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Challenges in the Management of Urinary Tract Infections

In this Issue...

Urinary tract infections (UTI), including uncomplicated and complicated infections, are a leading cause of outpatient primary care visits in developed countries. Uncomplicated UTIs occur in healthy non-pregnant women without underlying congenital or acquired urinary tract abnormalities whereas UTIs in all other patients, (including men) except pregnant women, are considered to be complicated UTIs.

In this issue, we focus upon several challenges in the management of UTIs, including adherence to treatment guidelines for uncomplicated UTI in adults and antimicrobial resistance commonly encountered when using recommended antimicrobials. Some special considerations reviewed include evaluating sexually active adolescents with UTI-like symptoms, UTIs in renal transplant patients, and a new vaccine on the horizon for prevention of recurrent UTIs in women. Pregnant women with bacteriuria and UTI are a special category and will not be discussed in this review.



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1.0 hours Physicians

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Commentary & Reviews:

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Guest Faculty Disclosures

Noreen A. Hynes, MD, MPH, DTM&H has disclosed no relevant financial relationships.

Unlabeled/Unapproved Uses

The author has indicated that there will be reference to unlabeled or unapproved uses of drugs or products in the presentation. The use of multi-valent vaginal suppositories for the prevention of recurrent UTIs is still in clinical trials and not available for general use; and the vaccine is not FDA-licensed.

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Describe the first-line antibiotic treatment of uncomplicated urinary tract infection and the impact of antibiotic resistance on treatment choice
- Identify UTI management issues in sexually active adolescents
- Review the importance of *Corynebacterium urealyticum* in renal transplant recipients

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In this audio interview, Dr. Noreen A. Hynes, an Assistant Professor (Part Time) of Medicine in the Division of Infectious Diseases at the Johns Hopkins University School of Medicine and an Assistant Professor of International Health in the Section on Epidemiology and Disease Control at the Bloomberg School of Public Health, at Johns Hopkins, discusses complicated and uncomplicated UTIs, the distinction between them, and the guidelines for treatment.

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COMMENTARY

In 2000, there were approximately 11 million outpatient visits among patients over the age of 19 years with a UTI, with over 80 percent of these visits made by women. The current inflation-adjusted direct-cost burden for the evaluation and treatment of UTI (based on dollars in 2000) is estimated to be \$4.3 billion per year.¹ Furthermore, more than 50 percent of women will have at least one UTI in their lifetime, and up to 5 percent of them will have recurring infections. *Escherichia coli*, predominantly the O, K, and H antigen serotypes, account for 80 to 90 percent of these infections;² the remaining 10 to 20 percent are caused by *Staphylococcus saprophyticus* (particularly among young, sexually active women), and other non-*E. coli* members of the Enterobacteraeae. Less common organisms such as *Enterococcus* species, *Pseudomonas sp*, *S. aureus*, and *Candida sp* are seen among person with complicated UTIs.

The epidemic of antimicrobial resistance, likely abetted by antibiotic misuse in both humans and food animals, continues to spread, presenting management challenges in both uncomplicated and complicated UTI.³ The *Guidelines for Antimicrobial Treatment of Uncomplicated Acute Bacterial Cystitis and Acute Pyelonephritis in Women*, issued by the Infectious Diseases Society of America (IDSA) 1999, provided evidence-based recommendations for treatment and also aimed to stem the tide of antimicrobial resistance among organisms commonly causing UTI.⁴ The study by Taur and colleagues (reviewed in this issue) provides the sobering finding that there is no evidence that providers have adopted the published guidelines. However, the fact that hospital-based providers and those caring for self-pay patients were significantly more likely to use the first-line recommended therapy (trimethoprim-sulfamethoxazole [TMP-SMX]), suggests that economic realities rather than concerns about evolving antimicrobial resistance may be a prime driver in antimicrobial selection. Notably, when comparing generic antibiotic costs of the first-line TMP-SMX with ciprofloxacin, a commonly used drug to treat UTI, the latter treatment (even in generic form) is 6 times more expensive than the former.

