



Summary of Proceedings

*Alliance for the Prudent Use of Antibiotics
June 10, 2003 Roundtable, Boston, MA*

UTI Treatment at a Turning Point:

Improving Antimicrobial Prescribing for Uncomplicated UTIs in an Era of Increasing Antibiotic Resistance

In June 2003, the Alliance for the Prudent Use of Antibiotics (APUA) hosted a national Summit on antimicrobial resistance in acute uncomplicated urinary tract infections. An expert national panel involving representatives from IDSA, CDC and the nation's top clinical specialists convened in Boston to consider presentations on current issues and suggest guidance for community practitioners.

Meeting Goals

States goals of the meeting were:

- To better understand the epidemiology of uncomplicated UTIs
- To discuss the merits of various antimicrobial treatment options to improve empiric treatment of UTIs and minimize antimicrobial resistance
- To consider how antimicrobial resistance should be factored in professional guidelines development for UTIs

Meeting Summary

Key themes and recommendations emerging from the meeting are summarized as follows:

Uncomplicated cystitis, one of the most common and easily cured infections, has recently presented clinicians with complex and far-reaching treatment decisions. Rising antibiotic resistance in its principal causative organism, *E. coli*, raises questions about antimicrobial choice – especially in light of the need to conserve an essential broad-spectrum class of antibiotics, the fluoroquinolones. Clinicians must weigh the appropriate use of trimethoprim-sulfamethoxazole (TMP/SMX), the current first line drug to which resistance is rising; nitrofurantoin, an older narrow-spectrum agent that has spawned little resistance but may be slightly less effective; and fluoroquinolones, highly reliable broad-spectrum drugs against which widespread resistance would spark a public health crisis.

The rising tide of antibiotic resistance worldwide is an urgent public health threat, threatening to cancel out decades of medical progress against many of the most frequent and deadly infectious diseases. In UTI treatment, antibiotic resistance increases patient morbidity, ranging from mild to severe; boosts the costs of reassessment and treatment; leads to higher rates of hospitalization; and invites the use of broader-spectrum therapies. More generally, the rising use of fluoroquinolones, both for upper respiratory infections and for uncomplicated cystitis, portends a dangerous synergy; this crucial class of drugs could become ineffective not only for these two common infections, but also for foodborne infections, sexually transmitted diseases, and hospital pneumonias.

On June 10, 2003, the Alliance for the Prudent Use of Antibiotics convened a private scientific meeting of leading experts in the field to better understand the epidemiology of uncomplicated cystitis, discuss the merits of various antimicrobial options to improve empiric treatment of UTIs and minimize antimicrobial resistance, and consider how resistance should be factored into professional guidelines development for UTIs. Participants discussed shifting resistance trends in UTI pathogens, examined gaps in our understanding of the causes and natural course of the disease, proposed a future research agenda – and, most important, suggested an updated algorithm for treatment. Among the questions that informed our thinking: How should rising resistance rates be factored into treatment guidelines? How should clinicians balance the risk of treatment failure against the threat of rising resistance? What social and economic factors drive prescribing behavior? Do today's surveillance programs overestimate resistance prevalence in community-acquired UTI, and if so what are the treatment implications?

And, finally, how can current IDSA guidelines for treating acute uncomplicated UTI take into account today's resistance trends?

What follows are key points made during this session, including an algorithm proposed by one of the presenters.

Epidemiology of UTIs

Acute uncomplicated urinary tract infection occurs primarily in young, healthy women. By age 24, 1 in 3 women receive the diagnosis, rising to at least 40-50% over a lifetime. In women, the peak of disease occurs during the sexually active years, between ages 18 and 39, while in men incidence increases with age. Among women over age 18, 11% have had a UTI in the past 12 months. A disproportionate number of UTI infections are repeats – that is, most UTIs occur in women who have had a previous infection. After an initial infection, 30-40% of patients will suffer a recurrence, usually more than twice.

