Lindsay Nicolle’s clinical and research interests in urinary tract infections reach back nearly a quarter century. During that time, she has witnessed ever-rising antibiotic resistance in *E. coli*, the most common pathogenic culprit in UTI patients. While drug resistance in developing nations is spawned by the easy availability of over-the-counter therapies and by underdosing, in industrialized countries the driving force is antibiotic overuse both in humans and in factory farm animals. Regardless of the cause, the challenge is formidable, says Nicolle, professor of internal medicine and medical microbiology at the University of Manitoba. “We need to recognize that urinary tract infections are the most common bacterial infections that occur in human beings.”

**Q: Are we at a turning point in the treatment of acute cystitis?**

**A:** For urinary tract infection, the most important pathogen in well people in the community is *E. coli*. Over the years we’ve seen serial development of resistance to antimicrobial agents in *E. coli*. More recently the concern has been trimethoprim and trimethoprim-sulfamethoxazole resistance – both having been mainstays of our treatment for urinary infection for several decades now.”

With the rise in resistance to trimethoprim (TMP) and trimethoprim-sulfamethoxazole (TMP/SMX), the issue is: If we want to use empiric therapy for acute uncomplicated cystitis, do we move forward with even broader spec-

**Antimicrobial Resistance in Urinary Tract Infections**

Kalpana Gupta, MD, MPH, University of Washington

Urinary tract infections (UTIs) are very frequent in the inpatient and outpatient settings. A 1997 ambulatory care survey found that UTIs resulted in over 7 million office visits and 1 million emergency room visits annually in the US (1). UTI is more common in women than men, especially among young adult sexually active women. The most common UTI syndrome in women is acute uncomplicated cystitis, affecting at least 50% of women sometime during their lifetime (1). The emergence of antimicrobial resistance among isolates causing UTI, particularly acute uncomplicated cystitis, is an important event that is making successful therapy of this infection more difficult.

*Resistance impacts treatment outcomes and options*  
Antimicrobial resistance has always been an important consideration in complicated UTIs, many of which occur in the nosocomial setting. However, the problem of antimicrobial resistance in uncomplicated, community-acquired UTI is a relatively new phenomenon with important implications. The most significant trend is an increase in trimethoprim-sulfamethoxazole (TMP/SMX) resistance among *E. coli*. TMP/SMX has traditionally been the drug of choice for treatment of these infections. Rates of TMP/SMX resistance were at about 5-7% in the early 1990’s, rising to 15% in the mid-1990s and to 18% by 1998. These rates vary geographically; certain areas such as the western and southern central regions of the US have even higher rates of resistance (22%) to TMP/SMX (2). Resistance has been linked to clinical and bacteriological outcomes (see Stamm article) and is necessitating changes in the management of acute uncomplicated cystitis (3). Resistance rates to ampicillin and cephalothin have always been relatively high and have continued to increase to approximately 40% over the past decade. In contrast, rates of resistance to nitrofurantoin and the fluoroquinolones in *E. coli* from acute uncomplicated cystitis are quite low at about 1% and have not increased appreciably in the US. A recent European survey of acute uncomplicated cystitis isolates also demonstrated little resistance to nitrofurans and ciprofloxacin in most of the countries studied (4). However, there is very high ciprofloxacin resistance in the community in Spain and Portugal (4, 5).

**Antimicrobial resistance trends** among *E. coli* causing acute uncomplicated pyelonephritis essentially mirror those seen in cystitis (3). The high level of resistance to ampicillin precludes usage of this drug unless the infecting uropathogen is known to be susceptible. Resistance to TMP/SMX has increased to about 20% and varies geographically, similar to the variation seen in cystitis strains (6). Resistance to the fluoroquinolones is negligible in uncomplicated...
APUA Editorial Comment

The World Health Organization (WHO) and the US Centers for Disease Control (CDC) have warned physicians to stop antibiotic misuse or risk more severe resistant infections and more treatment failures. WHO considers antibiotic resistance one of the three major public health threats of the 21st century and in collaboration with the CDC and others, has developed action plans to address this threat.

The April 2003 Annals of Medicine documented the good news that community physicians in the US now prescribe fewer antibiotics for unwarranted conditions such as colds and flu.* The bad news is that when they do, they are increasingly choosing broad-spectrum agents such as the fluoroquinolones and third generation cephalosporins when older, less costly drugs may still be effective.

