The microbial etiology of urinary infections has for several decades been regarded as well established, reasonably consistent, and of limited interest. *Escherichia coli* remains the predominant uropathogen isolated. Although new pathogens have been appearing with remarkable frequency in other illnesses, research to identify new agents underlying unexplained urinary tract clinical syndromes has been limited. Stemming from recent advances in molecular biology, clues to a variety of potential new pathogens are being identified, and expectations for identifying new and important etiologic agents for urinary syndromes will be substantial over the next several years. In addition, the pathogens traditionally associated with urinary tract infection (UTI) are changing many of their features, particularly because of antimicrobial resistance. As a result, empiric treatment will undergo change during the next several years in an attempt to limit the occurrence of resistance and prevent its spread.

The etiology of UTI is also affected by underlying host factors that complicate UTI, such as age, diabetes, spinal cord injury, or catheterization. Consequently, complicated UTI has a more diverse etiology than uncomplicated UTI, and organisms that rarely cause disease in healthy patients can cause significant disease in hosts with anatomic, metabolic, or immunologic underlying disease. The majority of community-acquired symptomatic UTIs in elderly women are caused by *E coli*. However, gram-positive organisms are common, and polymicrobial infections account for up to 1 in 3 infections in the elderly. In comparison, the most common organisms isolated in children with uncomplicated UTI are *Enterobacteriaceae*. Etiologic pathogens associated with UTI among patients with diabetes include *Klebsiella* spp., Group B streptococci, and *Enterococcus* spp., as well as *E coli*. Patients with spinal cord injuries commonly have *E coli* infections. Other common uropathogens include *Pseudomonas* and *Proteus mirabilis*.

Recent advances in molecular biology may facilitate the identification of new etiologic agents for UTI. The need for accurate and updated population surveillance data is apparent, particularly in light of concerns regarding antimicrobial resistance. This information will directly affect selection of empiric therapy for UTI. *Am J Med.* 2002;113(1A):14S–19S. © 2002 by Excerpta Medica, Inc.

**UNCOMPROMISED URINARY TRACT INFECTIONS**

The etiology of uncomplicated UTIs has generally remained constant over the past 2 decades, albeit with a noticeable increase in antimicrobial resistance in both community-acquired and nosocomial UTIs. The etiology of complicated UTI is more diverse and directly affected by underlying host characteristics than that of uncomplicated UTI.

The majority of acute community-acquired, uncomplicated infections in the United States and abroad are caused by *E coli* (80%) or *Staphylococcus saprophyticus* (10% to 15%). *Klebsiella, Enterobacter,* and *Proteus* species and enterococci infrequently cause uncomplicated cystitis and pyelonephritis. Fungal pathogens, and par-
During the period 1994 to 1997, it should be noted that fluoroquinolone susceptibility remains high (>99%).

The increasing resistance trends are likely to have important clinical implications to the empiric use of TMP-SMX for uncomplicated UTI and pyelonephritis. In fact, recent research has already demonstrated significantly greater bacteriologic and clinical cure rates for a 7-day course of the fluoroquinolone ciprofloxacin than a 14-day regimen of TMP-SMX for the treatment of acute uncomplicated pyelonephritis in premenopausal women.10

E. coli resistance to TMP-SMX was significantly greater (18%) than to ciprofloxacin (0%; \(P < 0.001\)), and there were significantly greater rates of clinical failures among patients receiving TMP-SMX who had TMP-SMX resistant E. coli infections (65%) as compared with susceptible E. coli infections (8%). Lower clinical cure rates and diminished bacterial eradication have also been demonstrated in TMP-SMX–treated women with uncomplicated UTI.10

Clinical failure rates of TMP-SMX for cystitis increased from 3% to 13% among susceptible E. coli to 27% to 40% among resistant strains.11 As a result, in geographic locations with known TMP-SMX resistance prevalence in the range of 10% to 20%, alternative antimicrobials, including a fluoroquinolone (3 days), nitrofurantoin (7 days), or fosfomycin (single-dose treatment), are preferred for cystitis.12

Although susceptibility is of critical importance in selecting an appropriate antimicrobial agent, clinicians must also first consider the established range of coverage for each agent. For example, despite established susceptibility, nitrofurantoin has not been shown to be effective in patients with acute pyelonephritis. In addition, nitrofurantoin is rarely the agent of choice in patients diagnosed with urinary infections other than acute cystitis. As a result, selection of an antibiotic must consider both susceptibility and known efficacy for the clinical syndrome.

