and safe. This use of antibiotics is associated with a significant reduction in recurrence rates. Additionally, intermittent dosing is associated with decreased risk of adverse events including gastrointestinal symptoms and vaginitis.

In a 1990 randomized double-blind placebo-controlled trial of 27 sexually active women with a median age of 23, post-coital antibiotics were shown to be more effective than placebo in reducing UTI recurrences.[147] Other older studies of post-coital antibiotic prophylaxis published between 1975 and 1989[172-175] were non-randomized but had similar results supporting post-coital dosing. In one study of 135 women, post-coital dosing was as effective as daily dosing.[107] Antibiotic prophylaxis should be offered to women with rUTIs temporally related to sexual intercourse, to be taken either before or after sexual activity. This prophylaxis approach targets the antibiotic to the time frame when these women are most vulnerable to UTIs, thus minimizing use of antibiotics, decreasing risk of adverse events, and potentially reducing direct and indirect costs of rUTIs.

Recommended instructions for antibiotic prophylaxis related to sexual intercourse include taking a single dose of an antibiotic immediately before or after sexual intercourse. Dosing options for prophylaxis include the following:

- TMP-SMX 40mg/200mg
- TMP-SMX 80mg/400mg
- Nitrofurantoin 50-100mg
- Cephalexin 250mg

Non-Antibiotic Prophylaxis

13. Clinicians may offer cranberry prophylaxis for women with rUTIs. (Conditional Recommendation; Evidence Level: Grade C)

There has been a growing concern regarding antibiotic resistance in the setting of recurrent UTI. In 2015 the World Health Organization increased awareness of the issue of the growing world-wide phenomenon of antimicrobial resistance through its publication Global Action Plan on Antimicrobial Resistance (AMR).[176] AMR is one factor that has led to an increasing interest in the scientific community to study non-antibiotic modalities in the prevention of rUTI, including the use of probiotics and the consumption of cranberry products.

Cranberries have been studied as a preventative measure for UTI for decades, but recently cranberry has been the subject of an increasing number of randomized clinical trials. These studies have used cranberry in a variety of formulations including juice, cocktail, and tablets. The proposed mechanisms of action is thought to be related to proanthocyanidins (PACs) present in cranberries and their ability to prevent the adhesion of bacteria to the urothelium. It must be noted that PACs are found in varying concentrations depending on formulation used, and many of the cranberry products used in the studies noted below were explicitly formulated for research purposes. The availability of such products to the public is a severe limitation to the use of cranberries for rUTI prophylaxis outside the research setting and must be discussed with patients. Juice studies have used a variety of juices and cocktails in varying volumes of daily consumption and have included cranberry of varying concentrations within the overall volume of product ingested. Likewise, cranberry tablets include variability in dosing and are not subject to the same regulatory environment as antimicrobial drugs. Many studies do not include validation of PAC dosage. Further, clinical studies have also not routinely reported side effects.

The systematic review identified eight randomized trials including cranberry versus placebo/no cranberry (6 RCTs, one with a lactobacillus arm)[177-182] and cranberry versus antibiotics (2 RCTs).[122,136] Four RCTs studied cranberry in a beverage form, and five studied cranberry tablets/capsules. Risk of bias was variable across the studies. Cranberry was associated with decreased risk of experiencing at least 1 UTI recurrence than placebo or no cranberry (5 trials, RR 0.67, 95% CI 0.54 to 0.83 ARD -11%, 95%CI -16% to 5%).[177-181] Kontiokari et al. found a 20% reduction in UTIs (versus control) with 50 mL of daily cranberry-lingonberry juice concentrate over six months.[177] Maki et al. used one 240mL serving of cranberry beverage daily versus placebo and found the antibiotic use-adjusted incidence rate ratio to be 0.61, 95% CI 0.41 to 0.91, P=0.016.[178] Stothers found that both cranberry juice and cranberry tablets significantly decreased the number of patients experiencing at least 1 symptomatic UTI per year (to 20% and 18%, respectively) compared with placebo (to 32%, $p<0.05$).[179] Takahashi et al. randomized women to 125 mL of daily cranberry juice (UR65) or placebo over 24 weeks. In a subgroup analysis of women aged 50 years or more, relapse of UTI was observed in 16 of 55 patients (29.1%) in the cranberry group versus 31 of 63 (49.2%) in the placebo group.[180] Cranberry fruit powder was also found to reduce UTIs significantly

(10.8% versus 25.8%, p = 0.04) in women who received 500 mg daily for 6 months.[181] This study noted that the cranberry fruit powder, which includes the pulp, seeds, and peel, had a PAC content of 0.56%.