As antimicrobial resistance is increasing, practitioners are advised to use an alternative therapy for the treatment of uncomplicated UTI when TMP-SMX antibiotic-resistance in *E. coli* isolates identified from their patient group exceeds 10 to 20 percent.⁴ This may be easier said than done in routine clinical practice, where the evaluation of an uncomplicated UTI usually does not include urine culture and sensitivity. Patients with complicated UTI, on the other hand, are routinely cultured at the time of presentation. The studies by Zhanel et al and Hames et al (both reviewed herein) highlight the widespread nature of antimicrobial resistance (in some regions to both TMP-SMX and the fluoroquinolones) and the important difference in antimicrobial resistance rates in uncomplicated versus complicated infections. The data presented suggest that local hospital laboratory antibiotic resistance rates among unselected urinary *E. coli* isolates may represent twice the rate seen in healthy women with uncomplicated UTI in that locality. If this estimated rate is accurate, then use of the recommended TMP-SMX is reasonable assuming contraindications for its use are absent.

There is one group of healthy patients for whom urine culture may be routinely needed for acute uncomplicated bacterial cystitis—sexually active adolescent females. Increasingly, this group of patients is seen by adult primary care physicians, in addition to usual settings such as middle-school, high-school, and university health clinics. In the study by Huppert and colleagues (reviewed in this issue), among university-aged sexually active women, found that it was not possible to distinguish an acute UTI from several different sexually transmitted infections (STI) based upon history, physical examination, and urinalysis alone. An STI was more common in this group than a UTI (33% vs 17%) and co-existence of the two was unusual. The authors conclude that testing for chlamydia, gonorrhea, trichomoniasis, genital herpes, candidiasis, and UTI in sexually active women with genitorurinary symptoms is warranted.

Complicated UTI, seen in the setting of a defect of the urinary tract or significant medical or surgical co-morbidities, are increasing due to expanding susceptible populations. Specific factors in complicated UTI include pregnancy, age, male gender, immunosuppression (including renal transplant patients), diabetes mellitus, indwelling urinary catheters, urolithiasis, urinary tract obstruction, renal insufficiency, and congenital and acquired anatomical defects.⁵ UTI is the most common bacterial infection seen in renal transplant recipients, and *Corynebacterium urealyticum* is a gram positive bacillus that has been recently recognized as a cause of UTI in this group. The infection can lead to obstructive uropathy, graft malformation, and graft rejection/loss. The increased recognition of this organism likely reflects both the increase in renal transplantation and provider requests that the organism be specifically sought (the organism requires 72 hours

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rather than 24 hours used for routine urine cultures). In the cohort study by Lopez-Medrano et al (herein reviewed), bacteruria was noted in 9.8% of patients, a much higher rate than was previously reported.⁶ Although rates of *C. urealyticum* were not high enough to lead to a recommendation of routinely requesting a search for this pathogen among symptomatic patients, the organism should be sought if their urine is alkaline or struvite crystals are noted on urinalysis. If suspected, the clinician will need to alert to the microbiology laboratory that this organism may be present. Antimicrobial sensitivities must be used to guide treatment, as almost all isolates are multidrug resistant.

Recurrent urinary tract infections are commonly seen in women, with pre-menopausal women constituting the largest proportion. Among these patients, most have no evidence of underlying urinary tract anatomical or physiological abnormalities. Prophylaxis is often given in the form of daily antibiotic suppression or post-coital single-dose treatment. Concerns about adverse effects of long-term exposure to antimicrobials, as well as the continuing spread of antibiotic resistance, particularly in *E. coli* urine isolates, has prompted continuing research into non-antimicrobial prevention strategies. Some currently employed strategies include avoidance of spermicidal contraceptives, post-coital voiding, and the intake of cranberry juice. A newer approach, a mucosally-applied vaccine, is in development; Hopkins et al (herein reviewed) report on the results of a Phase II randomized trial of a non-FDA-licensed multi-valent vaccine. The vaccine containing 10 uropathic strains, 6 of which were *E. coli*, was found to be most effective in preventing *E. coli* UTI in the group that received primary immunization followed by booster intravaginal dosing.

Urinary tract infections are commonly seen by both primary care providers and specialists, and present an increasingly difficult management challenge. Determining the best approach for the patient in an era of ever-increasing costs and ever-expanding antimicrobial resistance is complicated. Although some promising new strategies for some types of UTI may soon be available (ie, vaccines), currently the use of the evidence-based practice guidelines will most effectively assist in the proper care for patients, while also ensuring sound antibiotic stewardship that may reduce the drivers of antimicrobial resistance.

