Dietary supplements to prevent recurrent UTI: The evidence

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Outline

• Epidemiology of UTI
• Pathophysiology of UTI
• Supplements - definition
• Cranberry
• Probiotics
• Other supplements
• Recommendations
Burden of Disease

- Estimated annual cost of UTI in both men and women is $US 3.5 billion *

- ♀:♂ 50:1

- Lifetime risk of a single UTI episode in women 50%


Pathophysiology
• Colonisation of periurethral tissue with uropathogenic organisms

• Ascension of these organisms up urethra into bladder

• E. coli causes over 95% of UTIs*


• Adhesion to uroepithelial cells

  • Type I fimbriae bind to mannose-like receptors

  • P-type fimbriae bind to oligosaccharide receptors

Stapleton S. Lancet 1999;353:7-8
Introduction

Urinary tract infections (UTIs) affect nearly 13 million women annually in the United States alone and can result in significant costs and morbidity [1–5]. Uropathogenic Escherichia coli (UPEC) is the predominant causative agent, responsible for up to 85% of community-acquired infections [6,7]. The majority of UTIs are thought to arise when uropathogens present in the fecal flora colonize the vaginal introitus, ascend into the bladder, and initiate a host response manifested by secretion of cytokines, pyuria, and the onset of symptoms [8].

Women have a 25% chance of experiencing a recurrent UTI within six months [9] of an index episode and a 44% chance of recurrence within one year [10] despite appropriate therapy of the initial infection and negative follow-up urine cultures. Over one-half of all recurrent episodes of acute uncomplicated cystitis are caused by the same bacterial strain as the initial infection [11,12]. As with initial UTIs, it is widely thought that recurrences occur through reascension and reinoculation of the bladder lumen by a UPEC strain that has persisted in the periurethral or fecal flora following the previous UTI.

Recently, it was demonstrated in a murine model of cystitis that UPEC utilize a multistep pathogen cycling infection in which they progress through an intracellular niche within the bladder (Figure 1) [13–15]. UPEC express adhesive fibers known as type 1 pili that mediate binding to and invasion of luminal facet cells of the bladder [16–18]. This intracellular niche is conducive to UPEC replication and formation of intracellular bacterial communities (IBCs) with biofilm-like properties [13]. IBCs exist only transiently before the bacteria dissociate and migrate out of the facet cell, many adopting a filamentous morphology [14]. The filamentous UPEC avoid engulfment by neutrophils, thus allowing them to reinvade the urothelium [14].

Upon infection, the host exfoliates and expels bladder epithelial cells into the urine. Ultimately, UPEC are able to form quiescent intracellular reservoirs composed of small rosettes of bacteria within Lamp-1–positive endocytic vesicles that can persist for several weeks protected from antibiotics and, presumably, undetected by the host immune system [15,19,20]. Epithelial turnover may cause the quiescent bacteria to revert to an actively replicative form, leading to recurrent bacteriuria [19].

To date, an intracellular bacterial pathway has not been

Why Supplements?

• Risk of recurrence within 1 year of index case 44%*

• Despite appropriate antibiotic therapy and negative post-treatment cultures

• Antibiotic prophylaxis works

• Continuous

• Post-coital

• Problem of emerging antibiotic resistance

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What is a supplement?

According to Health Canada:

• “a plant or a plant material, an alga, a bacterium, a fungus or a non-human animal material, vitamins, an amino acid, an essential fatty acid, a mineral or a probiotic” and “that supplements the diet.”

• Definition varies by country

FDA Dietary Supplement Health and Education act (DHSEA) 1994

• “manufacturer is responsible for ensuring that its dietary supplement products are safe before they are marketed”

• Unlike drug products that must be proven safe and effective for their intended use before marketing, there are no provisions in the law for FDA to "approve" dietary supplements for safety or effectiveness before they reach the consumer”
Other than the manufacturer's responsibility to ensure safety, there are no rules that limit a serving size or the amount of a nutrient in any form of dietary supplements. This decision is made by the manufacturer and does not require FDA review or approval.