Finally, approximately 25% to 35% of initial UTI episodes are followed by recurrent episodes within 3 to 6 months.13 In up to 60% of cases of recurrent UTI (RUTI), the second infection is caused by a strain identical to that which caused the prior infection. With E. coli, the 6-month risk of a second UTI is 23.7% versus 7.7% for non–E. coli infections (\(P = 0.02\)).14

In conclusion, although the etiology of UTI remains constant, knowledge of local resistance trends is now an integral component in the successful empiric treatment of uncomplicated UTI. Selection of a therapeutic agent must now take into account geographic location and in vitro susceptibility, in addition to potential adverse effects and cost-effectiveness. Substituting a fluoroquinolone or nitrofurantoin for TMP-SMX in uncomplicated UTI may be necessary.
COMPLICATED UTI

Overview
Underlying host factors, including age, diabetes, spinal cord injury, or catheterization, have a significant impact on the etiology of UTIs. Less virulent organisms that rarely cause disease in an anatomically or metabolically normal urinary tract can cause significant illness and invasive disease in an abnormal urinary tract. In addition, research in Spain has identified an increase in group B streptococcal bacteremia in nonpregnant adults during the 1985–1994 time period, particularly among elderly patients and patients with diabetes and other underlying comorbidities.15 International studies also suggest an increase in *Candida* spp. and *Enterococcus* spp. as uropathogens.16

Pediatric Populations
The most common organisms isolated in children with uncomplicated UTI are Enterobacteriaceae.17 In contrast, children with comorbidities are more likely to have complicated infections, frequently caused by organisms not otherwise associated with UTI among healthy children. *Staphylococcus aureus* is more commonly seen among children with indwelling catheters or other sources of infection than healthy children. Coagulase-negative staphylococci and *Candida* spp. are commonly associated with infections after instrumentation of the urinary tract.17

Nosocomial UTI (NUTI) has been associated with urethral instrumentation among pediatric patients. However, a recent prospective study in Canada determined that only 50% of pediatric NUTI had prior instrumentation.18 The most common uropathogens included *E coli* (28%), *Candida* spp. (18%), *Enterococcus* (13%), gram-negative nonfermenters (13%), *Enterobacter* (approximately 10%), and *Pseudomonas* (9.7%). It is important to note that fungi have become the second most common pathogen isolated in pediatric NUTI.

More than 90% of acute nonobstructive *E coli*-induced pyelonephritis in children is caused by *E coli* possessing P fimbriae.19 P fimbriae allow the bacteria to adhere to the uroepithelial cell lining; children with acute nonobstructive pyelonephritis caused by P-fimbriated *E coli* have heavy colonization of P-fimbriated *E coli* in both periurethral areas and stool. In fact, this study demonstrated that poor sanitary habits from hospital workers in a neonatal ward facilitated epidemic outbreaks of acute pyelonephritis.

Elderly
The etiology of UTI among the elderly depends on their overall health status and whether they reside independently in the community or require long-term care arrangements. The majority of community-acquired symptomatic uncomplicated infections in elderly women are caused by *E coli*.20 *S saprophyticus* is a rare uropathogen in this subpopulation. Gram-positive organisms are common and account for 10% to 20% of UTIs in the elderly. Polymicrobial infections affect up to 1 in 3 patients. In contrast, the high rate of urinary catheterization among the elderly in long-term care facilities (7%),21 in combination with the frequent use of systemic antibiotics, increases the risk of UTI caused by resistant gram-negative rods, that is, *Pseudomonas aeruginosa, Proteus* spp., and nonfermenting gram-negative rods.

