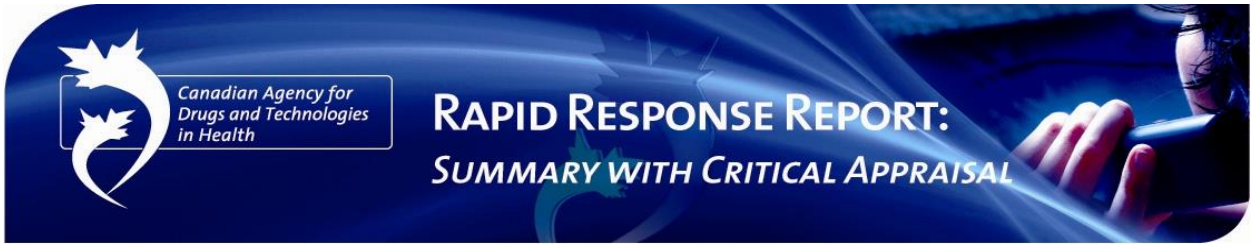

TITLE: Cranberry Products or Topical Estrogen-Based Therapy for the Prevention of Urinary Tract Infections: A Review of Clinical Effectiveness and Guidelines

DATE: 27 October 2016

CONTEXT AND POLICY ISSUES

Urinary tract infections (UTIs) are a substantial health burden, with total annual cost estimate of over US$3.5 billion in the US, and the second most common infection of any organ system.[1] UTIs occur in a wide variety of patient populations, however some populations are at increased risk including patients with bladder dysfunctions,[2] patients with urologic anatomical abnormalities,[2] residents of long-term care facilities,[3] patients with a urinary catheter,[4,5] and normal healthy women.[1] The risk of UTI in normal healthy adult women is approximately 50 times higher than in normal healthy adult men, with 50% of the general healthy female population experiencing at least one UTI in their lifetime, and 25-53% of women who experience a UTI having a recurrent UTI (rUTI) within one year.[1,6] For postmenopausal women risk factors for UTI include estrogen deficiency, cystocoele, urogenital surgery, and a previous UTI.[6] While antibiotics are commonly used for treatment and prophylaxis of UTIs,[4] concerns of promoting antimicrobial resistance,[3] side-effects,[3] alterations of healthy commensal microbiome,[7] and expense[6,8] suggest a role for successful non-antibiotic strategies for UTI prophylaxis.[1]

Cranberries (*Vaccinium macrocarpon* Aiton) have been used for hundreds of years to address urological health issues.[9] Proanthocyanidins (PACs) are a group of compounds recently isolated from cranberries that have demonstrated anti-adhesion activity against antibiotic susceptible and resistant strains of uropathogenic bacteria.[9] Cranberry juice and other cranberry products therefore represent a readily available and relatively safe source of PACs that may prevent UTIs in at-risk patients.[10]

Postmenopausal women, especially postmenopausal women with estrogen deficiency, are at an increased risk of both UTI and rUTI.[6] Topical estrogen can normalize vaginal flora changes that may have become unfavourable due to decreased estrogen.[11] It is suggested that the presence of normal vaginal flora may prevent uropathogenic bacterial colonization of the vagina which can then lead to an ascending infection and a subsequent UTI.[12] Topical estrogen therefore represents another potential alternative to antibiotic UTI prophylaxis.

The purpose of this report is to retrieve and review existing evidence of the clinical efficacy, safety and guidelines for the use of cranberry products and topical estrogen-based therapies for UTI prophylaxis.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of cranberry products for the prevention of urinary tract infections?

2. What is the clinical effectiveness of topical estrogen-based therapy for the prevention of urinary tract infections?

3. What are the evidence-based guidelines regarding the prevention of urinary tract infections?

KEY FINDINGS

Evidence of the clinical effectiveness of cranberry products for the prevention of urinary tract infection was identified in three systematic reviews. One high quality systematic review with a meta-analysis found a lack of evidence to support clinical efficacy of cranberry products for all examined populations including women with recurrent urinary tract infections and children. Another high quality systematic review with a meta-analysis found evidence of efficacy for urinary tract infection prophylaxis in children and in women with recurrent urinary tract infections. One additional systematic review specifically focused on pediatric populations also identified evidence of cranberry product prophylaxis. Seven of eight identified randomized controlled trials and all five identified non-randomized studies found statistically significant reductions in urinary tract infection incidence in a variety of patient populations administered cranberry product prophylaxis. The identified guidelines provided mixed recommendations for the use of cranberry product prophylaxis of urinary tract infections. Evidence identified in two systematic reviews on topical estrogen prevention of urinary tract infections in women consistently supported statistically significant clinical efficacy. The identified guidelines provided mixed recommendations for the use of topical estrogen prophylaxis of urinary tract infections. There were no reported observations in the identified evidence of significant adverse events in patients treated with cranberry products or topical estrogen for urinary tract infection prophylaxis.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. For research questions 1 and 2 no methodological filters were applied to limit retrieval by study type. For research question 3 methodological filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and September 28, 2016.

Selection Criteria and Methods

Titles and abstracts identified by the literature search strategy were screened by one reviewer. Articles determined to be potentially relevant were selected for full-text retrieval. Upon review, retrieved full-text articles that satisfied the selection criteria presented in Table 1 were included in the final selection for this report.

Table 1: Selection Criteria

Population	Any patient (adult or child); *Subgroup of interest: Post-menopausal women with frequent UTIs*
Intervention	Q1: Cranberry-containing products (e.g., cranberry juice, cranberry extract) Q2: Topical estrogen-based therapy (e.g., vaginal estrogen suppository, cream, tablet, extended-release insert) Q3: Cranberry-containing products, topical estrogen-based therapy, vaginal probiotics, D-mannose, blueberry-containing products.
Comparator	Q1: Topical estrogen-based therapy, vaginal probiotics, D-mannose, blueberry-containing products, placebo, or no treatment. Q2: Cranberry-containing products, vaginal probiotics, D-mannose, blueberry-containing products, placebo, or no treatment
Outcomes	Q1, 2: Clinical effectiveness – clinical benefits and harms (e.g. reduction in frequency and/or severity of recurrent UTIs, reduction in antibiotic use, adverse events) Q3: Evidence-based guidelines (i.e. practice recommendations)
Study Designs	Health Technology Assessments (HTA)/Systematic review (SR)/Meta-analysis (MA); Randomized controlled trials (RCTs); Non-randomized studies; and Evidence-based Guidelines

Exclusion Criteria

Studies that did not meet the selection criteria presented in Table 1 were excluded. Additionally studies published in a language other than English, published prior to 2011, guidelines without relevant recommendations, guidelines without reported methodology, and articles already included in at least one selected systematic review (SR), or meta-analysis (MA) were excluded.

Critical Appraisal of Individual Studies

Critical assessment of the included SR and HTAs used the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool.[13] The quality of the RCTs and non-randomized studies (NRSs) included in this report were assessed using the Downs and Black checklist.[14] Critical appraisal of the included guidelines used the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument.[15] All critical appraisals described study strengths and limitations narratively instead of assigning a numerical score.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search strategy initially identified 294 titles and abstracts of potential interest. Based upon titles and abstracts, 251 of these citations were excluded. Searching grey literature identified an additional nine potentially relevant articles resulting in a total of 52 articles for which full-text was retrieved. Applying the selection criteria (Table 1) to the full text of these articles resulted in exclusion of a further 30 studies. This report therefore includes 22 relevant articles; three SRs,[16-18] two SRs with MAs,[10,19] eight RCTs,[2-5,15,20-22] five NRSs,[7,11,23-25] and four guidelines with relevant recommendations.[26-29]

The excluded 30 full-text articles consisted of 11 reviews,[1,6,30-38] five studies that examined irrelevant outcomes,[8,9,39-41] one that examined an irrelevant comparator,[42] nine that were included in a more recent SR,[12,43-50] two that examined an irrelevant intervention,[51,52] and two commentary articles.[53,54]

Summary of Study Characteristics

A summary of included study characteristics is provided in Appendix 2.

Study design

SRs

Three SRs,[16-18] and two SRs that included an MA,[10,19] were identified as meeting the selection criteria. Jepson et al. included 24 RCTs and quasi-RCTs published between 1994 and 2011 that examined cranberry juice or cranberry products and conducted an MA on those studies.[10] Wang et al. included 13 RCTs, also published between 1994 and 2011, that examined cranberry containing products and provided an MA of these included studies.[19] Durham et al. identified seven RCTs and one RCT crossover study on cranberry product prophylaxis.[17] Rahn et al. identified 44 studies, published between 1993 and 2012, on commercially available vaginal estrogen products,[18] and the most recent SR, Duenas-Garcia et al, identified five RCTs examining topical estrogen for UTI prophylaxis, the most recent identified evidence was from a 2013 RCT.[16]

RCTs

Eight identified RCTs met the selection criteria and were not included in an identified SR.[2-5,15,20-22] All of these RCTs were two arm studies, with the longest follow-up being 1 year in two RCTs,[2,3] followed by six months in one RCT,[21] 24 weeks in two RCTs,[20,22] 12 weeks in one RCT,[15] six weeks in one RCT,[4] and 30 days in the shortest follow-up of the RCTs.[5] The most recently published RCT identified was conducted in India,[15] two were from the US,[4,20] one from the Czech Republic,[21] one was from Spain,[5] one from the Netherlands,[3] one from France,[2] and one from Japan.[22]

NRSs

Five NRSs are included in this report.[7,11,23-25] One of the identified NRSs was a prospective comparative study from Italy that followed patients for six weeks.[11] One study, published in

2015, also from Italy was described as a registry, supplement study and followed patients for 60 days.[23] Another NRS was conducted in the US and contained both an uncontrolled before and after, as well as a case-controlled analysis with a six month follow-up.[7] Two studies used a before and after analysis where the number of UTIs before prophylaxis was compared to the number of UTIs after initiation of prophylactic intervention. One was an uncontrolled before and after analysis from Spain that followed patients for six months after initiation of prophylaxis and compared the incidence of UTI to the three months prior to enrollment.[24] The other before and after study was from Germany and had a before and after analysis, using UTI incidence over the course of one year prior to enrollment, as well as control data for a retrospective comparison analysis of patients over 1 year.[25]

Guidelines

Four guidelines met the selection criteria.[26-29] The most recent guidelines were from the Group for the Study of Infection in Transplant Recipients (GESITRA) in Spain, published in 2015.[26] The European Association of Urology Nurses (EAUN) published guidelines meeting the selection criteria in 2013.[27] The Scottish Intercollegiate Guidelines Network (SIGN) published relevant guidelines in 2012.[28] The Working Group of the Clinical Practice Guidelines for Urinary Tract Infection in Children, also from Spain, published relevant guidelines in 2011.[29]

Population

SRs and MAs

Two of the five SRs included in this report had inclusion criteria for rUTI patients,[10,16] one of which had inclusion criteria that only specified rUTI patients,[10] and one that specified community dwelling, post-menopausal female rUTI patients.[16] Another SR focused on pediatric patients, both with and without urogenital abnormalities and identified studies that included a total of 685 patients.[17] One SR focused on genitourinary syndrome of menopause patients and identified 14 studies on vaginal estrogen that enrolled a total of 2136 patients.[18] Three SRs had explicitly stated exclusion criteria.[10,16,19] Duenas-Garcia et al. examined the evidence for community dwelling, post-menopausal women and excluded spinal cord injury, self-intermittent catheterization, chronic indwelling catheters, dementia, surgery within 30 days, and mixed population studies. The authors identified nine RCTs that examined a total of 1028 patients.[16] Jepson et al. identified 24 RCTs with trial data on a total of 4473 rUTI patients excluding studies that had patients that were on UTI treatment and patients that had a urinary tract condition that was not caused by bacterial infection.[10] Wang et al. identified 13 RCTs with data on a total of 1494 patients at risk for UTI and excluded RCTs that reported data unsuitable for the author's methods of quantitative analysis.[19]

