CHAPTER 1

General introduction

Urinary tract infections (UTI) are among the most frequently reported infections among older persons.[1-6] The incidence of UTI increases with age in both men and women[7-9] and ranges from 12-29 per 100 person-years at risk in community-dwelling older people[9,10] up to 44-58 per 100 person-years at risk in long-term care facilities (LTCF).[11,12] UTI account for 25% to 40% of all bacterial infections in LTCF.[2,13-15] Infections in LTCF contribute to higher morbidity and mortality rates, to more infection outbreaks, higher antimicrobial use, and additional costs.[1,16]

However, it is still generally accepted that diagnosing UTI in vulnerable very old persons is challenging. Factors such as impaired communication due to dementia, high prevalence of incontinence, chronic genitourinary symptoms, and a high frequency of positive urine cultures due to bacteriuria without complaints,[17-19] makes diagnosing UTI even more difficult. In addition, since clinical symptoms of UTI are frequently absent,[20] this makes differentiation between asymptomatic and symptomatic UTI in this population rather complicated.[17,21] As a result, for LTCF populations, there is no generally accepted standard for the diagnosis of UTI.

In these older residents, most clinical symptoms to ascertain UTI are based on consensus as presented in clinical guideliness.[22-27] Currently, these guidelines define a clinical UTI as the presence of specific and non-specific symptoms and signs of UTI, such as dysuria, change in character of urine, and change in mental status, confirmed with a urinalysis to evaluate the evidence of the presence of nitrite and leukocyte esterase. A positive nitrite and leukocyte esterase test may indicate the presence of clinical UTI and treatment with antibiotics may start. Although UTI are often treated empirically,[28] a urine culture may be necessary in LTCF residents with recurrent UTI to confirm the diagnosis and guide antibiotic treatment.

In vulnerable LTCF residents, clinical UTI not only cause several days of illness, but may have more severe consequences such as delirium, dehydration, urosepsis, hospitalization, or even death.[4,29] Infections also lead to a general decline in functioning,[30] which is often irreversible and can cause a cascade of general deterioration, more care dependency, and a higher mortality risk. In addition, disability in activities of daily living (ADL) is independently associated with the development of infections.[3,30,31] The relation between infections and ADL disability seems to present a negative spiral. Older people with dependency in ADL, depression, urine incontinence and impaired cognition are at higher risk of being admitted to a LTCF.[32]

Different factors predispose older persons to infections, such as age-associated changes in the adaptive and innate immune system, the presence of multiple comorbid diseases, the use of indwelling devices (e.g. urinary catheter, feeding tubes), and 24-hour grouped living in close proximity (e.g. participating in social activities, and close contact between residents and staff).[28,33,34]

Considering this negative impact of clinical UTI, we are particularly interested in how to prevent clinical UTI in vulnerable very old persons. Since the incidence of clinical UTI in LTCF residents is high, general hygienic precautions are important in these facilities, e.g. hand hygiene, toilet hygiene, timely change of incontinence material, and urinary catheter care.[35,36] Also, ensuring adequate fluid intake (hydration), regular toilet visits, and sufficient urination

(bladder emptying), is essential to eliminate bacteria and prevent UTI in this population.[37] In addition, an adequate infection surveillance program can provide insight into the incidence and prevalence of infections in LTCF. Surveillance data should be frequently monitored and reviewed to identify changing trends in infections.[38,39] Surveillance results often provide tools for targeted infection prevention strategies.

To more efficiently prevent clinical UTI and their subsequent negative consequences, it is important to identify older persons at risk for UTI. Among vulnerable older persons, an increasing age,[7,34] diabetes mellitus,[40,41] stroke,[42] urine incontinence,[14,43,44] prior history of UTI,[14,43] and impaired functional and cognitive status[3,30,31,34,43] are predictive for the development of clinical UTI.