The cumulative probability of UTI in women rises dramatically between ages 15 and 50 – most likely because these years represent the peak of sexual activity, the most important behavioral risk factor. In young women, 75-90% of UTIs can be ascribed to sexual intercourse. Another important variable – spermicide use – may alter normal vaginal flora. Diaphragms, often used with spermicides, appear to independently raise risk. Studies of both young, unmarried university women and older, married women in HMOs show a clear dose-response curve: the more sexual intercourse a woman has, the greater her chance of infection.

Genetic factors also elevate UTI risk. Patients have a higher frequency of first-degree female relatives (mothers, sisters, daughters) with the disease. Women with the diagnosis are also more likely to be non-secretors, and to have ABO blood-group antigens.

Natural History of UTI

Several studies have tracked the natural history of UTI. Brumfitt and Mabeck found that 50-70% of infections clear spontaneously, though symptoms may persist for months. Asbach showed that 26% of patients clear bacteriuria in two weeks, though the

study offers no data on symptoms or long-term follow-up. Nicolle has found that 28% of patients clear bacteriuria, and that 43% are asymptomatic at eight to ten days.

Microbiology of UTI

The microbiology of acute uncomplicated UTI is highly consistent: 80-85% of these infections are caused by *E. coli*. Among the important associated virulence factors in this pathogen is the type I fimbriae (Fim H). Another 5-15% of cases are caused by *Staphylococcus saprophyticus*, an organism that appears to strike seasonally, peaking at the end of the summer and in the fall. *Klebsiella pneumoniae*, *Proteus mirabilis*, group B streptococcus and other pathogens account for the remainder of cases.

Costs

Acute uncomplicated UTI is primarily a woman's health issue. While morbidity may be low compared to other diseases, the disease's impact is widespread. According to a study by Foxman, episodes average 6.1 symptomatic days each, including 2.4 days of restricted activity. Annual direct and indirect costs total \$1.6 billion.

Pre-Therapy Urine Cultures?

Rising antimicrobial resistance prompts the question: Should clinicians order routine pre-therapy urine cultures for UTIs? Arguing against this practice is that most cultures will predictably grow *E. coli* or *S. saprophyticus*. In addition, 10-20% of women who present with symptoms will test negative, even though they experience the same response to antimicrobial therapy as women with positive cultures. Thus, negative cultures are dubious grounds for withholding antimicrobial therapy. Another 10-30% of patients will have low counts of organisms, further suggesting that standard quantitative counts confuse the microbiology of this infection.

Another argument against performing pre-therapy cultures concerns timing. Physicians typically prescribe three-day treatment regimens – though it takes two to three days before the results of a urine culture come back, by which time it's already known whether a patient has responded to therapy. Moreover, UTI patients – most of whom understand their symptoms well and can self-diagnose – want and deserve the

convenience of simply asking for an antibiotic without having to go out of their way to submit a urine specimen.

Other experts counter that pre-therapy urine cultures are important, especially from a public health viewpoint. These cultures both confirm the diagnosis and reveal antibiotic susceptibility patterns and trends in a community. Ironically, current IDSA guidelines, which advise physicians not to culture uncomplicated UTI, may have impaired surveillance efforts.

Treatment Trends

International studies reveal wide variability in the treatment of acute uncomplicated urinary tract infections. Nations with equally modern health care systems use different agents as their number one choice. While fluoroquinolones are popular in Spain and Portugal, for example, TMP/SMX is most frequently used in Denmark and Canada, and cephalosporins are among the most popular agents in Germany and France. In the United States, treatment varies as well, according to 1989-1998 National Ambulatory Medical Care Survey data. In that survey, TMP/SMX use decreased, fluoroquinolone use increased, and non-recommended treatments such as beta-lactams made up one-third of prescriptions.

