Urinary Tract Infections in Patients with Chronic Renal Insufficiency

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Despite an increasing population of patients with chronic renal insufficiency, the literature on the management of urinary tract infections (UTI) in these patients is sparse. Patients with underlying diabetes are a specific population at risk. Antimicrobial treatment of UTI requires adequate serum, renal, parenchymal, and urine concentrations of drugs with antibacterial activity versus the etiologic organism. Sulfamethoxazole and nitrofurantoin are examples of drugs with low and likely inadequate urine concentrations in patients with creatinine clearances of <50 ml/min. Urine concentrations of ciprofloxacin and levofloxacin remain sufficient as renal function fails, whereas the concentrations of gemifloxacin and moxifloxacin are too low to predict efficacy. More investigative work is needed in the management of UTI in patients with poor renal function.

There are more than 7 million uncomplicated urinary tract infections (UTI) per year in the United States (1). The total includes more than 250,000 episodes of acute pyelonephritis per year. The incidence in patients with chronic renal insufficiency is unclear.

The management of UTI in patients with chronic renal insufficiency has attracted little to no attention. An in-depth electronic literature review identified only one publication that addressed the subject (2). There are a few studies of the treatment of infected polycystic kidneys (3,4). This is despite large numbers of patients with GFR between 10 and 50 ml/min as a result of diabetes, hypertension, and other disease entities. UTI in these patients seems not to be a problem that is sufficient to generate academic interest. This article highlights and comments on the issues that are involved in the management of UTI in patients with chronic renal insufficiency.

The Issues

Epidemiology

After adjustment for age, the frequency of UTI in patients with chronic renal insufficiency is not known to be different from that in the general population. On the one hand, the chronic disease that causes the renal insufficiency could reduce the risk for UTI as a result of reduction of risk factors such as sexual activity. Alternatively, the risk might be increased by disease factors (e.g., papillary necrosis, nephrolithiasis, neurogenic bladder) and the management of comorbidities with Foley catheters and intravenous lines. No literature that addressed this question was found.

There is documentation of increased risk for UTI in female patients with diabetes (5–8). Asymptomatic bacteriuria in women with diabetes is roughly three-fold greater than in women without diabetes, regardless of the degree of control of the hyperglycemia (9). Women with diabetes are more prone to severe cystitis, ascending pyelonephritis, and severe forms of pyelonephritis (e.g., perinephric abscess, papillary necrosis) (9). Despite the frequency of renal impairment as a result of diabetes, suggested treatment in such patients has not been a focus of published literature.

Types of UTI and Treatment Implications

The comments that follow focus on urethritis, cystitis, and pyelonephritis. The management of asymptomatic bacteriuria, chronic Foley catheter–related bacteriuria, and prostatitis is not discussed.

A long-standing issue is whether UTI represent surface mucosal (uroepithelial) or parenchymal infections or both. Infections of the urethra are viewed as superficial, whereas pyelonephritis is considered a parenchymal infection. Cystitis ranges from mild (superficial) to invasion of the wall of the bladder. So, which is more important: Adequate urine or serum concentrations of antimicrobial agents?

Data from UTI in animal models are helpful. High urine drug concentrations are necessary to sterilize urine; for pyelonephritis, it is necessary to have effective tissue concentrations of the antimicrobial agent. The serum concentrations of anti-infectives correlate with the drug concentration in renal tissue (10). Glomerular filtration ± net tubular secretion determines urine concentration. Thus, for patients who have renal insufficiency with therapeutic serum drug levels and adequate arterial perfusion of the renal parenchyma, the delivery of therapeutic
drug concentrations to both the parenchyma and the urine should not be a problem. For patients with chronic insufficiency and cystitis, there is a possibility that the urine drug concentration may be too low to eradicate the etiologic organism.

Management
Pyelonephritis

General principles apply regardless of the GFR. Blood cultures and an uncontaminated urine specimen are collected and submitted for culture and sensitivity. Obstruction of the urine collecting system by stone, tumor, stricture, necrotic renal papillae, or other pathology is considered and excluded.

