

# Urinary Tract Infection (UTI) and Pyelonephritis

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## **Introduction**

The topic 'renal tract infections', with all its subtopics, is huge. There is a lot of information published each year related to renal tract infections and their diagnosis and treatment. Unfortunately, there is a paucity of good quality trials and research. Much of the literature is in the form of reviews, and a lot of recommendations are not backed up with reasonable evidence. Standard practice seems to be historically based.

This document is a reasonable review of the literature and reasonably represents current evidence and views. It is by no means comprehensive: this topic itself has many Cochrane review topics in it.

Urinary tract infections affect 10-20% of women at some stage in their lifetime. The incidence of symptomatic urinary infection in men is quite low. This difference is explained by the anatomic differences between the sexes.

I have chosen the following areas for discussion.

## **Specimen collection**

The third edition of the CARPA Standard Treatment Manual recommends perineal cleansing before collection of first pass urine (FPU) and mid-stream urine (MSU) specimens. This practice is accepted as the gold standard in specimen collection by many people and aims to increase the validity of subsequent testing by minimizing perineal contamination. In clinical practice this is rarely how specimens are collected (personal observation).<sup>49</sup>

A review of the available literature reveals only a few studies in this area. Baerheim et al.<sup>1</sup> studied 864 morning urine samples from 110 female students. Each morning a different collection technique was used (holding labia apart, soap, disinfectant and saline). Only holding the labia apart decreased the contamination rate and the number of colony-forming units at culture. (Previous studies by the same authors came to similar conclusions). Morris et al.<sup>2</sup> compared specimen collection without instruction, to collection after perineal cleansing with sterile water. The results between the two groups were virtually identical. Schlaeger et al.<sup>3</sup> studied asymptomatic pregnant adolescents, comparing MSU collection before and after perineal cleansing. The results were similar for both groups. Schlaeger cites other studies that have similar conclusions. The results of a study by Winkens et al.<sup>49</sup> concludes that in practice few specimens are actually MSU, but this has no effect on urinalysis or MCS anyway.

This information suggests not only that perineal cleansing is not indicated, but perhaps also that instruction on mid-stream is not important

as it is not often adhered to. Further study needs to be done to ascertain if holding the labia apart yields better results.

Dr Lum, microbiologist with NT Department of Health and Community Services (pers. comm.), has observed that the normal flora in Indigenous women seems to vary from the non-Indigenous population. He suggests that even though perineal cleansing and mid-stream collection is not often performed, it should still be recommended until studies like the above are performed on the Indigenous population.

It would be interesting to know if contamination increased the yield of PCR testing for STI on urine samples.

### **Processing of urine specimens**

Ideally the urine needs to be plated onto the dipslide within 20 minutes of collection or be placed in the refrigerator until this can be done.<sup>52</sup> The quicker the urine is plated the more accurate the colony counts of pathogen, and the less the overgrowth of contaminants.

Microscopy is also more accurate if done within one to two hours. Cells tend to lyse if left in urine for periods longer than this, underestimating actual urine cell counts.

I did not look into whether delay in plating/cell counting has an impact on clinical decision making.

### **Urine dipstick analysis**

Leukocytes, nitrites, protein, blood and ketones can be present in UTI. Of these, leukocytes and nitrites are usually helpful diagnostically. Protein is positive usually because of increased cell counts. Blood on dipstick can be related to inflammation or false-positive. Ketones indicate starvation and an increased catabolic state from being unwell [Editor: Or marked lack of insulin].

### **Leukocytes**

The reaction reveals the presence of esterases that occur in granulocytes. False-positives can occur (vitamin C, high levels of protein/glucose/ketones).<sup>7</sup> With respect to UTI, the leukocyte esterase test has a reported sensitivity of 75-96% and specificity of 94-98%<sup>8</sup> for detecting significant pyuria. Hooten and Stamm<sup>8</sup> state that there is some evidence that this test does not perform this well in daily practice.

Note: Skov<sup>64</sup> found that the leukocyte esterase test was positive (>trace) in 50% of screening (STI) urine samples from Central Australian women, and 40% of Central Australian men. In these groups 75-87% had STI. On discussion of this issue with Knox<sup>6</sup>, she states that Tristate sexual health program and other audit information suggests that Leukocyte positivity in symptomatic individuals is a very poor discriminator in this population and should be omitted from treatment algorithms. In a female, the symptom of dysuria indicates UTI, although in the 15-40 year age group they may also have an asymptomatic STI. In a male, the symptom of dysuria is more consistent with STI, with or without leukocytes.

### **Nitrites**

The reaction reveals the presence of nitrite and therefore nitrite-forming bacteria (*E. coli*, *Klebsiella*, *Proteus*, *Staphylococcus* and *Pseudomonas*). Accuracy improves with prolonged retention of urine in the bladder (four to

eight hours).<sup>7</sup> Antibiotics should not have been taken within the preceding three days.<sup>7</sup> False-positives are seen in contaminated specimens, and false-negatives in very dilute or very concentrated urine specimens, ascorbic acid, high bacterial count, pH<6, high urobilinogen, and high specific gravity.<sup>10</sup>

There are many trials looking at sensitivity and specificity of the nitrite test for UTI. In the literature I reviewed<sup>11,12,13</sup>, sensitivity ranged from 27-39.5% and specificity from 92.9-99%. Bachellor<sup>14</sup> cites sensitivity 35-85% and specificity 92-100%. So, if the nitrite is positive, it's very likely a UTI is present, but if it is negative, the chances of UTI are still quite reasonable.