A recent study of insurance claims from a large preferred provider organization found that for acute sporadic cystitis, 37% of patients received trim sulfa and 32% received fluoroquinolones. For recurrent infections, 18% received trim sulfa, 38% fluoroquinolones, and 23% nitrofurantoin. Only 10% of the acute and 5% of the recurrent patients were given the recommended three-day regimen.

IDSA guidelines cite cost in arguing against fluoroquinolones as initial empiric therapy except when resistance exceeds 20%. Yet when factoring in recurrences and side effects, the cost difference between a three-day regimen of fluoroquinolones and other agents is negligible.

Many factors drive treatment variability. Women who receive TMP/SMX are more likely to be under 45 years of age and have had no prior history of UTI infection; women are more likely to receive fluoroquinolones if they suffer dysuria, and are less likely to receive the drugs if they are younger and non-white. Fluoroquinolones are more

likely to be prescribed by internists and general practitioners, and less likely to be prescribed by ob/gyns (who may be concerned about safe pregnancies). Nitrofurantoin is more likely to be prescribed by ob/gyns and HMO clinicians, and less likely to be prescribed by internists. Non-recommended treatments are more likely to be prescribed to nonwhite women and to those with a prior UTI; these drugs are also more likely to be prescribed by ob/gyns than by general practitioners or internists.

Larger structural forces may also drive variability in antimicrobial use: differences in regulatory approval; marketing pressures; reimbursement policies; and individual practice experience.

E. coli and UTIs

The *E. coli* that cause UTIs constitute a special subset of organisms. *E. coli* is an unusually large species designation, phenotypically similar (in most cases) but genetically heterogeneous. Though *E. coli* found in bowel flora are generally distinct from uropathogenic strains, there appears to be some overlap in these two groups.

Foxman looked at nine different virulence factors reported to be more frequent in strains causing cystitis than in commensal bowel flora. Calculating the potential combinations of these virulence factors, she found 36 different combinations. RFLPs yielded 125 different patterns. In other words, there is no way to characterize a strain as specifically uropathogenic. While different virulence factors occur more frequently among uropathogenic than non-uropathogenic *E. coli*, none contain unique markers.

Susceptibility to Disease

In humans, *E. coli* in asymptomatic infections are often spontaneously cleared. Bacteria introduced into the body may not necessarily interact with the host and cause infection. Humans are universally susceptible to urinary tract infections from some organism; though one *E. coli* strain may not infect a particular individual, another might. Women who have contracted their first urinary tract infection had an average of four previous sex partners – suggesting that sex itself wasn't the deciding factor, but rather the organism.

In addition, patients shift between asymptomatic bacteriuria and disease susceptibility. This movement suggests that different factors enhance exposure to potential pathogens, followed by changes in host response and bacterial characteristics. An individual may become immune to a specific organism but remain susceptible to others. Molecular studies of first and second infections have found that in only half of cases is the second causative organism the same as the first.

Among the factors that influence bacterial growth: trauma (which permits the organism to interact with the host immune system); obstruction of urine flow; prostate size; other anatomical features. Vaginal flora help determine whether *E. coli* can colonize. Host response varies according to different uropathogenic features. Host susceptibility may be modified by diet, by drinking cranberry juice, even by exposure to cold. Bacteria may also have special features that enable transmission between individuals. Foxman's group has found a gene associated with co-colonization. Persistent colonization and movement within individuals also appear to be crucial.

Several factors influence exposure to community uropathogens. Chief among these is recent vaginal intercourse. Pathogens found in urine (essentially a pure culture) can be transmitted by hand in potentially large counts. A recent study on co-colonization of sex partners shows that if at least one partner has a urinary tract infection, the couple is twice as likely to share the organism than if urinary tract infection is not present.

Condom use also affects UTI recurrence rates. Non-spermicidal condoms produce a trauma effect, which may increase symptomatic infections. One study found that while condoms were protective for infection with a different organism, they raised the risk of infection with the same organism – suggesting that individuals may harbor an internal reservoir of the organism that is disturbed by trauma. Oral sex may also be an important transmission factor.