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PROVIDER ADHERENCE TO UNCOMPLICATED UTI GUIDELINES

Taur V, Smith MA. [Adherence to the Infectious Diseases Society of America guidelines in the treatment of uncomplicated urinary tract infection](#). *Clin Infect Dis*. 2007;44:769-774.

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In a study utilizing cross-sectional data collected in the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey, the authors studied antibiotic use in the treatment of uncomplicated urinary tract infection (UTI) among women in outpatient settings before and after the introduction of the 1999 Infectious Disease



Society of America (IDSA) *Guidelines for Antimicrobial Treatment of Uncomplicated Acute Bacterial Cystitis and Acute Pyelonephritis in Women*. Excluded patients were those with recurrent UTI, indwelling urinary catheter, urinary tract malignancy, renal stones, or pregnant women. The primary outcome was the change in the use of the IDSA guideline first-line treatment (trimethoprim-sulfamethoxazole [TMP-SMX]), before and after issuance of the recommendations. The secondary outcome was the change in use of other commonly prescribed antibiotics for UTI over the 6-year study period beginning in 1996.

A weighted probability sample of 2,339 women ≥ 18 years, representing approximately 7 million UTI outpatient visits per year, was analyzed using an adjusted logistic regression model to examine changes in usage of five antibiotic categories (TMP-SMX, ciprofloxacin [CIP], nitrofurantoin [NF], non-CIP fluoroquinolones [FQ], and amoxicillin [AMX]) over the study period. The investigators report that after introduction of the IDSA Guideline, the use of TMP-SMX, NF, FQ, and AMX did not change significantly, whereas there was a 66% increase in CIP use. These results were unchanged after adjusting for potential UTI risk factors including the presence of diabetes mellitus, human immunodeficiency virus infection or acquired immunodeficiency syndrome, or among patients >60 years. Notably, use patterns differed significantly by provider type, practice setting and patient characteristics. Use of TMP-SMX was significantly more likely among hospital-based physicians than office-based providers (54.7% vs 27.6%, $p < 0.001$), general practice physicians than other physicians (32.4% vs 21.5%, $p < 0.04$), among self-paying patients compared with those with a third-party health care payer (42.4% vs 27.9%, $p < 0.05$), and among non-white patients compared with white patients (40.8% vs 27.8%, $p < 0.02$). No regional prescribing differences were noted.

This study demonstrates that no change occurred in the outpatient prescribing habits of providers for uncomplicated UTI after the introduction of the IDSA Guideline, and further notes a significant increase in ciprofloxacin use. The study did not provide an analysis of antibiotic selection based on regional antimicrobial resistance patterns for the most common cause of UTI, *Escherichia coli*; therefore, it is not possible to determine the role, if any, this played in the increasing use of ciprofloxacin. However, the differences in prescribing choices did correlate consistently over the entire study period with provider and patient characteristics, suggesting that regional resistance patterns may not have had a significant impact on the findings of this study. Notably, the outcomes here demonstrate that the practice guidelines did not have the intended effect of altering practice patterns, and highlight the need for applying a performance measure for guideline compliance such as that outlined in the IDSA Guideline.

ANTIBIOTIC RESISTANCE AMONG *ESCHERICHIA COLI* URINARY TRACT ISOLATES

Zhanel GG, Hisanaga TL, Laing NM, et al; for the NAUTICA Group, Hoban DJ. **Antibiotic resistance in *Escherichia coli* outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA)**. *Int J Antimicrob Agents*. 2006;27(6):468-475.

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Hames L, Rice CE. **Antimicrobial resistance of urinary isolates in acute uncomplicated cystitis among college-aged women: choosing a first line therapy**. *J Am Coll Health*. 2007;56(2):153-156.