The study found that by the end of the 1990s half of all community antibiotic prescriptions for adults were broad-spectrum agents and 40% for children. Over reliance on broad-spectrum agents for simple community infections creates a strong selective pressure for resistant organisms of many different types, including those not causing disease. These may be reservoirs of resistance determinants transmissible to other bacteria able to cause disease. Clinically relevant antibiotic resistance increases patient morbidity and mortality, and results in longer hospital stays and more readmissions, all of which makes the cost of treating a drug-resistant infection far greater than that of a susceptible infection.

In this edition, several of the nation’s leading clinicians examine the range of physician treatment options for urinary tract infections and give guidance to help interpret related antibiotic resistance trends. Within the complexities of this guidance, you will discern some simple antibiotic prescribing principles that public health authorities and professional societies increasingly advise: only prescribe an antibiotic when necessary; choose a narrow-spectrum agent when effective; and consult antibiotic susceptibility data including antibiograms to monitor local resistance and guide antibiotic choice. By practicing targeted therapy, individual physicians can effectively treat the patient now while helping to preserve the future power of antibiotics.


By Walter E. Stamm, MD

Professor of Medicine

Head, Division of Allergy and Infectious Diseases; University of Washington School of Medicine

For much of the last two decades, trimethoprim-sulfamethoxazole (TMP/SMX) has been the empiric treatment of choice for management of uncomplicated urinary tract infections in women. Previously used drugs, including sulfonamide alone, amoxycillin, and cephalothin, became less useful as 30-40% of community acquired E. coli have developed resistance to TMP/SMX. For this reason, it was necessary to reassess empiric therapy options for uncomplicated UTIs.

ASK the EXPERT continued on page 3

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ASK the EXPERT continued on page 3
ASK the EXPERT continued from page 2

– the organism responsible for 80% of these infections – became resistant to these drugs.

In 1999, the Infectious Diseases Society of America (IDSA) conducted a comprehensive review of available treatment studies of uncomplicated UTI in women and recommended three days of TMP/SMX as the empiric regimen of choice in regions where resistance was less than 20% (1). The IDSA guidelines also called attention to the increasing prevalence of TMP/SMX resistance among E. coli causing these infections, and to the lack of data correlating in vitro resistance with actual treatment failure. Some experts argued that the very high and prolonged levels of drug that could be delivered to the site of this superficial mucosal infection would be sufficient to effect a cure despite resistance in vitro.

In a recently published study from Israel, Raz and colleagues addressed the latter issue, namely whether resistance in vitro predicted clinical and microbiological failure (2). The study enrolled 618 women with acute uncomplicated UTI, and all were treated with the standard regimen used in the region, namely TMP/SMX for five days.

After treatment, women were reevaluated for both clinical and microbiological cure at 5 to 9 and 28 to 42 days after the completion of therapy. Overall, 29% of the women had infecting organisms (mostly E. coli) that were TMP/SMX resistant, while the remainder had susceptible strains. The cure rates were dramatically different in the two groups. Thus, at the earlier follow up visit, the microbiological cure rate was 86% in the women with susceptible strains and 42% in those with resistant strains. A similar differential in clinical response was seen at both the first and second follow-up visit.

These findings demonstrate that TMP/SMX resistance results in clinical and microbiological failure in women with acute uncomplicated cystitis, and that the drug should not be used for empiric therapy in geographic areas where resistance is frequent.

Recent data indicate that rates of TMP/SMX resistance among uropathogenic E. coli vary widely. For example, though rates in Northern Europe are only 5-10%, in Spain and Portugal they are 25-30% (3). In the United States, rates appear to be higher in the West and Southwest (15-25%) and lowest in the Midwest and East Coast (8-12%). This points to a need for surveillance data to understand when and where resistance to antimicrobials becomes a clinical treatment concern in E. coli that cause community-acquired UTI. There are also few data identifying how drug-resistant uropathogenic E. coli enter a community, how they are transmitted, and what factors drive persistence and increase prevalence.

Unfortunately, there have been few recent controlled trials of the use of nitrofurantoin in treatment of acute uncomplicated UTI, and such trials comparing nitrofurantoin with current short-course regimens such as nitrofurazones would be of interest.

In conclusion, Gupta and colleagues have presented an approach to the selection of empiric treatment for acute cystitis (5). Local surveillance data are needed to determine resistance prevalence, particularly to TMP/SMX, among uropathogenic E. coli. Where the prevalence is below 20%, TMP/SMX can be used. Risk factors for TMP/SMX resistance – namely, recurrent UTI, recent antibiotic use, recent travel to areas with higher resistance, and daycare exposure – can also be used to identify individual patients at higher risk. In areas with high resistance prevalence, an alternative drug, usually a fluoroquinolone or nitrofurantoin, should be selected based on the considerations noted above.

