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CHAPTER 1

General introduction
Urinary tract infections (UTI) are among the most frequently reported infections among older persons.\textsuperscript{1-6} The incidence of UTI increases with age in both men and women\textsuperscript{7-9} and ranges from 12-29 per 100 person-years at risk in community-dwelling older people\textsuperscript{8,10} up to 44-58 per 100 person-years at risk in long-term care facilities (LTCF).\textsuperscript{11,12} UTI account for 25% to 40% of all bacterial infections in LTCF.\textsuperscript{2,13-15} Infections in LTCF contribute to higher morbidity and mortality rates, to more infection outbreaks, higher antimicrobial use, and additional costs.\textsuperscript{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,\textsuperscript{17-19} makes diagnosing UTI even more difficult. In addition, since clinical symptoms of UTI are frequently absent,\textsuperscript{20} this makes differentiation between asymptomatic and symptomatic UTI in this population rather complicated.\textsuperscript{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 guidelines.\textsuperscript{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,\textsuperscript{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.\textsuperscript{4,29} Infections also lead to a general decline in functioning,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{7,34} diabetes mellitus,\textsuperscript{40,41} stroke,\textsuperscript{42} urine incontinence,\textsuperscript{14,43,44} prior history of UTI,\textsuperscript{14,43} and impaired functional and cognitive status\textsuperscript{3,30,31,44,45} 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.\textsuperscript{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.\textsuperscript{46,47} Methenamine hippurate is not effective for UTI prevention in patients with neurogenic bladder or renal tract abnormalities,\textsuperscript{48} but is often present in LTCF residents. Also, other non-drug preventive measures can be considered, such as vitamin C, \textit{Lactobacilli} and cranberry. However, vitamin C was shown to be not effective in the prevention of UTI,\textsuperscript{49} and the use of \textit{Lactobacilli} in post-menopausal women had no effect in UTI prevention compared with antibiotics.\textsuperscript{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.\textsuperscript{51-55} Cranberries contain proanthocyanidins (PACs), which are stable compounds with anti-adhesion activity against e.g. \textit{Escherichia coli}.\textsuperscript{56-58} Two studies reported that cranberry juice may be protective in older adults\textsuperscript{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.
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General introduction


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