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Zhanel et al report results from NAUTICA, an ongoing urinary tract infection (UTI) surveillance study among 10 Canadian and 30 US medical centers, assessing antibiotic resistance rates to common agents used to treat outpatient UTI. Data from a 15-month period (April 2003 to June 2004) characterize antimicrobial resistance in *E. coli* isolates to ampicillin (AMP), trimethoprim-sulfamethoxazole (TMP-SMX), ciprofloxacin (CIP), levofloxacin (LEV), and nitrofurantoin (NF). Up to 50 consecutive *E. coli* isolates were submitted to the central study laboratory from each participating center. There were no exclusion criteria for isolates identified from mid-stream urine specimens collected as part of routine care of outpatients. However, as treatment guidelines do not recommend urine cultures in healthy, pre-menopausal women with symptoms of acute bacterial cystitis,



these data include a high proportion of persons with complicated UTI (evidenced by >20% of isolates from males). There were 1,142 *E. coli* isolates evaluated; 862 (76%) from the U.S. and 280 (24%) from Canada.

The investigators report that overall *E. coli* resistance was highest to AMP (37.7%), followed by TMP-SMX (21.3%); resistance rates to CIP, LEV, and NF were 5.5%, 5.1%, and 1.1%, respectively. CIP resistance was highest among those >65 years compared with other age groups ($p < 0.05$). There was great regional variability in resistance rates across the spectrum of antibiotics assessed (see Table 1), with overall resistance significantly lower in Canada than the US. ($p < 0.05$). The West South-Central region of the US (AR, LA, OK, TX) had the highest resistance rates across all 5 antibiotics examined.

Table 1: *E. coli* antibiotic resistance rates, NAUTICA Study of routine laboratory urine isolates

Country, Province or Census Region	Number of <i>E. coli</i> Isolates	Percent Antibiotic Resistance				
		AMP	TMP-SMX	CIP	LEV	NF
CANADA						
British Columbia	29	27.6	20.7	3.4	3.1	0.0
Alberta	23	34.8	13.0	0.0	0.0	0.0
Saskatchewan	33	33.3	12.1	0.0	0.0	0.0
Manitoba	33	51.5	48.5	0.0	0.0	0.0
Ontario	38	34.2	21.0	2.6	2.1	0.0
Quebec	57	22.0	10.2	1.7	1.3	0.0
New Brunswick	31	41.9	6.4	0.0	0.0	0.0
Nova Scotia	36	27.8	13.9	0.0	0.0	0.0
UNITED STATES						
Pacific	115	36.5	21.2	6.1	5.2	2.6
Mountain	103	54.4	28.2	2.9	1.9	1.0
West North Central	143	37.1	15.4	4.2	4.2	1.4
East North Central	145	37.9	20.0	4.8	4.8	0.7
Mid Atlantic	111	39.6	27.9	11.7	10.8	1.8
South Atlantic	186	31.0	18.2	5.9	5.3	0.0
West South Central	59	52.5	42.4	20.3	20.3	5.1

Hames and Rice investigated the West South-Central region of the US, reporting the results of a study conducted in a university student health service examining antibiotic resistance of urine isolates collected over a 24-month period (July 2002 — June 2004) to TMP-SMX, CIP and NF among women, age 18-24 years, with acute, uncomplicated bacterial cystitis (AUC). Criteria for culture included the presence of nitrite or >10 white cells per high power field or by physician request. A positive result was $\geq 10^4$ cfu/mL of each of up to 2 pathogens. Excluded were women with fever, pregnancy, vomiting, flank tenderness, vaginal discharge, urine specimens with >2 organisms, or organisms deemed to be contaminants such as gram positive bacilli.

Among the 179 urinary isolates, 90% (n=161) were *E. coli*; the remaining 10% (n=18) included 15 non-*E. coli* gram negative isolates (*Proteus mirabilis*, *Klebsiella pneumoniae*, and *K. ozonae*), and 3 gram positive cocci (*Staphylococcus saprophyticus* and *S. aureus*). Of the 161 *E. coli* isolates, resistance was >20% to TMP-SMX and low or absent to CIP and NF, respectively (see Table 2).

Table 2: Antibiotic Resistance among *Escherichia coli* Urinary Isolates in Women with Uncomplicated UTI at a US University

Percent Antibiotic Resistance (n=161)		
TMP-SMX	CIP	NF
23.0	0.6	0.0

Among the 15 other gram negative organisms, 13% were resistant to TMP-SMX, 0% resistant to CIP, and 80% resistant to NF.

