Bacterial Interference for Prevention of Urinary Tract Infection

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The concept of bacterial interference, both passive and active, embodies the use of bacteria of low virulence to compete with and protect against colonization and infection by disease-causing organisms. Passive bacterial interference is achieved when naturally present commensal bacteria help defend against host infection by pathogenic organisms. Examples of bodily sites that are protected by normal flora include the skin, oral cavity, upper respiratory tract, vagina, bladder, and bowels. In instances where natural bacterial flora may not afford adequate resistance to colonization and/or infection, active bacterial interference can be useful by intentionally administering into the human body bacteria of low virulence that could replace pathogens. The potential benefit of bacterial interference in preventing infection has been explored with variable success in differently designed studies of various conditions (including urinary tract infection, vaginosis, burn, and antibiotic-associated colitis) by using different agents (including Escherichia coli, Lactobacillus species, Streptomyces species, and skin flora) [1–3].

Not only is urinary tract infection (UTI) the most common healthcare-acquired infection, but it also accounts for 8–11 million patient visits each year in the United States [4]. Because the risk-benefit analysis does not favor the general use of antimicrobial-based measures to prevent UTI, there exists a pressing need to explore the role of nonantimicrobial preventive approaches. To eliminate uropathogens, a number of studies have aimed at deliberate colonization of the bladder with bacteria of low virulence. This approach is supported by the fact that treatment of asymptomatic bacteriuria is not only contraindicated in general, but can also lead to emergence of uropathogens and development of symptomatic infection [5–7]. This review focuses on the role of bacterial interference in preventing UTI by using E. coli in patients with neurogenic/dysfunctional bladder or Lactobacillus species mostly in healthy women. It assesses the role of different agents of bacterial interference, explores the potential mechanisms of action, summarizes the results of clinical studies, compares different bacterial applications, and highlights future research.

AGENTS OF BACTERIAL INTERFERENCE

The 2 bacterial organisms that have been clinically tested as agents of bacterial interference for specifically preventing UTI include E. coli (E. coli strains 83972 and HU2117) and a variety of Lactobacillus species (mostly L. crispatus CTV05, L. casei var rhamnosus GR1 and GG, and L. fermentum B54).

Escherichia coli

Bacterial interference utilizing nonpathogenic E. coli for prevention of UTI was originally established by using E. coli 83972, an organism that had caused asymptomatic bacteriuria for 3 years in a young girl without altering renal function [8]. Although E. coli 83972 has not been reported to cause symptomatic UTI and usually does not express P fimbriae, it contains the full chromosomal pap gene that encodes P fimbriae [9, 10]. Escherichia coli HU2117 is a
genetically engineered strain created from wild-type *E. coli* 83972 that has an 800-base pair deletion mutation in the chromosomal *papG* gene [9]. As a result, it cannot make functional P fimbriae, which are associated with pyelonephritis and bacteremia. Based on in vitro data, *E. coli* HU2117 seems to be indistinguishable from *E. coli* 83972 with respect to bladder colonization and ability to prevent biofilm formation on urinary catheters by uropathogens [11].

*Lactobacillus* species

Lactobacilli are the dominant vaginal flora and possess antimicrobial properties that regulate other urogenital microbes. Although a variety of *Lactobacillus* species have been reported as healthy vaginal flora, *L. crispatus*, *L. gasseri*, *L. inners*, and *L. jensenii* appear to be most common [12]. *Lactobacillus casei* var *rhamnosus* strains have been evaluated as potential probiotic agents in the vagina but have not been reported as part of normal vaginal flora [12]. Since high concentrations of *Lactobacillus* species in the vagina correlate with a lower rate of UTI, the use of *Lactobacillus*-containing probiotics to restore commensal vaginal flora has been proposed for the treatment and prophylaxis of bacterial urogenital infections [4, 13]. In most occasions, however, *Lactobacillus* species is intentionally introduced into the human body for reasons other than prevention of UTI, including control of bacterial vaginosis and regulation of bowel flora. Because the potential for preventing UTI using bacterial interference by probiotic *Lactobacillus* is based primarily on the displacement of potential uropathogens from the vagina, this approach is utilized exclusively in women. An attempt to colonize the urethra or bladder directly through intravesicle inoculation with *Lactobacillus* was unsuccessful in men [13].