### **Diagnosis of UTI**

Kass and colleagues (1957, cited by Rubin<sup>43</sup>) did a lot of research into UTI and MSU and bacterial counts. The presence of  $>10^5$  cfu/ml of urine is widely accepted as the traditional standard for defining significant bacteriuria (sensitivity 99% and specificity 51%). Kass also noted that in a minority of patients a true bacteriuria was present with  $<10^5$  cfu/ml.

Stamm (1980, as cited by Rubin<sup>43</sup>) found that approximately 30% of women with symptoms of UTI, positive urinalysis and good response to antimicrobial treatment have true infection with  $10^2$ - $10^5$  cfu/ml. If the definition of significant bacteriuria was extended to include most of this group (i.e.  $\geq 10^3$ ), sensitivity would decrease to 90% but specificity would increase to 80%.

It is worth noting that *S. saprophyticus* is usually found in smaller numbers ( $10^2$  - $10^4$ ) when it is found to be the cause of UTI (Rubin<sup>43</sup> citing Hovelius 1979).

Bacterial counts can vary with any circumstance that alters the concentration of bladder urine, and as discussed above, with delay to plating on culture medium.

### **UTI versus STI**

The differential diagnosis of dysuria is UTI, STI and vaginitis/vulvitis. UTI and pelvic inflammatory disease (PID) can also both be associated with lower abdominal pain. In a standard population, history-taking can help identify vaginal/pelvic symptoms that make STI and vaginitis/vulvitis more likely, and UTI less likely. In the NT Aboriginal population it is my personal experience that accurate and detailed history-taking to the degree that is necessary to help differentiate between these diagnoses is mostly not possible.

Generally, the best predictor of STI risk is based on age (15-40 years old, but especially 15-25 years old).<sup>6,64</sup> According to Knox<sup>6</sup>, chlamydia and gonorrhoea may present with dysuria, but it is still more likely that a patient with dysuria has a UTI than a symptomatic STI. Hence, the best predictor of UTI in a female is dysuria, and although in the age groups above STI should be tested for (concomitant asymptomatic infection), empiric treatment should be for UTI. In a male, dysuria is predictive of STI, and should be treated as such.

Examination is limited in distinguishing between these clinical syndromes. Mild PID causes suprapubic pain, as does cystitis in at least 10% of women. Often, in remote clinics, it is impracticable (workforce issues, staff gender issues, lack of privacy in clinic examination rooms)

or unacceptable (patient refusal) to perform a full women's check-up with every presentation, to try and ascertain if cervicitis/pain on balloting the uterus is present.

### **In summary**

In the Aboriginal population, dysuria in women indicates UTI, and this is confirmed by a positive nitrite test. Negative nitrites means that the diagnosis is still UTI, but there is a small chance it could be STI. Treat for UTI, but test for STI if in the at-risk age groups. In men, dysuria indicates STI regardless of urinalysis. A UTI should be expected only if symptoms do not resolve with adequate treatment of the person and contacts.

Aside from difficulties distinguishing between STI/vaginitis and UTI, there is the added problem that they often co-exist. UTI is a common infection in any population, and seems to at least be as common in Aboriginal people. The STI rates in this population are extremely high. It is conceivable then that a patient with a symptomatic UTI may also have an asymptomatic STI.

I could find few studies (and none of significant quality) looking at UTI versus STI in causing dysuria, let alone studies in a similar patient population (with respect to disease rates and cultural aspects). Wong<sup>4</sup> performed a small study on a population of women with UTI, and compared their clinical presentation to those with gonorrhoea, chlamydia, and vaginitis. It was found that UTI was significantly associated with suprapubic tenderness (as with PID), and that there was considerable overlap between symptoms and signs in all groups. Accurate differentiation required pelvic examination, examination of vaginal fluid, and urine analysis.

Berg<sup>5</sup> similarly found no difference between the symptoms and signs of patients with STI and UTI. In this study it was also found that in those diagnosed with a UTI who had a full pelvic examination and STI screen, 53% were found to have STI when microbiological results were available. It was not clear what proportion had both UTI and STI.

Knox<sup>6</sup> (unpublished audit from Central Australia) looked at investigation and microbiological results for women presenting with abdominal pain and/or dysuria. She suggests that lower abdominal pain without dysuria is more indicative of an STI. Conclusions regarding dysuria are found above. The audit involved small numbers and was by no means comprehensive, but the most striking result was inadequate work-up of more than 50% of women presenting with genitourinary symptoms.

As noted above, Skov<sup>64</sup> found high rates of leukocyte positivity on screening urinalysis in asymptomatic individuals, with subsequent high STI rates in this group. However, as far as I am aware, there is no data relating to the predictive value of leukocytes with negative nitrites on urinalysis for STI vs UTI in symptomatic individuals (i.e. dysuria).

### **Sending MSU samples**

It is worth considering whether to recommend sending an MSU in young women with a single uncomplicated UTI where the clinical diagnosis is certain (nitrite positive on UA). The general rule is that a test should be ordered if it changes management.