Several options are available to reduce the risk of clinical UTI in those at high risk. With the discovery of penicillin by Fleming in 1928 and, later, other antibiotics for the treatment of infections, it became possible to cure and prevent UTI. For many years preventive treatment with antibiotics was the regular preventive care. However, an increasing problem arose with uropathogens that became resistant to antibiotic treatment. Also, prophylactic prevention with antibiotics in residents with recurrent UTI is not preferred because of side-effects, antibiotic resistance, and the related costs.[28,45]

With the expected increase in antimicrobial resistance there is a need for alternative non-antibiotic methods for UTI prevention. Prophylaxis with the vaginal application of estrogens is effective in post-menopausal women, but its safety and feasibility in geriatric populations has not yet been studied.[46,47] Methenamine hippurate is not effective for UTI prevention in patients with neurogenic bladder or renal tract abnormalities,[48] but is often present in LTCF residents. Also, other non-drug preventive measures can be considered, such as vitamin C, *Lactobacilli* and cranberry. However, vitamin C was shown to be not effective in the prevention of UTI,[49] and the use of *Lactobacilli* in post-menopausal women had no effect in UTI prevention compared with antibiotics.[50]

Centuries ago American Indians were aware of the medicinal working of cranberries and cranberry-containing products have long been used as a folk remedy to prevent clinical UTI. However, the question remains: are cranberry capsules a new alternative for the prevention of clinical UTI in LTCF residents? There is some evidence that prophylaxis with cranberry products is a potential prevention strategy.[51-55] Cranberries contain proanthocyanidins (PACs), which are stable compounds with anti-adhesion activity against e.g. *Escherichia coli*.[56-58] Two studies reported that cranberry juice may be protective in older adults[54,59] but the effectiveness of cranberry capsules in the protection against clinical UTI in vulnerable very old persons in LTCF has not yet been studied.

Aims of this thesis

The overall aim of this thesis is to study the possibilities for and effects of the prevention of clinical urinary tract infections in vulnerable very old persons.

The first part of this thesis investigates the effect of infections on functioning and explores which vulnerable very old persons would benefit most from UTI prevention. Chapter 2 describes a prospective follow-up study which explores the characteristics of LTCF residents on the natural course of care dependency. Within the Leiden 85-plus Study (a population-based prospective follow-up study of 85-year-old inhabitants of Leiden) we studied whether clinical infections predict an increase in disability in ADL among the oldest-old (Chapter 3), and which vulnerable older persons are at risk for UTI (Chapter 4).

The second part of this thesis describes the results of the effectiveness and costs of cranberry capsule use in the prevention of UTI in LTCF residents. The CRANBERRY study, a double-blind randomized placebo-controlled multi-center trial was conducted in 21 LTCF from the University Network for the Care sector in South Holland (UNC-ZH). The effectiveness of cranberry capsules in preventing UTI, stratified for UTI risk at baseline, is presented in Chapter 5. The use of cranberry capsules requires not only evaluation of its clinical effectiveness but also of its cost-effectiveness. The economic evaluation presented in Chapter 6 investigated the effect of UTI on health and related costs, and whether the preventive use of cranberry capsules in LTCF is cost-effective.

Chapter 7 presents a general discussion on the main results of the studies, considers the clinical implications of our findings for daily practice in long-term care, and makes some recommendations for future research.

REFERENCES

1 Eikelenboom-Boskamp A, Cox-Claessens JH, Boom-Poels PG, Drabbe MI, Koopmans RT, Voss A. Three-year prevalence of healthcare-associated infections in Dutch nursing homes. *J Hosp Infect* 2011; 78:59-62.

2 Cotter M, Donlon S, Roche F, Byrne H, Fitzpatrick F. Healthcare-associated infection in Irish long-term care facilities: results from the First National Prevalence Study. *J Hosp Infect* 2012; 80:212-216.