**MECHANISMS OF ACTION**

Figure 1 displays a humorous scientific version of potential mechanisms of bacterial interference. Mechanisms of action, listed in a clockwise fashion starting at the right upper corner, include competition for nutrients, production of antibacterial agents (including bacteriocins, antiseptics, and acidic substances), competition for attachment sites, regulation of gene expression, immunomodulation, and biofilm disruption. Coaggregation of organisms could also enhance the goal of bacterial interference. *Escherichia coli* and *Lactobacillus* species share some but not all mechanisms of bacterial interference.

*Escherichia coli* 83972

**Competition for Nutrients**

It has been suggested that the primary mechanism for bacterial interference by *E. coli* 83972 is competition with other bacteria for nutrients [14]. This concept was based on the observation that *E. coli* 83972 grew faster than several tested uropathogenic *E. coli* strains and significantly outperformed 1 uropathogenic *E. coli* strain in cocultures, both in vitro and in a murine bladder colonization model. However, human colonization trials indicate that *E. coli* 83972 may not eliminate other bacteria from the urine after relatively few generations.

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**Figure 1.** Potential mechanisms of bacterial interference: The Bladder Inn. Abbreviations: G, good; B, bad.
During long-term colonization in human subjects, *E. coli* 83972 colonized the bladder along with other bacteria that coexisted at the same or lower concentration [15–17]. In some instances bladder cocolonization along with *E. coli* 83972 was transient, whereas in others cocolonizers persisted for extended periods of time in the absence of symptomatic UTI.

**Bacteriocin Production**

Bacteriocins, including colicins and microcins, are antibiotic proteins produced by many species of bacteria that kill susceptible bacteria of the same species. An in vitro study showed that coating a urinary catheter with a colicin-producing strain of *E. coli* completely prevented catheter colonization by a susceptible clinical isolate but not by a colicin-resistant isolate [18]. *Escherichia coli* 83972 does not produce detectable levels of bacteriocin when studied in vitro, but genomic studies suggest that it has the genetic potential for expressing 3 microcins, namely, H47, M, and B17 [19].

**Competition for Attachment Sites**

A recent report suggested that attachment of probiotic *E. coli* Nissle to host tissue may prevent attachment of pathogenic bacteria [20]. Although *E. coli* Nissle has been used for prevention of various intestinal diseases, its use as a probiotic agent for prevention of UTI has been proposed but not evaluated experimentally [21]. The role of specific adherence in stable colonization of the human bladder by *E. coli* 83972 has been examined in several studies. In support of the attachment-competition model, *E. coli* 83972 was reportedly capable of adherence, albeit at a moderate level, to exfoliated uroepithelial cells and urinary catheters [22]. However, others suggested that specific bacterial adherence was not required for bladder colonization [8]. A subsequent report indicated that P fimbriae were not required for bladder colonization since a P negative null mutant of *E. coli* 83972 exhibited the same colonization attributes as wild type [23]. *Escherichia coli* 83972 derivatives that contain P-fimbrial genes on a plasmid exhibited enhanced early colonization of the bladder but the P adherence phenotype was lost shortly thereafter [14]. Genes for other *E. coli* fimbriae classes associated with specific adherence in the urinary tract, including type 1, type 1c, S, Dr, and M adhesions, are either not present in *E. coli* 83972 or are defective [19, 24]. Recent DNA sequence analysis of *E. coli* 83972 revealed a fimbrial gene cluster similar to an uroepithelial cell adhesin called Uca that is found in *Proteus mirabilis* [25].

