Recurrent Urinary Tract Infections Among Adult Women: Comparative Effectiveness of Five Prevention and Management Strategies Using A Markov Chain Monte Carlo Model

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Recurrent Urinary Tract Infections Among Women: Comparative Effectiveness of 5 Prevention and Management Strategies Using a Markov Chain Monte Carlo Model

Keywords: urinary tract infection; recurrent management.
Background: Urinary Tract Infection (UTIs)

- Common infection in adult women
  - 10-13% experience a UTI annually
  - Lifetime risk > 50%
  - Annually in U.S.
    - >6 million outpatient visits
    - 479,000 hospitalizations

Background: Urinary Tract Infection (UTIs)

- UTIs cause
  - Pain
  - Restriction of work and school
  - Bed rest
  - $2.4 billion in U.S. annually


Background: Recurrent UTIs

- Common problem in clinical practice
- Among women w/ UTI in next 6 months
  - 20-30% Have a second UTI
  - 3% will experience a third UTI
- Defined by experts as ≥ 3 UTIs during a one-year time span

Background: Recurrent UTIs

- Represent challenge for treating physicians
- No clear ideal prevention strategy
- No comparative trials of strategy

Background: Recurrent UTIs

- Treatment Prevention Strategies
  - Antibiotic prophylaxis
  - Estrogens
  - Cranberry juice/supplement
  - Self-diagnosis/self-treatment
  - Acupuncture
  - Lactobacillus
  - Vaccine
Hypothesis

- We hypothesized that preferred treatment strategies to prevent recurrent UTIs would differ depending on the outcome of preference.

Investigation Aim

- Quantify outcomes of recurrent UTI strategies
  - Effectiveness
  - Cost
  - HRQOL
Methods

- Markov decision analysis
- Monte Carlo simulation
  - Cohort of patients undergoing each strategy
  - Cohort of “control” patients with no intervention
- Systematic review of literature of efficacy
Markov Model
Methods

- Outcomes measured:
  - Number of UTIs/year
  - Annual cost from the payer’s (i.e., health plan’s) perspective
  - Annual cost from the patients’ perspective
  - Quality-adjusted life-days (QALD).
    - As opposed to QALY (QALD=QALY/365)

Methods

- Software program
  - DATA (version 4.0, TreeAge Software, Williamstown, MA)
Methods

- Systematic literature review
  - MEDLINE, Embase, and Cochrane Library databases
  - Searched for articles from 1966 to Jan. 2012
  - Keywords:
    - recurrent [recur*]
    - urine or urinary [urin*] AND
    - infectious or infection(s) [infectious, infection*].

- Two reviewers assessed each abstract
  - If both believed abstract might contain:
    - Data on management strategy for recurrent UTIs or
    - Review article that may reference such data
  - Then article was pulled for review
  - If the reviewers differed, 3rd reviewer tie-broke
  - Reference lists of retrieved articles also reviewed for additional (missed) studies
Methods

- Inclusion criteria for study population
  - Adult (>18 years of age) non-pregnant females
  - Study population with ≥ 3 UTIs per year
  - Comparative clinical trial:
    - Using either an untreated/placebo control group or
    - Quantified patients’ pre-intervention and post-intervention UTI incidence
  - English abstract and/or text

Methods

- Probability of UTI prevention
  - Obtained from articles presenting original data
  - Risk reduction calculated by comparing Tx strategy to control or pre-intervention group
  - Pooled mean risk reduction weighted by study sample size
  - Only modeled interventions with >2 published investigations
Methods

- Monte Carlo simulation
  - 10,000 subject simulations
  - One day Markov cycle
  - Untreated group has mean 3 UTIs/year
  - Second set of models with 8 UTIs/year
  - Probabilities from literature search
    - Risk reduction decreased UTI risk by x%

- Patients present with Sx's of UTI
  - Most with cystitis, small probability of STI, vaginitis