3 Chami K, Gavazzi G, Carrat F, de Wazieres B, Lejeune B, Piette F, Rothan-Tondeur M. Burden of infections among 44,869 elderly in nursing homes: a cross-sectional cluster nationwide survey. *J Hosp Infect* 2011; 79:254-259.

4 Engelhart ST, Hanses-Derendorf L, Exner M, Kramer MH. Prospective surveillance for healthcare-associated infections in German nursing home residents. *J Hosp Infect* 2005; 60:46-50.

5 Eriksen HM, Koch AM, Elstrom P, Nilsen RM, Harthug S, Aavitsland P. Healthcare-associated infection among residents of long-term care facilities: a cohort and nested case-control study. *J Hosp Infect* 2007; 65:334-340.

6 Richards CL, Jr. Infection control in long-term care facilities. *J Am Med Dir Assoc* 2007; 8:S18-S25.

7 Nationaal Kompas. Acute urineweginfecties. Omvang van het probleem. Incidentie en sterfte naar leeftijd en geslacht. [Acute urinary tract infections. Extent of the problem. Incidence and mortality by age and gender] (online).

8 Gardner ID. The effect of aging on susceptibility to infection. *Rev Infect Dis* 1980; 2:801-810.

9 Nicolle LE. Urinary tract infections in the elderly. *Clin Geriatr Med* 2009; 25:423-436.

10 Cools HJ, van der Meer JW. [Infections and aging]. *Ned Tijdschr Geneeskd* 1998; 142:2242-2245.

11 Nicolle LE, Strausbaugh LJ, Garibaldi RA. Infections and antibiotic resistance in nursing homes. *Clin Microbiol Rev* 1996; 9:1-17.

12 Stevenson KB. Regional data set of infection rates for long-term care facilities: description of a valuable benchmarking tool. *Am J Infect Control* 1999; 27:20-26.

13 Nicolle LE. Urinary tract infections in long-term care facilities. *Infect Control Hosp Epidemiol* 2001; 22:167-175.

14 Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Am J Med* 2002; 113 Suppl 1A:5S-13S.

15 Ruben FL, Dearwater SR, Norden CW, Kuller LH, Gartner K, Shalley A, Warshafsky G, Kelsey SF, O'Donnell C, Means E. Clinical infections in the non-institutionalized geriatric age group: methods utilized and incidence of infections. The Pittsburgh Good Health Study. *Am J Epidemiol* 1995; 141: 145-157.

16 Rothan-Tondeur M, Piette F, Lejeune B, de WB, Gavazzi G. Infections in nursing homes: is it time to revise the McGeer criteria? *J Am Geriatr Soc* 2010; 58:199-201.

17 Buhr GT, Genao L, White HK. Urinary tract infections in long-term care residents. *Clin Geriatr Med* 2011; 27:229-239.

18 Nicolle LE. Urinary infections in the elderly: symptomatic of asymptomatic? *Int J Antimicrob Agents* 1999; 11:265-268.

19 Petersen EE. Bacteriological finding. *Dtsch Arztebl Int* 2010; 107:824.

20 D'Agata E, Loeb MB, Mitchell SL. Challenges in assessing nursing home residents with advanced dementia for suspected urinary tract infections. *J Am Geriatr Soc* 2013; 61:62-66.

21 Rowe TA, Juthani-Mehta M. Diagnosis and management of urinary tract infection in older adults. *Infect Dis Clin North Am* 2014; 28:75-89.

22 Loeb M, Bentley DW, Bradley S, Crossley K, Garibaldi R, Gantz N, McGeer A, Muder RR, Mylotte J, Nicolle LE, Nurse B, Paton S, Simor AE, Smith P. Development of minimum criteria for the initiation of antibiotics in residents of long-term care facilities: results of a consensus conference. *Infect Control Hosp Epidemiol* 2001; 22:120-124.

23 McGeer A, Campbell B, Emori TG, Hierholzer WJ, Jackson MM, Nicolle LE, Peppler C, Rivera A, Schollenberger DG, Simor AE. Definitions of infection for surveillance in long-term care facilities. *Am J Infect Control* 1991; 19:1-7.