The selection of the drug for empiric therapy is based on efficacy versus the likely infecting organism plus the patient’s allergy history, drug toxicity profile, drug excretory pathway, drug cost, and other factors. *Escherichia coli* remains the most common pathogen for both outpatients and hospitalized patients (11,12). Enterococci and other aerobic Gram-negative bacilli (e.g., *Klebsiella, Enterobacter, Proteus* species) constitute the bulk of the non–*E. coli* infections. The increasing resistance of *E. coli* and *Klebsiella* species to penicillins and cephalosporins as a result of the production of extended-spectrum β-lactamases is noteworthy (13). *Pseudomonas aeruginosa* is usually encountered in patients with chronic indwelling Foley catheters or patients with complicated UTI. Activity versus *Staphylococcus saprophyticus* is important for patients with cystitis/urethritis.

The Gram stain of the well-mixed but uncentrifuged urine can be helpful. Detection of one or more bacteria per high-power field correlates with a bacterial density of >100,000 bacteria/ml urine (14). Furthermore, it is often possible to distinguish between Gram-positive cocci (e.g. enterococci), large Gram-negative bacilli (e.g., *E. coli*), small Gram-negative bacilli (e.g., *P. aeruginosa*), and yeast.

At present, the recommended empiric therapy is a fluoroquinolone that achieves both adequate serum and urine concentrations. Hence, moxifloxacin or gemifloxacin should not be used because of their low urine concentrations (Table 1). The dose of drug is adjusted for the degree of renal insufficiency as suggested by the drug package insert or standard reference sources (15,16). The primary goal is to achieve predictably effective serum and urine concentrations. Ciprofloxacin urine concentrations, 24 h after an adjusted dose, are reported as above the minimum inhibitory concentration (MIC) of urinary pathogens in patients with a creatinine clearance of <50 ml/min (17,18).

Trimethoprim-sulfamethoxazole is often administered for uncomplicated pyelonephritis in young women. However, for reasons described below, trimethoprim-sulfamethoxazole may not be effective in patients with renal insufficiency.

The fluoroquinolones do not have predictable efficacy versus enterococci. If enterococcal infection is suspected on the basis of the urine Gram stain, positive blood culture, or other factors, then empiric therapy with piperacillin-tazobactam, ticarcillin-clavulanate, or ampicillin-sulbactam is suggested. For severely penicillin-allergic patients, vancomycin is reasonable. Daptomycin, although not licensed to treat UTI, does achieve high urine concentrations.

In the bacteremic patient with septic shock, an empiric carbapenem (imipenem or meropenem) is reasonable because of the high level of predictive efficacy versus *E. coli*, other Enterobacteriaceae, many enterococci, and *P. aeruginosa*. Ertapenem is another option with the caveat that ertapenem does not have predictive activity versus *P. aeruginosa* or *Enterococcus* species (18).

Patients with polycystic renal disease and infected cysts are a special population. Published reports indicate that effective concentrations of trimethoprim-sulfamethoxazole, ciprofloxacin, and chloramphenicol can be achieved in the cyst fluid (3,4). In contrast, penicillins, cephalosporins, and aminoglycosides do not achieve adequate cyst concentrations (19).

Specific management depends on the culture and sensitivity results plus the ability to resolve underlying or associated comorbid states. For “uncomplicated” pyelonephritis in young women, 7 d of therapy with an effective fluoroquinolone is as effective as 14 d of trimethoprim-sulfamethoxazole (20). The appropriate duration of fluoroquinolone therapy in patients with renal insufficiency is unknown. There are no duration studies with β-lactams; the penicillins, cephalosporins, and carbapenems are generally given for 14 d, especially when accompanied by bacteremia.

In short, the management of pyelonephritis in patients with GFR in the 10- to 50-ml/min range requires only reduction of dosage to avoid high serum concentrations and the concomitant increased risk for concentration-dependent adverse drug events. Ciprofloxacin or levofloxacin are suggested as first choices for empiric therapy.