- UTIs
  - Required visit to MD
  - Treated with systemic antibiotics
  - Most present with cystitis, some w/ pyelo
  - Small proportion require hospitalization
Costs

- Program (payer) perspective
- Patient perspective
Methods

Costs:
- Hospitalization: American Hospital Association
  - 10% cost burden on patient
- MD visits: CMS
- Pharmaceutical costs: Red Book
  - Patient co-pay
- Cranberry: pill costs from 3 national commercial pharmacies (mean costs)
- Acupuncture: survey of 30 clinics (mean cost)
- Lab costs: survey of 2 major commercial labs

HRQOL:
- Taken from generic health states from the literature

Kaplan RM et al. J Chronic Dis 1984;37:85-95
Methods

- Taken from generic health states from the literature
- HRQOL states examples
  - Perfect health 1.0
  - UTI (“Painful, burning, or frequent urination”) 0.9673
  - Pyelonephritis (“fever or chills with aching all over and vomiting or diarrhea”) 0.9288


Methods

- One-way sensitivity analyses:
  - Performed for each
    - Probability
    - Cost
    - QALD value
  - Each value ranged over the minimal & maximal values determined from the literature or cost survey

Kaplan RM et al. J Chronic Dis 1984;37:85-95
RESULTS

2,673 Abstracts reviewed

144 Articles reviewed in full

20 Articles on rUTI management strategies

2,529 Abstracts Excluded:
- 956 Non-UTI studies
- 477 Pediatric studies
- 303 Review articles/opinion pieces
- 256 Basic science studies
- 261 Case report/series
- 129 Epidemiologic studies
- 57 Studies of UTIs in men
- 36 No untreated control or pre/post comparison group
- 21 UTI vaccination studies
- 24 study population with < 3 recurrent UTIs/year

124 Articles Excluded:
- 51 Review articles/opinion pieces
- 30 Did not use TMP-SMX
- 19 Study population with < 3 recurrent UTIs/year
- 10 No untreated control or pre/post comparison group
- 8 Pediatric studies
- 3 Studies of UTIs in men
- 2 Epidemiologic studies
- 1 Basic Science study
Results

- The systematic literature review yielded 2,791 articles.
- We found 20 articles that were clinical trials of UTI prophylaxis for UTIs that met our criteria:
  - Antibiotic prophylaxis (n=6)
  - Estrogen prophylaxis (n=5)
  - Acupuncture prophylaxis (n=2)
  - Cranberry prophylaxis (n=4)
  - Self-treatment (n=3)