Komaroff<sup>52</sup> cites a cost-effectiveness analysis showing that the small benefit of sending an MSU in this situation (that is, reduces duration of symptoms by 10%), does not warrant the increased cost (40%) of laboratory

confirmation. A large proportion of practitioners using this manual will be working remotely, and results of MSU are unlikely to have any impact on duration of symptoms as results arrive well after the fact. Even patients who fail to respond to first-line therapy are likely to re-present before results are available, and treatment with a second-line agent is likely to have been started empirically. Also, I suspect that the cost of remote collection of MSU gives less reliable results and incurs a greater cost than seen in the above study.

On the other hand, results of MSU are important in surveillance of organism prevalence and antibiotic sensitivity. Also, in a population where there is a high prevalence of STI, MSU processing is important for gonorrhoea isolates and sensitivities, to confirm dysuria is indeed from UTI rather than STI or other causes of dysuria, and also the specimen can be used for PCR testing to diagnose STI (either symptomatic or asymptomatic). It also helps in clinical audits such as the one performed by Knox<sup>6</sup> where, if investigation were complete for each patient, conclusions could be drawn on predictive value of symptoms, signs and UA. Sending an MSU on all patients presenting with dysuria would also mean a more straightforward protocol for the manual. It is also my own personal observation that MSU in symptomatic individuals are often not requested, which becomes difficult when working out who really gets recurrent UTI and should receive further attention. Perhaps the greater cost of sending an MSU on each person with symptoms could be balanced out by more clearly stating that only a pregnant asymptomatic woman should have an MSU for MCS and be treated if there is indeed evidence of infection.

For the current protocol I have recommended that an uncomplicated UTI (see below) does not need an MSU, but all others do. [Editor: This position is supported by the editorial committee for the above reasons.] This could be changed in future if there was evidence that this resulted in compromised patient care.

### **Complicated versus uncomplicated UTI**

Patients with UTI can be divided into two broad groups. There are those who are more likely to respond poorly to standard treatment regimens and have a higher incidence of severe complications (the complicated UTI), and those that are more likely to respond quickly to treatment with a very low risk of complications (the uncomplicated UTI).

There are several host factors that have been identified as markers of complicated UTI:<sup>8</sup>

- Anatomic abnormalities of the renal tract: obstruction, urolithiasis, polycystic kidney disease etc.
- Neurological disorders affecting bladder function
- Pregnancy
- Male gender
- Instrumentation: stents, indwelling urinary catheters
- Unusual or multi-resistant organisms (including hospital acquired infections)
- Chronic renal failure
- Immunosuppressive therapy or disease
- Childhood

There is some debate regarding the following groups:

- Diabetics
- Elderly women
- Postmenopausal women
- Duration of symptoms

### **Diabetics**

Some of the literature I viewed included diabetes as a host factor associated with complicated UTI. Patterson<sup>15</sup> reviewed the literature and found that bacteriuria and UTI are more common (up to threefold) in diabetic women. Pyelonephritis was also more common (up to fivefold). Hence their recommendation that people with diabetes should be included in the definition of uncomplicated UTI.

Ronald<sup>16</sup> agrees that there is an increased incidence of all renal tract infections in diabetic patients. However, he concludes that, because of the poor quality of data and the lack of trials with alternate treatment durations, most diabetics should be classified as uncomplicated UTI. He follows this recommendation with a call for more research.

Nicolle et al.<sup>17</sup> looked at hospitalisation rates for pyelonephritis in Manitoba over a three year period and found that rates among Native American women with treaty status was five to 20 times greater than those among other women, and that this difference was partially attributable to a greater frequency of pregnancy and diabetes. This study was flawed but indicates that further study needs to be done in this subpopulation. Subsequent study may be easily extrapolated to our patient population.

Data regarding hospitalisation rates for Aboriginal women in the Northern Territory was not looked at for the purpose of this document. Analysis of hospital separation data is problematic as there are multiple variables in addition to diabetes that could influence outcomes (delay to presentation, access to health care, diabetes, diabetic control, antibiotic compliance, renal disease and other co-morbidities).

The third edition of CARPA and the eleventh edition of Australian Therapeutic Guidelines: Antibiotic<sup>33</sup> don't distinguish between complicated and uncomplicated, let alone diabetic versus non-diabetic patients.

Due to the lack of good evidence, it is my recommendation that diabetics with UTI are uncomplicated unless they qualify for complicated status on other grounds. This will result in an easier protocol to follow and better compliance.

### **Elderly women**

Being elderly is often quoted as an independent risk for complicated UTI.<sup>8</sup> 'Elderly' is not defined in most articles, but Beier<sup>18</sup> implies elderly is over 65 years of age. He cites a review article by Nicolle (1992) that concludes elderly women have lower rates of eradication of UTI with any duration of therapy, and tend to fare poorly after short-course therapy.

The Cochrane review<sup>19</sup> on this topic defines elderly as over 60 years of age, and states 'Many Authors do not recommend single dose treatments in elderly women because these seem to be less effective . . . This attitude is based on either previous review articles or on results from three trials which did not specifically assess the efficacy in women over 60 years with symptomatic uncomplicated UTI'.

Institutionalised women and those with debilitating disease tend to have increased rates of UTI (Nicolle 1992, cited by Hatton et al.<sup>23</sup>). Beier points out that there are many factors that lead to nursing home residents as being classified as complicated; stroke, prior antibiotic use, bladder

catheterisation, incontinence, residual urine, decreased functional status. There may be a case for classifying nursing home residents as complicated in an effort to make CARPA guidelines more straightforward.

