract infection is a common finding in elderly people living in the community: In the cross-sectional survey we found asymptomatic bacteriuria, according to the recognised definition, in one out of five women and in one out of ten men.
- In elderly women, reduced mobility and urinary incontinence were both associated with the presence of asymptomatic bacteriuria: In a woman with reduced mobility and urinary incontinence the estimated risk of finding asymptomatic bacteriuria was almost 50%.
- In elderly women, the odds of having bacteriuria increased with the frequency of incontinence. Urge incontinence was associated with bacteriuria, while stress incontinence was not.
- Asymptomatic bacteriuria often persists: Of subjects with asymptomatic bacteriuria at baseline, 60% also had asymptomatic bacteriuria in the two subsequent surveys at 6 and 18 months.
- In the three repeated surveys over 18 months, asymptomatic bacteriuria was found at least once in one third of women and in one fifth of men.
- There was a frequent change of strains in those with “persisting” E. coli-bacteriuria: At the 18-month follow-up only 40% carried the same strain.
- In elderly women, the risk of developing a symptomatic urinary tract infection within 24 months was higher among women with asymptomatic bacteriuria at baseline than in those without bacteriuria.
- Urinary levels of CXCL1, CXCL8 and IL-6 were higher in patients with acute cystitis than asymptomatic bacteriuria, and were also higher in subjects with asymptomatic bacteriuria than in negative controls.
- Urinary leukocyte esterase >2 in a patient with bacteriuria indicates a symptomatic infection.
- Measurement of urinary IL-6 and leukocyte esterase in combination could be even more useful in discriminating between symptomatic and asymptomatic bacteriuria.
Sammanfattning (in Swedish)

Antibiotika och antibiotikaresistens
Under 1900-talet har kunskapen om infektionssjukdomarna och deras behandling förbättrats i snabb takt. Många stora infektionssjukdomar har, åtminstone i de rika delarna av världen, minskat i betydelse pga. förbättrad hygien, minskad trångboddhet och andra sociala faktorer. Upptäckten av sulfa på 1930-talet och penicillinet, som kom i användning första gången på 1940-talet, revolutionerade våra möjligheter att behandla allvarliga och tidigare livshotande infektioner. Nya antibiotika (antibakteriella medel) utvecklades under 1900-talets senare hälft och vi fick nu goda möjligheter att behandla såväl allvarliga lunginflammationer och blodförgiftningar som lindriga men besvärande infektioner som halsfluss och blåskattarr.


Urinvägsinfektioner
Urinvägarnas omfattar njurarna där urinen produceras, urinledarna som leder urinen till urinblåsan där urinen lagras i väntan på att få kissas ut via urinröret. Även prostatakörteln hos mannen är en del av urinvägarna.

Vid en urinvägsinfektion etablerar sig bakterier i urinvägarna. Oftast är det tarmbakterier av typen Escherichia coli (E. coli), speciellt hos kvinnor, som tar sig den korta vägen från tarmöppningen till urinröret och vidare upp i urinvägarna. Symtomen vid urinvägsinfektion orsakas, som vid de flesta andra infektioner, främst av kroppens reaktion på bakterierna.


Ytterligare en form av urinvägsinfektion är när bakterier etablerar sig i urinvägarna utan att det ger några symtom – asymtomatisk bakteriuri.

Asymtomatisk bakteriuri

Asymtomatisk bakteriuri är vanligast hos kvinnor. Det förekommer hos någon procent av skolflickor och hos 1-5 % av unga och medelålders kvinnor. Från 50-60 år ökar förekomsten successivt till ca 20 % hos 80-åriga kvinnor. Hos yngre män är det ovanligt med asymtomatisk bakteriuri, men från 50-60 år ökar förekomsten successivt till 5-10 % hos 80-åriga män. Hos sjuka och skropliga äldre är asymtomatisk bakteriuri ännu vanligare. På sjukhem och motsvarande har 30-50 % av kvinnorna och 20-30 % av männen bakterier i urinen utan att det ger några symtom. Kvinnor med diabetes har oftare asymtomatisk bakteriuri än kvinnor utan diabetes.