**Biofilm Prevention**

*Escherichia coli* 83972 shows a low but detectable level of adherence to silicone urinary catheters. Pretreatment of urinary catheters with *E. coli* 83972 reportedly prevented colonization of the catheters in vitro after challenge with a variety of uropathogens [26]. These results suggest that presence of an *E. coli* 83972 biofilm interferes with subsequent colonization of catheters by pathogenic bacteria. Enhancement of the capacity of *E. coli* 83972 to form a biofilm on catheter material by adding type 1 fimbriae was associated with improvement in bacterial interference in a dose-responsive manner [27]. Although these findings are consistent with the hypothesis that *E. coli* 83972 biofilm presents a physical barrier to attachment by pathogenic bacteria, other interpretations remain possible.

**Lactobacillus species**

The topic of potential mechanisms for the therapeutic effect of probiotic *Lactobacillus* at sites other than the urinary tract has been the subject of several recent reviews [28–30]. Many of the mechanisms that have been suggested to speak head the activity of *Lactobacillus* probiotics against organisms and infections outside the urinary tract may also apply to prevention of UTI. Potential mechanisms by which *Lactobacillus* species cause bacterial interference are described below.

**Immunomodulation**

Recent studies suggest that modulation of host immune functions may contribute to the therapeutic effect of probiotic *Lactobacillus* [31]. The authors of a 2-patient pilot study suggested that immunomodulation by *Lactobacillus*-induced downregulation of proinflammatory cytokines such as tumor necrosis factor α, interleukin 6, interleukin 8, interleukin 10, and interleukin 12 (p70) may be beneficial [32]. However, factors that were not assessed in this study, such as the presence/absence of bacteriuria during the 90-day trial period, could have confounded the interpretation of results.

**Gene Regulation**

Increasing evidence indicates that bacterial products from probiotic *Lactobacillus* may induce downregulation in expression of virulence factors [30, 33]. Spent culture supernatants from probiotic *Lactobacillus* reportedly downregulated the promoter activity of *E. coli* type 1 and P fimbriae genes [34]. Type 1 and P fimbriae are associated with urinary tract colonization and infection, but their role in vaginal colonization has not been investigated. The extent to which *Lactobacillus* products can prevent specific adherence of uropathogens to the vaginal epithelium or suppress subsequent expression of fimbrial genes after the bacteria migrate to the urinary tract is unknown. Type 1 fimbriae also contribute to colonization of urinary catheters [27]. Additional studies are required to show whether probiotic *Lactobacillus* can suppress bacterial colonization of urinary catheters in vivo by use of a gene regulation mechanism.

**Biofilm Prevention**

Biofilms formed by pathogenic bacteria can facilitate bacterial colonization of tissues and complicate management of
established infection. It is theoretically possible that introduction of nonpathogenic organisms could displace biofilm-embedded pathogens in the vagina and, subsequently, prevent UTI. A recent in vitro study showed that application of probiotic L. rhamnosus GR-1 to biofilms formed in vitro by a uropathogenic E. coli strain interfered with the integrity of the biofilm and caused significant killing of E. coli [35].

Production of Antibacterial Agents

The mechanism by which Lactobacillus species kill bacterial pathogens could be multifactorial and may include production of bacteriocin-like molecules, hydrogen peroxide, and lactic acid. In a dose- and pH-dependent manner, lactic acid, hydrogen peroxide, and spent culture supernatants from urogenital probiotic strains L. casei var rhamnosus GR-1 and L. reuteri RC-14 all strongly inhibited growth of uropathogenic E. coli strains and increased the promotor activity of outer membrane proteins A and X (porins that are normally upregulated in response to stress by uropathogens) [34]. That same study also showed that lactic acid and Lactobacillus spent culture supernatants could downregulate the promoter activity of the major subunits of type 1 and P fimbriae virulence factors. In another study, hydrogen peroxide acted individually and in cooperation with lactic acid to kill uropathogenic E. coli [36].