There was no statistically significant difference between daily cranberry versus antibiotics in risk of experiencing ≥1 UTI after 6 or 12 months, but the pooled estimate was based on only two trials, favored antibiotics (not statistically significant), and was imprecise (RR 1.30, 95% CI 0.79 to 2.14, I^2=68%)[122,136] The Beerepoot trial[122] compared cranberry versus TMP-SMX (RR 1.09, 95% CI 0.92 to 1.28). The study found cranberry was associated with a greater number of clinical UTI recurrences (mean 4.0 versus 1.8, p=0.02) and shorter time to first recurrence (median 4 versus 8 months, p=0.03); however, effects were no longer present in the 3 months following discontinuation of treatment. Researchers noted cranberry was associated with a lower risk of resistance in E. coli isolates than TMP-SMX in patients with symptomatic recurrence (resistance to TMP or TMP-SMX ~15% versus ~90% and resistance to amoxicillin ~25% versus ~80%). The McMurdo trial[136] compared cranberry to TMP (RR 1.76, 95% CI 1.00 to 3.09) and found no difference in time to recurrence (median 84 versus 91 days, p=0.48). Additionally, it was found that 31.6% of microbial isolates in symptomatic UTI recurrences were TMP-susceptible in the TMP and cranberry groups combined.

Not all studies have included a methodology to examine a hypothesized mechanism of action in humans, which have included both inhibition of adherence mechanisms and urinary content changes that make the urine generally less habitable to uropathogens. Clinical studies have also not routinely reported side effects. Cranberry, in a formulation that is available and tolerable to the patient, may be offered as prophylaxis including oral juice and tablet formulations as there is not sufficient evidence to support one formulation over another when considering this food-based supplement. In addition, there is little risk to cranberry supplements, further increasing their appeal to patients. However, it must be noted that fruit juices can be high in sugar content, which is a consideration that may limit use in diabetic patients.

Lactobacillus

While lactobacillus probiotics have been studied with greater interest in recent years given growing concerns for antibiotic resistance, the Panel is unable to recommend the use of lactobacillus as a prophylactic agent for rUTI given the current lack of data indicating benefit in comparison to other available agents. The systematic review identified five trials evaluating lactobacillus for prevention of recurrent UTI.[124,183-186] Sample sizes ranged from 30 to 238 (total N=464) and the duration of treatment ranged from 5 days to 12 months. Three trials compared lactobacillus versus placebo,[183,184,186] one trial compared lactobacillus versus an antibiotic,[124] and one trial compared lactobacillus versus skim milk-based lactobacillus growth factor.[185] All of the trials evaluated lactobacillus via vaginal suppository, except for one trial[124] of oral lactobacillus versus an antibiotic. lactobacillus species were rhamnosus, reuteri, and crispatus.

There was no difference between lactobacillus vaginal suppositories versus placebo in risk of experiencing ≥1 UTI in 3 trials of younger (mean age in 20's or 30's) women (RR 1.01, 95% CI 0.45 to 2.26, I^2=55%.[183,184,186] The lactobacillus species and dosing schedules varied across trials (twice weekly, daily for 5 days, or daily for 5 days then weekly for 10 weeks).

One trial (n=138, mean age 64 years) found no differences between daily oral lactobacillus (rhamnosus GR-1 and reuteri RC-14) versus TMP-SMX at 12 months in mean number of clinical UTI recurrences (3.3 versus 2.9, mean difference 0.4, 95% CI -0.4 to 1.4) or likelihood of experiencing ≥1 UTI (79% versus 69%, RR 1.15, 95% CI 0.98 to 1.34), though lactobacillus was associated with shorter time to first recurrence (median 3 versus 6 months, p=0.02).[124]

Increased Water Intake

One medium risk of bias trial of women with recurrent UTIs who reported <1.5 L/day of fluid intake at baseline (n=140, mean age 36 years) found increased water intake associated with fewer UTI recurrences compared with no additional fluids (mean 1.7 versus 3.2 UTI episodes over 12 months, p<0.001).[67] Increased water take was also associated with lower likelihood of having at least 3 UTI episodes over 12 months (<10% versus 88%) and greater interval between UTI episodes (143 versus 84.4 days, p<0.001). The increased fluid intake intervention was based on provision of three 500 mL bottles of water to be consumed daily. Daily fluid intake increased from 0.9 L/day to 2.2 L/day in the increased water intake group compared with no change in the no additional fluids group. While these data are promising, no conclusions can be drawn as to whether or not increased water intake is beneficial to women who regularly drink higher quantities of fluids than those reported in this study or those who may be at a lower risk for UTI recurrence.