#### **Postmenopausal women**

Hormonally induced changes in the vaginal flora associated with menopause may play a role in UTI in older women (increased pH and decreased Lactobacilli).<sup>20</sup> This has been linked to recurrent UTI. Postmenopausal women may have a cystocele or ureterocoele, which by definition constitutes a structural abnormality of the renal tract and hence indicates complicated UTI.

There is no evidence that menopausal status alone should influence duration of antibiotic treatment. However, Naber<sup>32</sup> cites a recommendation by Raz that, in postmenopausal women with recurrent UTI (>3 episodes per year), the acute episode should be treated with a conventional treatment course.

#### **Recent UTI or recent antibiotic treatment**

'Recent' is not qualified in any of the literature.<sup>8,21,22</sup> Relapse UTI is defined as recurrence of symptoms within two weeks of finishing antibiotics. Hence 'recent antibiotic use' could also be defined as two weeks, as I assume the implications are the same (resistant infection and treatment failure). Fihn et al.<sup>55</sup> noted a UTI in the preceding six weeks was more often associated with treatment failure, possibly indicating a period as long as six weeks where more resistant infection is selected for.

#### **Duration of symptoms**

The longer the duration of symptoms, the greater the possibility of occult upper tract infection/invasive tissue infection (this is not a variable that has been studied well on its own). Hooten and Stamm<sup>8</sup> suggest symptoms longer than seven days identifies patients at higher risk of complication/treatment failure. They use this cut-off in their own randomised trial of three-day antimicrobial treatment in uncomplicated cystitis in women.<sup>58</sup> Caron and Humbert<sup>24</sup> suggest infection longer than four days indicates complicated UTI (based on Nicolle). Bump<sup>30</sup> sits between, recommending that infection longer than five to seven days be regarded as complicated infections (five references cited). Komaroff<sup>52</sup> recommends greater than seven to ten days be regarded as complicated UTI.

Rubin et al.<sup>54</sup> used antibody-coated bacteria (ACB) as an indicator of occult upper tract infection when comparing short-course versus conventional-course antibiotics. Those positive for ACB were excluded from the study but it was noted that ACB-positive patients had a significantly longer duration of symptoms, had less access to medical care and more severe symptoms at presentation. However, I did not look at the validity of ACB in diagnosing occult upper tract infect

#### **Temperature**

With respect to pyelonephritis, Hoang and Pollack<sup>48</sup> use a temperature above 38.8°C as an indicator of severe pyelonephritis. There was no other discussion about this issue in the literature reviewed.

## **Infecting organisms**

A report in the Australian Family Physician<sup>25</sup> based on data from 1993 National Antimicrobial Resistance Surveillance Program (28 laboratories from around Australia) found:

<b>Uncomplicated UTI</b>	(% of total)
<i>E. coli</i>	80-90%
<i>S. saprophyticus</i>	5-15%
Other	<i>Klebsiella</i> , <i>Enterobacter</i> , <i>Proteus</i>

Complicated UTI (no percentages available)

*E. coli*, *Proteus*, *Pseudomonas*, *Klebsiella*, *Enterobacteria*, *Serratia*.  
*Enterococci* and *Staphylococcus* are more likely multi-resistant

Pyelonephritis

*E. coli*

Note 1: Central Australian Children/Adult data 2001 from THS<sup>26</sup> found *E. coli* 85%, *S. saprophyticus* 5.2%, *Klebsiella* 1.3%, *Enterobacteria* 3.9%, *Proteus* 2.6%.

Note 2: Western Diagnostic Pathology MSU Isolates from an Alice Springs Aboriginal Medical Service (CAAC) in 2001<sup>27</sup> found: *E. coli* 85%, *S. saprophyticus* 4.7%, *Klebsiella* 2.2%, *Enterobacteria* 2.2%, *Proteus* 2.2%

## **Sensitivity to antibiotics of the infecting organisms**

The antibiograms presented are from DHCS laboratory data for Central Australia<sup>28</sup>, DHCS NT-wide data for 2000, and Western Pathology data for CAAC 2001.<sup>27</sup> It is worth noting that it is not routine practice for MSU to be sent on all patients with potential UTI, and an MSU is more likely to be sent in the cases of a recurrent or resistant infection. Also, the DHCS 2000 NT-wide data predominantly includes urine samples from hospital in-patients. Hence these results are an indication only of what is seen in the primary care setting and should be interpreted cautiously.

It should also be noted that even organisms seen to be resistant on Kirby-Bauer disk testing in vitro, can still be sensitive to the very high urinary concentrations of antibiotic in vivo.<sup>52</sup>

### **Resistance (per cent)**

<i>E. coli</i>	Ampi/amoxicillin	53-70%
	Trimethoprim	23-41%
	Cephalexin	1.0-1.5%
	Amoxicillin/clavulanate	1.0-1.5%
	Gentamycin	4.0-5.5%
<i>S. saprophyticus</i>	Trimethoprim	85%
<i>Klebsiella</i>	Ampi/amoxicillin	100%
<i>Proteus</i>	Nitrofurantoin	100%
<i>Enterococci</i>	Cephalexin	100%

## **Natural history of UTI**

There is evidence of spontaneous resolution of UTI in up to 40% of cases (20-40 year old age group).<sup>23</sup> Naber<sup>32</sup> discusses the few placebo-controlled

studies and concludes that 20-50% of patients become asymptomatic within one week. Hooten and Stamm<sup>8</sup> suggest that 50-70% of lower UTI clear spontaneously, although symptoms may persist for several months. This conclusion was based on information from two studies (1972, 1984). They also cite a placebo-controlled study by Asbach (1991) that showed 26% of women on placebo treatment cleared their bacteriuria at two weeks (nil information on symptoms, complications, further follow-up).