24 Juthani-Mehta M, Tinetti M, Perrelli E, Towle V, Van Ness PH, Quagliarello V. Interobserver variability in the assessment of clinical criteria for suspected urinary tract infection in nursing home residents. *Infect Control Hosp Epidemiol* 2008; 29:446-449.

25 Went P, Achterberg W, Bruggink R, Ellen-van Veelen J, Pelzer D, Rondas A, Schep-de Ruiter E. Richtlijn Urineweg-Infecties [Guideline Urinary Tract Infections] Utrecht, the Netherlands: Verenso, Dutch Association of Elderly Care Physicians, 2006.

26 High KP, Bradley SF, Gravenstein S, Mehr DR, Quagliarello VJ, Richards C, Yoshikawa TT. Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities: 2008 update by the Infectious Diseases Society of America. *J Am Geriatr Soc* 2009; 57: 375-394.

27 Genao L, Buhr GT. Urinary Tract Infections in Older Adults Residing in Long-Term Care Facilities. *Ann Longterm Care* 2012; 20:33-38.

28 van Buul LW, van der Steen JT, Veenhuizen RB, Achterberg WP, Schellevis FG, Essink RT, van Benthem BH, Natsch S, Hertogh CM. Antibiotic use and resistance in long term care facilities. *J Am Med Dir Assoc* 2012; 13:568-13.

29 Mylotte JM. Nursing home-acquired bloodstream infection. *Infect Control Hosp Epidemiol* 2005; 26: 833-837.

30 Bula CJ, Ghilardi G, Wietlisbach V, Petignat C, Francioli P. Infections and functional impairment in nursing home residents: a reciprocal relationship. *J Am Geriatr Soc* 2004; 52:700-706.

31 Maziere S, Couturier P, Gavazzi G. Impact of functional status on the onset of nosocomial infections in an acute care for elders unit. *J Nutr Health Aging* 2013; 17:903-907.

32 Young Y. Factors associated with permanent transition from independent living to nursing home in a continuing care retirement community. *J Am Med Dir Assoc* 2009; 10:491-497.

33 Juthani-Mehta M, Quagliarello VJ. Infectious diseases in the nursing home setting: challenges and opportunities for clinical investigation. *Clin Infect Dis* 2010; 51:931-936.

34 High KP, Bradley S, Loeb M, Palmer R, Quagliarello V, Yoshikawa T. A new paradigm for clinical investigation of infectious syndromes in older adults: assessment of functional status as a risk factor and outcome measure. *Clin Infect Dis* 2005; 40:114-122.

35 Went PBM, Caljouw MAA. Urineweginfecties. *Tijdschrift voor Ouderengeneeskunde* 2013; 38:37-38.

36 Smith PW, Bennett G, Bradley S, Drinka P, Lautenbach E, Marx J, Mody L, Nicolle L, Stevenson K. SHEA/APIC Guideline: Infection prevention and control in the long-term care facility. *Am J Infect Control* 2008, 36:504-535.

37 Cools HJ. [The elimination of bacteria from the bladder in geriatric patients]. *Ned Tijdschr Geneeskd* 1984; 128:1835-1839.

38 Haenen A, Alblas J, De Greeff SC, Veldman MJ. Surveillance van infectieziekten in verpleeghuizen, aan de slag met infectiepreventie. [Surveillance of infectious diseases in nursing homes, get started with infection prevention]. *Infectieziekten bulletin* 2013; 24:244-247.

39 Montoya A, Mody L. Common infections in nursing homes: a review of current issues and challenges. *Aging health* 2011; 7:889-899.

40 Geerlings SE. Urinary tract infections in patients with diabetes mellitus: epidemiology, pathogenesis and treatment. *Int J Antimicrob Agents* 2008; 31 Suppl 1:S54-S57.