Patients with Diabetes
UTIs are considered to be 1 of the top 10 concurrent or complicating illnesses with diabetes.22 Etiologic pathogens associated with UTI among patients with diabetes include *Klebsiella* spp., *P* streptococci, and *Enterococcus*, as well as *E coli*. It is believed that *Klebsiella* and group B streptococci are 2 to 3 times more common among patients with diabetes than patients without diabetes.22 A recent prospective study found *E coli* was the most frequent causative agent among patients both with diabetes (56.1%) and without diabetes (56.8%).23 As yet, the reasons underlying an increased propensity to cause UTI among most uropathogens are unknown.

Women with diabetes who have asymptomatic bacteriuria are at increased risk of developing symptoms.22 It has been suggested that organisms currently found in asymptomatic women with diabetes have the potential to invade the renal parenchyma and cause illness. Patients with diabetes are more likely to have UTIs by non-albicans *Candida* species than patients without diabetes. Finally, the high rate of bladder catheterization among patients with diabetes also impacts etiologic factors.

Patients with Spinal Cord Injuries or Catheters
Patients with spinal cord injuries commonly present with *E coli* infections. Other common uropathogens include *Pseudomonas* and *Proteus mirabilis*. Patients with indwelling catheters or structural abnormalities of the urinary tract are more vulnerable to infection by *P mirabilis*.24,25 Unique virulence factors produced by this organism contribute to its pathogenicity. *E coli* remains the predominant causative agent. Other common pathogens include *Candida* species, enterococci, *P aeruginosa, Klebsiella* spp., *Enterobacter* spp., and *S aureus*.

A recent microbiologic survey of long-term care facilities identified numerous gram-negative isolates (*P aeruginosa, P mirabilis, E coli,* and *Klebsiella pneumoniae*), as well as gram-positive isolates (enterococci and *S aureus*).21 Approximately 7% of residents had urinary catheters; 38% had recently taken, or were currently receiving, antibiotics, facilitating significant antibiotic pressures within this population.

Results from a surveillance database in a Midwest university hospital covering 1982 through 1991 demonstrated a significant increase in NUTI, from 2.63 of 1,000...
patient-days to 4.35 of 1,000 patient-days ($P = 0.0023$). An overwhelming majority (88%) of NUTIs were catheter related. There was a reduction in the prevalence of UTI caused by *E. coli*, *Proteus* spp., and *Pseudomonas* spp., and an increase in UTI caused by yeasts, *K. pneumoniae*, and group B streptococcus.

### PATHOGENESIS OF UTI

Individual susceptibility to UTI is complex, depending on genetic, biologic, and behavioral factors (Table 2). The interaction between bacterial virulence and host defense factors can ultimately result in UTI. Each bacterial species has distinct pathogenic mechanisms that facilitate UTI. Colonization is determined by the specific bacterial adhesive characteristics, the receptor repertoire on the epithelial surface, and the surrounding fluids. Vaginal colonization of uropathogens frequently precedes UTI. Genotypic traits for epithelial cell receptivity have been identified as an important susceptibility factor in UTI.

#### Pathogenesis of *E. coli* Infections

A critical initial step in the pathogenesis of both acute and recurrent UTI involves colonization of the urinary tract or vaginal introitus with *E. coli*. Uropathogenic *E. coli* strains generally possess filamentous surface adhesive organelles called fimbriae or pili. In the case of type 1 fimbriae, the adhesin molecule FimH, which is located at the tip of the type 1 pilus, directly interacts with host receptors and facilitates bacterial attachment on the luminal surface of the bladder epithelium. This may also mediate the internalization of bacteria into epithelial cells, where *E. coli* can replicate and escape host defense mechanisms. Research has shown that women with RUTI have 3-fold more *E. coli* adhering to vaginal, buccal, and voided uroepithelial cells than women without recurrent infection. Further, women with RUTI also have longer durations of vaginal colonization with uropathogenic *E. coli*, even during asymptomatic periods.

