Women with recurrent urinary tract infections: antibiotic resistance and non-antibiotic prophylaxis
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Introduction and outline of the thesis
Introduction

Urinary tract infections (UTI) are common and are among the most frequent medical conditions requiring outpatient treatment. Approximately 80% of all UTIs occur in women. The shorter female urethra is often seen as the cause of this increased incidence. Sexual intercourse is a well-known risk factor for the development of a UTI. By the age of 24, it has been estimated that 1 in 3 women will have had a UTI. About half of all women will experience one or more UTIs during their lifetime. The incidence of UTIs increases with age. In postmenopausal women lower estrogen levels lead to disappearance of lactobacilli from the vaginal bacterial flora. This results in a higher chance of colonization of the vagina with Enterobacteriaceae, which is associated with the occurrence of UTIs. Moreover, there is an increased risk of UTIs in certain patient groups, such as patients with an indwelling catheter, diabetes mellitus, urinary obstruction or neurogenic bladder. Given the increase in life expectancy and the increase in the number of patients with diabetes in the coming years, it is expected that the absolute number of cases of UTI will continue to rise. In addition to impact on quality of life, UTIs have a substantial financial and economic impact on society.

Recurrent UTIs

Approximately 20-30% of the women with a UTI will have a recurrence. Recurrent UTIs (rUTIs) are defined as at least three episodes of a UTI in twelve or at least two episodes in six months. rUTIs can be subdivided into relapses and reinfections. A relapse is defined as a UTI caused by the same microorganism after adequate treatment. Reinfection refers to recurrence of a UTI caused by a different microorganism or a rUTI caused by a previously isolated microorganism after treatment and a subsequent negative urine culture. To prevent reinfections, women with rUTIs can be recommended to use daily low-dose antibiotic prophylaxis, to start a short course of antibiotics immediately at the onset of symptoms, or to take postcoital antibiotic prophylaxis.

Use of antibiotics is effective in the treatment of UTIs, but leads to an increase in antibiotic resistance in microorganisms. This is also the case for low-dose antibiotic prophylaxis. In a study with 86 healthy students, 82 of them had resistant microorganisms in their feces after 2 weeks of trimethoprim (with or without sulfamethoxazole) prophylaxis. In addition, antibiotics can cause side effects. Women with rUTIs are increasingly asking their healthcare professionals about the value of taking non-antibiotic products. Clearly, there is a need to target alternative pathways involved in the pathogenesis of UTIs.

Pathogens

The majority of the UTIs is caused by bacteria from the intestine that ascend through the urethra to the bladder and sometimes to the kidneys. UTIs can be
divided into uncomplicated and complicated UTIs. An uncomplicated UTI is cystitis in a woman who is not pregnant, is not immunocompromised, has no anatomical and functional abnormalities of the urogenital tract and does not exhibit signs of tissue invasion and systemic infection. Complicated UTIs are UTIs in all other patient groups. The most common pathogen is *Escherichia coli*, causing 70 to 90% of uncomplicated UTIs. Also, in about half of all women with a complicated UTI *E. coli* can be isolated. Other common pathogens are enterococci, *Staphylococcus saprophyticus*, *Proteus mirabilis* and *Klebsiella* species.

**Pathogenesis**
The first step in the pathogenesis is the colonization of the vaginal introitus and urethral meatus with uropathogens, after which the bladder can be colonized through the urethra. The vaginal flora plays an important role in the prevention of UTIs. The lactobacilli-dominated vaginal flora in premenopausal women impedes the colonization of uropathogens due to competitive exclusion and by a decrease in the vaginal pH. The main defense mechanisms of the host against colonization of the bladder are dilution and micturition. Anatomical or functional abnormalities that prevent complete emptying of the bladder increase the chance for colonization with uropathogens.

After colonization, the next step in the pathogenesis of a UTI is the adhesion of uropathogens to the epithelial bladder cells. After adherence, uropathogens are protected against being removed by micturition. The adhesion of *E. coli* to the uroepithelial cell receptors of the host is accomplished by hair-like organelles called fimbriae. The most important are type 1 fimbriae and P-fimbriae. Type 1 fimbriae mainly play a role in the pathogenesis of cystitis and P-fimbriae in pyelonephritis.

**Non-antibiotic prevention of (recurrent) UTIs**

**Prevention of colonization by uropathogens**

*Estrogens*
In premenopausal, non-pregnant women the vaginal flora consists for 90% of lactobacilli, which protect against urogenital infections. A loss or absence of lactobacilli has been associated with increased colonization by uropathogenic *E. coli*. Other conditions that disturb the lactobacilli dominated vaginal flora, for example recent antibiotic use, are also associated with an increased risk of UTIs.