Cystitis/Urethritis

With the import of adequate urine drug concentration as a significant factor in success in treating urethritis and cystitis, I contacted several pharmaceutical manufacturers with drugs that are licensed as safe and effective for the treatment of UTI. The companies indicated that their UTI-controlled studies excluded patients with impaired renal function. None of the respondents had data on urine drug concentrations in patients with renal insufficiency; none of the companies had data on clinical or bacteriologic response rates stratified by the degree of renal insufficiency.

There are published data on the urine concentrations of antimicrobials in patients with normal renal function (Table 1) (21–23). With normal renal function, filtered drug is concentrated many-fold such that urine concentrations can reach many thousands of micrograms per milliliter. The MIC for 90% of the bacteria that commonly cause UTI is usually <16 μg/ml. Hence, there is a large safety range as long as the kidney can concentrate urine to some degree. Even though it is unlikely that cystitis would require parenteral therapy, it is pertinent to comment on the data in Table 1.

Urine drug concentrations can be hard to interpret. Urine is collected over variable time periods, and the concentration measured reflects an average for the time involved (23). Renal excretion is also measured as the percentage of unchanged drug excreted over 24 to 48 h rather than as an average concentration. In addition to drug concentration, urinary pH and
osmolality can affect antibacterial efficacy in urine, especially of aminoglycosides (24).

All of the penicillins listed in Table 1 achieve high urine concentrations, and it is unlikely that subtherapeutic levels would occur in patients with renal insufficiency. Recall that reports indicate an inferior performance of amoxicillin-clavulanate as compared with ciprofloxacin in the treatment of uncomplicated cystitis in women (25).

Although active in vitro versus E. coli, none of the four oral cephalosporins listed has Food and Drug Administration approval for UTI. Note that percentage of renal excretion for all four is <50%.

Cefazolin and ceftriaxone achieve very high urine concentrations; hence, subtherapeutic concentrations with renal insufficiency is unlikely. Imipenem and ertapenem are approved for the treatment of UTI, whereas meropenem is not. Imipenem requires the presence of cilastatin to maintain therapeutic drug concentrations. For both imipenem and ertapenem, no more than 40% of a dose is present in the urine of patients with normal renal function. Even though the drugs’ MIC may be low, in patients with renal insufficiency, the urine concentrations may not be adequate and should be studied.

Among the fluoroquinolones, attention is focused on gemifloxacin and moxifloxacin. Both have low urine concentrations and are not indicated in the treatment of UTI in patients with normal or abnormal renal function. In contrast, ciprofloxacin and levofloxacin achieve high urine concentrations with oral or parenteral therapy. Of interest, there is documentation of the posttreatment isolation of a fluoroquinolone-resistant E. coli from the feces of a patient who was treated for cystitis (26). In