Nitrofurantoin is unique among antimicrobials in that it has been used to treat acute cystitis for more than 40 years and is perhaps the only drug that has been used for that length of time to which resistance has not emerged. From an ecological perspective, it is thus an excellent choice to use to treat TMP/SMX-resistant E. coli. However, it is not as effective as fluoroquinolones when administered as a three-day regimen and usually must be given for seven days to achieve desired cure rates. Mild gastrointestinal side effects are not uncommon with seven-day treatments and more serious pulmonary hypersensitivity occasionally occurs.

References
pyelonephritis and these drugs are now considered the antimicrobial class of choice for oral treatment of pyelonephritis in women (7).

Factors promoting resistance

Antimicrobial use is one of the strongest predictors of resistance, with a 5-17 fold increased odds of isolating a TMP/SMX resistant uropathogen from women who recently used TMP/SMX (8, 9). However, the equation is not so simple, because even women who use antimicrobials other than TMP/SMX have an increased risk of having a TMP/SMX-resistant uropathogen (8). Laboratory surveys examining multidrug resistance in UTI have found that the most common resistance phenotype among multidrug-resistant E. coli UTI isolates includes resistance to ampicillin, tetracycline, and TMP/SMX. The fact that the resistance genes for these drugs can travel on plasmids supports the epidemiologic data suggesting that exposure to any one of several antimicrobial agents can promote resistance to a single agent. In addition, decreased prescribing of TMP/SMX does not necessarily lead to decreased TMP/SMX resistance rates (10, 11), probably because the antimicrobials used in lieu of TMP/SMX continue to create a selective pressure for TMP/SMX-resistant isolates.

So what factors other than antimicrobial use drive TMP/SMX resistance among uropathogenic E. coli? A recent study found that certain E. coli clones are more likely to be uropathogenic and drug-resistant and thus can result in outbreaks of drug-resistant UTI (12). Other studies have not found clonality among their UTI strains, but have reported increased rates of TMP/SMX-resistant UTIs in patients who have recently traveled to areas with endemic high rates of TMP/SMX resistance and among patients of Asian or Latin American ethnicity (13, 14). Finally, the use of antimicrobials in animal feeds is an important potential determinant of increased resistance in E. coli causing human infections (15, 16). One study found that cephalosporin-resistant E. coli strains from food animals and humans carried a homologous CMY-2 gene and a similar plasmid, suggesting that transfer of resistance from food animals to humans may occur. Interestingly, one of the human E. coli strains was isolated from a woman with uncomplicated UTI (17).

The future of resistance in UTI

Although TMP/SMX resistance in acute uncomplicated cystitis has been troubling, the availability of effective alternative antimicrobial agents has made it possible to continue to provide effective empiric therapy for these infections. However, emerging trends of fluoroquinolone resistance and multidrug resistance threaten to make the situation even more difficult. With increased usage of fluoroquinolones for cystitis as well as for other infections, it is likely that the currently low fluoroquinolone resistance rates among E. coli will increase. Studies of complicated UTI have clearly demonstrated the emergence of fluoroquinolone-resistant E. coli strains after exposure to fluoroquinolones for treatment or prophylaxis of UTI. To date, no published studies have demonstrated that a short duration of fluoroquinolone exposure for treatment of acute uncomplicated cystitis results in fluoroquinolone-resistant isolates, but it is likely that such selection pressure does occur. An increase in fluoroquinolone resistance rates in uncomplicated cystitis would markedly hamper the ability of a clinician to effectively treat the infection with short-course therapy, since ciprofloxacin-resistant E. coli isolates also tend to be resistant to TMP/SMX and other drugs (17). Fortunately, such isolates usually retain susceptibility to nitrofurantoin; however, this drug needs to be given for seven days. Multidrug resistance in UTI is still infrequent, especially in cases of uncomplicated cystitis, but is a very significant concern as antimicrobial resistance continues to evolve.

Research Priorities

It is clear that we need a better understanding of the factors promoting the acquisition and dissemination of antimicrobial-resistant uropathogens in the community. To date, few studies have focused on this issue. In addition, although there are several laboratory surveys estimating the rates of resistance among uropathogens isolated from different settings, more information is needed on factors determining resistance.
BRIEFS

Employer Data Information Set) performance measures:

1. Rate of antibiotic prescribing for children over 3 months and under 18 years diagnosed with upper respiratory infection.