The results from these studies are consistent with other reports of increasing antibiotic resistant among major urinary tract pathogens, as well as regional variation in resistance patterns. The high *E. coli* resistance rates found among isolates from the West South-Central region of the US in these two studies highlights the important distinctions between uncomplicated and complicated UTI resistance patterns. TMP-SMX resistance was approximately two-fold lower in the AUC university health service study than in the NAUTICA study; CIP resistance was more than 20 times less. Given the rates of CIP and LEV resistance in the US reported in the NAUTICA study, prudent use of fluoroquinolones is needed and should be based on region-specific and target group-specific urinary isolate antimicrobial resistance data.

APPROACH TO THE SEXUALLY ACTIVE YOUNG WOMAN WITH URINARY SYMPTOMS

Huppert JS, Biro F, Lan D, Mortensen JE, Reed J, Slap GB. **Urinary symptoms in adolescent females: STI or UTI?** *J Adolesc Health*. 2007,40(5):418-424.

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Huppert et al conducted a cross-sectional study among sexually-active adolescent or young adult females with and without urinary symptoms (dysuria, urgency, or frequency) to determine the most effective approach for differentiating a urinary tract infection (UTI) from 3 common sexually transmitted infections (STI), *Chlamydia trachomatis* (CT), *Trichomonas vaginalis* (TV), and *Neisseria gonorrhoea* (GC) in this group. Exclusion criteria were age <18 years or >24 years, urinary isolate with <10⁴ cfu/mL of the predominant isolate, presence of a complicated UTI risk factor, or urine cultures that grew 3 or more microorganisms. Patients were interviewed regarding relevant current and past history. Specimens were collected for laboratory assessment which included urinalysis, urine culture, and urine nucleic amplification testing for CT and GC, as well as TV culture from clinician-collected or patient self-administered vaginal swabs and saline wet mount for microscopic detection of motile trichomonads. Univariate, multivariate backward stepwise and exact logistic regression, and multi-level decision tree analyses were performed. The 2 primary outcome variables were UTI (>10⁴ colonies of a single pathogenic organism on urine culture) and STI (a positive test result for CT, GC — or, for TV, either a positive culture or saline wet mount).

Over the 20-month study period (May 2003 to January 2005), 305 females were enrolled in the study and 296 (97%) had evaluable results. Overall, 52% had urinary symptoms and 48% did not. However, urinary symptoms were neither sensitive nor specific for the presence or absence of infection — 33% had a STI, 17% had an UTI (4% had both), and 55% had no documented infection.

Among the patients presenting without urinary symptoms, 76% were also free of vaginal symptoms (vaginal discharge or pruritis). There was no difference in the proportion of study STI among patients with and without urinary symptoms (36% vs 29%, p <0.02). Women with sterile pyuria (negative urine culture with white cells on urinalysis) and urinary symptoms were more likely to have a study STI than those without symptoms or sterile pyuria (65% vs 27%, $\chi^2 = 14$, p<0.001). Among the patients with urinary symptoms and who had complete laboratory data for further analysis, 20% had only a UTI, 30% had only



a study STI, and 6% had both. In this symptomatic group, 38% had a normal urinalysis — of these, 33% had a UTI or study STI. Among the participants without a diagnosed UTI or study STI, 22% received a clinical diagnosis of genital herpes simplex virus infection, vaginal candidiasis, or pelvic inflammatory disease.

Additionally, risk factors for STI, including past history of STI, current use of oral contraceptives, condom use at last intercourse, history of a new partner in the last 3 months, or >1 partner in the past 3 months did not predict who should be screened for an STI in this group.

This study demonstrates that among sexually active adolescents, urinary symptoms alone, or in combination with urinalysis data, are inadequate to differentiate UTI from CT, GC, or TV. The authors do not recommend empiric treatment for either UTI or study STI in this group, whether seen in an office visit or evaluated by telephone triage. The office-based evaluation recommended by these authors includes a history to elicit UTI and STI risk factors and symptoms, and a urinalysis and urine culture along with laboratory testing for CT, GC and TV, with the results guiding treatment decisions.