RCTs

None of the identified RCTs specifically examined post-menopausal rUTI patients. Four RCTs included populations of rUTI patients,[15,20-22] and four included only female patients.[4,20-22] Singh et al. included 72 patients with subclinical asymptomatic bacteriuria and/or rUTI that did not respond to antimicrobials.[15] Maki et al. included 373 female rUTI patients aged 20 to 70 years, with a BMI less than 40, and specified exclusion of patients that had a current UTI and patients that were on antimicrobials.[20] Vostalova included 62 female rUTI patients aged 18 to 75 years and had comprehensive criteria that excluded patients such as pregnant patients, patients with potentially relevant anatomical abnormalities, GI abnormalities, catheterization, and diabetes

mellitus (DM).[21] Takahashi et al. examined 227 female rUTI patients aged 20 to 79 years including patients with acute exacerbation of acute uncomplicated or chronic complicated cystitis.[22] Other populations examined in the RCTs included in this report were 160 adult females undergoing elective gynecologic surgery,[4] 62 patients requiring urethral catheter placement,[5] 928 long term care facility (LCTF) patients over 65 years old,[3] and 171 multiple sclerosis patients with symptoms of pollakiuria, urgency, dysuria, or urinary incontinence.[2]

NRSs

None of the five identified NRSs specifically examined post-menopausal rUTI patients. Four NRSs examined rUTI patients,[7,23-25] two of which included only adult female patients.[7,24] Sanchez et al. included 20 adult female patients with recurrent symptomatic postcoital urinary tract infections (rPCUTI).[24] Pagnonas et al. examined 82 renal transplant patients with rUTI,[25] while the largest study included 370 males with prostatic adenocarcinoma treated with radical, adjuvant, or salvage radiotherapy.[11] Ledda et al. enrolled 44 rUTI patients,[23] while Burleigh et al. enrolled 17 female rUTI patients.[7]

Guidelines

No identified guidelines were specific to post-menopausal rUTI patients, however one guideline with a broad focus of UTI management, diagnosis, and prophylaxis, provided a recommendation specific to this population.[29] The most recently published guidelines from GESITRA focused on UTIs in solid organ transplant patients,[26] while one focused on adult catheterization,[27] and another focused on children aged one month to 18 years.[29]

Intervention and comparators

SRs and MAs

Three SRs included only studies that examined cranberry products for UTI prophylaxis,[10,17,19] while one SR included only studies that examined commercially available vaginal estrogen products.[18] Duenas-Garcia et al. examined topical estrogen, systemic estrogen, and antibiotic UTI prophylaxis.[16] The SRs and MAs of this report identified studies using comparators of placebo,[10,16-19] no treatment,[10,16-19] and any other treatment.[10] Wang et al. included a separate pooled analysis of studies that examined cranberry juice vs placebo/control and cranberry capsule/tablet vs placebo/control,[19] and both Wang et al. and Jepson et al., included separate pooled analysis different dose frequencies.[10,19] Rahn et al. included studies of commercially available vaginal estrogen products and identified studies that employed systemic estrogen, non-hormonal moisturizers, and non-hormonal lubricants as controls.[18]

RCTs

All of the identified RCTs examined cranberry product interventions for UTI prophylaxis.[2-5,15,20-22] Singh et al. used Cranpac (IPCA, Mumbai, India) that specified a proantocyanidin (PAC) content of 60mg, twice per day. The study used *Lactobacilus acidophilus* probiotic as a placebo.[15] Vostalova et al examined cranberry powder capsules (NATUREX-DBS, Sagamore, USA) with a PAC content of 1.4mg taken twice per day,[21] Foxman et al. used TheraCran (Theralogix, LLC, Rockville, MD) capsules with a PAC content equivalent to 240mL cranberry juice taken twice per day,[4] Caljouw et al. used cranberry capsules containing 9mg PAC taken twice daily.[3] These three RCTs compared cranberry capsule efficacy to placebo capsules.[3,4,21] Maki et al. used

240mL cranberry juice (Ocean Spray Cranberries, Inc., Lakeville-Middleboro, MA) with an unspecified PAC content and compared it to a similar placebo beverage.[20] Takahashi et al. also examined cranberry juice (Kikkoman Food Products and Nisshin Oillio Group, Tokyo, Japan) that contained more than 40mg PAC, once per day, and compared it to a color and taste adjusted placebo juice of unreported PAC content.[22] One RCT used cranberry extract powder to make an oral solution containing 18mg PAC, which was administered to participants twice per day, and compared efficacy to a matching placebo.[2] Another RCT used 120mg American cranberry extract with an unreported PAC content in conjunction with unspecified routine prophylactic therapy, and compared it to routine prophylactic therapy alone.[5]

NRSs

All NRSs included in this report examined cranberry products for UTI prophylaxis.[7,11,23-25] Anthocran (Indena Spa, Milan, Italy) with no reported PAC content,[23] sweetened dried cranberries (Ocean Spray Cranberries Inc., Lakeville-Middleboro, MA) with no reported PAC content,[7] Cysticlean (Vita Green, Hong Kong) with 118mg/day PAC,[7] cranberry extract tablets with 60mg/day PAC,[11] and twice daily 50mL of cranberry juice[25] were the interventions of interest in the included NRSs. The comparators used in these studies were from retrospective analysis of patients prior to prophylactic intervention,[7,24,25] and no treatment,[11,23,25] while one NRS utilized a vaccine study control group for case-control analysis.[7]

Guidelines

The guidelines included in this report examined the available evidence for any UTI prophylaxis intervention.[26-29] All four guidelines provided a recommendations relevant to cranberry product prophylaxis of UTI,[26-29] while two of these also formulated a recommendation relevant to topical estrogen UTI prophylaxis.[26,28]

Outcomes

SRs and MAs

The primary outcome investigated in four of the five included SRs was UTI incidence.[10,16,17,19] Jepson et al. also specifically defined UTI incidence as specimen confirmed but without specifying a CFU concentration.[10] Three SRs reported UTI incidence or reduction without specifying a more precise definition of infection.[16,17,19] Rahn et al. reported rUTI incidence as reported by included studies as one of many outcomes relating to vaginal estrogen treatment for genitourinary syndrome of menopause including vaginal dryness, dyspareunia, dysuria, urgency, frequency, urodynamic measures and adverse events.[18] Three SRs included adverse event outcomes as reported by the included studies.[10,16,18] Other outcomes evaluated in the SRs included symptomatic bacteriuria,[16] urinary urgency,[16] dysuria,[16] antibiotic consumption,[17] and compliance.[10]

RCTs

The primary outcome in all of the included RCTs was UTI incidence.[2-5,15,20-22] Four RCTs defined the outcome of UTI only upon confirmation by culture,[2,5,15,21] whereas one RCT used a clinical definition based upon symptomatic presentation.[20] Two RCTs reported both a clinical definition and a culture-confirmed UTI outcome.[3,4] Takahashi et al. recorded administration of antibiotics to treat UTI, as diagnosed by an undescribed method, as an UTI occurrence.[22] Maki et al.

reported diverse measures of UTI outcomes including clinical UTI incidence density with pyuria, time to first clinical UTI, time to first clinical UTI with pyuria, time to first symptomatic, and culture-confirmed UTI.[20] Foxman et al. also reported time to first UTI, and UTI caused by *Escherichia coli*.[4] Vostalova also reported time to first UTI,[21] and Caljouw reported incidence of rUTI.[3] Adverse event outcomes were reported in six RCTs.[2,4,15,20-22] Two RCTs investigated outcomes possibly relevant to the hypothesized efficacy of cranberry product prophylaxis of UTI and included a bacterial adhesion measure,[15] catheter biofilm formation,[15] haematological and biochemical markers of PAC consumption,[21] and free and total urine phenolics.[21] Compliance was reported in four RCTs.[2-4,20] Secondary outcomes reported in a study by Gallien et al., who investigated prophylaxis for MS patients, included UTI rate, UTIs/patient, quality of life (QoL), Expanded Disability Status Scale (EDSS) scores, urinary disorder symptoms, MS relapse incidence, and antibiotic consumption.[2]

NRSs

All five included NRSs reported outcomes of UTI incidence.[7,11,23-25] A clinically defined UTI was reported in one study,[23] while a culture-confirmed UTI outcome was reported in three studies.[11,24,25] One study used UTI rates pre and post invention, and time to first UTI based upon patient reported UTI incidence.[7] Adverse event outcomes were reported in one NRS.[23] Additional outcomes reported in the NRSs included symptom-free patients during registry,[23] UTI duration,[23] urinalysis at end of registry,[23] compliance,[23] intestinal flora changes,[7] tolerability,[24] QoL,[24] urinary symptoms,[11,25] and pyuria/nitrituria.[25]

Guidelines

All included guidelines had graded recommendations associated with a level of evidence.[26-29] Two guidelines provided relevant recommendations based on expert opinion.[28,29]

Summary of Critical Appraisal

A summary of the critical appraisal of the identified articles is provided in Appendix 3.

SRs and MAs

All five included SRs conducted a systematic literature search and reported the methodology used.[10,16-19] All five also reported inclusion criteria,[10,16-19] three reported exclusion criteria,[10,16,19] and all reported search terms used for the literature search.[10,16-19] Both study selection and data extraction were done in duplicate in three of the included SRs.[10,18,19] One SR reported data extraction methodology that was not done in duplicate,[16] while the data extraction methodology was not reported in one included SR.[17] The process of study selection was reported in a PRISMA flowchart in three SRs,[16,18,19] described narratively in Jepson et al.,[10] and not described in Durham et al.[17] The majority of the included SRs provided a description of a valid critical appraisal system and applied it included studies,[10,18,19] one SR did not include any critical appraisal,[17] and Duenas-Garcia et al. reported a critical appraisal score (Jadad) without clarifying the particular risks of bias in each included study.[16] Jepson et al. provided tabulated study characteristics of both included and excluded studies.[10] A defined research question and a defined patient population of interested was provided by four SRs,[10,16,18,19] however it was unclear in Durham et al. if these were predefined before the literature search.[17] All included SRs contained a statement of no potential COIs.[10,16-19] A MA was included in two SRs.[10,19] Of the two MAs, one assessed publication bias and conducted sensitivity analysis.[19] A sensitivity analysis

was described in the methodology of Jepson et al. however it was unclear why it was not conducted.[10] Both MAs examined study heterogeneity.[10,19]

RCTs

Of the eight RCTs identified and included in this report,[2-5,15,20-22] four were multicenter studies.[2,3,20,22] Recruitment and enrollment data for the trials were reported in CONSORT diagrams in six RCTs,[2-4,15,20,21] while two provided no recruitment data.[5,22] Tabulated patient characteristics were provided by seven RCTs,[2-5,15,20-22] statistical analysis revealed no statistically significant differences in baseline characteristics in five of these,[3,5,15,20,21] while one RCT accounted for potential confounding.[4] One RCT was an open-label study.[5] Allocation concealment methodology was provided in four RCTs, and these RCTs also provided information on the roles of blinded investigators.[2-4,20] Three RCTs did not clarify the role of blinded investigators,[20-22] while one RCT had incomplete blinding.[15] All of the included RCTs provided sufficient details on the statistical methods used,[2-5,15,20-22] while two did not sufficiently describe randomization methods.[5,22] Six RCTs reported the methodology used for assessing compliance when the intervention was self-administered.[2-4,15,20,22] Five used the empty cranberry product packaging returned by the patient as a measure of compliance,[2-4,15,20] while one RCT did not provide details other than the doctors strictly confirmed regular intake of the intervention.[22] Two RCTs did not report a method for assessing compliance,[5,21] however Barnoiu et al. examined inpatients where the intervention was not self-administered.[5] Six RCTs clearly defined patient eligibility,[2-4,20-22] seven clearly defined the intervention,[2-4,15,20-22] and six clearly defined the outcomes of interest.[2-4,15,20,22] A statistical power calculation conducted a priori was described in six of the included RCTs.[2-4,15,20,21] Five RCTs conducted an ITT analysis,[2-4,20,21] and two had no loss to follow-up.[15,22] A discussion of study limitations was provided by seven of the eight RCTs.[2,3,5,15,20-22] Adverse events were discussed and quantified in four RCTs,[2,4,20,22] while adverse events were discussed without quantification in two RCTs.[3,15] Methods for collecting adverse event data were not available in two RCTs,[15,21] while one RCT had no mention of adverse events.[5] All RCTs provided a statement regarding potential COIs, six stated the authors had no potential COIs,[2-5,15,21] while two reported industry support for the study.[20,22]