After menopause only 25 to 30% of women have lactobacilli in the vagina. With estrogen replacement therapy this percentage may increase to 60 to 100%, which will lead to a lower risk of UTIs. In a placebo-controlled study with intravaginal estrogens in postmenopausal women with rUTIs, no intravaginal lactobacilli were present at baseline. After one month of treatment, in 22 out of 36 women in the estrogen group intravaginal lactobacilli were present, compared with 0
of 24 women in the placebo group (difference 61%, 95% CI 45 to 77%). In the estrogen group the vaginal pH decreased from 5.5 to 3.8 (p <0.001), while there was no change in the placebo group. The percentage of women with vaginal colonization with *Enterobacteriaceae* in the estrogen group decreased from 67 to 31%, but was virtually unchanged in the placebo group. The main result of this study was that the incidence of UTIs was lower in the estrogen-compared to the placebo group: 0.5 versus 5.9 episodes per patient year (p <0.001).

**Lactobacilli**

The above mentioned study shows that estrogen replacement results into increased numbers of lactobacilli and decreased numbers of potentially pathogenic microorganisms in the vagina. Exogenous administration of lactobacilli might also have this effect. Lactobacilli are live microorganisms which, when administered in adequate amounts, may confer a health benefit to the host. The mechanisms of their probiotic action remain to be further elucidated. However, several laboratory studies have indicated that some lactobacilli strains may affect pathogens by means of competitive inhibition (i.e., by competing for growth). Several lactobacillus strains have anti-pathogenic properties, but not all possess the ability to colonize the vagina. Promising for urogenital use are the strains *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14. *L. rhamnosus* GR-1 is able to colonize the intestines and vagina, can adhere to vaginal and uroepithelial cells and can inhibit the adhesion and growth of intestinal and urogenital pathogens. *L. reuteri* RC-14 is an adherent strain that inhibits the adhesion of a range of uropathogens. An additional advantage is that this strain produces hydrogen peroxide, which can interfere with the growth of pathogens. In recent decades it has become clear that intravaginally administered *L. rhamnosus* GR-1 and *L. reuteri* RC-14 can colonize the vagina, are able to compete with uropathogens and reduce the incidence of UTIs. It has also been shown that after oral intake, the strains *L. rhamnosus* GR-1 and *L. reuteri* RC-14 can be cultured from the vagina. A randomized, placebo-controlled study demonstrated that oral intake of these lactobacilli restored a disturbed vaginal flora into a lactobacilli dominated flora. Furthermore, women in the lactobacilli group had a significant reduction in the number of potentially pathogenic bacteria and yeasts in the vagina.

**Prevention of adherence of uropathogens**

**Cranberries**

For centuries, cranberries are consumed for their medicinal properties. It has long been thought that the beneficial effect of cranberries in the prevention of UTIs was due to the excretion of hippuric acid in urine. In 1984, it was suggested that cranberries might exert their beneficial effects through the inhibition of bacterial adherence to host cells. Subsequently, two substances in cranberries were identified which could inhibit the adhesins of *E. coli*. The first is fructose, which can interfere with the adherence of type 1-fimbriae of *E. coli* to the uroepithelial cells, the second is a high molecular weight substance, the so-called A-type
proanthocyanidins (PACs), which interfere with the attachment of P-fimbriae to uroepithelial cells. In a laboratory study it was shown that *E. coli* can grow on culture media with cranberries, but fimbriae are not longer expressed. The anti-adherence properties of cranberries may help in two ways in the prevention of UTIs: first, there is a selection of less adherent bacterial strains in the stool, and second, the adherence of *E. coli* to uroepithelial cells is inhibited.

Several attempts have been made to assess the efficacy of cranberry products in the prevention of UTIs. In small observational studies and randomized clinical trials favorable results were found for the prevention of recurrences in women with rUTIs. A small crossover trial analyzed 10 women with rUTIs. The women were given either 400 mg cranberry extract or placebo daily for three months before switching treatments. A total of 21 UTIs were recorded during the time they were taking cranberry (2.6 per patient year), compared to 15 UTIs while on placebo (6.0 per patient year).

In an open randomized study in women (mean age 30.5 years) with rUTIs, 50 women received cranberry juice (50 ml = 7.5 g cranberry concentrate/day) and 50 women did not receive therapy. After 6 months 16% of the women in the cranberry group had at least one UTI, compared with 36% of untreated women (difference 20%, 95% CI 3 to 37%). Comparable results were found in a double blind study comparing cranberry products with placebo in women (mean age 42.3 years) with rUTIs.