**FDA 2010**

- Dietary supplements must comply with "good manufacturing practices", and be produced under "controls that result in a consistent product free of contamination, with accurate labeling"
- Report to the FDA "all serious dietary supplement related adverse events"
Supplements
• Cranberry

• Probiotics

• Other - Uva ursi, Forskolin, Juniper, Golden Rod, D-Mannose
- *Vaccinium macrocarpon*

- Historically used for disorders of stomach, blood, liver; fever, scurvy

- 1800’s treatment for bladder disorders

- Ocean Spray earnings 2008 US$1.9 Billion

- 90% of world’s annual production from MA, NJ, WI (USA); 8% from Quebec and BC

- 95% of berries are used for juice

- 5% left whole
Mechanism of Action

- Initial studies focused on the potential role of hippuric acid.
- Quinic acid in cranberry is a precursor of hippuric acid, a known potent bacteriostatic agent.
- Requires ingestion of 240ml of cranberry juice at 80% concentration.*
- Subsequent studies did not reproduce these results.


- Anti-adherence properties - human studies showed 68% adherence inhibition after ingestion of cranberry juice cocktail.*

*Sobota AE. J Urol 1984;131:1013-16
• **Fructose** - inhibits Type 1 (mannose-specific) fimbriated E. coli in vitro*, but no in vivo studies to support this


• **Proanthocyanidins** (PACs)
  - Flavonoid compounds in tannin-rich foods
  - Conjugated dimers and trimers of anthocyanidins
  - PACs derived from cranberry exhibit A-type linkages
    - superior anti-adhesion properties compared to B-type linkages found in PACs from apples, grapes, green tea*

• Inhibit adhesion of P fimbriated E. coli (as well as Proteus, Klebsiella, Enterbacter, Pseudomonas)

• Competitively binding to fimbriae or reduce adhesion capabilities by altering P-fimbriae

• Cranberry PAC levels related to:
  
  • pH
  
  • Temperature
  
  • Light
Pharmacokinetics of PACs

- Not well studied in humans
- Peak urinary PAC concentrations seen 3-6 hours after intake; completed by 12 hours
- Approximately 5% of oral dose excreted in urine
- Colonic excretion - potential role for selection of non-pathogenic E coli in gut

Formulations

- Pure juice - pH <2.5
- Cranberry juice cocktail - most common 25-27%, sweetened
- Tablets, capsules
The Evidence

- Cochrane review 2008*
  - 10 RCTs - 5 cross-over, 5 parallel group
    - 7 juice vs placebo or water
    - 2 tablets vs placebo
    - 1 juice vs tablets vs placebo

*Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database of Systematic Reviews 2008(1)

- Cochrane review 2008
  - 4 studies included in meta-analysis
  - UTI incidence at 12 months RR 0.66 (0.47-0.92)
  - Women with recurrent UTI had 39% risk reduction
<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Primary Outcome</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT CJC (27%) vs placebo (multi-dosing)*</td>
<td>188 pregnant women &lt;16/40</td>
<td>Asymptomatic bacteriuria Symptomatic UTI</td>
<td>IRR for all UTI 0.59 (95% CI 0.22-1.6)</td>
<td>61% completed study High dropout due to GI SE Underpowered</td>
</tr>
<tr>
<td>RCT cranberry capsules 500mg vs trimethoprim 100mg for 6 months**</td>
<td>137 women ≥45yo with recurrent UTI</td>
<td>Antibiotic treated UTI Time to UTI</td>
<td>RR for UTI 1.61 (95% CI 0.93-2.79)</td>
<td>Adequately powered Previous studies confirm efficacy of Trimethoprim in prophylaxis</td>
</tr>
<tr>
<td>Crossover RCT cranberry capsule 500mg vs placebo***</td>
<td>47 SCI men</td>
<td>Symptomatic UTI</td>
<td>Incidence UTI 0.3 vs 0.9 UTI per person-year (p= 0.01)</td>
<td>Incidence rate in Placebo phase(0.9) not significantly different from that prior to study(1.3)</td>
</tr>
</tbody>
</table>


**Limitations**

- Comparison between studies difficult because
- No universally accepted standard method for quantification of PACs in commercial cranberry products; currently no requirement to state PAC content
- Cranberry tablets vary their PAC content from levels that are similar to pure juice, down to undetectable levels
• No objective measure of adherence to treatment protocol (measurement of urinary output of PACs)

• No systematic evaluation of the frequency of dose-administration or dose-response relationship