NRSs

The NRSs included in this report had additional limitations to those inherent in a non-randomized study design.[7,11,23-25] Ledda et al. was an unclear study design with no description of patient selection or allocation methodology, additionally this NRS did not report baseline patient characteristics, blinding, or outcome assessment methodology.[23] Burleigh et al. used an undescribed patient control group for one outcome and did not provide any patient characteristics, any mention of blinding, and used patient reported and unclearly defined outcomes.[7] An uncontrolled before and after study by Sanchez et al. also used patient reported and unclearly defined outcomes with no mention of blinding or compliance.[24] Bonetta et al. insufficiently described allocation methods, did not mention blinding, and did not provide baseline patient characteristics.[11] Pagonas et al did not sufficiently define patient eligibility, the intervention used, compliance, blinding, or adverse events, and did not report baseline patient characteristics for the control group.[25] One NRS did not provide a COI statement,[25] one reported that the authors had no potential COIs,[11] and three were industry supported studies.[7,23,24] A discussion of limitations, although not necessarily comprehensive, was provided in all included NRSs.[7,11,23-25] Strengths of some NRSs included a clearly stated objective,[7,11,22-24] clear patient

inclusion and exclusion criteria,[7,11,23,24] a description of statistical methodology,[7,11,23-25] and a discussion and quantification of adverse events.[11,24]

Guidelines

The guidelines identified and included in this report all had many strengths and included a systematic literature search upon which assessed evidence levels were linked to each graded recommendation.[26-29] Only three of these provided an adequately defined literature selection criteria.[27-29] All identified guidelines also stated the target audience of the recommendations.[26-29] Three guidelines provided a clear scope, defined goals, and defined patient population,[26,28,29] Three guidelines provided COI statements from the guideline development group,[26,27,29] while one guideline offered COI statements for individual authors upon request.[28] Two guidelines had a variety of stakeholder representation involved in guideline development.[28,29] Some guidelines also provided information on guideline implementation,[28,29] updating,[26,28,29] and limitations.[27]

Summary of Findings

A more detailed summary of the findings described below is tabulated in Appendix 4.

Three SRs included in this report examined evidence regarding cranberry product prophylaxis of UTIs.[10,17,19] Durham et al., 2015, found one RCT that reported a statistically significant greater prevention of UTI and reduction of antimicrobials using cranberry-lingonberry juice for UTI prophylaxis as compared to no treatment or probiotic. Two RCTs identified by Durham et al. found a statistically significant reduction in UTI incidence when cranberry juice was used as prophylaxis compared to placebo.[17] One of these RCTs also found a significant reduction in the requirement for antimicrobials favouring cranberry juice, however no statistically significance was demonstrated in outcomes of time to first UTI, incidence of at least one UTI, and more than one UTI.[17] Cranberry extract capsules demonstrated statistically superior prophyaxis for UTI incidence than placebo in another RCT identified by Durham et al., however two additionally identified studies found no statistically significant differences between UTI incidence when cranberry concentrate was used as prophylaxis as compared to water or placebo.[17] The authors partially explain the mixed results by the different patient populations in the identified trials stating,"…cranberry products may be an effective option for preventing recurrent UTIs in pediatric patients, especially for otherwise healthy patients with no anatomical abnormalities." Jepson et al., 2012, conducted an MA of 13 studies of 2,462 patients and reported no statistically significant difference for patient UTI incidence or adverse events when using cranberry products for prophylaxis as compared to a control. The lack of statistically significant difference remained when subpopulations, including women and pregnant women, were analyzed independently. The authors did note the largely unexplained, moderate statistical heterogeneity of 53% while asserting that cranberry products do not significantly reduce the risk of UTI.[10] Wang et al. also note the substantial heterogeneity across trials while identifying data from 9 studies of 1,175 patients that, when pooled, support a statistically significant UTI reduction from cranberry product prophylaxis. When subpopulations were examined Wang et al. found statistically significant UTI prophylaxis of cranberry products in women with rUTI and children, but not in patients with neuropathic bladder, elderly patients, or pregnant patients. The authors conclude their analyses support the consumption of cranberry-containing products for prophylaxis of UTIs in certain populations.[19]

Duenas-Garcia et al. identified two studies reporting a statistically significant reduction in UTI incidence associated with vaginal estriol prophylaxis. Neither study identified by Duenas-Garcia et al. reported any side effects specific to vaginal estriol prophylaxis. The authors conclude, "Regarding nonantibiotic interventions, the use of topical estrogen appears to be the most effective, and it may even have a residual effect when stopped." However the authors also note a dearth of high-quality studies of prevention interventions for rUTI in postmenopausal community-dwelling women.[16] Rahn et al. identified 14 studies of 4,232 women and concluded that moderate-quality evidence suggests that UTI incidence is reduced with the use of vaginal estrogen with no increased adverse events. The authors conclude that, "these data are a significant endorsement for vaginal estrogen therapy in postmenopausal patients with recurrent cystitis."[18]

The primary outcome of UTI incidence was reduced with statistically significance in six of the RCTs included in this report,[3-5,15,20,21] and not significantly reduced in two RCTs,[2,22] for patients using cranberry product UTI prophylaxis as opposed to control prophylaxis. One RCT used antibiotic use as an outcome of UTI occurrence and reported no statistically significant difference for women. In a subgroup analysis however this study found statistically significant prophylactic activity of cranberry juice for women over 49 years.[22] Six RCTs reported no statistically significant differences in adverse events or serious adverse events attributable to cranberry products.[2-5,15,20-22] Two RCTs examined outcomes of UTI severity and observed statistically significant improvement for patients using cranberry product UTI prophylaxis including outcomes of UTI with pyria,[20] and QoL.[2]

Outcomes of statistically significant UTI incidence reduction with cranberry product UTI prophylaxis were observed in all five NRSs included in this report.[7,11,23-25] No adverse events were reported in two NRSs that recorded adverse event data.[23,24] Outcomes of UTI severity in the NRSs that were significantly improved for patients using cranberry product UTI prophylaxis included UTI with pyria,[25] symptoms,[23,25] QoL,[24] dysuria,[11] urgency,[11] and urine flow.[11]

All relevant evidence based recommendations identified in this report are quoted in Appendix 4, Table A4.3

GESITRA guidelines reported an evidence level of II, and a grade C recommendation that non-antibiotic therapies including cranberry extract could be provided to transplant patients with rUTI.[26] SIGN produced a recommendation of the highest grade and level of evidence to advise women with rUTI to consider cranberry products for UTI prophylaxis. The SIGN guideline development group also produced a grade D recommendation that patients on warfarin should avoid cranberry products unless it is determined that the benefits outweigh the risks. Based on expert opinion, SIGN also formulated good practice points to advise women that cranberry capsules may be more convenient and effective than cranberry juice and to consider increased monitoring of warfarin patients also taking cranberry products. The SIGN guidelines cited reports of suspected interactions of cranberry juice and warfarin resulting in increased prothrombin time to support the warfarin related recommendation and good practice point.[28] The EAUN guidelines have formulated a grade A recommendation based upon a level of evidence of 1b to not recommend cranberry supplementation for UTI prevention or treatment for catheterized adults.[27] The GDG for UTIs in children stated that there is insufficient evidence to support a recommendation of cranberry juice for UTI prophylaxis in children.[29]

GESITRA guidelines report an evidence level of II, and a grade C recommendation that non-antibiotic therapies including topical estrogens could be provided to transplant patients with

rUTI.[26] SIGN formulated a grade A recommendation and 1++ level of evidence to not use estrogens for rUTI prevention in postmenopausal women as evidence suggests antibiotic prophylaxis is superior and the evidence for estrogens over placebo is mixed and possibly has harmful effects.[28]

Limitations

The identified evidence presented significant heterogeneity, as has been previously identified by the included MAs. These studies pooled data examining different patient populations and different cranberry products that may have complicated interpretation of the results. The quality of evidence as assessed by the included SRs was relatively free from significant bias but one high quality MAs identified loss to follow-up and per-protocol analysis of some included studies as the largest potential sources of bias.[10] The analysis in this report lacks the methods to quantify the heterogeneity of the evidence to enable a more sophisticated comparison of the more recently published evidence with the included MAs. The evidence used to support guideline recommendations was older and outside of search timeframe of this report, therefore contradictory recommendations remained unaccounted for. None of the guidelines identified in this report were developed specifically for a Canadian healthcare setting.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The evidence identified in this report examining the clinical efficacy of cranberry products for UTI prophylaxis is mixed. The identification of this mixed evidence from RCTs and guidelines agrees with the two included high-quality SRs with MAs that identified substantial and unexplained heterogeneity across trials.[10,19] When analyzing defined subpopulations of patients,[10,19] or when different definitions of UTI are used,[3,4] the evidence remains mixed. In review published in 2016, Liska et al. examined the methodological differences between Wang et al., Jepson et al., and other MA evidence that may be related to the conflicting findings. The authors identified patient population variations as a possible source of conflicting results. The authors also suggested additional research on cranberry prophylaxis of rUTIs in women is necessary as the substantial heterogeneity in SRs presents a challenge for healthcare professionals and policymakers to apply current evidence.[1] This challenge is evidenced by the relevant contradicting guideline recommendations identified in this report.[26-28]

This report identified evidence supporting clinical efficacy of cranberry product UTI prophylaxis in the following populations; women with rUTI,[7,19-21,24] women with rUTI over 49 years old,[22] children,[17,19] rUTI,[15,23] post-gynecological surgery patients,[4] patients carrying a double-J ureteral stent,[5] high-UTI-risk long-term care facility (LTCF) patients,[3] prostatic adenocarcinoma patients treated with radiotherapy,[11] and renal transplant patients with rUTI.[25] An absence of clinical efficacy for cranberry product UTI prophylaxis was observed in populations of; women with rUTI,[10,22] elderly males and females,[10,19] neuropathic bladder/spinal injury patients,[10,19] pregnant women,[10,19] children,[10] radiotherapy patients,[10] low-UTI-risk LTCF patients,[3] and MS patients with neurogenic bladder.[2] While Foxman et al. observed a clinically effective prophylactic effect of cranberry products when defining a UTI by symptomatic presentation or by UTI confirmed by culture,[4] Caljouw et al. observed that clinical efficacy was only evident when UTI outcomes were defined by symptomatic presentation.[3] There was consensus identified in the evidence included in this report with regards to the safety of cranberry products. No significant adverse events specific to a cranberry product intervention for prophylaxis were reported. A contraindication for cranberry products was identified in the SIGN guidelines for patients taking warfarin.[28]

Two identified SRs examined topical estrogen for UTI prophylaxis in women. Both SRs identified evidence to support its clinical efficacy.[16,18] Rahn et al. had less methodological quality limitations and concluded that moderate-quality evidence supports vaginal estrogen use to decrease UTI frequency.[18] Duenas-Garcia et al. also found consistent evidence from two studies demonstrating vaginal estriol superiority to placebo in the prevention of UTIs in postmenopausal women.[16] No identified RCTs or NRSs examined the evidence for the UTI prophylactic efficacy of topical estrogen. No studies compared cranberry products to topica estrogen. While GESITRA recommended that topical estrogens could be provided to transplant recipients with rUTI,[26] SIGN guidelines published a strong recommendation based upon high-quality evidence from 2001 against estrogen use for routine UTI prophylaxis in postmenopausal women.[28] Evidence from high-quality studies published after 2001 were identified by the two previously mentioned SRs and used to support conclusions of vaginal estrogen efficacy for the prevention of UTIs in postmenopausal women.[16,18]