CORYNEBACTERIUM UREALYTICUM INFECTION IN KIDNEY TRANSPLANT RECIPIENTS

López-Medrano F, García-Bravo M, Morales JM, et al. **Urinary tract infection due to *Corynebacterium urealyticum* in kidney transplant recipients: an underdiagnosed etiology of obstructive uropathy and graft dysfunction—results of a prospective cohort study.** *Clin Infect Dis.* 46:825-830.

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Corynebacterium urealyticum is a gram positive bacillus with strong urease activity and urinary tract tropism, requiring 72 hours of culture incubation for identification. Infection with this organism has been recently recognized as a cause of obstructive uropathy, graft malformation, and graft rejection/loss in renal transplant recipients. López-Medrano et al report the results of a prospective cohort study to determine risk factors for and outcomes following infection with *C. urealyticum* among renal transplant patients. Prospectively recruited patients, all of whom received prophylactic cotrimoxazole (sulfamethoxazole-trimethoprim) for 6 months post-transplantation, had urine and inguinal skin cultures performed on the day of study enrollment. Standard and selective culture media was used and subsequent antimicrobial resistance testing was performed for all cultures positive for *C. urealyticum*. Participants with a positive *C. urealyticum* culture from either site were evaluated monthly. Forward stepwise logistic regression was used to identify independent risk factors for *C. urealyticum* bacteremia.

Of the 163 patients enrolled over the 13-month study period, baseline urine cultures were positive in 16 (9.8%) and baseline skin cultures were positive in 22 patients (13.5%). Bacteriuria at baseline was an independent risk factor for developing long-term urinary tract symptoms (Odds Ratio [OR] = 27.7, Confidence Interval = [CI] 2.55-300.58, $p = 0.006$) and obstructive uropathy (OR=25.97, CI = 4.43-152.31, $p < 0.001$). On multivariate analysis, independent risk factors for *C. urealyticum* bacteremia included antibiotic therapy in the last month (OR = 8.4, CI = 1.57-41.06, $p = 0.012$), having undergone a nephrostomy (OR = 51.59, CI = 3.62-736.06, $p = 0.004$), and skin colonization (OR = 208.3, CI = 21.54-2015.2, $p < 0.001$). The following characteristics, found to be significant on univariate analysis, were not found to be independent risk factors: age, sex, urinary tract infection in the previous month, and urethral catheterization for >1 month. Factors that were not found to be significant in univariate analysis, and therefore not used in the analytic regression model, included serum creatinine levels >1.5 mg/dL, acute rejection, immunosuppression with 3 drugs, presence of a urethral catheter at any time, having undergone cystoscopy or urological surgery, the presence of a lymphocele, obstructive uropathy, or perirenal hematoma. Among the 16 patients with bacteremia, 6 were asymptomatic, 9 had acute cystitis, and 1 had encrusting pyelitis. Struvite crystals were found only in those with symptomatic disease. Use of selective medium increased recovery of *C. urealyticum* five-fold compared to standard sheep blood agar. All isolates were susceptible to vancomycin and teicoplanin with high rates of resistance (ie $\geq 40\%$) among most other antimicrobial classes.

The results of this prospective study demonstrated a much higher rate of *C. urealyticum* bacteremia (9.8%) than previously reported in less robust studies. The incidence of infection may have been greater in this cohort because those with negative cultures at



both sites on study entry did not undergo subsequent testing. Importantly, skin colonization with this organism in the absence of bacteruria at baseline was an independent risk factor for subsequent development of bacteruria. The finding of struvite crystals, chronic urinary tract symptoms, obstructive uropathy, crusting pyelitis, pyelitis, and sterile pyuria with negative standard urine culture should alert the clinician to ask the microbiology laboratory to look for this organism. The results of sensitivity testing should guide treatment decisions.

PROGRESS IN NON-ANTIBIOTIC APPROACHES TO PREVENTING RECURRENT URINARY TRACT INFECTIONS

Hopkins WJ, Elkahwaji J, Beierle LM, Levenson GE, Uehling DT. **Vaginal mucosal vaccine for recurrent urinary tract infections in women: results of a Phase 2 clinical trial.** *J Urol.* 177:1349-1353.