### Table 1. Serum and urine concentrations of selected antimicrobials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose, Route</th>
<th>Excretion via</th>
<th>Peak Serum Concentration (μg/ml)</th>
<th>% Renal Excretion of Unchanged Drug</th>
<th>Urine Concentration (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactams</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ampicillin</td>
<td>0.5 g p.o.</td>
<td>GF, TS</td>
<td>3 to 6</td>
<td>75 to 92</td>
<td>1000 to 2250</td>
</tr>
<tr>
<td>amoxicillin</td>
<td>0.5 g p.o.</td>
<td>GF, TS</td>
<td>6 to 10</td>
<td>60 to 98</td>
<td>300 to 1300</td>
</tr>
<tr>
<td>aztreonam</td>
<td>1 g IV</td>
<td>GF, TS</td>
<td>125</td>
<td>65 to 94</td>
<td>1000 to 5000</td>
</tr>
<tr>
<td>piperacillin</td>
<td>3 g IV</td>
<td>GF, TS</td>
<td>209</td>
<td>74 to 89</td>
<td>8000</td>
</tr>
<tr>
<td>ticarcillin</td>
<td>3 g IV</td>
<td>GF, TS</td>
<td>257</td>
<td>80 to 99</td>
<td>650 to 2500</td>
</tr>
<tr>
<td>cephalixin</td>
<td>1 g p.o.</td>
<td>GF, TS</td>
<td>32</td>
<td>91 to 100</td>
<td>5000 to 10,000</td>
</tr>
<tr>
<td>cefuroxime</td>
<td>1 g p.o.</td>
<td>GF, TS</td>
<td>14</td>
<td>50</td>
<td>1000 to 7000</td>
</tr>
<tr>
<td>cefixime</td>
<td>0.2 g p.o.</td>
<td></td>
<td>1 to 4</td>
<td>20 to 50</td>
<td></td>
</tr>
<tr>
<td>cefdinir</td>
<td>0.3 g p.o.</td>
<td></td>
<td>1.6</td>
<td>18</td>
<td>21 to 139</td>
</tr>
<tr>
<td>cefpodoxime</td>
<td>0.2 g p.o.</td>
<td></td>
<td>2.3</td>
<td>29 to 33</td>
<td>20</td>
</tr>
<tr>
<td>cefazolin</td>
<td>1 g IV</td>
<td>GF, TS</td>
<td>188</td>
<td>90 to 96</td>
<td>700 to 2000</td>
</tr>
<tr>
<td>ceftriaxone</td>
<td>1 g IV</td>
<td>GF</td>
<td>130</td>
<td>65 to 95</td>
<td>549 to 995</td>
</tr>
<tr>
<td>imipenem</td>
<td>0.5 g IV</td>
<td>GF, TS</td>
<td>21 to 58</td>
<td>5 to 42</td>
<td>500</td>
</tr>
<tr>
<td>meropenem</td>
<td>1 g IV</td>
<td>GF, TS</td>
<td>50</td>
<td>62 to 83</td>
<td>N/D</td>
</tr>
<tr>
<td>ertapenem</td>
<td>1 g IV</td>
<td></td>
<td>154</td>
<td>38</td>
<td>N/D</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>0.5 g p.o.</td>
<td>GF, TS</td>
<td>1.6 to 2.9</td>
<td>30 to 50</td>
<td>350</td>
</tr>
<tr>
<td>gatifloxacin</td>
<td>0.4 g p.o.</td>
<td></td>
<td>4.2</td>
<td>65</td>
<td>N/D</td>
</tr>
<tr>
<td>gemifloxacin</td>
<td>0.320 g p.o.</td>
<td></td>
<td>0.7 to 2.6</td>
<td>&lt;35</td>
<td>N/D</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>0.5 g p.o.</td>
<td>GF</td>
<td>5.7</td>
<td>61 to 86</td>
<td>286</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>0.4 g p.o.</td>
<td></td>
<td>4.5</td>
<td>20</td>
<td>N/D</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitrofurantoin</td>
<td>0.1 gm p.o.</td>
<td>GF, TS, TR</td>
<td>&lt;2</td>
<td>27 to 56</td>
<td>50 to 200</td>
</tr>
<tr>
<td>trimethoprim</td>
<td>0.16/0.8 g p.o.</td>
<td>9/105</td>
<td>50 to 75/10 to 30</td>
<td>31 to 165/10 to 133</td>
<td></td>
</tr>
<tr>
<td>sulfamethoxazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trimethoprim</td>
<td>0.2 gm p.o.</td>
<td>GF, TS</td>
<td>2</td>
<td>50 to 75</td>
<td>70 to 100</td>
</tr>
<tr>
<td>sulfamethoxazole</td>
<td></td>
<td></td>
<td>46</td>
<td>N/D</td>
<td>400 to 2000</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amikacin</td>
<td>0.5 g IV</td>
<td>GF, TR</td>
<td>17 to 25</td>
<td>&gt;90</td>
<td>170 to 1720</td>
</tr>
<tr>
<td>gentamicin</td>
<td>0.08 g IV</td>
<td>GF, TR</td>
<td>4 to 8</td>
<td>&gt;90</td>
<td>400 to 500</td>
</tr>
<tr>
<td>tobramycin</td>
<td>0.08 g IV</td>
<td>GF, TR</td>
<td>4 to 8</td>
<td>&gt;90</td>
<td>94 to 443</td>
</tr>
</tbody>
</table>

*aThe urine concentration is expressed as the range of concentrations achieved after a standard dose in patients with normal renal function. Single values represent the average urine concentration over a standard dosage interval (21–23). GF, glomerular filtration; IV, intravenously; N/D, no data; p.o., orally; TR, tubular reabsorption; TS, tubular secretion.*
the past, an advantage of fluoroquinolones was their ability to eradicate infecting E. coli from vaginal, perineal, and presumably rectal sites of colonization.