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ABBREVIATIONS

BMI	body mass index
CFU	colony forming units
DM	diabetes mellitus
EAUN	European Assocation of Urology Nurses
EBRT	external beam radiotherapy
EDSS	Expanded Disability Status Scale
FU	follow-up
GDG	guideline development group
GESITRA	Group for the Study of Infection in Transplant Recipients
GI	gastrointestinal
Hx	history
LTCF	long-term care facility
MA	meta-analysis
MS	multiple sclerosis
PAC	proantocyanidins
QoL	quality of life
RCT	randomized controlled trial
rPCUTI	recurrent postcoital urinary tract infection
rUTI	recurrent urinary tract infection
SDC	sweetened dried cranberry
SEM	standard error of the mean
SIGN	Scottish Intercollegiate Guidelines Network
SOT	solid organ transplant
SR	systematic review
TMP-SMX	trimethoprim-sulfamethoxazole
UTI	urinary tract infection
VAS	visual analogue scale

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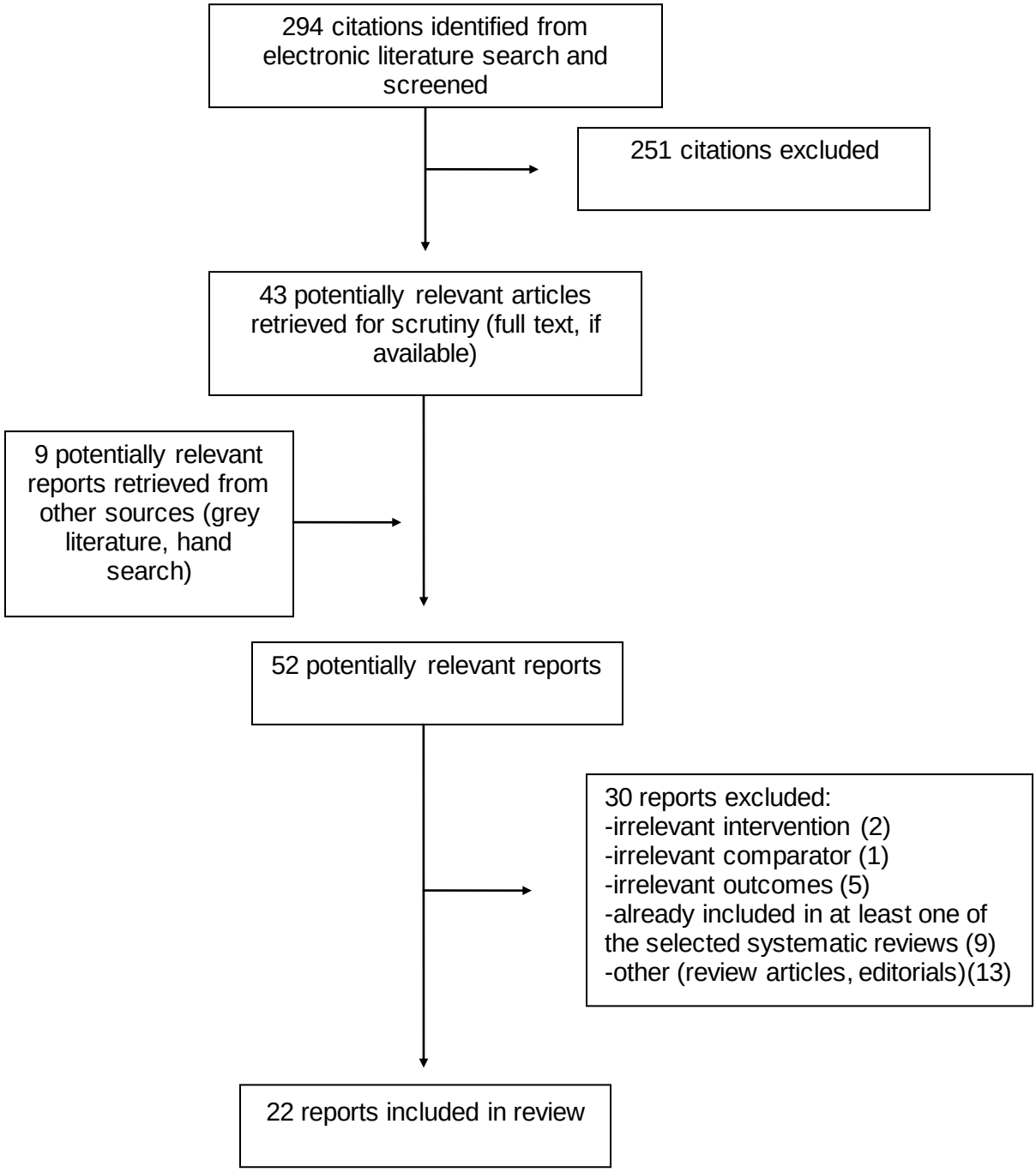
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Study Characteristics

Table A2.1: Summary of Study Characteristics of Included SR, and MAs

Study Design	Population (sample size)	Intervention	Comparator(s)	Outcomes
Systematic Reviews and Meta-analyses				
Duenas-Garcia et al., 2016[16]				
SR: (9 RCTs) Literature search from 1970 to August 1, 2015	rUTI in community dwelling postmenopausal women Exclusions: spinal cord injury, self-intermittent catheterization, chronic indwelling catheters dementia, surgery within 30 days, mixed population studies (Study size ranged from 40 - 252, median 106 patients)	Topical estrogen (5 RCTs) Systemic estrogen (2 RCTs) Antibiotics (3 RCTs)	Placebo or baseline Placebo Vaginal estrogen *Lactobacillus* Alternative dosing schedules	• UTI (definition varied) • Symptomatic bacteriuria (definition varied) • Urinary urgency and dysuria • Adverse events
Durham et al., 2015[17]				
SR: (7 RCTs, 1 RCT crossover) Literature search 1966 to June 2015	Healthy children (3 trials) Children with urogenital anatomical abnormalities (5 trials)	Cranberry products	*Lactobaciluus* No treatment Placebo Cefaclor Trimethoprim suspension	• UTI incidence • Antibiotic consumption • Asymptomatic bacteriuria
Rahn et al., 2014[18]				
SR: (44 studies, 14 studies on vaginal estrogen)	Genitourinary Syndrome of Menopause patients	All commercially available vaginal estrogen products	Placebo No treatment Systemic estrogen Moisturizers and	• Vaginal dryness • Dyspareunia • Dysuria • Urgency • Frequency

Table A2.1: Summary of Study Characteristics of Included SR, and MAs				
Study Design	**Population (sample size)**	**Intervention**	**Comparator(s)**	**Outcomes**
Literature search up to April 22, 2013			lubricants	• rUTI incidence • Atrophy • Urodynamic measures • Endometrial effects • Serum estradiol changes • Adverse events
Jepson et al., 2012[10]				
SR with MA: (24 RCTs and quasi-RCTs) Literature search to June 4, 2013	rUTI patients (n = 4473) Exclusions: UTI treatment, urinary tract condition not caused by bacterial infection	Cranberry juice or cranberry product taken for at least one month	Placebo, no treatment, water, methenamine hippurate, antbiotics, or *Lactobacillus*	• UTI incidence confirmed by specimen • Prophylaxis adherence • Adverse events
Wang et al., 2012[19]				
SR with MA: (13 RCTs) Literature search to November 2011	Patients at risk for UTI (n = 1494) Exclusions: results not expressed or reported or not suitable for quantitative analysis	Cranberry containing products for UTI prophylaxis	Placebo or nonplacebo control	• UTI incidence
MA=meta-analysis; **RCT**=randomized controlled trial; **SR**=systematic review; **rUTI**=recurrent urinary tract infection; **UTI**=urinary tract infection				

Table A2.2: Summary of Study Characteristics of Included RCTs and RCS				
Study Design, Location, Follow-up	**Patient Characteristics, Sample Size**	**Intervention**	**Comparator(s)**	**Outcomes**
RCTs				
Singh et al., 2016[15]				
2 arm RCT Outpatients in India FU: 12 weeks	Patients with subclinical asymptomatic bacteriuria and/or rUTI not responding to antimicrobials (n = 72)	Cranpac™ (IPCA, Mumbai, India) (PAC 60mg, 2 x per day) (n = 36)	*Lactobacilus acidophilus* (Placebo) ($4x10^8$/capsule, 2 x per day) (n = 36)	Primary: • Culture-confirmed UTI incidence Secondary: • Bacterial adhesion • Catheter biofilm formation • Tolerability • Adverse events
Maki et al., 2016[20]				
2 arm, multicenter RCT Outpatients in 17 US centers, 1 France center FU: 24 weeks	Female rUTI patients (20-70 years) with ≥ 2 UTIs/previous year and ≥ 1 UTI treated within 6 months BMI <40.0 Exclusions: current UTI and current antibiotic use (n = 373)	240mL cranberry juice (Ocean Spray Cranberries Inc., Lakeville-Middleboro, MA) per day (n = 185)	240mL placebo beverage per day with similar caloric content, designed to look, smell, and taste like intervention (n = 188)	Primary: • Clinical UTI incidence density Secondary: • Clinical UTI incidence density with pyuria • Time to first clinical UTI • Time to first clinical UTI with pyuria • Time to first symptomatic, culture confirmed UTI • Compliance • Adverse events
Vostalova et al., 2015[21]				
2 arm RCT Outpatients in Czech Republic FU: 6 months	Female (18 - 75 years) rUTI patients (≥2 UTIs in previous year) Exclusions: UTI at baseline, antibiotic usage during study, pregnant or breast	Cranberry fruit powder capsule (NATUREX-DBS, Sagamore, USA) (1.4mg PAC 2 x per	Placebo capsules (n = 93)	Primary: • UTI incidence ($\geq 10^5$ CFU/mL with symptoms) Secondary: • Time to first UTI

Table A2.2: Summary of Study Characteristics of Included RCTs and RCS				
Study Design, Location, Follow-up	**Patient Characteristics, Sample Size**	**Intervention**	**Comparator(s)**	**Outcomes**
	feeding, potentially relevant anatomical anomalies, DM, cardiovascular disease, GI problems, metabolic, renal, hepatic, neurological, or sexually transmitted disease, immunocompromised condition, catheterization, surgery within 6 months, narcotic use, heavy alcohol consumption, clinical trial participation within 30 days (n = 182)	day) (n = 89)		• Compliance • Haematological and biochemical markers • Free and total phenolics in urine • Adverse events
Foxman et al., 2015[4]				
2 arm RCT USA FU: 6 weeks following gynecological surgery	Female patients (≥ 18 years) undergoing elective gynecologic surgery Exclusions: fistula repair or vaginal mesh removal procedures, pregnancy, cranberry allergy, anticoagulant medications, Hx of nephrolithiasis, congenital urogenital anomaly, neurogenic bladder (n = 160)	TheraCran® (Theralogix, LLC, Rockville, MD)) 2 x 2 capsules/day equivalent to two 240mL servings of cranberry juice based upon PAC content (n = 80)	Placebo capsules (n = 80)	Primary: • Clinical UTI incidence • Culture-confirmed UTI incidence Secondary: • Compliance • UTI caused by *E.coli* • Time to first UTI • Adverse events
Barnoiu et al., 2015[5]				
2 arm RCT Inpatients in Spain FU: average 30 days	Patients requiring urethral catheter placement Exclusions: Renal transplant, reconstructive surgery	Routine prophylactic therapy with adjuvant 120mg of American cranberry	Routine prophylactic therapy	Primary: • Culture-confirmed UTI incidence Secondary: • Risk factors