• Different definitions of UTI - asymptomatic bacteriuria, symptomatic UTI, colony count

• Varying study duration

• High withdrawal rates - up to 47% (GI symptoms)

Adverse Events

• Allergic reaction

• GI upset 10-40%
Adverse Events

- Interaction with warfarin
  - May inhibit activity of CYP2C9
  - Case reports detailing increased INR in patients taking cranberry products concurrently
  - 2 RCTs do not support this

- Close monitoring of INR in patients taking warfarin and cranberry

Nephrolithiasis

- Cranberry contains high levels of oxalate
- Conflicting results in literature
  - Increased urinary excretion of oxalate, but also of magnesium, potassium*
  - Decreased excretion of oxalate and phosphate, increased citrate excretion**

**McHarg TA, et al. BJU Int 2003;92:765-68
What are they?

- “live microorganisms which when administered in adequate amounts confer a health benefit to the host” (FAO/WHO criteria for probiotic)
  - bacteria, yeasts
  - dairy products, probiotic fortified foods
  - freeze-dried form - tablets, capsules, powders
Lactobacilli

- Anaerobic, gram-positive bacteria
- Predominant bacteria found in genital flora of healthy, premenopausal women

\[ \text{Lactobacilli} \]

- \textbf{L rhamnosus GR-1, L fermentu RC-14}
- \textbf{L crispatus}
- \textbf{L rhamnosis GG}
- \textbf{L casei Shirota}
- \textbf{L acidophilus}

\textbf{Urogenital}

- \textbf{Intestinal}
• Competitively bind to vaginal epithelial cells
• Compete for nutrients
Role in Genitourinary health

• Women with history of recurrent UTI have altered vaginal flora
  • reduced Lactobacillus species
  • prolonged vaginal colonization with uropathogens, predominantly E coli*
  • So, theoretically use of probiotics restores normal vaginal flora, inhibits overgrowth of uropathogens and prevents recurrent UTIs


The Evidence

• L. rhamnosus GR-1/L fermentum RC-14
• L crispatus
L rhamnosus GR-1/L fermentum RC-14

- **L rhamnosus GR-1**
  - adheres to vaginal epithelial cells
  - bacteriostatic properties

- **L fermentum RC-14**
  - produces surface-active proteins, preventing adhesion of uropathogens to vaginal epithelial cells


- For probiotics to be clinically effective vaginal colonization has to occur irrespective of route of administration
  - Both oral and vaginal administration has been shown to result in conversion of abnormal to normal vaginal flora
  - This change is shown to persist following cessation of probiotic administration

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<tbody>
<tr>
<td>RCT L rham PV weekly vs LGF for 12 months*</td>
<td>55 premenopausal women</td>
<td>UTI incidence</td>
<td>No intergroup difference in UTI incidence</td>
<td></td>
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<td></td>
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<td></td>
<td>UTI 1.6/1.3 with treatment (p=0.001)</td>
<td></td>
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<tr>
<td>RCT norfloxacen or TMP/SMX for 3 days then L rham PV twice weekly x 4 doses then 1 PV at 2 months vs placebo**</td>
<td>41 premenopausal women with culture-confirmed UTI</td>
<td>Bacterial eradication UTI recurrence</td>
<td>No difference between antibiotic groups</td>
<td>Study underpowered</td>
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<tr>
<td></td>
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<td></td>
<td>No significant difference in rec UTI between L rham (21%) and placebo (47%)</td>
<td></td>
</tr>
<tr>
<td>RCT L rham# PV twice weekly vs placebo for 26 weeks***</td>
<td>47 premenopausal women</td>
<td>UTI incidence</td>
<td>IRR 1.41 (95%CI 0.88-1.98)</td>
<td>Strain not demonstrated to inhibit E coli in vitro</td>
</tr>
</tbody>
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**L crispatus**

- Adheres strongly to vaginal epithelial cells
- Lowers pH of vaginal environment
Before and after study of 9 women with history of recurrent UTI*

- L crispatus PV 2 nightly for 1 year
- Incidence of UTI pre vs during treatment 5.0 per patient year to 1.3 per patient year (p<0.01)

Adverse Events

- Systemic infection
  - Lactobacillus infection is rare
  - When it occurs usually in patients with underlying chronic disease or immunocompromise