Other Mechanisms

Probiotic mechanisms for vaginal Lactobacilli that prevent colonization by vaginal pathogens may also prevent vaginal colonization with uropathogens. These include bacteriocin production and aggregation. Whereas both mechanisms have been associated with probiotic Lactobacillus at other bodily sites, their role in UTI prophylaxis has not been investigated.

CLINICAL TRIALS

The attributes and results of important clinical trials of bacterial interference using E. coli [9, 10, 15, 16, 37–39] or Lactobacillus species [40–45] are summarized in Tables 1 and 2, respectively. Neither E. coli nor Lactobacillus species have reportedly caused symptomatic UTI. Not unexpectedly, all listed studies were relatively small in size (≤100 patients), particularly the E. coli–based trials as they required either direct bladder inoculation of nonpathogenic bacteria twice a day for 3 consecutive days (1 set of inoculation) up to 3 sets, or immersion of a bladder catheter in a bacterial suspension of nonpathogenic E. coli for 24 hours before inserting the E. coli–coated catheter into the bladder. As a corollary, the finding of an insignificant trend of efficacy in some studies could be attributed to their insufficient power. Although all listed trials were pilot studies intended to generate preliminary data before embarking on pivotal comparative trials, some trials significantly reduced the incidence of UTI by several-fold. Whereas many listed studies were randomized, placebo-controlled, double-blind studies, others suffered from a suboptimal single-arm design that dictated comparison of generated data to historic control.

Recent Infectious Diseases Society of America guidelines on UTI [46] utilized a systematic weighting of the quality of evidence that can be strong (I), moderate (II), or weak (III). Although this review is not intended to provide clinical recommendations, it would be reasonable to use that system to partially assess the quality of evidence emanating from particular subcategories of studies that share the same interfering agent and mode of intervention. Although 2 of the 5 studies that assessed bladder inoculation by E. coli were randomized controlled and demonstrated significant efficacy [9, 15], the small number of evaluable patients disallows a high quality of evidence. The 2 studies [38, 39] that assessed insertion of an E. coli–treated catheter were open-label and very small, and, therefore, generated evidence that would be of moderate quality at best. Although all 4 randomized controlled studies [40, 43–45] that evaluated Lactobacillus-containing vaginal suppository indicated some level of efficacy, they were not optimally conducted, thereby minimizing the quality of evidence to moderate. The single randomized controlled trial [42] of an oral drink that contains Lactobacillus is the largest published study on bacterial interference, but other studies need to be done before establishing a high quality of evidence.