Table A2.2: Summary of Study Characteristics of Included RCTs and RCS				
Study Design, Location, Follow-up	**Patient Characteristics, Sample Size**	**Intervention**	**Comparator(s)**	**Outcomes**
	using bowel tissue, UTI prior to surgery, carrying any catheter at discharge (n = 62)	extract		
Caljouw et al., 2014[3]				
2 arm, multicenter RCT LTCFs in Netherlands FU: 1 year	LTCF residents ≥ 65 years Patients stratified by UTI risk. High risk defined as > 1month catheterization, DM, ≥ 1 UTI/previous year Exclusions: coumarin use, life expectancy < 1month (n = 928)	Cranberry capsules (500mg with 9mg PAC) twice daily High risk n = 253 Low risk n = 205	Placebo capsules twice daily High risk n = 263 Low risk n = 207	Primary: • Clinical UTI incidence • Culture-confirmed UTI incidence Secondary: • Compliance • rUTI incidence • Hospitalization • Mortality
Gallien et al., 2014[2]				
2 arm, multicenter RCT Outpatients in France FU: 1 year	MS patients (18 - 70 years), EDSS ≥ 3, clinically stable for ≥ 3 months, with pollakiuria, urgency, dysuria or urinary incontinence Exclusions: pregnancy or breast feeding, renal failure, risk of uric acid lithiasis, peptic ulcer, cranberry intolerance, UTI antibioprophylaxis, oral anticoagulants, cranberry product consumption within 3 months, indwelling catheter, current UTI (n = 171)	Powder for oral solution of cranberry extract twice per day (18mg PAC twice per day) (n = 82)	Matching placebo (n = 89)	Primary: • 1 year culture-confirmed UTI incidence Secondary: • Compliance • UTI rate • UTIs/patient • QoL (Qualiveen scale) • EDSS • Urinary disorder symptoms • MS relapse incidence • Antibiotic consumption • Adverse events
Takahashi et al., 2013[22]				
2 arm, multicenter	Females (20 - 79 years) rUTI and acute	Cranberry juice	Placebo juice	Primary: • UTI incidence

Table A2.2: Summary of Study Characteristics of Included RCTs and RCS				
Study Design, Location, Follow-up	**Patient Characteristics, Sample Size**	**Intervention**	**Comparator(s)**	**Outcomes**
RCT Outpatients in Japan FU: 24 weeks	exacerbation of acute uncomplicated or chronic complicated cystitis Exclusions: Hx of uric acid stone disease, urological intervention for obstruction or malignant disease, indwelling catheter, concomitant urogenital infection, systemic diseases, allergy to cranberry, non-eligibility for this trial as judged by doctor in clinic (n = 227)	(Kikkoman Food Products and Nisshin Oillio Group, Tokyo, Japan) (>40mg PAC 1x per day)		(based on administration of antibiotics) Secondary • Adverse events
NRSs				
Ledda et al., 2015[23]				
Registry, supplement study Outpatients in Italy FU: 60 days	rUTI patients (≥3 UTIs/previous year or 2 in last six months) Exclusions: any chronic condition or risk factors, immune-compromising disease, infection of any nature, blood in urine, antibiotics within six months, corticosteroids within 6 months, allergy/intolerance to cranberry (n = 44)	Fosfomycin for one day Day 5: upon negative urinary culture lifestyle advice and patients were suggested to take Anthocran® (Indena Spa, Milan, Italy) for 60 days (n = 22)	Fosfomycin for one day Day 5: upon negative urinary culture lifestyle advice and patients were suggested to take Anthocran® (Indena Spa, Milan, Italy) for 60 days [the comparator group chose not to take intervention] (n = 22)	• Clinical UTI incidence before and after • Symptom-free patients during registry • UTI duration • Urinalysis at end of registry • Compliance • Adverse events

Table A2.2: Summary of Study Characteristics of Included RCTs and RCS				
Study Design, Location, Follow-up	**Patient Characteristics, Sample Size**	**Intervention**	**Comparator(s)**	**Outcomes**
Burleigh et al., 2013[7]				
Uncontrolled before and after study and case-controlled analysis US outpatients FU: six months	rUTI female patients (≥ 18 years) Exclusions: immunocompromised status, co-morbidities, chronic inflammatory bowel disease, DM, cranberry allergy (n = 17)	42g/day sweetened dried cranberries (Ocean Spray Cranberries Inc., Lakeville-Middleboro, MA) for two weeks (n = 17)	Retrospective analysis of intervention group patient records for uncontrolled before and after analysis (n = 17) Previous trial control group for case-control analysis (n = 24)	Primary: • Self-reported UTI rate pre and post intervention (uncontrolled before and after) • Time to first UTI (case-control) Secondary: • Intestinal bacterial flora changes
Sanchez et al., 2013[24]				
Uncontrolled before and after study Outpatients in Spain FU: 6 months	Female (18 - 60 years) rPCUTI (≥2 PCUTI/previous year) with confirmed current UTI Exclusions: Intervention used within 3 months, bladder neoplasm, urinary stones, postvoid residual volume > 100mL, obstructive urinary symptoms (n = 20)	Cysticlean® (Vita Green, Hong Kong) containing 118mg/day PAC for 6 months as follows: 1st sexual intercourse in a week 1x118mg for 3 days, subsequent sexual intercourse per week 1x118mg (n = 20)	Retrospective analysis of intervention group records (n = 20)	Primary • Culture-confirmed rPCUTI incidence Secondary • Tolerability • QoL
Bonetta et al., 2012[11]				
2 arm prospective nonrandomized comparative study Outpatients in	Males with prostatic adenocarcinoma treated with radical, adjuvant, or salvage radiotherapy Exclusions: Hx of	Enteric-coated tablet containing 200mg cranberry extract (30% PAC)/day	No treatment (n = 186)	Primary • Culture-confirmed UTI incidence (≥10^5 CFU/mL) • Urinary symptoms

Table A2.2: Summary of Study Characteristics of Included RCTs and RCS				
Study Design, Location, Follow-up	**Patient Characteristics, Sample Size**	**Intervention**	**Comparator(s)**	**Outcomes**
Italy FU: 6 weeks	pelvic EBRT, previous pelvic malignancy, Karnofsky score < 80, renal failure, treatment refusal (n = 370)	(n = 184)		(frequency, dysuria, nocturia, urgency)
Pagonas et al., 2012[25]				
Retrospective comparison and before and after study Outpatients in Germany FU: 1 year	Renal transplant patients with rUTI (≥2 UTIs/year) (n = 82)	L-methionine (n = 25) Cranberry (2x50mL/day) (n = 39) L-methionine + Cranberry (n = 18)	No prophylaxis (n = 30) Baseline (year prior to prophylaxis)	Primary • Culture-confirmed UTI incidence (≥10^5 CFU/mL) • Urinary symptoms • Pyuria/nitrituria

BMI=body mass index; **CFU**=colony forming units; **EBRT**=external beam radiotherapy; **DM**=diabetes mellitus; **EDSS**=Expanded Disability Status Scale; **FU**=follow-up; **GI**=gastrointestinal; **Hx**=history; **LTCF**=long-term care facility; **MS**=multiple sclerosis; **PAC**=proantocyanidins; **QoL**=quality of life; **RCT**=randomized controlled trial; **rPCUTI**=recurrent postcoital urinary tract infection; **rUTI**=recurrent urinary tract infection; **UTI**=urinary tract infection; **TMP-SMX**=trimethoprim-sulfamethoxazole;

Table A2.1: Summary of Study Characteristics of Included Guidelines			
Origin, Publication Date	**Interventions of Interest**	**Evidence Levels and Recommendation Grading**	**Target Population**
Guidelines			
GESITRA, 2015[26]			
Spanish Society of Infectious Dieseases and Clinical Microbiology (SEIMC) Spanish Network for Research in Infectious Diseases (REIPI) Spain, 2015	Prophylaxis, diagnosis and management of UTIs in solid organ transplant patients	**Levels of Evidence:** **I:** At least one well-designed and executed trial **II:** At least one non-randomized controlled comparative or cohort study, or a non-controlled experimental study with non-conclusive results **III:** Expert opinion, descriptive studies, or reports **Levels of Recommendations:** **A:** Solid evidence of efficacy and clinical benefit **B:** Solid or moderately solid evidence of efficacy with limited clinical benefit **C:** Insufficient evidence of efficacy, or benefits do not outweigh risks, valid alternatives are available **D:** Moderately solid evidence of lack of efficacy or poor outcomes **E:** Strong evidence for a lack of efficacy	Physicians, including primary care, involved in the care of solid organ transplant recipients
EAUN Guidelines, 2013[27]			
European Association of Urology Nurses Europe, 2013	Adult catheterization for all indications	**Levels of Evidence:** **1a:** MA of RCTs **1b:** ≥1 RCT **2a:** ≥1 well-designed nonrandomized study **2b:** ≥1 well-designed quasi-experimental study **3:** Evidence from well-designed non-experimental studies **4:** Expert committee, opinions, or clinical experience of authorities **Grade of Recommendations:** **A:** Based on clinical studies of good quality, addressing the specific recommendation including ≥ 1 RCT **B:** Based on well-conducted studies other than RCTs **C:** Recommendations made despite absence of directly applicable good quality evidence	Urology nurses, patients, caregivers

Table A2.1: Summary of Study Characteristics of Included Guidelines			
Origin, Publication Date	**Interventions of Interest**	**Evidence Levels and Recommendation Grading**	**Target Population**
SIGN Guidelines, 2012[28]			
Scottish Intercollegiate Guidelines Network Scotland, July 2012	Interventions aimed at UTI management, diagnosis, and prophylaxis	**Levels of Evidence** **1++:** High quality MAs, systematic reviews of RCTs or RCTs with very low bias risk **1+:** Well conducted MAs, systematic reviews of RCTs or RCTs with low bias risk **1-:** MAs, systematic review of RCTs or RCTs with high bias risk **2++:** High quality systematic reviews of case control or cohort studies with very low bias risk **2+:** Well conducted case control or cohort studies with low bias risk **2-:** Case control or cohort studies with high bias risk and/or significant risk that relationship is not causal **3:** non-analytic studies **4:** expert opinion **Grade of Recommendations** **A:** At least one MA, systematic review of RCTs or RCT rated as **1++**, consistent evidence rated as **1+** **B:** Evidence overall consistent studies of **2++**, or extrapolated evidence from **1++** or **1+** **C:**Evidence overall consistent studies of **2+**, or extrapolated evidence from **2++** **D:** Evidence **3** or **4**, or extrapolated evidence from **2+** **Good practice point**: Expert opinion	Healthcare professionals in primary and secondary care, officers in charge of residential and care homes, policy makers, clinical effectiveness leads, caregivers, and patients
GDG for UTIs in children, 2011[29]			
Working Group of the Clinical Practice Guidelines for Urinary Tract Infection in Children Spain, 2011	Interventions aimed at UTI management, monitoring, diagnosis, and prophylaxis in children (1month - 18 years)	**Levels of Evidence** **1++:** High quality MAs, systematic reviews of RCTs or RCTs with very low bias risk **1+:** Well conducted MAs, systematic reviews of RCTs or RCTs with low bias risk **1-:** MAs, systematic review of RCTs or RCTs with high bias risk **2++:** High quality systematic reviews of case control or cohort studies with very low bias risk **2+:** Well conducted case control or cohort studies with low bias risk **2-:** Case control or cohort studies with high bias risk and/or significant risk that	Health professionals in primary care and specialist care for children with suspected UTI, patients, and caregivers

Table A2.1: Summary of Study Characteristics of Included Guidelines			
Origin, Publication Date	**Interventions of Interest**	**Evidence Levels and Recommendation Grading**	**Target Population**
		relationship is not causal **3:** non-analytic studies **4:** expert opinion **Grade of Recommendations** **A:** At least one MA, systematic review of RCTs or RCT rated as **1++**, consistent evidence rated as **1+** **B:** Evidence overall consistent studies of **2++**, or extrapolated evidence from **1++** or **1+** **C:**Evidence overall consistent studies of **2+**, or extrapolated evidence from **2++** **D:** Evidence **3** or **4**, or extrapolated evidence from **2+** **Good practice point**: Expert opinion	

GDG=guideline development group; **EAUN**=European Assocation of Urology Nurses; **GESITRA=**Group for the Study of Infection in Transplant Recipients; **MA**=meta-analysis; **RCT**=randomized controlled trial; **SIGN**=Scottish Intercollegiate Guidelines Network; **UTI**=urinary tract infection;

APPENDIX 3: Summary of Critical Appraisal

Table A3.1: Summary of Critical Appraisal of Included SRs and MAs using AMSTAR tool[55]