Other Supplements

Uva Ursi (Bearberry)
• Species of Arctostaphylos

• Woody shrub high altitudes circumpolar

• Leaves are proposed therapeutic portion based on arbutoside content

Uva Ursi (Bearberry)

Hydroquinone (glucuronidated)

Hydroquinone glucuronide

Arbutoside

Glucose + aglycone hydroquinone

Hydroquinone glucuronide in pH > 7

Hydroquinone (proposed antimicrobial agent)

Yamell E. World J Urol 2002;20:285-93
• In Vitro studies

• Increases hydrophobicity of E coli, decreases ability of bacteria to adhere to urothelial cells*

• Antimicrobial activity against S aureus, S typhi, C albicans**

* Turi M, et al. APMIS 1997;105;956-62

• In Vivo study

• RCT 57 women with recurrent UTI*

• Uva-E (Arbutin & Dandelion) 3 tabs tid vs placebo for 1 month

• F/u 12 months

• UTI 0% vs 23% (p<0.05)

• No reported side effects

• Concerns regarding long term use of Uva Ursi relate to hydroquinone

  • Excessive doses: GI upset, tinnitus, liver dysfunction

  • Mutagenic/carcinogenic effects

  • Interaction with CYP450 isoenzymes

  • Bull’s eye maculopathy

  • Avoid in pregnancy, lactation, children < 12yo

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**Forskolin**

• Extract from Colue’s forskohlii

• Basic science studies

  • Elevator of Cyclic AMP

  • May have a role in decreasing IBCs

• No human RCT to support use
Juniper Berries

- Conifers
- Over 60 species in the Northern hemisphere
- Leaves contain antimicrobial and diuretic properties of terpenoids (animal studies)
- Human clinical trials not reported on efficacy or safety in UTI

Golden Rod

- Flowering perennial (Solidago spp)
- North American Native

Yamell E World J Urol 2002;20:285-93
• 1 Double blind RCT
  • Increase urine flow

• No single active ingredient isolated, mechanisms still undetermined

• Side effects: allergic reaction, renal failure

D Mannose

• Natural sugar

• Competitively blocks adhesion of E Coli

• Large literature in vivo and animal models

• Lacking human RCT

Bone K Br J Phytoth. 1994
Current Trials

Cranberry

- Current NIH/NCCAM* funded studies addressing limitations of published studies

  Quality control of the product
  Dose response
  Documentation of compliance
  Urine quantification of PACs
  Tracking of symptomatic UTI's
  Bacterial analysis (virulence)

*National Centre for Complementary and Alternative Medicine
**Cranberry**

- Effects of Cranberry-Containing Products in Women with Recurrent Urinary Tract Infection
- Cranberry for Prevention of Urinary Tract Infections in MS Patients
- Effect of Cranberry Capsules on Urinary Infection Rates in Spinal Cord Injured Patients During Post Acute Rehabilitation
- Cranberry Juice for the Prevention of Recurrent Urinary Tract Infections
- Dosing Study of Cranberry Capsules for the Prevention of Bacteriuria in Nursing Home Residents
- Cranberry Juice for Treatment of Urinary Tract Infections

**Probiotics**

- Probiotics as a Prophylactic Aid in Women with Recurrent Urinary Tract Infections
- Bacteriuria Eradication through Probiotics
- Intravaginal LACTIN-V for Prevention of Recurrent Urinary Tract Infection
- Probiotics for Girls with Recurring Urinary Tract Infections
- Probiotics in Girls With Spina Bifida
- Low Dose Estriol with Lactobacilli Treatment for Preventing Recurrent Urinary Tract Infection in Postmenopausal Women
Conclusions

• Cranberry
• Few high quality studies
• Conflicting results regarding efficacy of cranberry products in UTI prevention - No standard method for quantification of PACs in commercial products
• No consensus as to juice vs capsules, dose or dosing schedule

• Use diluted pure cranberry juice (1:4) 60ml bid

• Probiotics

• Specific for genitourinary tract (L Rhamnosus/L fermentum)
Useful Resources

• National Centre for Complementary and Alternative Medicine (NCCAM) nccam.nih.gov

• The Office of Dietary Supplements ods.od.nih.gov

• Health Canada Natural health products www.hc-sc.gc.ca/dhp-mps/prodnatur/index-eng.php

Questions