COMPARISON OF BACTERIAL APPLICATIONS

Table 3 compares the attributes of E. coli–based vs Lactobacillus–based applications. In contrast to E. coli that could be inoculated into the bladder either directly or via a catheter covered by a biofilm containing E. coli, Lactobacillus species could be introduced in the form of a vaginal suppository or an oral drink. Because the protective effect by nonpathogenic E. coli is based on controlling vaginal pathogens at the site of infection, the achieved urinary concentrations of nonpathogenic strains of E. coli are usually the same or higher than those of other bacteria that may coexist in the bladder [15]. A different mode of action, control of the source of pathogens, applies to Lactobacillus species which replace virulent vaginal flora that could migrate from the vagina to the bladder and cause symptomatic UTI in women. Although intentional bladder colonization with nonpathogenic E. coli strains has been reported to cause local inflammatory symptoms (bladder irritability) and signs (pyuria), we know of no similar issues in patients who receive Lactobacillus-containing supplements. There is no evidence that bacterial interference adversely affects kidney function. Notwithstanding the impact of differences in study design and size on outcome, the protective efficacy of intentional bladder
<table>
<thead>
<tr>
<th>Ref</th>
<th>Author/Year</th>
<th>E. coli Strain</th>
<th>Study Design</th>
<th>Enrolled Patients</th>
<th>Intervention</th>
<th>Reported Safety</th>
<th>Reported Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Darouiche 2011</td>
<td>HU2117</td>
<td>Randomized, placebo-controlled, double-blind</td>
<td>65</td>
<td>Bladder inoculation</td>
<td>Yes</td>
<td>Average no. of episodes of symptomatic UTI per patient-year was lower in the experimental group than in the control group (0.50 vs 1.68, $P = .02$).</td>
</tr>
<tr>
<td>37</td>
<td>Sundén 2010</td>
<td>83972</td>
<td>Crossover, placebo-controlled, double-blind</td>
<td>20</td>
<td>Bladder inoculation</td>
<td>Yes</td>
<td>The time to first symptomatic UTI was longer with than without E. coli 83972 bacteriuria (median 11.3 vs 5.7 mo, sign test $P = .013$). There were fewer reports during 1 year of symptomatic UTI with than without E. coli 83972 bacteriuria (13 vs 35 episodes; paired t test, $P = .009$, 95% CI: 0.31–1.89).</td>
</tr>
<tr>
<td>38</td>
<td>Prasad 2009</td>
<td>83972</td>
<td>Open-label, compared E. coli colonizers to historic control</td>
<td>13</td>
<td>Insertion of a coated bladder catheter for 3 d in patients practicing intermittent bladder catheterization</td>
<td>Yes</td>
<td>Lower rate of symptomatic UTI while colonized with E. coli 83972 than during presstudy period (0.77 vs 2.27 episodes per patient-year). Statistical comparison not provided.</td>
</tr>
<tr>
<td>39</td>
<td>Trautner 2007</td>
<td>HU2117</td>
<td>Open-label, compared E. coli recipients to historic control</td>
<td>12</td>
<td>Insertion of a coated bladder catheter for 28 d in patients with indwelling bladder catheters</td>
<td>Yes</td>
<td>Calculated rate of symptomatic UTI in the experimental group was lower than the reported historic rate in spinal cord-injured subjects with indwelling bladder catheters (0.15 vs 2.72 cases per 100 patient-days). Statistical comparison not provided.</td>
</tr>
<tr>
<td>15</td>
<td>Darouiche 2005</td>
<td>83972</td>
<td>Randomized, placebo-controlled, double-blind</td>
<td>27</td>
<td>Bladder inoculation</td>
<td>Yes</td>
<td>Mean number of symptomatic episodes of UTI per year was lower in experimental group than in control group (1.6 vs 3.5, $P = .036$).</td>
</tr>
<tr>
<td>16</td>
<td>Darouiche 2001</td>
<td>83972</td>
<td>Open-label, compared E. coli colonizers to noncolonizers and historic control</td>
<td>44</td>
<td>Bladder inoculation</td>
<td>Yes</td>
<td>A lower mean rate of symptomatic UTI in patients colonized with E. coli 83972 vs patients who could not be colonized (0.06 vs 1.80 episodes of UTI/patient-year, $P &lt; .001$).</td>
</tr>
<tr>
<td>10</td>
<td>Hull 2000</td>
<td>83972</td>
<td>Open-label, compared E. coli colonizers to noncolonizers and historic control</td>
<td>21</td>
<td>Bladder inoculation</td>
<td>Yes</td>
<td>Mean rates of symptomatic UTI per patient-year were 0 in patients colonized with E. coli 83972 vs 3.1 in the same patients before colonization. Statistical comparison not provided.</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; E. coli, Escherichia coli; UTI, urinary tract infection.

* Safety: Intervention is considered safe if inoculated E. coli strain does not cause symptomatic UTI.