Table 1. Probability values for variables in model

<table>
<thead>
<tr>
<th>Description</th>
<th>Probability</th>
<th>Range of probabilities tested</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acupuncture risk reduction</td>
<td>0.68</td>
<td>0.6-0.7</td>
<td>24,25</td>
</tr>
<tr>
<td>Cranberry risk reduction</td>
<td>0.50</td>
<td>0.4-0.8</td>
<td>9,10,18,17</td>
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<tr>
<td>Daily antibiotics/Nitrofurantoin, 100 mg bid risk reduction</td>
<td>0.86</td>
<td>0.6-1.0</td>
<td>11,19-23</td>
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<tr>
<td>Estrogen use risk reduction</td>
<td>0.65</td>
<td>0.3-1.0</td>
<td>12-15,18</td>
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<tr>
<td>Description</td>
<td>Mean cost per unit (US dollars)</td>
<td>Range tested (US dollars)</td>
<td>References</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>---------------------------------</td>
<td>---------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Acupuncture, initial session for gynecology visits</td>
<td>2.51/day</td>
<td>1.37-4.40</td>
<td>See text</td>
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<tr>
<td>Clindamycin (oral)</td>
<td>0.75/day</td>
<td>0.37-1.25</td>
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<tr>
<td>Estrogen</td>
<td>0.50/day</td>
<td>0.14-3.63</td>
<td>See text</td>
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<tr>
<td>Daily antibiotics/Neosporin 100 mg bid (AEDP)</td>
<td>1.94/day</td>
<td>1-4</td>
<td>See text</td>
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<td>Ciprofloxacin, 250 mg bid (AEDP)</td>
<td>4.44/day</td>
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<td>See text</td>
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<tr>
<td>Ciprofloxacin, 500 mg bid (AEDP)</td>
<td>5.38/day</td>
<td>3-41</td>
<td>See text</td>
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<td>Self-treatment for yeast infection</td>
<td>16.14</td>
<td>8-32</td>
<td>See text</td>
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<tr>
<td>Hospitalization for pyelonephritis</td>
<td>1782.28/day</td>
<td>829-3600</td>
<td>See text</td>
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<tr>
<td>Outpatient treatment for infection unresponsive to fluoroquinolones or pyelonephritis</td>
<td>29.77/day</td>
<td>15-60</td>
<td>See text</td>
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<tr>
<td>Follow-up physician visit</td>
<td>97.77</td>
<td>65-132</td>
<td>See text</td>
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<td>Initial urinalysis</td>
<td>20.76</td>
<td>10-42</td>
<td>See text</td>
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<tr>
<td>Follow-up urinalysis</td>
<td>20.76</td>
<td>10-42</td>
<td>See text</td>
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<tr>
<td>Urine culture</td>
<td>16.42</td>
<td>37-93</td>
<td>See text</td>
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<tr>
<td>Vaginal smear</td>
<td>13.50</td>
<td>10.65-18.25</td>
<td>See text</td>
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<tr>
<td>STI test</td>
<td>67.60</td>
<td>26-135</td>
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<table>
<thead>
<tr>
<th>Description</th>
<th>Duration (days)</th>
<th>Range (days)</th>
<th>References</th>
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<tbody>
<tr>
<td>Hospitalization for pyelonephritis</td>
<td>3</td>
<td>1-8</td>
<td>See text</td>
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<tr>
<td>Outpatient treatment for infection unresponsive to fluoroquinolones</td>
<td>5</td>
<td>3-10</td>
<td>See text</td>
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<tr>
<td>Outpatient treatment for pyelonephritis</td>
<td>7</td>
<td>5-14</td>
<td>See text</td>
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</tbody>
</table>
Number of UTIs per year

Management Strategy

Mean payer cost per year

Management Strategy
### Change in cost to payer

- **Ref.**
- **No strategy used**: $319
- **Daily antibiotics**: $327
- **Daily estrogen**: $502
- **Daily cranberry pills**: $421

### Mean payer cost per UTI prevented

- **Ref.**
- **No strategy used**: $168
- **Daily antibiotics**: $172
- **Daily estrogen**: $218

#### Management Strategy

- Daily antibiotics
- Daily estrogen
- Daily cranberry pills
- Acupuncture
- Symptomatic self-treatment
Total QALDs in 1 year

- No strategy used: 353
- Daily antibiotics: 361
- Daily estrogen: 361
- Daily cranberry pills: 360
- Acupuncture: 362
- Symptomatic self treatment: 355

QALD gained per year

- No strategy used: 9.8
- Daily antibiotics: 7.6
- Daily estrogen: 6.6
- Daily cranberry pills: 8.3
- Acupuncture: 1.1
- Symptomatic self treatment: 0
Mean payer cost per QALY gained