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The authors conducted a randomized, double-blind Phase II clinical trial comparing the efficacy of a vaginal mucosa-delivered vaccine versus placebo in preventing recurrent urinary tract infections (RUTI). The vaccine contained 10 strains of heat-killed uropathic strains (1×10^8 of each) — including 6 *E. coli* strains and 1 each of *Proteus mirabilis*, *Morganella morganii*, *Klebsiella pneumonia*, and *Enterococcus faecalis* — compounded as a suppository in a polyethylene glycol base. Placebo suppositories contained only the base. Women with a history of >3 UTI in the previous 12 months were eligible to receive 6 suppositories over approximately 4 months (1 per week for 3 weeks followed by 1 per month for 3 months) during the 6 month enrollment period that began one week after stopping all prophylactic antibiotics. Patients were randomly assigned to one of 3 groups. Women in the placebo group received suppository with no vaccine. Vaccine treatment groups received 3 weekly vaccine suppositories followed by either monthly placebo (primary vaccination) or vaccine for 3 months (primary-boost). Samples of urine and vaginal secretions were collected before dosing, at 2 weeks, and then at every 4 weeks. Exclusion criteria were indwelling catheter, kidney stones, urinary tract anatomical defect, neurogenic bladder, or urinary diversion. The primary outcome was time to RUTI.

Seventy-five patients, evenly distributed among the 3 groups, were included in the Kaplan-Meier analysis of infection-free periods. Study participants had history of 6 to 20 RUTI per year prior to study entry, or at least 1 RUTI every 2 months. The proportion of women remaining infection-free in the placebo group, primary vaccination group, and primary-boost group were 30.0%, 57.0%, and 72.5%, respectively. On sub-group analysis of *E. coli* RUTI prevention, the vaccine-boost strategy was found to be the most efficacious when compared with placebo ($p < 0.0016$) among sexually-active women 20 to 52 years who were using oral contraceptives or estrogen and who had neither a history of childhood RUTI nor hysterectomy. There were no statistically significant increases in urinary or vaginally secreted immunoglobulin A (IgA) anti-*E. coli* antibodies in any of the 3 groups over the course of the trial. Adverse effects attributable to the vaccine were minimal.

This study demonstrates that a multivalent vaginal mucosal vaccine is effective in delaying or preventing RUTI over a 6-month period when compared with placebo. The greatest difference was seen among women who received boosted vaccine doses at monthly intervals. Although the vaccine was broad spectrum, it appeared to have the greatest efficacy in preventing *E. coli* RUTI, the most common cause of RUTI. The authors suggest that the vaccine-boost strategy may provide an alternative strategy to chronic antibiotics in women with RUTI. The failure to illicit a significant increase in mucosal IgA antibodies suggests that this may not be the correct correlate of protection for this vaccine. Large, multi-center clinical efficacy trials with longer follow-up periods and additional dosing schedules likely will be needed before licensure of this product by the Food and Drug Administration. In an era of increasing uropathogenic antimicrobial resistance to commonly used agents, new strategies such as this vaccine-based approach are needed.



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This activity has been developed for the Primary Care Physician, Internist, and Infectious Disease Specialist.

Learning Objectives — [back to top](#)

At the conclusion of this activity, participants should be able to:

- Describe the first-line antibiotic treatment of uncomplicated urinary tract infection and the impact of antibiotic resistance on treatment choice
- Identify UTI management issues in sexually active adolescents
- Review the importance of *Corynebacterium urealyticum* in renal transplant recipients

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- **John G. Bartlett, MD** has disclosed that he has served on the HIV Advisory Board for GlaxoSmithKline, Abbott, Bristol-Myers Squibb, Pfizer and Tibotec. He is also on the Policy Board for Johnson & Johnson.
- **Paul G. Auwaerter, MD** has disclosed that he has served as a consultant for Novartis, Pfizer, Ortho-McNeil, Schering-Plough, and Genzyme. He is on the Speakers' Bureau for Schering-Plough and has also disclosed that he is a Stock Shareholder for Johnson & Johnson.
- **Sara E. Cosgrove, MD, MS** has disclosed that she has received grants or research support from Merck and served on the Advisory Boards for Ortho-McNeil, Cadence Pharmaceuticals, and Theravance/Astellas.

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