41 Ronald A, Ludwig E. Urinary tract infections in adults with diabetes. *Int J Antimicrob Agents* 2001; 17:287-292.

42 Powers JS, Billings FT, Behrendt D, Burger MC. Antecedent factors in urinary tract infections among nursing home patients. *South Med J* 1988; 81:734-735.

43 Stamm WE, Raz R. Factors contributing to susceptibility of postmenopausal women to recurrent urinary tract infections. *Clin Infect Dis* 1999; 28:723-725.

44 Moore EE, Jackson SL, Boyko EJ, Scholes D, Fihn SD. Urinary incontinence and urinary tract infection: temporal relationships in postmenopausal women. *Obstet Gynecol* 2008; 111:317-323.

45 Carlet J, Collignon P, Goldmann D, Goossens H, Gyssens IC, Harbarth S, Jarlier V, Levy SB, N'doye B, Pittet D, Richtmann R, Seto WH, van der Meer JW, Voss A. Society's failure to protect a precious resource: antibiotics. *Lancet* 2011; 378:369-371.

46 Raz R. Postmenopausal women with recurrent UTI. *Int J Antimicrob Agents* 2001; 17:269-271.

47 Perrotta C, Aznar M, Mejia R, Albert X, Ng CW. Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. *Obstet Gynecol* 2008; 112:689-690.

48 Lee BS, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database Syst Rev* 2012; 10:CD003265.

49 Castello T, Girona L, Gomez MR, Mena MA, Garcia L. The possible value of ascorbic acid as a prophylactic agent for urinary tract infection. *Spinal Cord* 1996; 34:592-593.

50 Beerepoot MA, ter Riet G, Nys S, van der Wal WM, de Borgie CA, de Reijke TM, Prins JM, Koeijers J, Verbon A, Stobberingh E, Geerlings SE. Lactobacilli vs antibiotics to prevent urinary tract infections: a randomized, double-blind, noninferiority trial in postmenopausal women. *Arch Intern Med* 2012; 172:704-712.

51 Beerepoot MA, ter Riet G, Nys S, van der Wal WM, de Borgie CA, de Reijke TM, Prins JM, Koeijers J, Verbon A, Stobberingh E, Geerlings SE. Cranberries vs antibiotics to prevent urinary tract infections: a randomized double-blind noninferiority trial in premenopausal women. *Arch Intern Med* 2011; 171:1270-1278.

52 Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev* 2012; 10:CD001321.

53 Wang CH, Fang CC, Chen NC, Liu SS, Yu PH, Wu TY, Chen WT, Lee CC, Chen SC. Cranberry-containing products for prevention of urinary tract infections in susceptible populations: a systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med* 2012; 172:988-996.

54 McMurdo ME, Bissett LY, Price RJ, Phillips G, Crombie IK. Does ingestion of cranberry juice reduce symptomatic urinary tract infections in older people in hospital? A double-blind, placebo-controlled trial. *Age Ageing* 2005; 34:256-261.

55 Beerepoot MA, ter Riet G, Verbon A, Nys S, de Reijke TM, Geerlings SE. [Non-antibiotic prophylaxis for recurrent urinary tract infections]. *Ned Tijdschr Geneeskd* 2006; 150:541-544.

56 Howell AB, Foxman B. Cranberry juice and adhesion of antibiotic-resistant uropathogens. *JAMA* 2002; 287:3082-3083.

57 Howell AB. Bioactive compounds in cranberries and their role in prevention of urinary tract infections. *Mol Nutr Food Res* 2007; 51:732-737.

58 Raz R, Chazan B, Dan M. Cranberry juice and urinary tract infection. *Clin Infect Dis* 2004; 38:1413-1419.

59 Avorn J, Monane M, Gurwitz JH, Glynn RJ, Choodnovskiy I, Lipsitz LA. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. *JAMA* 1994; 271:751-754.