Number of UTIs per year (Baseline = 8 UTIs/yr)
Mean payer cost per UTI prevented

Management Strategy

Total QALDs in 1 year

Management Strategy
QALD gained per year

Management Strategy

Mean payer cost per QALY gained

Management Strategy
## Results from Payer’s Perspective (3 UTIs/Year)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Number of UTI/year</th>
<th>Mean payer cost/year</th>
<th>Change in cost to payer</th>
<th>Mean payer cost/UTI prevented</th>
<th>Total QALDs in 1 year</th>
<th>QALD gained/year</th>
<th>Mean payer cost/QALY gained</th>
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</thead>
<tbody>
<tr>
<td>No strategy used</td>
<td>3.0</td>
<td>$771</td>
<td>REF</td>
<td>REF</td>
<td>353</td>
<td>REF</td>
<td>REF</td>
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<tr>
<td>Daily antibiotics</td>
<td>0.4</td>
<td>$821</td>
<td>-$50</td>
<td>$19</td>
<td>363</td>
<td>9.8</td>
<td>$1,859</td>
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<tr>
<td>Daily estrogen</td>
<td>1.1</td>
<td>$452</td>
<td>-$319</td>
<td>-$168</td>
<td>361</td>
<td>7.6</td>
<td>-$15,320</td>
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<tr>
<td>Daily cranberry pills</td>
<td>1.1</td>
<td>$444</td>
<td>-$327</td>
<td>-$172</td>
<td>360</td>
<td>6.6</td>
<td>-$18,079</td>
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<tr>
<td>Acupuncture</td>
<td>0.7</td>
<td>$269</td>
<td>-$502</td>
<td>-$218</td>
<td>362</td>
<td>8.3</td>
<td>-$22,054</td>
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<tr>
<td>Symptomatic self treatment</td>
<td>3.0</td>
<td>$350</td>
<td>-$421</td>
<td>N/A</td>
<td>355</td>
<td>1.1</td>
<td>-$139,828</td>
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</table>

## Results from Payer’s Perspective (8 UTIs/Year)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Number of UTI/year</th>
<th>Mean payer cost/year</th>
<th>Change in cost to payer</th>
<th>Mean payer cost/UTI prevented</th>
<th>Total QALDs in 1 year</th>
<th>QALD gained/year</th>
<th>Mean payer cost/QALY gained</th>
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<tr>
<td>No strategy used</td>
<td>8.0</td>
<td>$2,008</td>
<td>REF</td>
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<td>336</td>
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<td>Daily antibiotics</td>
<td>1.3</td>
<td>$1,014</td>
<td>-$994</td>
<td>-$148</td>
<td>360</td>
<td>24.2</td>
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<tr>
<td>Daily estrogen</td>
<td>3.1</td>
<td>$946</td>
<td>-$1062</td>
<td>-$217</td>
<td>353</td>
<td>17.5</td>
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<tr>
<td>Daily cranberry pills</td>
<td>4.4</td>
<td>$1,074</td>
<td>-$934</td>
<td>-$259</td>
<td>358</td>
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<td>Acupuncture</td>
<td>2.8</td>
<td>$736</td>
<td>-$1272</td>
<td>-$245</td>
<td>355</td>
<td>19.3</td>
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<tr>
<td>Symptomatic self treatment</td>
<td>8.0</td>
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<td>-$1067</td>
<td>N/A</td>
<td>338</td>
<td>2.2</td>
<td>-$177,008</td>
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</table>
## Results from Patient’s Perspective (3 UTIs/Year)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Mean patient cost/year</th>
<th>Change in cost to patient</th>
<th>Mean patient cost/UTI prevented</th>
<th>Mean patient cost/QALY gained prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>No strategy used</td>
<td>$139</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>Daily antibiotics</td>
<td>$140</td>
<td>$1</td>
<td>$0</td>
<td>$19</td>
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<tr>
<td>Daily estrogen</td>
<td>$169</td>
<td>$30</td>
<td>$15</td>
<td>$1,412</td>
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<tr>
<td>Daily cranberry pills</td>
<td>$341</td>
<td>$202</td>
<td>$106</td>
<td>$11,121</td>
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<tr>
<td>Acupuncture</td>
<td>$946</td>
<td>$807</td>
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<td>$35,467</td>
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<td>Symptomatic self treatment</td>
<td>$69</td>
<td>-$70</td>
<td>N/A</td>
<td>-$23,260</td>
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</table>