2. Rate of group A streptococcus tests given to children over 2 years and under 16 years diagnosed with pharyngitis and prescribed an antibiotic.

The measure specifications, to be published in summer of 2003, are intended to be applicable to health care organizations, such as medical groups, as well as health plans.

FDA Requires Label Warning about Antibiotic Misuse Causing Resistance

After a two-year public comment process, the U.S. Food and Drug Administration, on February 5th, issued the final rule on “Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use”.

The final rule pertains to both oral and IV antibiotics and warns that misuse can cause resistance. It applies to all systemic antibacterials that are indicated for the treatment of bacterial infections, even if, like clarithromycin and rifampin, they are also indicated for the treatment of mycobacterial infections.

“Antibacterial resistance is a serious and growing public health problem in the United States and worldwide,” said FDA Commissioner, Mark McClellan, M.D., Ph.D. “Without effective antibiotic drugs, common infections that were once easily treated can cause serious health threats to children and adults alike.”

Full text of this ruling can be found on the APUA website: www.apua.com.


Q: Are vaccines a promising alternative?
A: I’m not convinced that vaccines will have a large role to play in acute cystitis. First, while E. coli is the most common organism, there are a number of others that can cause acute cystitis. So you

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would not expect a vaccine to be fully efficacious ever. Secondly, a vaccine works because of the development of immunity in women who are vaccinated—and since we’re talking about vaccinating women who have recurrent urinary tract infections with *E. coli*, you would assume that they already have a good immune response to *E. coli* because they’re constantly being infected with *E. coli*. So what additional immunity does vaccination give you?

**Q: What about probiotics?**

**A:** Probiotics are even murkier. It’s always very attractive to restore the flora to normal. But I don’t think anybody has convincingly shown a way to use that to help prevent infection. The studies that have been done to date—studies that have looked at vaginal suppositories or at swallowing lactobacillus—have not been systematic enough in standardization of dosage, documentation of levels that are achieved, and diagnosis of urinary tract infection. The idea with probiotics is that you restore normal colonization to the vagina and potentially the gut. Well, *E. coli* is normal in anybody’s gut—although not necessarily uropathogenic *E. coli*. And restoration of vaginal flora often relates to the use of spermicides and bacterial vaginosis—and there are other ways to deal with that.

**Q: What’s the current thought on cranberry juice?**

**A:** There’s one study from Scandinavia that looked at lingonberries—the active substance in lingonberries is similar to that in cranberries. It suggested there was a decrease in the frequency of recurrent infection in women who had increased lingonberry intake. So maybe there is a role for it, especially in women who have less frequent infections. It has not been effective in older individuals.

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**Q: Are there other innovative treatments you would like to see explored?**

**A:** If we can create spermicides that greatly increase the frequency of urinary infections, we should be able to create spermicides or other topical agents that could potentially prevent infection. This is all very theoretical. It could relate to what you coat the spermicides with, or to an ingredient that would interfere with the binding of bacteria to cells. If you could come up with something that would prevent both STDs and urinary tract infections, that would be a big plus for younger women.

**Q: What changes today would most improve clinical practice?**

**A:** We should limit our use of antibiotics, especially for acute cystitis. Wherever possible, avoid fluoroquinolone antimicrobials and use alternate agents such as nitrofurantoin, which has been around for quite some time and is still clearly efficacious?"
APUA New Chapters

APUA welcomes two new international chapters:
Kazakhstan: Led by Dr. Bakytgul Yermekbaeva, a Pharmacologist with the Drug Information Center in Kazakhstan.
Tbilisi, Georgia: Led by Dr. Nanuashvili Alexander of the Infectious Disease Department of Tbilisi Medical Academy.

APUA Small Grants for Chapter Research

APUA provides small grants and technical assistance to support APUA Chapter research intended to guide clinical policy and practice at the local level. Recently 100% of APUA Chapters involved in field research reported progress on their work. Highlights include:

APUA-Uruguay chapter member Dr. Rosario Palacio of the University Hospital in Montevideo reported progress of their research “Cost of S. aureus hospital-acquired infections”. This study will compare costs associated with MRSA and MSSA in a University Hospital. As of June 30, 2002, 30 patients had been enrolled in the study and 50 isolates reported.