Food may contain uropathogens. The inability to perform accurate strain typing is an obstacle to investigating this question. Using current methods, it is difficult to prove that one *E. coli* is the same as another. Epidemiological proof that two people had contact with each other would strengthen the case that two *E. coli* strains are the same. Sampling *E. coli* from different organs, such as the bowel, bladder, and vagina, yields oversamples and undersamples, suggesting that the pathogens thrive in specific niches.

Most likely, uropathogens do not solely originate in bowel flora. Foxman has observed that condom use makes a difference, and that not all sexual intercourse leads to infection. Thus, there must be some inherent feature of the organism that raises the risk of infection. Contact tracing would help illuminate how uropathogens get into women's bowel flora.

In general, researchers don't understand the circulation of *E. coli*. If scientists had markers, as they do with *E. coli* O157:H7, they could help track uropathogenic *E. coli*.

The Science Behind Antimicrobial Resistance

E. coli and *Klebsiella* have developed a wide range of resistance traits against today's most commonly used agents.

Klebsiella have shown increasing resistance in the form of transmissible beta-lactamases. Among these enzymes are extended spectrum beta-lactamases (ESBLs), which can hydrolyze many agents, including third-generation cephalosporins. Plasmid-mediated beta-lactamases, which in the United States are more prevalent in *Klebsiella* than in *E. coli*, have the potential to cause outbreaks in such places as rehabilitation centers.

Multidrug resistance is common on these plasmids. ESBL-producing strains are twice as resistant to TMP/SMX, ciprofloxacin, and gentamicin, and are more resistant in general than other strains. A urine isolate of *Klebsiella pneumoniae* recovered in Alabama in 1994 contained a protein, dubbed qnr, that is capable of protecting gyrase, the target enzyme of ciprofloxacin and other fluoroquinolones used to treat *E. coli* infections.

TMP/SMX resistance springs from several potential mechanisms. These include efflux of one or both drugs; mutations in one or both of the enzymes that are targets of these drugs; and alterations in cell permeability. *E. coli* strains that are resistant to TMP/SMX are also ten times more resistant to ciprofloxacin, and substantially more resistant to nitrofurantoin. Such findings suggest that, through long-term exposure, *E. coli* have acquired resistance to several drugs. A 2003 study analyzed 400,000 isolates (non-catheter specimens) of *E. coli* from female outpatients. Ampicillin resistance was 38%; TMP/SMX resistance was 17.5%; ciprofloxacin resistance was 2.3%.

Quinolone resistance in *E. coli* may spring from mutations in DNA gyrase, the target of fluoroquinolone drugs. Efflux pumps may remove quinolones from the cell, and permeability factors may prevent the drugs from entering. Thus, in Gram-negative rods, a two-step process takes place: the cell erects a blockade to keep the drug from coming in, and up-regulates efflux mechanisms for pumping the drug out. In fluoroquinolone-resistant *E. coli*, rates of resistance to nitrofurantoin increase dramatically. The mechanism for such resistance isn't completely understood.

The mechanisms of antimicrobial resistance are broad. These include an accumulation of unrelated traits in strains that have circulated for a relatively long period of time; acquisition of linked unrelated traits on transmissible elements; and expression of multidrug resistance traits, such as an efflux pump. Because these mechanisms are already in place, clinicians driven to use less common agents, or those agents to which resistance is relatively uncommon in the United States, will increasingly encounter resistance to these substitute agents as well.

The Value of Surveillance

Most estimates of resistance prevalence are drawn from surveillance studies. But these studies vary dramatically in where data originate and how data are filtered. This variation calls into question the reliability of numbers routinely cited in prevalence estimates.