## Results from Patient’s Perspective (8 UTIs/Year)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Mean patient cost/year</th>
<th>Change in cost to patient</th>
<th>Mean patient cost/UTI prevented</th>
<th>Mean patient cost/QALY gained prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>No strategy used</td>
<td>$365</td>
<td>REF</td>
<td>REF</td>
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<td>Daily antibiotics</td>
<td>$178</td>
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<td>-$28</td>
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<td>Daily estrogen</td>
<td>$261</td>
<td>-$104</td>
<td>-$21</td>
<td>-$2,167</td>
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<tr>
<td>Daily cranberry pills</td>
<td>$458</td>
<td>$93</td>
<td>$26</td>
<td>$1,541</td>
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<tr>
<td>Acupuncture</td>
<td>$998</td>
<td>$633</td>
<td>$122</td>
<td>$11,971</td>
</tr>
<tr>
<td>Symptomatic self treatment</td>
<td>$181</td>
<td>-$184</td>
<td>N/A</td>
<td>-$30,444</td>
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</table>
Results: Sensitivity Analysis

- **Payer costs sensitive to:**
  - Estrogen costs ($0.50/day)
    - 30% reduction if estrogen cost was $0.14/day or a 2400% increase if the cost was $32/day
  - Antibiotic prophylaxis
    - 43% cost reduction to 89% cost increase

- **Other costs had lesser effects**

Results: Sensitivity Analysis

- **Patient costs sensitive to:**
  - Cranberry pills
    - 64% cost reduction to 155% cost increase
  - Acupuncture
    - 43% cost reduction to 79% cost increase

- **Other costs had lesser effects**
Results: Sensitivity Analysis

- Probabilities with influence on results
  - Antibiotic prophylaxis
    - 0.0 to 1.2 UTIs/year
  - Pyelonephritis probability
    - 23% decrease to 346% increase in payer costs
  - QALD affected by FQ treatment cure %
    - 348-361 QALD (baseline 353)

Summary

- Daily antibiotics
  - Least expensive for patient
  - Cost for payer
    - Cost savings for 8 UTI/year model
    - Modest cost ($50 year) for 3 UTI/year model
Summary

• Acupuncture
  ○ Least expensive for payer
  ○ Very expensive for patient
  ○ Of note
    ● Access to treatment poorly understood
    ● Efficiency of intervention poorly understood
    ● Ideal regimen unclear
      • In studies, Rx administered 2x/week x 4 weeks & women then followed x 6 months

Summary

• Daily estrogens, cranberry
  ○ Similar reductions in UTIs
    ● 1.1 UTIs/year for 3 UTI/year model
  ○ Similar payer costs, QALY gained
  ○ But cranberry very expensive to patient
Summary

Daily estrogens

- Optimal method unclear
  - Oral, transdermal, vaginal
- May not be tolerated by some women

Summary

Symptomatic self-treatment

- No reduction in UTIs
- Minimal improvement in QALY
- Very cost effective to patient, provider
- May be very attractive to some persons, very unattractive to other
Limitations

- Model had many many assumptions
- Only based on published data
  - Publication bias
- Quality of some clinical trials relatively poor
  - Double blind placebo controlled RCTs ideal but rare
- Cost of medications not as clear as expected

Limitations

- Long term tolerability, efficacy not modeled
  - But rare events have minimal effects on cost in prior studies
- CAM interventions not well standardized
- No disease specific HRQOL measures
- Models not stratified by patient related factors, e.g., age
  - Model assumed patients in perfect health
- Didn’t perform credibility ranges
Strengths

- Multiple complementary outcomes
- Multiple perspectives
- Systematic review of the literature
- Summary, comparative outcomes

Implications

- Interventions to prevent UTIs
  - Generally efficacious
  - Cost-effective
- Data will help patients/provider partnership individualize treatment strategy