Strengths	Limitations
Systematic Reviews and Meta-analyses	
Duenas-Garcia et al., 2016[16]	
• Systematic literature search methodology described with inclusion/exclusion criteria and search terms • Data extraction methodology described • PRISMA flowchart of study selection provided • Valid critical appraisal system described and applied • Discussion on study limitations • Defined research question and patient population • Tabulated study characteristics • Reported adverse event data • Statement of no COIs	• Study selection and data extraction not done in duplicate • Unclear which studies had which risk of bias as identified by critical appraisal
Durham et al., 2015[17]	
• Systematic literature search methodology described with inclusion criteria and search terms • Tabulated study characteristics • Discussion on study limitations • Reported adverse event data • Statement of no COIs	• No assessment of bias of included studies • Data extraction methodology not described • No duplication of study selection or data extraction • No details on literature selection process • Unclear if research question and patient population were predefined
Rahn et al., 2014[18]	
• Systematic literature search methodology described with inclusion criteria and search terms • Study selection and data extraction done in duplicate • Data extraction methodology described • PRISMA flowchart of study selection provided • Valid critical appraisal system described and applied • Tabulated study characteristics • Defined research question and patient population • Reported adverse event data • Provide some evidence-based, graded guidelines • Acknowledged limitations • Statement of no COIs	• Some methodology in supplemental material

Table A3.1: Summary of Critical Appraisal of Included SRs and MAs using AMSTAR tool[55]	
Strengths	**Limitations**
Jepson et al., 2012[10]	
• Systematic literature search methodology described with inclusion/exclusion criteria and search terms • Study selection and data extraction done in duplicate • Included studies published in languages other than English • Data extraction methodology described • Tabulated characteristics of included and excluded studies provided • Valid critical appraisal system described and applied • Defined research question and patient population • Analyzed pooled results - meta-analysis • Examined study heterogeneity • Reported adverse event data • Statement of no COIs	• No PRISMA flowchart of study selection provided • No analysis of publication bias
Wang et al., 2012[19]	
• Systematic literature search methodology described with inclusion criteria and search terms • Study selection and data extraction done in duplicate • Data extraction methodology described • PRISMA flowchart of study selection provided • Valid critical appraisal system described and applied • Tabulated study characteristics • Defined research question and patient population • Analyzed pooled results - meta-analysis • Analyzed potential publication bias • Examined study heterogeneity and performed sensitivity analysis • Reported adverse event data • Statement of no COIs	
COI=conflict of interest; **PRISMA**=Preferred Reporting Items for Systematic Reviews and Meta-Analyses;	

Table A3.2: Summary of Critical Appraisal of Included RCTs and NRSs using Downs and Black checklists[14]	
Strengths	**Limitations**
RCTs	
Singh et al., 2016[15]	
• CONSORT diagram for patient recruitment/enrollment • Patient characteristics tabulated - no significant differences between groups • Statistical methods described • Randomization methodology described • Clearly defined intervention • Method for assessing compliance • Clearly defined outcomes • Statistical power determined a priori • Discussion of study limitations • No loss to follow-up • Adverse events discussed • Statement of no COIs	• Single center study • Not completely blinded • No allocation concealment protocol described • Unclear patient eligibility • No methodology for collecting adverse event data • No gender information on patient groups
Maki et al., 2016[20]	
• Multicenter study • CONSORT diagram for patient recruitment/enrollment • Patient characteristics tabulated - no statistically significant differences between groups • Allocation concealment methodology described • Statistical methods described • Randomization methodology described • Method for assessing compliance • Clearly defined patient eligibility • Clearly defined intervention • Clearly defined outcomes • Statistical power determined a priori • Provided ITT analysis • Discussion of study limitations • Adverse events discussed and quantified • COI statement provided	• Unclear role of blinded investigators • Industry supported study
Vostalova et al., 2015[21]	
• CONSORT diagram for patient recruitment/enrollment • Patient characteristics tabulated - no statistically significant differences between groups • Randomization methodology described • Statistical methods described • Clearly defined patient eligibility • Clearly defined intervention	• Single center study • Allocation concealment method not described • Unclear role of blinded investigators • No methodology for assessing compliance • No methodology for collecting adverse event data

Table A3.2: Summary of Critical Appraisal of Included RCTs and NRSs using Downs and Black checklists[14]	
Strengths	**Limitations**
• Provided ITT analysis • Statistical power determined a priori • Discussion of study limitations • Statement of no COIs	
Foxman et al., 2015[4]	
• CONSORT diagram for patient recruitment/enrollment • Patient characteristics tabulated - confounding accounted for • Allocation concealment methodology described • Randomization methodology described • Role of blinded investigators outlined • Clearly defined patient eligibility • Clearly defined intervention • Clearly defined outcomes • Statistical power determined a priori • Statistical methods described • Method for assessing compliance • Provided ITT analysis • Adverse events discussed and quantified • Statement of no COIs	• Single center study • No discussion of study limitations
Barnoiu et al., 2015[5]	
• Patient characteristics tabulated - no statistically significant differences between groups • Statistical methods described • Discussion of study limitations • Statement of no COIs	• Single center study • No patient recruitment data • Open-label study - no blinding or allocation concealment • Randomization methodology not described • Patient eligibility not described • Intervention not clearly described • Outcome not clearly defined • No statistical power calculation to determine sample size • No mention of adverse events
Caljouw et al., 2014[3]	
• Multicenter study • CONSORT diagram for patient recruitment/enrollment • Patient characteristics tabulated - no statistically significant differences between groups • Allocation concealment methodology described • Statistical methods described • Randomization methodology described • Role of blinded investigators outlined	• No adverse event or tolerability data

Table A3.2: Summary of Critical Appraisal of Included RCTs and NRSs using Downs and Black checklists[14]	
Strengths	**Limitations**
• Clearly defined patient eligibility • Clearly defined intervention • Clearly defined outcomes • Method for assessing compliance • Provided ITT analysis • Statistical power determined a priori • Discussion of study limitations • Statement of no COIs	
Gallien et al., 2014[2]	
• Multicenter study • CONSORT diagram for patient recruitment/enrollment • Patient characteristics tabulated • Allocation concealment methodology described • Statistical methods described • Clearly defined patient eligibility • Randomization methodology described • Role of blinded investigators outlined • Clearly defined outcomes • Clearly defined interventions • Statistical power determined a priori • Provided ITT analysis • Method for assessing compliance • Comprehensive discussion on study limitations • Adverse events discussed and quantified • Statement of no COIs	• Baseline characteristics not assessed for statistically significant differences • Significant numbers lost to follow-up
Takahashi et al., 2013[22]	
• Multicenter study • Statistical methods described • Patient characteristics tabulated • Clearly defined patient eligibility • Clearly defined intervention • Clearly defined outcomes • Complete follow-up • Comprehensive discussion on study limitations • Adverse events discussed and quantified • COI statement • Method for assessing compliance	• No patient recruitment data • No statistical power calculation to determine sample size - acknowledgement of underpowered sample size • Patient characteristics not evaluated for significant differences • No allocation concealment mentioned • Unclear role of blinded investigators • Randomization methodology not described • Industry supported study
NRSs	
Ledda et al., 2015[23]	
• Objective stated • Intervention described • Patient inclusion/exclusion criteria described • Outcomes defined • Discussion of study limitations • Statistical methods described	• Very unclear patient selection and allocation methodology • No mention of blinding • Method of compliance observation not provided • Patient characteristics not reported

Table A3.2: Summary of Critical Appraisal of Included RCTs and NRSs using Downs and Black checklists[14]	
Strengths	**Limitations**
	• Assessment of outcomes and adverse events unclear • Industry funded study
Burleigh et al., 2013[7]	
• Objective stated • Intervention described • Patient inclusion/exclusion criteria described • Statistical methods described • Adverse events discussed • Discussion of study limitations • COI statement provided	• Used a insufficiently described control group for one outcome • No mention of blinding • No patient characteristics provided • Patient reported and unclearly defined outcomes • Industry funded study • Uncontrolled before and after study
Sanchez et al., 2013[24]	
• Objective stated • Patient inclusion/exclusion criteria described • Intervention described • Adverse events discussed and quantified • Patient characteristics reported • Statistical methods described • Discussion of study limitations • COI statement provided	• Patient reported unclearly defined outcomes • No mention of compliance • No mention of blinding • Industry funded study • Uncontrolled before and after study
Bonetta et al., 2012[11]	
• Objective stated • Patient inclusion/exclusion criteria described • Intervention described • Defined outcomes • Statistical methods described • Adverse events discussed and quantified • Compliance monitored (inpatients) • Discussion of study limitations • Statement of no COI	• Unclear allocation • No patient characteristics provided • No mention of blinding
Pagonas et al., 2012[25]	
• Objective stated • Patient characteristics of study group tabulated • Statistical methods described • Defined outcomes • Discussion of study limitations	• Unclear patient eligibility • Patient characteristics of control group not reported • Intervention not sufficiently described • No mention of compliance • No mention of blinding • No mention of adverse events • No COI statement
COI=conflict of interest; **NRS**=non-randomized study; **PRISMA**=Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RCT**=randomized controlled trial;	

Table A3.3: Summary of Critical Appraisal of Included Guidelines using AGREE II[13]	
Strengths	**Limitations**
Guidelines	
GESITRA, 2015[26]	
• Evidence levels for recommendations • Evidence levels and grades of recommendations tabulated • Levels of evidence and grades of recommendations linked • COI statement provided • Clear scope and patient population • Defined goals • Explicitly stated target audience • Systematic literature search • Recommendations and information relevant to specific patient population including drug interactions and complications • Authors recommend timeframe for updating	• Limited stakeholder representation in guideline development • Literature selection and exclusion criteria not provided • No discussion on limitations, recommendation implementation
EAUN Guidelines, 2013[27]	
• Evidence levels for recommendations • Evidence levels and grades of recommendations tabulated • Levels of evidence and grades of recommendations linked • COI statement provided • Explicitly stated target audience • Systematic literature search • Defined literature selection and exclusion criteria • Discussion on guideline limitations	• Limited stakeholder representation in guideline development • Very broad scope with no explicit goal • Limited information on guideline implementation and updating
SIGN Guidelines, 2012[28]	
• Evidence levels for recommendations • Evidence levels and grades of recommendations tabulated • Levels of evidence and grades of recommendations linked • Specific information on guideline implementation and updating • Explicitly stated target audience • Stakeholder representation in guideline development group • Clear scope and patient population • Defined goals • Systematic literature search • Defined literature selection and exclusion criteria	• No specific discussion on guideline limitations • No patient representation in guideline development • Information on potential COIs only available upon request
GDG for UTIs in children, 2011[29]	
• Evidence levels for recommendations • Evidence levels and grades of	• No explicit discussion on limitations of recommendations

Table A3.3: Summary of Critical Appraisal of Included Guidelines using AGREE II[13]	
Strengths	**Limitations**
recommendations tabulated • Levels of evidence and grades of recommendations linked • COI statements provided • Clear scope and defined patient population • Defined goals • Explicitly stated target audience • Stakeholder representation in guideline development group • Systematic literature search • Defined literature selection and exclusion criteria • Specific information on guideline implementation and updating	
COI=conflict of interest; **PRISMA**=Preferred Reporting Items for Systematic Reviews and Meta-Analyses;	