### **Which antibiotic to use: Pyelonephritis**

In contrast to lower urinary tract infection there has been less study of treatment options for pyelonephritis.<sup>31, 45, 34, 47, 8</sup>

The ideal antibiotic is bacteriocidal with high penetration and concentration in both urine and renal tissue.<sup>45</sup> The choices therefore are aminoglycosides, penicillins/clavulanate, monobactams (aztreonam), carbapenems (imipenem), cephalosporins (third generation, although second generation is acceptable in areas where resistance is low<sup>38</sup>), flouroquinolones, trimethoprim/sulphamethoxazole. Nitrofurantoin does not satisfy these criteria.

Tolkoff-Rubin and Rubin<sup>34</sup> recommend that empiric therapy for pyelonephritis must cover >95% of possible infecting organisms. Hence, ampicillin alone is not appropriate. All the other agents listed above fulfill this criterion. It is worth noting that in acute uncomplicated community-acquired pyelonephritis, Enterococcus is very uncommon.<sup>50</sup>

As far as the length of therapy goes, most clinicians continue IV therapy until afebrile then switch to oral therapy. Up to 12% of patients are bacteraemic - bacteraemia does not attribute a worse prognosis, and blood cultures rarely change treatment and are therefore not routinely recommended.<sup>8</sup> There is no evidence to guide optimal IV treatment lengths. The duration of therapy in total is usually two weeks. Again, there is little evidence upon which to recommend an appropriate total treatment time so it stands that, until research is done, two weeks is standard practice. It has been noted that in severe cases of pyelonephritis, two-week therapy is associated with up to 50% relapse. Four to six weeks of therapy is associated with >95% cure rates but with higher side effects.<sup>34</sup>

Warren et al.<sup>47</sup> made recommendations on behalf of the Infectious Diseases Society of America. Based on available evidence they recommend:

Two weeks' treatment appears to be adequate for most women (A,I)

1. Mild cases can be managed with oral treatment - Flouroquinolone (A,II), co-trimoxazole (B,II) or amoxicillin/clavulanate if organism is gram positive (B,III).
2. Severe cases should be admitted to hospital (A,II) for parenteral therapy - flouroquinolone, aminoglycoside +/- ampicillin, third generation cephalosporin +/- aminoglycoside (B,III).

It should be noted that, in Australia, first-line treatment with a flouroquinolone is unacceptable due to concerns regarding emerging resistance with widespread use, and cost.

The eleventh edition of the Australian Therapeutic Guidelines: Antibiotic<sup>33</sup> recommends:

1. For mild to moderate infection, oral treatment with cephalixin, amoxycillin/clavulanate or trimethoprim (duration: two weeks).

2. For severe infection, parenteral therapy with ampicillin and gentamycin, or ceftriaxone.

In view of the resistance patterns detailed above, trimethoprim is not a valid choice. For severe pyelonephritis diagnosed remotely it would be quite acceptable to give IV or IM either gentamycin or ceftriaxone stat while awaiting transfer. Ceftriaxone is a little more expensive, and needs to be mixed with lignocaine for intramuscular administration, but is acceptable and effective as a first-line option, with the advantage over other cephalosporins being its longer half-life. Dr Lum, Microbiologist for DHCS (pers. comm.), notes that a lot of ceftriaxone is used in the NT and perhaps cephalosporins is a better choice. A drawback of cephalosporins is the need for eight-hourly dosing, which may compromise treatment if the patient is delayed in getting to hospital. Perhaps this is an issue better addressed in the hospital setting.

### **UTI in men**

A UTI in a male is by definition a complicated infection. Most infections are associated with urological abnormalities, bladder outlet obstruction or instrumentation. Anatomical features of the male urinary tract protect from UTI (that is, a long urethra). There are a small number of 15-50-year-old men who suffer acute uncomplicated UTI. Factors associated with this include homosexuality, intercourse with an infected partner, and lack of circumcision (as cited in Hooten and Stamm<sup>8</sup>).

Due to the low frequency of UTI in men, good quality treatment trials are non-existent.<sup>8</sup> Hence, most reviews recommend empiric use of antibiotics as for complicated UTI or pyelonephritis. Nitrofurantoin should not be used in men as it doesn't achieve reliable tissue concentration and hence is not useful in occult prostatitis or pyelonephritis.

Recommendations regarding length of therapy vary. Hooten and Stamm<sup>8</sup> suggest an initial seven days of treatment. Other authors<sup>14,23,33</sup> suggest between seven and 14 days. All agree that relapse needs investigation for pyelonephritis/prostatitis/epididymitis and treatment for four to six weeks (or up to three months in the case of chronic prostatitis<sup>14</sup>).