There is evidence for an intestinal habitat for uropathogenic bacteria, as strains of uropathogenic *E. coli* have been found in the colonic microflora. In addition, new molecular assays have identified 29 virulence factor genes of *E. coli*. Research comparing UTI among non-immunocompromised, immunocompromised, and renal disease patients found *E. coli* was the most frequently isolated pathogen among all groups. All virulence factors of *E. coli* were more common among nonimmunocompromised versus immunocompromised patients; the highest degree of discrimination between the groups involved genes for bacterial adhesive proteins. It was suggested that less virulent *E. coli* strains can cause UTI more frequently in immunocompromised patients or patients with renal disease. Additional research also found low virulence strains to be prevalent in patients with diabetes and signs of renal complications.

A limited number of P-fimbriated *E. coli* strains have been strongly associated with pediatric pyelonephritis. Each *E. coli* clone has distinct characteristics, including O and K serotype, similar outer membrane protein patterns, and hemolysins. Some O and K serotypes of *E. coli* are more common uropathogens than others. Nevertheless, P fimbriation appears to be a virulence factor. Further, there appears to be a correlation between colonization of the gastrointestinal tract with P-fimbriated *E. coli* and acute pyelonephritis.

A recent surveillance study in Spain assessed the etiology of community-acquired UTI for the *E. coli* serotype O15:K52:H1 over a 1-year period. This specific serotype accounted for only 1.4% of community-acquired *E. coli* UTIs, but these infections were more likely to present as...
pyelonephritis. E coli O15:K52:H1 strains had a limited repertoire of virulence factors, but extensive and diverse antimicrobial resistance profiles.

There are, as yet, no prospective population-based studies on the pathogenesis of UTI among patients with diabetes. In some patients with diabetes, Tamm-Horsfall protein is markedly reduced, allowing adherence and cell entry of type 1 fimbriated E coli.22 Whereas P fimbriation and hemolysin production have been identified as important virulence factors among patients with diabetes,33 there is, as yet, no evidence identifying differences in bacterial virulence factors for E coli among patients with or without diabetes.

Pathogenesis of Non-E coli Infections

In contrast to the pathogenesis of E coli UTI, S saprophyticus and enterobacterial species adhere to uroepithelial cells through different adhesive mechanisms. After attachment, Proteus spp., K pneumoniae, and S saprophyticus each produce urease, which catalyzes the hydrolysis of urea in urine and causes the release of ammonia and CO2. As a result, the urinary pH is elevated, which can eventually lead to the formation of bladder or kidney stones.

CONCLUSIONS

The majority of UTIs are uncomplicated infections. UTIs are considered complicated when patients have functional, metabolic, or structural abnormalities. Throughout the recent past, the most common causative pathogens associated with uncomplicated cystitis or acute pyelonephritis have been, and remain, E coli (80%) and S saprophyticus (5% to 15%). In comparison, the etiology of complicated UTI is more diverse and frequently polymicrobial in nature. Specific host factors, such as the extremes of age (pediatric or elderly), pregnancy, diabetes, catheterization, or spinal cord injuries, can impact on etiology. Patients with diabetes are more likely to have infections involving Klebsiella spp., whereas patients with urinary catheters are more frequently diagnosed with Pseudomonas infection. Although there have been minimal changes in the predominant uropathogens over the past decades, there have been significant changes in the resistance patterns to antimicrobials. The changes in resistance patterns need to be considered when determining the most appropriate empiric therapy. This is particularly important given the increasing resistance to TMP-SMX.

Recent advances in molecular biology may facilitate the identification of new etiologic agents for UTI. A renewed interest in the etiology and management of UTI has surfaced over the past few years. The need for accurate and updated population surveillance data is apparent, particularly in light of concerns regarding antimicrobial resistance. This information will ultimately direct selection of empiric therapy for UTI.

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