APPENDIX 4: Summary of Findings

Table A4.1: Summary of Findings of Included SRs and MAs	
Findings	**Author's Conclusions**
SRs and MAs	
Duenas-Garcia et al., 2016[16]	
Clinical Effectiveness **Topical Estrogen vs Placebo** 2 studies Vaginal estriol vs placebo (p< 0.001) Vaginal estriol: 0.5 UTI/patient year Placebo: 0.9 UTI/patient year Vaginal estriol vs placebo (p< 0.005) Vaginal estriol: 10/50 total UTIs Placebo: 102/43 total UTIs Vaginal estriol ring vs placebo Vaginal estriol ring: 27/53 total UTIs Placebo: 44/55 total UTIs Vaginal estriol ring vs placebo (p< 0.008) Vaginal estriol ring: Cummulative proportion of patients free of UTIs was higher **Adverse Events** 2 studies No side effects were noted specific to vaginal estriol however 0 - 36% of treatment groups and placebo groups experienced local reactions of itching or burning.	**Clinical Effectiveness** "In this review, we found a dearth of high-quality studies evaluating the prevention of recurrent UTI in postmenopausal community-dwelling women. Typically, no more than 1 study was available to assess the effectiveness of any intervention, making it difficult to form conclusions about the optimal clinical approach for reducing the number of UTIs or symptomatic bacteriuria in postmenopausal women." (pp. 67) "Regarding nonantibiotic interventions, the use of topical estrogen appears to be the most effective, and it may even have a residual effect when stopped." (pp. 68) **Adverse Events** Topical Estrogen "Most of the side effects of these medications are minimal and well tolerated." (pp. 68)
Durham et al., 2015[17]	
Clinical Effectiveness **Probiotic vs Cranberry juice** 1 RCT Probiotic vs Cranberry-lingonberry juice vs no treatment UTI risk favours cranberry ($p < 0.05$) Cranberry: 5/27 (18.5%) Probiotic: 11/26 (42.3%) No treatment: 18/27 (66.7%) Requirement for antimicrobials favours cranberry ($p < 0.05$) Cranberry: 1/27 (3.7%) Probiotic: 5/26 (19.2%) No treatment: 7/27 (26.0%)	**Clinical Effectiveness** "Based on the results of 8 clinical trials identified, cranberry products may be an effective option for preventing recurrent UTIs in pediatric patients, especially for otherwise healthy patients with no anatomical abnormalities." (pp. 1355) [Two studies used an irrelevant comparator (antibiotics)]

Table A4.1: Summary of Findings of Included SRs and MAs	
Findings	**Author's Conclusions**
Placebo vs Cranberry juice 1 RCT Cranberry juice (300mL/day) UTI incidence density favours cranberry ($p = 0.03$) (n = 228) Antimicrobial days per year favours cranberry ($p < 0.001$) (n = 228) Incidence of at least one UTI NS Time to first UTI NS More than one UTI NS 1 RCT UTI incidence - Cranberry juice w/37% PAC vs w/o PAC ($p = 0.045$) Cranberry w/37% PAC: 5/5 Cranberry w/o PAC: 15/8 1 RCT UTI incidence - Cranberry concentrate vs water NS 1 Study - UTI incidence - Cranberry concentrate vs placebo NS 1 RCT - UTI incidence - Cranberry extract capsule vs placebo (n = 20) ($p = 0.012$) Cranberry: 0.45 ± 0.82 infections/year Placebo: 0.7 ± 0.92 infections/year	
Rahn et al., 2014[18]	
Clinical Effectiveness 14 studies Vaginal estrogen vs placebo or no treatment (n = 4 232) The frequency of UTI was reduced with use of vaginal estrogen (moderate-quality evidence) Insufficient data to compare different estrogen formulations **Adverse Events** 14 studies Vaginal estrogen vs placebo or no treatment (n = 4 232) No differences in reported adverse events (variably reported data)	**Clinical Effectiveness** "There was moderate-quality evidence that UTIs were less frequent with use of vaginal estrogen in women with vulvovaginal atrophy. The few studies including patients with recurrent UTI were relatively small and used different types of estrogen application… these data are a significant endorsement for vaginal estrogen therapy as a preventive therapy in postmenopausal patients with recurrent cystitis." (pp. 7)

Table A4.1: Summary of Findings of Included SRs and MAs	
Findings	**Author's Conclusions**
Jepson et al., 2012[10]	
Clinical Effectiveness **One or more UTIs at follow-up (RR>1 favours cranberry)** Cranberry products vs placebo/control (13 studies) (n = 2 462) RR (95% CI): 0.86 (0.71, 1.04) (I^2 = 53%) Patient subpopulations of above Women with rUTI (4 studies) (n = 594) RR (95% CI): 0.74 (0.42, 1.31) (I^2 = 65%) Elderly males and females (2 studies) (n = 413) RR (95% CI): 0.75 (0.39, 1.44) (I^2 = 48%) Neuropathic bladder/spinal injury patients (2 studies) (n = 353) RR (95% CI): 0.95 (0.75, 1.20) (I^2 = 0.0%) Pregnant women (2 studies) (n = 674) RR (95% CI): 1.04 (0.93, 1.17) (I^2 = 0.0%) Children (2 studies) (n = 309) RR (95% CI): 0.48 (0.19, 1.22) (I^2 = 73%) Radiotherapy patients (1 studies) (n = 119) RR (95% CI): 1.15 (0.75, 1.77) **Symptomatic UTI incidence** Cranberry dose: ≥ 2/day vs 1/day (3 studies) (n = 208) RR (95% CI): 1.12 (0.75, 1.68) (I^2 = 0.0%) **Adverse Events** **Adverse events** Cranberry products vs placebo/control (5 studies) (n = 597) RR (95% CI): 0.83 (0.31, 2.27) (I^2 = 5%) Cranberry dose: ≥ 2/day vs 1/day (1 study) (n = 44) Weakness and abdominal pain RR (95% CI): 0.30 (0.03, 2.70) Mild fever RR (95% CI): 6.42 (0.35, 117.34) Heart burn RR (95% CI): 4.58 (0.23, 90.30)	**Clinical Effectiveness** "…cranberry products do not significantly reduce the risk of repeat symptomatic UTI compared to placebo or no treatment in groups of people at risk of repeat UTI (overall RR 0.86, 95% CI 0.71 to 1.04) or for any of the subgroups analysed. There was however moderate heterogeneity (53%), which is largely unexplained." (pp. 12)

Table A4.1: Summary of Findings of Included SRs and MAs	
Findings	**Author's Conclusions**
Wang et al., 2012[19]	
Clinical Effectiveness **Patients ≥ 1 UTI (RR<1 favours cranberry)** Cranberry users vs nonusers (9 studies) (n = 1 175) RR (95% CI): 0.62 (0.49, 0.80) (I^2 = 43%) Patient subpopulations of above Women with rUTI (2 studies) (n = 150) RR (95% CI): 0.53 (0.33, 0.83) (I^2 = 0%) Neuropathic bladder (4 studies) (n = 307) RR (95% CI): 0.80 (0.57, 1.14) (I^2 = 37%) Children (1 studies) (n = 54) RR (95% CI): 0.28 (0.12, 0.64) Elderly patients (1 studies) (n = 376) RR (95% CI): 0.51 (0.21, 1.22) Pregnant patients (1 studies) (n = 188) RR (95% CI): 4.57 (0.25, 83.60) **P values were not significant in the meta-regression for the following analyses:** Cranberry juice vs placebo/control (5 studies) (n = 748) RR (95% CI): 0.47 (0.30, 0.72) (I^2 = 2%) Cranberry capsule/tablet vs placebo/control (3 studies) (n = 277) RR (95% CI): 0.79 (0.44, 1.44) (I^2 = 57%) **Cranberry dose frequency** Once daily vs placebo/control (1 study) (n = 135) RR (95% CI): 1.03 (0.64, 1.66) > twice daily vs placebo/control (1 study) (n = 668) RR (95% CI): 0.58 (0.40, 0.84) (I^2 = 18)	**Clinical Effectiveness** "In conclusion, the results of the present meta-analysis support that consumption of cranberry-containing products may protect against UTIs in certain populations. However, because of the substantial heterogeneity across trials, this conclusion should be interpreted with great caution." (pp. 995)
CI=confidence interval; RCT=randomized controlled trial; RR=risk ratio; UTI=urinary tract infection;	

Table A4.2: Summary of Findings of Included RCTs and NRSs	
Findings	**Authors' Conclusions**
RCTs	
Singh et al., 2016[15]	
Clinical Effectiveness UTI incidence ($p < 0.001$) Cranpac™: 12/36 (33%) Placebo: 32/36 (89%) Bacterial adhesion score at 12 weeks ($p < 0.001$) Cranpac™: 0.28 Placebo: 2.14 Catheter biofilm formation number at 12 weeks ($p = 0.018$) Cranpac™: 3 Placebo: 6 **Adverse Events** No adverse events were noted No clear tolerability results presented	**Clinical Effectiveness and Adverse Events** "The overall efficacy and tolerability of standardized cranberry extract containing (PAC-A) were superior to placebo in terms of reduced bacterial adhesion; bacterial MRHA negativity; urine pH reduction; and in preventing recurrent UTI (dysuria, bacteriuria and pyuria)."
Maki et al., 2016[20]	
Clinical Effectiveness Investigator diagnosed annualized UTI incidence density (95% CI) ($p = 0.017$) Cranberry juice: 0.48 (0.33, 0.63) Placebo beverage: 0.75 (0.56, 0.94) Incidence rate ratio: 0.62 (0.42, 0.92) UTIs with pyria ($p = 0.037$) Incidence rate ratio (95% CI): 0.63 (0.40, 0.97) Time to first UTI ($p = 0.078$) Hazard ratio (95% CI): 0.67 (0.43, 1.05) Time to first UTI with pyria ($p = 0.131$) Hazard ratio (95% CI): 0.69 (0.43, 1.12) Time to first symptomatic culture confirmed UTI ($p = 0.914$) Hazard ratio (95% CI): 0.97 (0.56, 1.67) Compliance (mean ± SEM) Cranberry: 98.1 ± 0.6% Placebo: 98.2 ± 0.5% **Adverse Events** **Adverse Events ≥5%** Headache	"In conclusion, the consumption of a cranberry juice beverage significantly reduced the clinical UTI incidence density in women with a history of ≥2 UTIs in the previous year. These results suggest that the consumption of cranberry is a useful strategy for reducing recurrent clinical UTI episodes and antibiotic use that is associated with the treatment of these events."

Table A4.2: Summary of Findings of Included RCTs and NRSs	
Findings	**Authors' Conclusions**
Cranberry: 8.6% Placebo: 6.4% Sinusitis Cranberry: 5.4% Placebo: 3.2% Upper respiratory infection Cranberry: 7.0% Placebo: 6.9% All serious adverse events: chest pain, ischemic colitis leading to septic shock, miscarriage, appendicitis, surgery for rectal prolapse were deemed unrelated or unlikely to be related to treatment.	
Vostalova et al., 2015[21]	
Clinical Effectiveness UTI incidence (p = 0.04) (ITT analysis using age standardized 12-month UTI history (p = 0.01)) Cranberry: 9/83 (10.84%) Placebo: 24/93 (25.81%) Time to first UTI (p = 0.04) 10% of cranberry group had 1st UTI: 133 days 10% of placebo group had 1st UTI: 65 days Haematological and biochemical markers NS and within range of normal Free and total phenolics in urine NS Compliance "Excellent" - no methods or data presented **Adverse Events** No adverse events recorded	**Clinical Effectiveness and Adverse Events** "In summary, results of this study showed that intake of 500mg of cranberry fruit powder containing 2.8mg of PACs/day for 6months was associated with a reduction in incidence of recurrent UTIs. The compliance with the study protocol was excellent and no adverse events were recorded." (pp. 1566)
Foxman et al., 2015[4]	
Clinical Effectiveness Clinical UTI incidence (p = 0.008) Cranberry: 15/80 (19%) Placebo: 30/80 (38%) Culture-confirmed UTI incidence (p = 0.04) Cranberry: 12/80 (15%) Placebo: 23/80 (29%) UTI caused by *E.coli* (p = 0.07)	**Clinical Effectivness** "This is the first report of a double-blind, placebo-controlled randomized clinical trial demonstrating a statistically and clinically significant benefit of taking cranberry in preventing UTI after elective gynecologic surgery where a urinary catheter is placed. This reduction in UTI risk is similar in magnitude to