One of the major surveillance programs relevant to UTIs is the SENTRY program. Initiated in 1997 by Bristol Myers Squibb, this global program tracks infection through a central laboratory. It collects data from North America, Latin America, Europe, Asia-Pacific, and South Africa. SENTRY collects data longitudinally not only on UTIs, but also infections of the bloodstream, respiratory tract, skin and soft tissue, and other sites. In SENTRY studies, data on UTIs predominantly come from hospitals, thus reflecting patients whose infections are serious, recurrent, or require hospitalization. This population sample may lead to overestimates of community resistance patterns.

Another surveillance program, TSN – The Surveillance Network – is a virtual program in which several hundred labs around the world are linked to a central database, which filters incoming data and generates millions of results.

Several recent studies have drawn on surveillance programs to estimate the prevalence of antibiotic resistance in UTI. In ECO-SENS (2003), Kahlmeter conducted a prospective study of European and Canadian outpatients with uncomplicated UTI. This two-year effort, drawing in 202 sites, reflects pathogen resistance rates among UTI outpatients. It concludes that neither ciprofloxacin nor nitrofurantoin resistance was high in *E. coli* (2% or lower).

In 2001, Gupta published a study of community-acquired urinary tract infection based on TSN. This nationwide analysis mined existing laboratory data and separated it out by region. Gupta found that TMP/SMX susceptibility varied significantly from region to region.

In a 2001 prevalence study targeted at outpatients, Karlowsky acquired from 202 TSN participating laboratories urinary tract isolates for standardized testing. Similarly, resistance rates varied dramatically from one region of the country to another.

The wide variation in prevalence rates has serious implications for treatment. Physicians working in community clinics are prescribing antibiotics based on inapplicable prevalence estimates generated from hospital patients. Urgently needed is more active longitudinal surveillance for uncomplicated community-acquired cystitis. Local antibiograms, which may primarily reflect physicians' experiences with failed treatments, may likewise distort the true resistance picture.

What Can We Learn from the CDC?

The UTI treatment community can take a lesson from the Centers for Disease Control and Prevention's successful campaign to reduce unnecessary antibiotic prescription for upper respiratory infections (which are typically caused by viruses). Beginning in 1995, the agency undertook a broad-based effort to change prescribing patterns by ferreting out the reasons providers choose certain drugs and then educating these providers about more prudent choices. CDC established partnerships with managed care organizations, pharmacy benefit management companies, pharmaceutical companies, large health care purchasers, medical schools, and professional societies to communicate the message to physicians. CDC has also initiated active population-based surveillance and enhanced passive surveillance of resistance trends, and has supported

such practices as physician profiling to raise individual awareness of prescribing habits. This comprehensive approach has led to a decline in overall antibiotic use.

Treatment Failure

Higher resistance rates do not strongly predict clinical failure. According to a paper by Gupta, with no TMP-SMX resistance, there is a 93% bacteriologic eradication rate and a 95% cure rate for symptoms. Even at 30% resistance, the bacteriologic eradication rate is 80% and the cure rate 85%. This raises the question: What should be the threshold for moving from empiric TMP/SMX to empiric fluoroquinolones or other drugs, if the treatment failure rate is lower than expected?

Studies suggest that in uncomplicated UTI, treatment failure is more likely if the uropathogen is resistant *in vitro*. In pyelonephritis, TMP/SMX-resistant strains likewise respond less well to the drugs. Not unexpectedly, many physicians have encountered cases of pyelonephritis that had originated in treatment failure with TMP/SMX, usually because the original resistant organism was not cultured.

Management Strategies: A Discussion

While TMP-SMX is the recommended drug of choice for uncomplicated cystitis, the use of fluoroquinolones to treat this common infection is rising – a trend that greatly concerns public health experts, who warn that selecting for increased resistance to fluoroquinolones could greatly impair treatment of hospital infections, foodborne disease, and STDs. How, then, can providers be reassured that non-fluoroquinolone drugs are valid choices against uncomplicated cystitis?