### **Further investigation in a male**

All men, after proven UTI, should be investigated for renal tract abnormalities or occult tissue infection (e.g. rectal examination for prostatic hypertrophy, culture of prostatic secretions, renal tract imaging US/IVP).<sup>14</sup> Hooten and Stamm<sup>8</sup> suggest this is not necessary in those with no obvious complicating factors with single uncomplicated UTI. Lipsky (cited by Stamm<sup>31</sup>) notes that urological evaluation in young men who respond to therapy is usually unrewarding.

Proteus UTI is associated with infected stones. All cases with a proteus UTI should receive appropriate treatment and subsequent imaging of the renal tract for stones.

### **Further investigation in a female**

Most women with recurrent uncomplicated UTI have no anatomic abnormality of the renal tract and therefore do not need an evaluation of their urinary tract.<sup>8,12</sup> Clinical suspicion of a complicating factor increases the yield of further investigation.

Similarly, further investigation of a young female with acute uncomplicated pyelonephritis is not cost-effective and has a low diagnostic yield (Johnson 1992, as cited by<sup>8</sup>). It is rare to find urological abnormalities in those who respond promptly to antimicrobial therapy (personal observation<sup>8</sup>). Some practitioners recommend a follow up MSU two weeks after antibiotic cessation<sup>50</sup>, but this doesn't seem to be based on any evidence. It would also be reasonable to image the urinary tract if pyelonephritis became a recurrent problem.

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## **Other therapies**

### **Hydration<sup>35</sup>**

Theoretically, dilution of microbes and frequent micturition should aid in recovery from UTI. However, antimicrobial concentrations and host bacterial response may also be diluted. There is limited trial information on this issue.

### **Urine acidification<sup>35, 23</sup>**

Acidification is antibacterial. Urine acidification is difficult to achieve and maintain and is therefore rarely attempted. It should be noted that high-dose ascorbic acid is associated with the formation of urate stones.

### **Urinary alkalinisation**

Urinary alkalinisation is used widely for 'symptom relief'. There is little trial evidence to support its use. Brumfitt et al.<sup>36</sup> found no correlation between pH and the incidence of symptoms of UTI, number of symptoms, symptomatic vs asymptomatic bacteriuria, and significant vs insignificant bacteriuria. This information casts doubt on the place of urinary alkalinisation in the treatment of UTI.

## **Asymptomatic bacteriuria**

Asymptomatic bacteriuria is the presence of  $>10^5$  CFU of a bacterial species on mid-stream urine, without symptoms or pyuria. The incidence of asymptomatic bacteriuria varies with age and sex. The incidence in schoolgirls is 1-2%, sexually active females 2-4%, over 60-year-old women 6-8%, over 80-year-old women  $>20\%$ , institutionalised women 30-50%. For males, childhood to middle age  $<1\%$ , over 60 year old men 1-3%, over 80-year-old men  $>10\%$ , institutionalised men 20-40%.<sup>21</sup>

Approaches to asymptomatic bacteriuria are varied. The concern with asymptomatic bacteriuria is progression pyelonephritis. The concerns with treatment are lack of evidence of benefits with respect to morbidity and mortality, the transient results, and emergence of resistance. The only population where treatment has decreased the incidence of complications is in pregnant women<sup>27</sup> - there is widespread agreement that in pregnancy asymptomatic bacteriuria should be screened for and treated if found. Another population where there seems to be widespread agreement on management is to not treat the institutionalised elderly.<sup>19</sup> Treatment of this group is associated with no change in mortality and treatment failures, and recurrences are common.<sup>35, 38</sup>

Opinions otherwise vary. Bachellor<sup>14</sup> recommends treatment in those with structural abnormalities of the renal tract, renal impairment, mechanical heart valves or joint prostheses, immunosuppressed patients and prior to instrumentation of the urinary tract. Korman and Grayson<sup>25</sup> suggest that pregnant women and men <50 years old should definitely be treated, but not the elderly. Auchenthaler<sup>21</sup> recommends not looking for it, and not treating it (the exception being pregnancy). Lutters and Vogt<sup>19</sup> state in the introduction to a Cochrane review on treatment of UTI in elderly women that ' . . . there is consensus in the medical literature that elderly patients without symptoms should not be treated'. Nicolle<sup>37</sup> feels that there is not sufficient evidence to make recommendations either way regarding screening for, or treatment of, asymptomatic bacteriuria.

### **Recurrent UTI**

Recurrent UTI is defined as three or more infections per year. Approximately 20% of young women with their first UTI will have a recurrent infection.<sup>31</sup> Only rarely do patients have an underlying renal tract abnormality (see above). The ongoing use of diaphragm with spermicide is associated with recurrences, possibly because spermicide promotes E.coli colonisation of the vagina. Other risk factors include<sup>39</sup> more than four episodes of sexual intercourse per month, a new sexual partner within the preceding 12 months, maternal history of recurrent UTI, first UTI at <15 years old, and shorter distance between urethra and anus. Of note, voiding patterns (e.g. after intercourse), bacterial vaginosis, STIs, douching, wiping patterns, tub bathing, types of underwear worn and lifetime sexual partners were not associated with recurrent UTI.