* Efficacy: Intervention is considered efficacious if bladder colonization by the inoculated E. coli strain significantly reduces the incidence of symptomatic UTI as compared with persons or periods without bacteriuria due to the inoculated strain of E. coli.
Table 2. Clinical Trials Using *Lactobacillus* species for Prevention of Urinary Tract Infection

<table>
<thead>
<tr>
<th>Ref</th>
<th>Author/Year</th>
<th>Lactobacillus Strain</th>
<th>Study Design</th>
<th>Enrolled Patients</th>
<th>Intervention</th>
<th>Reported Safety</th>
<th>Reported Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>Stapleton 2011</td>
<td><em>L. crispatus</em> CTV05</td>
<td>Randomized, placebo-controlled, double-blind</td>
<td>100</td>
<td>Vaginal suppository</td>
<td>Yes</td>
<td>Recurrent symptomatic UTI during a 10-week treatment period occurred in 15% of patients in the experimental group vs 27% in the control group (RR = 0.5; 95% CI: 0.2–1.2)</td>
</tr>
<tr>
<td>41</td>
<td>Uehara 2006</td>
<td><em>L. crispatus</em> c</td>
<td>Open-label, compared to historic control</td>
<td>9</td>
<td>Vaginal suppository</td>
<td>Yes</td>
<td>Average number of recurrent episodes of symptomatic UTI per year was 1.3 in the experimental group vs 5.0 in historic control group (P = .0007)</td>
</tr>
<tr>
<td>42</td>
<td>Kontiokari 2001</td>
<td><em>L. casei</em> var <em>rhamnosus</em> GG</td>
<td>Randomized, controlled, compared to cranberry-lingonberry drink or no drink</td>
<td>150</td>
<td>Oral drink</td>
<td>Yes</td>
<td>At 6 mo, the likelihood of recurrent symptomatic UTI was lower (P = .023) in cranberry-lingonberry group (16%) than in <em>Lactobacillus</em> group (38%) or control group (36%)</td>
</tr>
<tr>
<td>43</td>
<td>Reid 1995</td>
<td><em>L. casei</em> var <em>rhamnosus</em> GRI &amp; <em>L. fermentum</em> BS4</td>
<td>Randomized, controlled, compared to <em>Lactobacillus</em> growth factor and historic control</td>
<td>55</td>
<td>Vaginal suppository</td>
<td>Yes</td>
<td>Rates of symptomatic UTI were comparable among recipients of <em>Lactobacillus</em> and recipients of <em>Lactobacillus</em> growth factor (1.6 vs 1.3 episodes per patient-year); in comparison, the historic control group had a 6.0 rate of symptomatic UTIs per patient-year (P &lt; .001)</td>
</tr>
<tr>
<td>44</td>
<td>Baerheim 1994</td>
<td><em>L. casei</em> var <em>rhamnosus</em> c</td>
<td>Randomized, placebo-controlled, double-blind</td>
<td>47</td>
<td>Vaginal suppository</td>
<td>Yes</td>
<td>A 1.41 ratio of the rate of symptomatic UTI in the placebo group vs the experimental group (95% CI: 1.08–1.98)</td>
</tr>
<tr>
<td>45</td>
<td>Reid 1992</td>
<td><em>L. casei</em> var <em>rhamnosus</em> GRI &amp; <em>L. fermentum</em> BS4</td>
<td>Randomized, placebo-controlled, blinded</td>
<td>41</td>
<td>Vaginal suppository</td>
<td>Yes</td>
<td>Recurrent symptomatic UTI occurred in 21% of patients treated with <em>Lactobacillus</em> suppository vs 47% in those who received skim-milk suppository (P = .27)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk; UTI, urinary tract infection.

a Safety: Intervention is considered safe if the introduced *Lactobacillus* strain does not cause symptomatic UTI.

b Efficacy: Intervention is considered efficacious if recipients of *Lactobacillus* species have significantly lower incidence of symptomatic UTI as compared to control.

c Uncharacterized *Lactobacillus* strain.
Table 3. Comparison of Approaches Using *Escherichia coli* vs *Lactobacillus* Species for Prevention of Urinary Tract Infection