It is surprising that clinicians are hesitant to use recommended fluoroquinolone-sparing medications, starting with nitrofurantoin. Even after 50 years of nitrofurantoin use, *E. coli* continue to demonstrate low levels of resistance to the drug. Moreover, nitrofurantoin's only indication is for uncomplicated urinary tract infection, meaning that clinicians needn't worry about selecting for resistant organisms in other infections. And nitrofurantoin has no cross-resistance with other antibiotics. Most reports demonstrate a consistently low level of resistance to the drug in *E. coli* and reasonable tolerance by patients³. Weighing against nitrofurantoin, there are insufficient data to demonstrate the

drug to be as effective in single-dose or 3-day regimens as TMP/SMX or fluoroquinolones. In its currently recommended 7-day regimen, nitrofurantoin continues to be more expensive than TMP/SMX and fluoroquinolones. Some clinicians are concerned that the 7-day regimen may lead to lack of patient compliance. And providers may worry about the safety of nitrofurantoin. Rare side effects include an acute pulmonary reaction, most common in the elderly. More severe subacute and chronic pulmonary reactions can develop if the drug is taken for long periods of time. Yet large-scale analyses put these risks into perspective. An evaluation of 121 million courses of nitrofurantoin treatment showed that the frequencies of major adverse reactions are very low, with the most common being acute pulmonary reactions, which occur in 0.00094% of exposed patients.

On balance, the Roundtable presenters noted that nitrofurantoin should be given more emphasis as a fluoroquinolone-sparing second-line agent for more women with uncomplicated cystitis, and an alternative when TMP/SMX cannot be used. This opinion was based on: 1) concerns about preserving fluoroquinolones 2) the low and stable level of resistance to nitrofurantoin among *E. coli* and *S. saprophyticus* and 3) increasing resistance of uropathogens to TMP/SMX (although this was noted to be somewhat exaggerated because surveillance data are from hospital patients).

Turning to fosfomycin, overall published and unpublished data suggest that the drug is inferior to first-line agents currently available for treatment of acute uncomplicated cystitis. In a meta-analysis of two trials in which fosfomycin single dose was compared with multiday regimens of norfloxacin, fosfomycin was found to have similar eradication and recurrence rates, but a significantly higher rate of adverse events. Data presented to the US FDA showed that single-dose fosfomycin was significantly less effective in eradicating bacteriuria compared to TMP-SMX for 10 days or ciprofloxacin for 7 days. In addition, fosfomycin is an expensive medication.

Trimethoprim and TMP-SMX have long been considered first-line agents for treatment of uncomplicated cystitis. Most studies have shown no difference in treatment outcomes between TMP-SMX and fluoroquinolones, although there are no cystitis treatment trials involving large numbers of women infected with TMP-SMX-resistant uropathogens. Though physicians outside the US often deride the use TMP-SMX because

of the purported danger of sulfa allergies, this danger was not confirmed in trials evaluated in the IDSA review. TMP-SMX is also the least expensive option in treatment of uncomplicated cystitis.

Finally, the fluoroquinolones have been shown to be highly effective in treating uncomplicated cystitis in three-day regimens. Although fluoroquinolones are more expensive than TMP-SMX, the cost differential may not be significant in practice when factoring in expenses associated with treatment failures and adverse events. On the other hand, there is an urgent need to preserve the fluoroquinolone class of drugs.

What is the likelihood of inducing fluoroquinolone resistance? No studies have shown that short course fluoroquinolone therapy for acute UTI selects for resistant flora. An unpublished paper by Gupta does suggest that a three-day regimen of ciprofloxacin selects out for ciprofloxacin-resistant *E. coli*, although genetically distinct from the initial strains. And selection for fluoroquinolone-resistant rectal *E. coli* has been seen following single dose prophylaxis in men undergoing urologic procedures and following 28-day treatment for prostatitis. Other studies have presented contradictory answers to this question.

In formulating treatment guidelines for uncomplicated cystitis, physicians and the public health community must try to glean how much fluoroquinolone use for upper respiratory infections contributes to rising fluoroquinolone resistance among UTI pathogens. This should be an area of future research, as the ultimate goal of reducing antibiotic selection pressure hinges in part on the answer to this question.