Raz et al. (as cited by<sup>31,39</sup>) found that in postmenopausal women anatomical differences are important. The presence of incontinence, residual urine and history of UTI before menopause were identified as risk factors. Also, in postmenopausal women, the lack of oestrogen results in a change in the vaginal normal flora with loss of lactobacilli and colonisation by E. coli.<sup>20</sup>

The management of recurrent UTI can take several forms.<sup>35, 25, 41, 39</sup>

- Intermittent (self) treatment of the acute infection (antibiotics according to the patient's individual status as complicated or uncomplicated)
- Continuous low-dose antibiotic prophylaxis e.g. trimethoprim 150 mg daily, cephalexin 250-500 mg daily, nitrofurantoin 50-100 mg daily
- Post-coital prophylaxis (stat dose of antibiotic e.g. trimethoprim 300 mg)
- Hormonal support (vaginal oestrogen)<sup>20</sup>

It should be noted that antibiotic prophylaxis is safe for periods of up to over five years. Once prophylaxis has ceased, most women revert back to experiencing recurrent infections.

### **A note on cranberries**

A Cochrane review exists regarding the place of cranberry products in the prophylaxis of recurrent UTI.<sup>44</sup> The authors conclude ' . . . the small number of poor quality trials gives no reliable evidence of the effectiveness of cranberry juice and other cranberry products. The large number of dropouts/withdrawals indicates that cranberry juice may not be acceptable over long periods of time . . . Cranberry juice cannot be recommended for

the prevention of UTI . . . Further properly designed trials with relevant outcomes are needed'.

### **Which antibiotic regimen?**

When choosing an antibiotic regimen, the following questions need to be addressed:

Which antibiotic?

This is mostly covered above because it is primarily decided by sensitivity data from Kirby-Bauer disc testing in the laboratory on MSU specimens from a representative population. As discussed above, in vivo and in vitro sensitivities vary in lower UTI because the antibiotics used achieve extremely high urinary concentrations. The general rule is that once resistance to an antibiotic by an organism is greater than 20%, treatment failure rates become too high for further use to be acceptable. Hence it seems that trimethoprim's days are over! Bump<sup>30</sup> reviewed single-dose treatment trials and found that many trials excluded patients with resistant organisms. Of the studies that didn't, some showed lower cure rates and others no significant difference (it should be noted, however, that there seems to be general agreement that most studies of single-dose therapy lacked sufficient power to draw accurate conclusions<sup>61</sup>). Hence, in the absence of specific trials that test the effectiveness of an antibiotic regardless of laboratory sensitivity, or until a new method of testing urinary pathogens for antibiotic sensitivity that takes into account this discrepancy is developed, these rules should be adhered to.

Antibiotic cost and the possibility of emerging resistance is also considered when choosing an antibiotic. This is especially the case where the flouroquinolones are involved.

What dose?

The main issue here is whether a lower overall dose and/or decreased frequency of daily dosing can be used to minimize side effects and improve treatment compliance. These changes can be made because of the fact that the antibiotics used achieve extremely high urinary concentrations. An example is twice-daily dosing of cephalexin<sup>60</sup>, nitrofurantoin 50 mg three times per day.<sup>57</sup>

What duration?

Single dose, short course (three days), conventional (five to seven days) or long (two weeks)? The duration has to be sufficient to have high cure rates and low relapse rates but also not so long that compliance and side effects are an issue. For high cure rates and low relapse rates, the duration must be sufficient to cover occult upper tract infection and vaginal/rectal colonisation by the pathogenic organism.<sup>22</sup> Up to 30% of patients with a clinical lower UTI are thought to have subclinical upper tract involvement.<sup>31, 34, 54</sup> Laboratory techniques for the non-invasive evaluation of anatomic site of infection have not proved sensitive enough to be useful in clinical practice<sup>34</sup>, so it remains impossible to identify this group of patients at the outset. Of the common antibiotics used in lower UTIs, it is worth noting that nitrofurantoin achieves poor tissue levels and performs poorly in upper tract/invasive tissue infections (e.g. prostatitis). However, it has performed well in clinical trials and remains a valid first-line option.

Stamm<sup>22</sup> discusses antibiotic performance with respect to elimination of pathogenic organisms from the vaginal/rectal reservoir. Further study needs to be done but it appears that trimethoprim and the flouroquinolones are concentrated in vaginal secretions. Some trials have evaluated vaginal and fecal carriage (as cited by Stamm<sup>22</sup>) and show that trimethoprim, trimethoprim/sulphamethoxazole and flouroquinolones effectively eradicate pathogenic organisms from these areas after three to 10 days' treatment. Beta-lactams and nitrofurantoin do not. Also, the former group of antibiotics has little impact on normal flora (anaerobes and lactobacilli), whereas the latter group can eradicate normal flora. Further study needs to be done to look at the significance of these points.

Compliance remains an issue and it is observed that particularly in the setting of UTI, patients often discontinue medication after symptoms subside (average three to four days). Compliance is approximately 75% for seven day treatment<sup>59</sup> (author states similar results in other studies).