Based on these studies it was concluded that cranberries may be effective in preventing UTIs in premenopausal women with rUTIs. Whether cranberry products are effective in other patient populations, as for example women without a history of rUTI, is still uncertain.

The optimal cranberry dose to prevent rUTIs is still not clear. In earlier studies with cranberry products the amount of proanthocyanidins used to prevent a UTI is often not described. In 2004 the French Food Authority (AFSSA) stated that a product containing at least 36 mg of PACs may carry the claim “help reduce the adhesion of certain *E. coli* bacteria to the urinary tract walls.” This claim was based on a study in older women without a history of rUTIs. In this study half of the women drank 300 ml cranberry juice daily (36 mg of PACs) and the other half placebo juice. Bacteriuria with pyuria was significantly less likely to occur in the cranberry group.

In a later (2010) ex-vivo study it was shown that the extent and duration of the anti-adhesion activity in urine following cranberry powder consumption was clearly dependent on the amount of PACs consumed. After intake of 72 mg of PACs anti-adhesion activity was present for 24 hours. Therefore, it was concluded that the administration of PAC-standardized cranberry powder at dosages containing 72 mg of PAC per day may offer some protection against bacterial adhesion and virulence in the urinary tract.
In 2008 McMurdo et al. were the first to compare cranberry prophylaxis (500 mg daily) with trimethoprim prophylaxis (100 mg daily) in 137 postmenopausal women with rUTIs. Twenty-five of 69 women in the cranberry group had a UTI, compared to 14 of 68 women in the trimethoprim group (relative risk 1.62 (95% CI: 0.93, 2.79)). Although trimethoprim had a small advantage over cranberry extract, there were more adverse events that led to withdrawal in the trimethoprim group.

Conclusion
Various options to prevent UTIs with non-antibiotic prophylaxis are available. However, only few studies have been performed in which non-antibiotic prophylaxis has been compared with antibiotic prophylaxis, which is standard of care to prevent UTIs in women with recurrent UTIs. The primary goal of the studies described in this thesis was therefore to determine whether cranberries and lactobacilli can be considered as a serious alternative to antibiotics in the prevention of rUTIs.

Outline of the thesis
Emerging antibiotic resistance necessitates studying non-antibiotic alternatives in the prevention of UTIs. This thesis focuses on non-antibiotic prophylaxis of UTIs in pre- and postmenopausal women with recurrent UTIs and the development of antibiotic resistance in women using long-term low-dose antibiotic prophylaxis. In addition, the predictive value of asymptomatic bacteriuria (ASB) and disease-related knowledge in women with rUTIs were investigated.

In Chapter 2 the literature will be reviewed. The aim of this systematic review is to review evidence from randomized trials on the efficacy and tolerability of non-antibiotic prophylaxis compared to placebo or no treatment in adults with rUTIs.

In the following two chapters we will describe the results of the two double-blind randomized trials of the NAPRUTI study (“Non-antibiotic versus Antibiotic Prophylaxis for Recurrent Urinary Tract Infections”). In these two interlinked non-inferiority trials, we investigated the effects of 12-months non-antibiotic prophylaxis on the rate of UTI recurrence and the development of antibiotic resistance. In Chapter 3 we first present the results of the trial in which we compared cranberry- with trimethoprim-sulfamethoxazole prophylaxis in premenopausal women with rUTIs. The results of the trial comparing lactobacilli prophylaxis with trimethoprim-sulfamethoxazole prophylaxis in postmenopausal women with rUTIs are described in Chapter 4.

The aim of the study in Chapter 5 is to assess the determinants of antimicrobial resistance in Escherichia coli isolated from urinary and fecal samples of women with rUTIs.
Chapter 6 focuses on the predictive value of asymptomatic bacteriuria (ASB). Currently, it is unknown whether information from an asymptomatic sample is useful in guiding antimicrobial therapy. In the study described in this chapter we investigate whether ASB is predictive for the development of a UTI and whether *Escherichia coli* ASB strains are predictive for the subsequent UTI-causing strain with regard to antimicrobial susceptibility and pulsed-field gel-electrophoresis pattern.

In Chapter 7 we assess the disease-related knowledge of the women with rUTIs participating in our trials. We sent them a knowledge questionnaire, and questioned them about the cause of UTIs, female pelvic anatomy, the incidence of UTIs, preventive practices, antibiotic use and resistance. Finally, in Chapter 8 we summarize the major findings of all studies and discuss remaining questions and the implications for future research.
References

Introduction