<table>
<thead>
<tr>
<th>Attribute</th>
<th><em>E. coli</em></th>
<th><em>Lactobacillus</em> species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site/method of inoculation</td>
<td>Direct bladder inoculation or coated catheter</td>
<td>Vaginal suppository or oral drink</td>
</tr>
<tr>
<td>Mode of action</td>
<td>Controls pathogens at the site of infection</td>
<td>Controls the source of pathogens</td>
</tr>
<tr>
<td>Safety</td>
<td>Could cause local inflammatory findings</td>
<td>No known issues</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Consistent reduction of urinary tract infection</td>
<td>Inconsistent results</td>
</tr>
<tr>
<td>Practicality</td>
<td>Could be cumbersome</td>
<td>Easy application</td>
</tr>
<tr>
<td>Cost</td>
<td>Could be high</td>
<td>Moderate</td>
</tr>
<tr>
<td>Coreceipt of antibiotics</td>
<td>Antibiotics consistently given before inoculation</td>
<td>Inconsistent</td>
</tr>
<tr>
<td>Applicability</td>
<td>Patients with neurogenic or dysfunctional bladder</td>
<td>Mostly in healthy women</td>
</tr>
<tr>
<td>Regulation</td>
<td>Food and Drug Administration(FDA)</td>
<td>FDA vs dietary supplement</td>
</tr>
</tbody>
</table>

Colonization with nonpathogenic *E. coli* strains seems to be more consistent than that afforded by introducing probiotic *Lactobacillus*. On the other hand, the practicality and cost of intervention favor the *Lactobacillus*-based approach, which is less invasive and expensive than bladder inoculation with nonpathogenic *E. coli* strains. As compared to direct bladder inoculation, the insertion of *E. coli*-coated bladder catheter is more practical and less costly. Routine administration of systemic antibiotics before bladder inoculation with *E. coli* 83972 or HU2117 with the aim of reducing the urinary concentration of preexisting bacteria not only augments the likelihood that the bladder will become colonized by these nonpathogenic strains, but also could contribute to higher urinary concentrations of inoculated *E. coli* strains vs co-colonizing bacteria [9, 15]. Systemic antibiotics, however, are inconsistently given in patients receiving probiotic *Lactobacillus*. Although bacterial interference is generally intended to improve the quality of life of patients who suffer from recurrent episodes of symptomatic UTI, these 2 particular approaches of bacterial interference apply to distinctly different patient populations; whereas nonpathogenic strains of *E. coli* have been utilized to prevent symptomatic UTI in patients with neurogenic/dysfunctional bladder (including those with spinal cord injury), the *Lactobacillus*-based strategy is applied mostly in healthy women. Finally, the use of nonpathogenic strains of *E. coli* for prevention of UTI requires approval from the Food and Drug Administration (FDA) through an Investigational New Drug application. Although current use of probiotic *Lactobacillus* for prevention or treatment of infection also requires FDA approval, it is, unfortunately, sometimes used as a “dietary supplement” to escape the stringent FDA evaluation.

**FUTURE DIRECTIONS**

No person is immune from developing UTI. In general, about a third of women have their first UTI by the age of 24 years, and more than a quarter of adult females with a first episode of UTI will have a recurrence [4]. The statistics are even worse in patients who suffer from neurogenic bladder, especially those with spinal cord injury in whom UTI is the most common infectious condition [16]. Preliminary data from the summarized pilot studies are promising, but in and by themselves are not sufficient to establish new standard-of-care practices. Although clinically protective against UTI, limitations to wide-scale implementation of bacterial interference using nonpathogenic strains of *E. coli* in patients with neurogenic bladder include relative impracticality and high cost of direct bladder inoculation, the possibility that nonpathogenic strains of *E. coli* could be inflammatory in patients with sensate bladder, and the small size of completed pilot studies. That is why we plan to conduct a randomized, placebo-controlled, double-blinded, multicenter trial that assesses the efficacy, safety, and economic implications of inserting a bladder catheter that contains a biofilm of nonpathogenic *E. coli*. As to *Lactobacillus* species, further work needs to be done to document the stability of probiotic products, assess the effects of specific strains, and explore the impact of probiotic concentration on efficacy.

**Note**

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Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**