#### **A note on single-dose therapy**

The advantages of single-dose therapy are cost, compliance and lower side effect profile. Single-dose therapy was widely evaluated in the 1970s and 80s with promising results. Amoxicillin and amoxicillin/clavulanate overall fared poorly, but trimethoprim, trimethoprim/ sulfamethoxazole and the flouroquinolones showed very promising results. Note that in the 1970s and 80s resistance to trimethoprim was extremely low.<sup>60</sup> Subsequently, reviewers have concluded that a majority of studies were of insufficient power due to small numbers and, to a certain degree, poor methodology.<sup>61,22,53</sup> When the few reasonable trials are compared with trials of longer duration, it seems that single-dose therapy is generally less effective than the same antibiotic used for longer duration.<sup>60,61</sup> This difference was less pronounced for trimethoprim. When patients have proven lower tract disease (patients selected with invasive or non-invasive localisation techniques), cure rates are >90-95%.<sup>63</sup> However, in clinical practice localisation isn't practical (see above). When relapse rates are significant, cost increases, because of the management of the relapse. Some authors have proposed single-dose therapy as a diagnostic tool for occult upper tract infection<sup>54,22</sup>, thereby identifying those that need treatment for mild pyelonephritis. This approach has not been integrated into clinical practice!

Past trials of single-dose therapy have focused mainly on trimethoprim, beta-lactams, nitrofurantoin and some study of flouroquinolones. There may still be a place for single-dose therapy in the future when flouroquinolones are indicated as first-line agents (e.g. increasing resistance levels to other agents), or with other poorly studied agents such as gentamycin or fosfomycin trometerol.

#### **A note on short-course therapy (three days)**

Again, short-course therapy has advantages of lower cost, better compliance and lower side effects compared to conventional course, with better results than single-dose therapy. Trimethoprim performs particularly well with three-day treatment having equivalent cure rates to seven-day treatment (1989)<sup>59</sup>, and it being superior (six-week cure rate 82%) to three-day treatments with amoxicillin, first generation cephalosporin, and nitrofurantoin (six-week cure rates 61-68%, 1991).<sup>58</sup> However, as noted above, sensitivities have changed since 1989-91 and trimethoprim may not perform so well overall today.

### **Notes on individual antibiotics**

**Amoxycillin.** Small trials in the 1970s showed great promise for single dose amoxycillin, but larger trials in the 1980s were less convincing with cure rates 60–80%. Longer durations of treatment improved cure rates but the rates remained inferior to trimethoprim.<sup>8</sup> Resistance since that time has been steadily climbing. Stamm<sup>22</sup> concludes that the lesser therapeutic effectiveness of amoxycillin is only partly explained by resistance, and proposes that the short urinary half-life (18 hours) may also be a factor. There is also the effect of this antibiotic on normal flora and the vaginal/rectal reservoir as discussed above. The precise role of each of these factors in the poor performance of amoxycillin is unknown.

Amoxycillin is no longer recommended for first-line use in UTI due to its failure rate and increasing resistance, and is not recommended in this protocol.

**Amoxicillin/clavulanate.** I ended up with little data on amoxicillin/clavulanate. Johnson and Stamm<sup>50</sup> reviewed two studies (details unknown) that had favorable cure outcomes but high frequency of side effects. Also, there was evidence for selection of resistant organisms in subsequent episodes of UTI. They conclude that the side effects and cost preclude it as a first-line agent. The paucity of trials indicates that further investigation into the exact place of amoxicillin/clavulanate in UTIs needs to be further evaluated, especially in the face of increasing resistance to trimethoprim. The Australian Therapeutic Guidelines: Antibiotic (TGA) recommends amoxicillin/clavulanate as first-line treatment as a five-day course.<sup>33</sup> In view of cost, side effects, availability of other agents and the remaining uncertainty about efficacy, I have recommend amoxicillin/clavulanate only for complicated UTI in the full-length course.

**Cephalosporins.** Cephalosporins have similar urinary half-lives, urinary concentrations and modes of action to amoxycillin. In the past they have not performed nearly so well as trimethoprim in treatment of any duration. Also, the longer the treatment course, the better the cure rates.<sup>60</sup> The current CARPA manual recommends three-day treatment with twice-daily cephalexin. The current TGA recommend five-day treatment with twice-daily cephalexin<sup>33</sup>, but fails to distinguish between complicated and uncomplicated infection. Cephalexin is pregnancy category A. Trials have been performed using multiple different dosing regimens, and twice-daily dosing for three days achieves reasonable cure rates. Hence, for uncomplicated UTI, I have not changed the recommendation of cephalexin from the previous CARPA manual.

**Trimethoprim.** Unfortunately trimethoprim is no longer a first-line agent because of decreasing sensitivity.

**Nitrofurantoin.** Nitrofurantoin does not achieve adequate urinary levels when the creatinine clearance is <40 ml/min, and serum concentrations increase causing problems in toxicity.<sup>23</sup> Hence, it should not be used in renal impairment/failure. It also achieves poor tissue levels and should not be used in upper tract infections and invasive disease (see above). Warren et al.<sup>47</sup> predict that nitrofurantoin will become an important agent with increasing resistance to trimethoprim, and I agree. Bailey<sup>57</sup> cites studies that have shown that lower doses of the macrocrystalline form of nitrofurantoin are as effective as higher doses, with less side effects

(that is, 50 mg three times daily compared with 100 mg four times daily). Nitrofurantoin performs reasonably well in short-course, but a five- to seven-day course is superior.<sup>32</sup>

**Norfloxacin/Fluoroquinolones.** Personal feedback from microbiologists and infectious disease physicians, and also TGA recommendations<sup>33</sup>, supports the recommendation that these agents not be used as first-line agents in the treatment of UTI.

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