Researching Antimicrobial Use and Resistance in Bangladesh

A comprehensive antibiotic use and resistance study in rural Bangladesh is underway. Project researcher, Amira Roess is being assisted by Dr. Nuriul Islam, president of the APUA-Bangladesh chapter. The study investigates: the extent of human and animal antibiotic use in the community; the prevalence of resistance of Streptococcus pneumoniae; and the effect of antibiotic use on resistance prevalence (at the individual, family, and community levels). Anthropological, survey, and microbiological methods will be used to learn about beliefs, patterns, and sources of antimicrobials for humans and animals and to understand the epidemiology and risk factors for neonatal carriage of antibiotic-resistant S. pneumoniae, and knowledge of neonatal treatment habits in Bangladesh. The information obtained will influence policy recommendations on the distribution and use of antibiotics for both humans and animals, the selection of drug treatments for this region, and the design of sustainable community-based education interventions targeting neonatal treatment habits.

APUA-Nepal Impacts National Antibiotic Policy

APUA-Nepal held its second general body meeting on February 15, 2003 in Kathmandu, where the General Body elected its new Executive Committee. APUA-Nepal has been cooperating closely with the His Majesty’s Government (HMG) of Nepal in drafting a National Antibiotic Policy and in categorizing antibiotics for different levels of prescribers in the past. The general body identified the following activities as next year’s main tasks:

1. Preparing National Antibiotics Guidelines and submission to HMG Nepal for implementation.
2. Training on rational use of antibiotics to the prescribers in 5 different regions of the country.
3. Preparing APUA-Nepal Charter and lobbying for commitment from all stakeholders.
4. Increasing awareness about prudent antibiotic use to the consumers through various activities.

Newly elected executive committee, some of which are pictured above: Kumud K. Kafle, MD – President, Asfaq Sheak, PhD – Vice President, Shyam P. Lohani, MPharm – General Secretary, Bimal M. Shrestha, BPharm – Treasurer, Bhupendra B. Thapa, MSc Pharm – Member, Radha R. Prasad, MPharm – Member, Dhrubalal Singh, FRCP – Member, Iswar Lal Acharya, FRCP – Member, Rewati M. Shrestha, DVM – MS Member, Pramila Pradhan, FRCOG – Member, Bharat M. Pokhrel, PhD – Member.

APUA-South Korea

Inauguration draws 500 healthcare workers

APUA-South Korea held an Inaugural Symposium on November 7, 2002. Over 500 attendees from more than 15 hospitals attended the meeting. At the invitation of Dr. Changgi D. Hong, Chairman of the Organizing Committee of APUA-South Korea, Dr. Stuart Levy presented along with Dr. Philip Jenkins of the WHO Anti-infective Drug Resistance Initiative.

APUA-South Korea’s workplan goals include the creation of a nationwide computer-based surveillance system for antimicrobial resistance and public education about the issue using the mass media.

APUA and Voice of America (VOA) in Developing Countries

In an effort to tackle antimicrobial resistance in the developing world, the RPM Plus AMR Partner Group, of which APUA is an active member, has begun working with VOA on an educational project funded by USAID. APUA chapters are assisting VOA on the ground to promote policy discussion, increase accurate reporting of drugs, and inform consumers, suppliers and the media in target countries. India, Ethiopia and Nigeria are targeted first.

Vancomycin-Resistant Enterococcus Identified in Lebanon

Vancomycin resistance among enterococcal isolates is an increasing problem and has been reported worldwide since 1988. Dr. Ziad Daud, of Saint George University Hospital in Beirut, recently reported the first case of isolation and identification of vancomycin-resistant gram-positive cocci in Lebanon.
Alliance for the Prudent Use of Antibiotics
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If you are concerned about the public health threat of antibiotic resistance, become part of the solution. Make a tax-deductible contribution and join our global network of citizens, clinicians, researchers and policy makers.

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APUA is a 501(c)3 non-profit, donations are US tax-deductible. APUA is the only organization in the world solely dedicated to strengthening society’s defenses against infectious diseases through research and education on antibiotic use and antibiotic resistance. APUA’s mission is to improve infectious disease treatment and control worldwide through promoting appropriate antibiotic access and use and reducing antibiotic resistance. With members in over 100 countries and numerous foreign affiliated chapters, APUA provides a unique network to support country-based activities and facilitate international planning and communication. APUA’s resources include an international scientific advisory board with members of national academies of medicine and science and a professional staff with specialized expertise. APUA’s global network of affiliated chapters serves to tailor interventions to local customs and practices.

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