Nitrofurantoin provides proof of principle. Patients with creatinine clearances <20 ml/min excrete little or no drug in the urine, suggesting that nitrofurantoin not be used in such patients (27,28).

There are two concerns regarding the use of trimethoprim-sulfamethoxazole. There is increasing documentation of resistance of E. coli. Surveillance surveys in the United States indicate in vitro resistance in the range of 15 to 17%, the rate in Portugal is nearly 35% (29). Second, the urine concentrations of sulfamethoxazole falls to subtherapeutic concentrations in patients with creatinine clearances <50 ml/min (30). Of interest, the urine trimethoprim concentration remains high even with marked renal insufficiency (30). Why this difference exists is unclear. Hence, the suggestion is to prescribe trimethoprim alone, in reduced dosage, for the treatment of uncomplicated cystitis in patients with a low creatinine clearance.

Aminoglycosides
The aminoglycosides are excreted by glomerular filtration. Roughly 5% of filtered drug is reabsorbed by the cells of the proximal renal tubules (31). The result is very high urine concentrations (Table 1). There are few data on urine concentrations in patients with renal disease. One paper reported a peak urine concentration of sisomicin (an aminoglycoside that is not available in the United States) of only 1.8 μg/ml in the ureteral urine from a severely damaged kidney (32).

Aminoglycosides are not indicated for the treatment of cystitis or urethritis. At present, E. coli, Klebsiella species, and other common Gram-negative causes of pyelonephritis are susceptible to fluoroquinolones and extended-spectrum β-lactam antibiotics, making unnecessary the use of potentially toxic aminoglycosides. Rarely, it might be necessary to use aminoglycosides in low synergistic doses in combination with an active penicillin for enterococcal pyelonephritis. Pyelonephritis that is caused by P. aeruginosa may require an aminoglycoside in the rare instance of resistance to both ciprofloxacin and anti-pseudomonal β-lactams. Adjustment of dosage should yield effective serum and renal parenchymal levels and adequate urine concentrations, lower the risk for further drug-induced renal injury, and minimize the chance of ototoxicity.

In summary, antimicrobials with anticipated effectiveness in patients with urethritis/cystitis and chronic renal insufficiency are selected fluoroquinolones (ciprofloxacin, levofloxacin) and trimethoprim alone. Nitrofurantoin should not be used because of low urine drug concentrations.

Conclusion
Clinical trials of new drugs that are under evaluation for efficacy for UTI usually exclude patients with chronic renal insufficiency. As a result, there are few data on the urine concentrations of drugs that are licensed for the treatment of UTI in patients with underlying renal disease. Of interest, there are only a few reports of clinical or microbiologic antimicrobial treatment failures in patients with renal insufficiency and cystitis or pyelonephritis. Perhaps this is not a serious problem, or, more likely, the sporadic nature of the problem has failed to generate a coordinated multicenter evaluation.

At present, a prudent approach is to treat the patient who has pyelonephritis with an active fluoroquinolone alone after appropriate dose reduction. Fluoroquinolones should also be effective in patients with urethritis/cystitis. Trimethoprim alone is an alternative for cystitis treatment, with the caveat that 15 to 20% of the isolates may be resistant. There is no need to add sulfamethoxazole as the patients with low creatinine clearances will likely have subtherapeutic urine concentrations. It is also suggested that nitrofurantoin not be used because of low urine concentrations. Regardless of the drug used, a patient’s failure to respond may represent resistant bacteria or inadequate urine concentrations of the prescribed drug. This subject deserves more attention.

References