Table A4.2: Summary of Findings of Included RCTs and NRSs	
Findings	**Authors' Conclusions**
Cranberry: 38% Placebo: 46% Median time to first UTI (p = 0.0005) Cranberry: 18 days Placebo: 8.5 days Compliance - pill counts (p = NS) Cranberry: 57 Placebo: 60 **Adverse Events** Gastrointestinal upset (p = NS) Cranberry: (56%) Placebo: (61%)	that reportedly obtained by administering antibiotics at time of catheter removal (6), and avoids the collateral damage associated with antibiotic use, including pressure for antibiotic resistance." (pp. 8)
Barnoiu et al., 2015[5]	
Clinical Effectiveness Culture-confirmed UTI incidence (p = 0.04) Cranberry: 4/31 (12.9%) Placebo: 12/31 (38.7%) Statistically significant risk factors Duration of JJ catheter -average days (p = 0.03) UTI : 35.9 days no UTI: 28.5 days	**Clinical Effectiveness** "As a conclusion of this study, we can state that American cranberry extract at a daily dosage of 120 mg has an adjuvant effect on UTI prevention in patients carrying a double-J ureteral stent after surgery." (pp. 117)
Caljouw et al., 2014[3]	
Clinical Effectiveness Clinical UTI incidence in high-UTI-risk group (p = 0.04) Cranberry: 98/205 (47.8%) Placebo: 125/207 (60.4%) Cuture-confirmed UTI incidence in high-UTI-risk group (p = NS) Cranberry: 45/205 (22.0%) Placebo: 46/207 (22.2%) Clinical UTI incidence in low-UTI-risk group (p = NS) Cranberry: 59/205 (28.8%) Placebo: 51/207 (24.6%) Cuture-confirmed UTI incidence in low-UTI-risk group (p = NS) Cranberry: 17/205 (8.3%) Placebo: 16/207 (7.7%) Compliance (p = NS) Mean capsule intake (95% CI): 97% (96.6, 97.6)	**Clinical Effectiveness** "In LTCF residents with high UTI risk, taking cranberry capsules twice daily results in a 26% lower incidence of clinically defined UTI than with placebo, although no difference was found in UTI incidence according to a strict definition. Cranberry capsules may offer an opportunity to decrease the incidence of this common infection in high- UTI-risk LTCF residents by using a well-tolerated treatment." (pp. 109)

Table A4.2: Summary of Findings of Included RCTs and NRSs	
Findings	**Authors' Conclusions**
Clinical rUTI in high-UTI-risk group (*p* = NS) HR (95% CI): 0.92 (0.71, 1.17) Clinical rUTI in high-UTI-risk group (*p* = NS) HR (95% CI): 1.14 (0.78, 1.68) No statistically significant differences in hospitalization or mortality	
Gallien et al., 2014[2]	
Clinical Effectiveness Culture-confirmed UTI (*p* = 0.72) Cranberry: 31/82 (37.8%) Placebo: 36/89 (40.4%) Compliance Cranberry: 60/72 (83%) Placebo: 51/64 (80%) QoL at 9 months (Qualiveen score) (*p* = 0.02) Cranberry: 0.91 ± 0.70 Placebo: 1.27 ± 0.86 No other timepoints had a statistically significant difference All other secondary outcomes did not demonstrate a statistically significant difference UTI rate UTIs/patient EDSS Urinary disorder MS relapse incidence Antibiotic consumption **Adverse Events** No statistically significant differences	**Clinical Effectiveness** "The daily administration of cranberry extract containing 36mg of proanthocyanidins did not prevent UTI occurrence in MS patients with neurogenic bladders." (pp. 1258)
Takahashi et al., 2013[22]	
Clinical Effectiveness UTI incidence (antibiotic use) (*p* = 0.4209) Cranberry: 32/107 (29.9%) Placebo: 38/106 (35.8%) Subgroup analysis Age ≥ 50 years UTI incidence (antibiotic use) (*p* = 0.0425) Cranberry: 16/55 (29.1%) Placebo: 31/63 (49.2%) No significant differences in UTI incidence in the	**Clinical Effectiveness** "In conclusion, although a preventive effect of cranberry juice against uropathogens has been shown, its clinical efficacy to prevent recurrent UTI remains controversial. In this study, cranberry juice prevented the recurrence of UTI in a limited female population with a 24-week intake of the beverage." (pp. 116)

Table A4.2: Summary of Findings of Included RCTs and NRSs	
Findings	**Authors' Conclusions**
follow subgroups analyzed: Age < 50 years Patients with acute uncomplicated cystitis **Adverse Events** Burning-like sensation following consumption of study beverage Cranberry: 1/107 Placebo: 0/106	
NRSs	
Ledda et al., 2015[23]	
Clinical Effectiveness Clinical UTI reduction frequency (before and after) (groups compared $p < 0.012$) Cranberry: 73.3% (before and after $p < 0.05$) No cranberry: 15.4% (before and after $p < 0.05$) Symptom-free patients ($p < 0.05$) Cranberry: 7/22 (31.8%) No cranberry: 0/22 (0%) Mean UTI duration ($p < 0.05$) Cranberry: 2.5 ± 1.3 days No cranberry: 3.6 ± 1.7 days Urinalysis negative for blood or bacteria ($p < 0.005$) Cranberry: 20/22 (90.9%) No cranberry: 11/22 (50.0%) Compliance >95% of cranberry doses taken **Adverse Events** None observed in either group	**Clinical Effectiveness** "Given the overall limited number of subjects and the short follow-up of this registry study, its results are to be considered preliminary." (pp. 77)
Burleigh et al., 2013[7]	
Clinical Effectiveness Patient reported six month mean UTI rate ($p = 0.004$) Before: 2.4 After: 1.1 Time to first UTI favours Cranberry over control (Kaplan-Meier ($p = 0.023$)) E.coli heterogeneity (no change in heterogeneity observed) Overall mean diversity measure 0.0080	**Clinical Effectiveness** "The results of this study indicate a potential beneficial effect of consuming SDC in reducing the number of recurrent UTIs in susceptible women; however, the results shown here are only preliminary and further studies are necessary. Daily SDC consumption is an inexpensive and readily available supplement to a woman's diet and may provide potential prophylactic effects.

Table A4.2: Summary of Findings of Included RCTs and NRSs

Findings	Authors' Conclusions
	Despite the observed clinical efficacy of SDC consumption, however, the underlying mechanism of SDC is still unclear." (pp. 6)
Sanchez et al., 2013[24]	
Clinical Effectiveness Culture-confirmed PCUTI at 3 and 6 months Baseline 20/20 (100%) 3 months 10/20 (50%) (0.0016) 6 months 3/20 (15%) ($p < 0.0001$)* * ($p = 0.0082$ vs 3 months) Mean number of culture-confirmed PCUTI Baseline 2.8 ± 1.3 3 months 0.7 ± 1.0 ($p < 0.0001$) 6 months 0.2 ± 0.5 ($p < 0.0001$) QoL change from baseline (VAS) 3 months 8.7 ± 13.7 ($p = 0.0110$) 6 months 15.8 ± 15.5 ($p < 0.0002$) **Adverse Events** No adverse events or side effects occurred during the study	**Clinical Effectiveness** "The use of AC products appears to be safe. The present study confirmed the safe profile of Cys as there were no adverse events at all. Prophylaxis of Cys seems to be a promising option to decrease the number of PCUTIs and therefore increase QoL. The results of this pilot study are not significant due to the short follow-up period and the limited number of patients. We believe is needed a randomized placebo controlled study with at least 50 patients and follow up should be one year." (pp. 5)
Bonetta et al., 2012[11]	
Clinical Effectiveness Culture-confirmed UTI incidence (authors state that this result is statistically significant) Cranberry: 16/184 (8.7%) Control: 45/186 (24.2%) Culture-confirmed rUTI incidence Cranberry: 0/184 (0%) Control: 8/186 (4.3%) Dysuria (Boyarsky scale) ($p < 0.0001$) Cranberry / Control Degree 0: 114 (61.9%) / 66 (35.9%) Degree 1: 49 (26.6%) / 60 (32.6%) Degree 2: 20 (10.9%) / 44 (23.9%) Degree 3: 1 (0.6%) / 14 (7.6%) All: 184 / 184 Urinary symptoms due to radiotherapy Nocturia incidence ($p < 0.001$) Cranberry: 31% increase Control: 54% increase	**Clinical Effectiveness** "Despite the lack of randomization in this study, a clear-cut reduction in the LUTIs and bladder discomfort associated with pelvic irradiation was observed, with statistically significant differences in terms of dysuria, nocturia, and urinary frequency. It is possible that, because of its strong antioxidant properties, cranberry could attenuate actinic damage to the bladder mucosa, reducing the inflammatory process and, as a consequence, its symptoms. Full evaluation of this issue will require a further ad hoc study." (pp. 285)

Table A4.2: Summary of Findings of Included RCTs and NRSs

Findings	Authors' Conclusions
Urgency ($p < 0.0001$) Cranberry: 31% increase Control: 54% increase Urine flow ($p = 0.0066$) Cranberry: 14% decrease Control: 21.5% decrease Urination frequency (average daily) ($p = 0.0006$) Cranberry / Control Before: 5.85 / 5.33 After: 7.55 / 8.74	
Pagonas et al., 2012[25]	
Clinical Effectiveness Culture-confirmed UTI incidence/year Baseline / Follow-up Cranberry: 3.6±1.4 / 1.3±1.3 (p<0.001) Met: 3.9±1.8 / 2.0±1.3 (p<0.001) Cranberry+Met: 3.1±1.3 / 1.1±1.1 (p=0.001) Control: 2.6±0.6 / 2.5±1.0 (p=0.85) Symptoms Baseline / Follow-up Cranberry: 56.4% / 33.3% (p=0.008) Met: 76.0% / 24.0% (p<0.001) Cranberry+Met: 72.2% / 33.3% (p=0.03) Control: 80% / 83.3% (p=1.0) Pyuria/Nitrituria Baseline / Follow-up Cranberry: 79.5% / 51.3% (p=0.02) Met: 76.0% / 28.0% (p<0.001) Cranberry+Met: 88.9% / 38.9% (p=0.008) Control: 100% / 96.7% (p=NA)	**Clinical Effectiveness** "The present analysis provided data on nonantibiotic prophylaxis of recurrent UTIs in renal transplant recipients. The findings indicated that L-methionine and cranberry may be potent agents in this setting to reduce the incidence of UTI episodes by about 50%." (pp. 3021) "To compare the efficacy of the different approaches, however, a prospective randomized, controlled study will be nece ssary." (pp. 3021)
EDSS=Expanded Disability Status Scale; **QoL**=quality of life; **SDC**=sweetened dried cranberry; **SEM**=standard error of the mean; **VAS**=visual analogue scale;	

Table A4.3: Summary of Relevant Recommendations of Included Guidelines
Guidelines
GESITRA, 2015[26]
For rUTI in SOT recipients **Evidence level: II; Grade of Recommendation: C** The use of non-antibiotic therapies, such as cranberry extract, L-methionine, topical estrogens, or topical application of Lacto-bacillus, could be provided to transplant patients with recurrent UTI.
EAUN Guidelines, 2013[27]
Infection Prevention **Evidence level: 1b; Grade of Recommendation: A** Do not recommend cranberry supplementation routinely to prevent or treat UTI.
SIGN Guidelines, 2012[28]
Cranberry Products **Evidence level: 1++; Grade of Recommendation: A** Advise women with recurrent UTI to consider using cranberry products to reduce the frequency of recurrence. **Good Practice Point** Women should be advised that cranberry capsules may be more convenient than juice and that high strength capsules may be most effective. **Evidence level: 4; Grade of Recommendation: D** Advise patients taking warfarin to avoid taking cranberry products unless the health benefits are considered to outweigh any risks. **Good Practice Point** Consider increased medical supervision and INR monitoring for any patient taking warfarin with a regular intake of cranberry products. Oestrogen **Evidence level: 1++; Grade of Recommendation: A** Do not use oestrogens for routine prevention of recurrent UTI in postmenopausal women.
GDG for UTIs in children, 2011[29]
Prophylaxis of UTI in children **Good Clinical Practice** There was insufficient scientific evidence to support a recommendation for the use of any of the following preventative measures: vaccines with uropathogenic strains, ascorbic acid, cranberry juice or probiotics.
rUTI=recurrent urinary tract infection; **SOT**=solid organ transplant;