Det kliniska problemet i samband med asymtomatisk bakteriuri är därför inte tillståndet i sig, utan att det ofta leder till antibiotikabehandling i onödan. Urinprov tas ofta mer eller mindre rutinmässigt inom sjukvården och hittar vi bakterier i urinen är vi vana att behandla. Många gånger kan det dessutom vara så att allmänna eller diffusa symtom hos äldre tillskrivs ett samtidigt fynd av bakterier i urinen, trots att detta fynd inte har något samband med symtomen. Det kan också ibland vara så att patienten på grund av t ex demenssjukdom inte själv kan berätta om hon har några symtom på blåskatarr.
Frågeställningar i denna studie

De flesta studier angående asymptomatisk bakteriuri hos äldre är gjorda på institutionsboende av olika slag. Vi ville med vår studie kartlägga förekomsten av asymptomatisk bakteriuri hos äldre som fortfarande bor i eget boende. Vi ville dessutom se om det fanns någon koppling mellan asymptomatisk bakteriuri och andra sjukdomar eller tillstånd hos individen. Vidare ville vi se vad som händer över tiden. Är det så att samma individ oftast har asymptomatisk bakteriuri konstant och i så fall med samma bakteriestam? Till sist ville vi undersöka om mängden vita blodkroppar i urinen, mätt som leukocytesteras med urinsticka, och halten i urinen av en typ av små signalämnen/inflammationsproteiner (cytokiner) skiljer sig åt mellan patienter med akut cystit och individer med asymptomatisk bakteriuri. Kan leukocytesteras användas i diagnostiken i tveksamma fall och kan mätning av cytokiner vara en ytterligare hjälp?

Hur studien gjordes


Leukocytesteras och cytokiner i urinen mättes hos 16 patienter som sökte vårdcentralen för en akut cystit, hos 24 individer med bakterier men utan symtom och hos 20 individer som varken hade bakterier eller symtom. Alla dessa var 80 år eller äldre.

Studiens resultat och något om hur de kan tolkas

Vi fann att vid varje undersökningstillfälle hade nästan var femte kvinna och var tionde man bakterier i urinen utan att det gav några symtom. Sammantaget hade mer än var tredje kvinna och var femte man bakterier i urinen utan symtom vid åtminstone ett av undersökningstillfällena. En statistisk analys (logistisk regression) av resultatet bland kvinnorna visade att nedsatt rörlighet, urininkontinens och behandling med östrogen alla hade en egen, oberoende koppling till förekomst av bakterier i urinen.

Orsaken till sambandet med nedsatt rörlighet skulle kunna vara att dessa individer har svårt att helt tömma urinblåsan och att det då blir lättare för bakterier att hålla sig kvar, men det kan också vara så att nedsatt rörlighet är ett tecken på dåligt allmäntillstånd och skröplighet, något som tidigare visats ha ett samband med bakterier i urinen.

Vi gjorde en närmare analys av sambandet med urininkontinens och fann att kvinnor som rapporterade tättare besvär av urinläckage ofta hade
bakterier i urinen. Det visade sig också finnas ett samband mellan trängningsinkontinens (bråttom – hinner inte till toaletten) och bakterier i urinen. Däremot fann vi inget motsvarande samband med stressinkontinens (läckage vid t ex hosta och lyft). Här skulle man kunna tänka sig att en del individer med trängningsinkontinens och bakterier, åtminstone om de har nyttillkomna besvär, i själva verket har en symtomgivande blåskatarr och då kan vara hjälpta av antibiotikabehandling. En alternativ förklaring kan vara att urininkontinensen och bakterierna i urinen har en annan, gemensam orsak. För detta senare talar att det finns tidigare studier där man antibiotikabehandlat kvinnor med urininkontinens och bakterier i urinen utan att det haft någon positiv effekt på inkontinensen.

Genom att typbestämma kolibakterierna kunde vi se att av de individer som hade upprepade fynd av E. coli i urinen hade 76 % kvar samma stam av E. coli efter 6 månader. Efter 18 månader hade de flesta bytt stam så att endast 40 % hade kvar ursprungsstammen.

Kvinnor som hade bakterier i urinen vid första undersökningstillfället visade sig i något högre utsträckning drabbas av en symtomgivande urinvägsinfektion inom 24 månader. Detta stämmer med vad andra funnit i yngre befolkningsskikt. Att behandla med antibiotika vid bakterier i urinen för att förebygga kommande urinvägsinfektioner har prövats i andra studier, dock utan positiva resultat.

Av de cytokiner som undersöks visade sig CXCL1 (GRO-α), CXCL8 (IL-8) och IL-6 förekomma i högre koncentrationer vid asymtomatisk bakteriuri jämfört med individer utan bakterier i urinen och i än högre koncentrationer vid akut cystit.

Vid både akut cystit och asymtomatisk bakteriuri sågs tecken på ett ökat antal vita blodkroppar i urinen mätt som utslag för leukocytetestas på urinstickan. Detta stämmer väl med tidigare studier. Om man emellertid tittade på graden av utslag för leukocytetestas visade det sig att de flesta med akut cystit hade mer än två på en femgradig skala (0-4) i motsats till individer med asymtomatisk bakteriuri som i regel hade två eller mindre.

För att i tveksamma fall skilja mellan symtomgivande urinväginfektion och asymtomatisk bakterieuri skulle därför mätning av leukocytetestas med skiljevärdena två kunna vara användbart. Ytterligare diagnostisk träffsäkerhet skulle kunna uppnås om man kombinerade mätning av leukocytetestas med mätning av IL-6 i urinen.