While surveillance data reflect population-wide resistance trends, clinicians need to be able to predict TMP/SMX resistance in individual patients. Studies suggest that recent hospitalization, diabetes, current use of antibiotics, and TMP/SMX use within the past three months can dramatically increase the likelihood of a TMP/SMX-resistant strain causing UTI. It is also reasonable to consider the following as risk factors for being infected with a TMP/SMX-resistant organism: travel to countries with known high prevalence of TMP/SMX resistance, such as Mexico or southern Europe; having children in daycare; having a family member who has recently been treated for a UTI caused by TMP/SMX-resistant *E. coli* strain.

To summarize, clinicians face new and puzzling dilemmas in empiric UTI therapy: They can choose somewhat less effective and more expensive antibiotics without other indications and without cross-resistance (fosfomycin and nitrofurantoin); or they can choose TMP/SMX despite apparently rising resistance; or choose fluoroquinolones, with rising resistance a major public health concern. With rising resistance in uropathogens and the threatened loss of fluoroquinolones, IDSA guidelines must be clarified and refined.

The panel determined that there was a need for an algorithm to help refine treatment discussions. The panelists noted that while guidelines can help shape

Suggested Algorithm for Treatment of Acute Uncomplicated Cystitis

Presented by Thomas Hooton, MD

TMP/SMX or TRIMETHOPRIM should be the first line treatment if:

- patient has no history of allergy to the drug
- no antibiotics in the past 3 months (for any reason)
- no recent hospitalization
- where rate of resistance to TMP/SMX in the community is not high (i.e., greater than or equal to 20%)

FLUOROQUINOLONES should be considered for women who

- have allergy or risk factors for TMP/SMX resistance or
- who live in communities with known high rate of resistance to TMP/SMX (i.e., greater than 20%)?
- have severe symptoms that clearly affect their daily routine or
- who might find it difficult to call or return for care

NITROFURANTOIN should be considered as a fluoroquinolone-sparing agent for women who have:

- allergy to, or risk factors for, TMP/SMX or
- who live in communities with known high rate of resistance to TMP/SMX (i.e., greater than 20%)?
- mild to moderate symptoms

Conclusions and Recommendations

- Fluoroquinolones are excellent drugs and have an important role in treating uncomplicated cystitis – but not as first-line therapies. Rising fluoroquinolone resistance is a serious public health threat. The routine use of fluoroquinolones for treating mild to moderate acute uncomplicated cystitis should be strongly discouraged.
- Rising – and possibly exaggerated – estimates of resistance to TMP/SMX are leading clinicians away from what remains an inexpensive and highly effective drug for the treatment of uncomplicated cystitis. Fluoroquinolone-sparing agents should be given higher priority.
- Although TMP/SMX resistance is increasing, current surveillance systems likely exaggerate resistance prevalences in community-acquired uropathogens because they depend on data from hospital settings and because of culture selection bias. Clinicians need resistance estimates based on data gathered from primary care clinics, school-based clinics, and university clinics. We recognize that such data are usually not available to practicing clinicians.
- Researchers should study the clinical outcomes and side-effects of shorter courses of nitrofurantoin than the currently recommended 7 days.
- Professional societies need to develop for clinicians algorithms – such as the one offered at this roundtable – that stratify patients by risk and predict which are more likely to harbor resistant vs. susceptible strains.
- Current IDSA guidelines do not help physicians decide when to use fluoroquinolone drugs vs. fluoroquinolone-sparing medications to treat uncomplicated cystitis. We recommend that IDSA refine and clarify its current guidelines to address that question. In treating uncomplicated cystitis, we must select treatments that make therapeutic sense and that serve the larger public health goal of containing antibiotic resistance and preserving essential antibiotics.

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UTI Treatment at a Turning Point:

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In an Era of Increasing Antibiotic Resistance**

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