Antalet individer som undersöks för cytokinhalten i urinen var litet och tolkningen av resultaten bör därför göras med viss försiktighet. Dock stämmer resultaten med vad andra funnit hos yngre individer. För att få bättre kunskap om och hur sådana mätningar kan tillföra något i diagnostiken bör en studie med fler deltagare och i en mer klinisk miljö göras.
Konklusion
Asymtomatisk bakteriuri är vanligt även hos äldre utanför institutioner. Många har bakterier i urinen tillfälligt men många har också detta fynd vid upprepad provtagning och då ofta med nya bakteriestammar. Detta stöder redan tidigare etablerad kunskap att inte behandla asymtomatisk bakteriuri. För att inte förledas till onödig antibiotikabehandling är det viktigt att inte rutinmässigt ta urinprov annat än när man verkligen misstänker att en urinvägsinfektion kan orsaka patientens besvär. I tveksamma fall kan man ha viss hjälp av leukocytesteras på urintickan, i framtiden eventuellt kombinerat med en urinsticka som mäter IL-6.

Framtida forskning för att ytterligare förbättra kunskapen om asymtomatisk bakteriuri hos äldre:

- Behandlingsstudie för att utvärdera effekten av antibiotikabehandling vid bakteriuri och trängningsinkontinens hos äldre kvinnor.
- Behandlingsstudie för att utvärdera effekten av antibiotikabehandling vid bakteriuri och allmänssymtom men där fokala urinvägsymtom saknas.
- Studier om förekomst och handläggning av asymtomatisk bakteriuri/symtomgivande urinvägsinfektioner hos äldre män.
- Studie för att bättre undersöka om det finns ett verkligt samband mellan asymtomatisk bakteriuri och senare tillkommande symtomgivande urinvägsinfektioner.
- Studie för att närmre utröna cytokinernas möjliga roll i diagnostiken genom att göra mätningar över tiden hos samma individer med och utan asymtomatisk bakteriuri och vid tillkommande symtomgivande urinvägsinfektioner.
Acknowledgements

Many people have contributed to this research project. Especially I wish to express my gratitude to:

Lars Englund, Sigvard Mölstad and Kurt Svärdsudd, my supervisors. Lars for strong, positive and immediate support when needed, Sigvard for sharing with me your broad knowledge in the subject and for your ability to see what is important, and Kurt for introducing me into the field of epidemiology.

Malin André, my colleague and friend. This would not have been done without having you as a source of inspiration.

Lena Olai, Lena Skoglund, Susanne Pantzar and Carina Anteskog who visited all the participants and carefully collected the data, and Lena, you are good to have as a roommate, both in dialogue and in silence.

Britta Loré at the microbiology laboratory of Falun. Always positive and interested, you introduced me to E. coli and gave me all support I needed, in spite of your heavy workload. Thank you also to the staff of the microbiology laboratory of Falun.

Maria Pilawa, Marianne Omne-Pontén and Staffan Nilsson at the Centre for Clinical Research, Dalarna for your continuous support in all possible ways.

All my friends and research colleagues at CKF for creating an inspiring and creative environment in seminars as well as around the kitchen table.

Eva Samuelsson, my friend and co-author. You showed me how to do.

Sture Löfgren, Andreas Matussek and Jan Strindhall at the microbiology laboratory of Jönköping for excellent research collaboration. Cytokines and E. coli really are interesting, believe it or not. Thank you also Sofia Nygren, Elisabeth Slänemyr and Marita Skarstedt for your technical support.

My colleagues and all the staff of Britsarvets Health Care Centre for your encouraging support in this project. Yes, I know I have been a bit absent from the real work.
Co-author Inger Kühn, for sharing your knowledge on phenotyping.

Research colleagues at the section of Family Medicine and Clinical Epidemiology, Uppsala University, for interesting discussions and seminars.

Jan Ifver for statistical advices, Linda Schenck for correcting my attempts in the English language and Britt-Marie Sandberg for help in assembling data from the population register.

Bernhard von Below, friend and conversation partner. Thank you for some wonderful wandering and working weeks in the Alps.

My dear wife Lisa and my children Axel, Elsa, Signe, Ebba and Agnes for your love and support in every way!

I am also grateful for the financial support for this study given by:

- The Centre for Clinical research, Dalarna (County Council of Dalarna).
- STRAMA (the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents).
References


88. Walker S, McGeer A, Simor AE, Armstrong-Evans M, Loeb M. Why are antibiotics prescribed for asymptomatic bacteriuria in institutionalized elderly


adequate diagnostic tool? Arch Gerontol Geriatr. 2008; [Epub ahead of print].


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)