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EDITORIAL

An infectious disease and pharmacokinetic perspective on oral antibiotic treatment of uncomplicated urinary tract infections due to multidrug-resistant Gram-negative uropathogens: the importance of urinary antibiotic concentrations and urinary pH

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Introduction

One of the most common reasons for infectious disease consultation for urinary tract infections (UTIs) from urologists is regarding the selection of antibiotic therapy for acute uncomplicated cystitis (AUC) or catheter-associated bacteriuria (CAB) due to multidrug-resistant (MDR) Gram-negative bacillary (GNB) uropathogens in hospitalized and ambulatory patients. The important therapeutic decisions for AUC or CAB due to MDR uropathogens are regarding the interpretation of susceptibility testing, i.e., in vitro susceptibility versus in vivo effectiveness, and the choice of oral versus intravenous antibiotic therapy. This commentary is based on my experience and pharmacokinetic (PK) principles. The importance of urinary antibiotic concentrations in determining the urinary spectrum of oral antibiotics and the effect of urinary pH are discussed as determinants of therapeutic efficacy.

Effective antibiotic therapy of AUC due to MDR GNB uropathogens depends on several factors, e.g., the inherent activity of the antibiotic against the uropathogen, absolute versus relative resistance, achievable urinary antibiotic concentrations (largely determined by renal function), and the effect of urinary pH on both bacterial multiplication and antimicrobial activity. In normal hosts with effective antibiotic therapy of AUC, bacteriuria is rapidly eliminated in 6–12 h. In both normal and compromised hosts, the therapeutic approach is the same, but in compromised hosts, rapidity of response, i.e., time to negative culture (TTNC), may be delayed and duration of therapy may need to be extended.

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Antibiotic urinary spectrum

Stamey was the first to advance the concept of urinary (vs. serum) antibiotic spectrum [1]. Clinically, it is important to appreciate that in vitro antibiotic susceptibility testing is based on achievable serum, not urinary, antibiotic concentrations. Furthermore, serum susceptibility testing is done in broth at a serum pH of 7.4, not human urine at urinary pH. Urinary antibiotic susceptibilities often differ considerably from serum susceptibilities [2–6]. Stamey reported that oral penicillin, due to high achievable urinary concentrations, easily eradicated *Escherichia coli* in urine, even though the *E. coli* was "resistant" by serum-derived susceptibilities [1, 4]. Stamey and others also showed that oral tetracycline, e.g., doxycycline, was effective in eradicating "tetracycline-resistant" *Pseudomonas aeruginosa* from urine. The minimum inhibitory concentration (MIC) of *P. aeruginosa* to tetracycline is 150 mcg/ml, a level which is not achievable in serum at any dose. However, with intact renal function, urinary tetracycline levels are >300 mcg/ml, well in excess of the MIC of *P. aeruginosa* [5, 6].

Uropathogen susceptibilities reported as "susceptible" even though based on serum susceptibilities are accurate and clinicians can rely on this interpretation and expect elimination of bacteriuria by the antibiotic [4–10]. If the antibiotic has inherent activity against the uropathogen, but the uropathogen is reported as "resistant" or "non-susceptible" by serum susceptibility testings, then the organism may, in fact, be "susceptible" in urine if urinary levels exceed the MIC of the organism; against *E. coli* in urine, oral amoxicillin is more effective than the same dose of oral ampicillin since

achievable urinary concentrations of amoxicillin greatly exceed those of ampicillin [11] (Table 1).

Antibiotic relative and absolute resistance of MDR Gram-negative organisms in urine

Antibiotic resistance makes therapeutic considerations complex [12, 13]. Natural absolute/high-level resistance refers to resistance beyond the spectrum of the antibiotic, independent of antibiotic concentrations, e.g., enterococci are naturally cephalosporin-resistant. Acquired absolute/high-level resistance also cannot be overcome, regardless of achievable antibiotic concentrations. Acquired "relative resistance" refers to resistance that is concentration-dependent, e.g., doxycycline-"resistant" *P. aeruginosa* (MIC = 150 mcg/ml) is easily eradicated from urine, but not serum with oral doxycycline, since urinary levels are greater than the MIC (urinary level = 300 mcg/ml) of the uropathogen [5, 6]. To be effective against "resistant" uropathogens by serum susceptibility testing, urinary concentrations of the antibiotic must exceed the MIC of the uropathogen [5, 7, 10]. However, if the uropathogen is an extended-spectrum beta-lactamase (ESBL)-producing organism, e.g., *E. coli* and *Enterobacter cloacae*, urinary concentration aside, the antibiotic selected must have *inherent* activity against ESBL-positive organisms, e.g., IV: carbapenems, aminoglycosides; PO: nitrofurantoin, fosfomycin. Antibiotics inactivated by ESBLs will be ineffective against such organisms, regardless of urinary antibiotic concentrations [14, 15]. In addition, clinicians should be aware of the differences between in vitro susceptibility and in vivo effectiveness of certain antibiotics, e.g., *Klebsiella pneumoniae* is usually reported as susceptible to trimethoprim–sulfamethoxazole (TMP-SMX) but is often clinically ineffective against this particular pathogen [15]. Other factors being equal, subinhibitory or low concentrations of antibiotics near or below the MIC predisposes to resistance [12, 13]. Resistance is less likely with high antibiotic concentrations since susceptibility is, in part, concentration0dependent [16]. For this reason, in vitro serum susceptibility data overestimate the resistance of urinary isolates in the presence of high urinary antibiotic levels [7–11, 17, 18].

The effect of urinary pH on the therapy of uncomplicated UTIs

After high urinary concentrations, which determine the antibiotic urinary spectrum, urinary pH is the most overlooked factor potentially affecting the therapeutic response and TTNC. Urinary pH not only affects uropathogen growth, but it also affects the antimicrobial activity of several antibiotics [19–22]. Spectrum is, in part, pH-dependent with some antibiotics. The spectrum of erythromycin in an acid urine is limited to anti-enterococcal activity, but in an alkaline urine, erythromycin has activity against several GNB uropathogens [20]. For some antibiotics, antibiotic activity is heavily pH-dependent [18, 22]. Some antibiotics have optimal antimicrobial activity in an acid urine (pH = 5–6), e.g., cephalosporins, but these antibiotics have decreased antibacterial activity in an alkaline urine (pH > 6). Similarly, antibiotics with optimal activity in an alkaline urine, e.g., erythromycin, have decreased activity in an acid urine (pH = 5–6). The antimicrobial effect of some antibiotics is completely dependent on the urinary pH, e.g., methenamine salts. Methenamine salts, in the presence of an acid urine, form formaldehyde, which is responsible for its antibacterial effects (Table 2). Furthermore, if the urinary pH decreases the activity of the antibiotic being used, it may have the same effect as subinhibitory urinary concentrations and may predispose to resistance [21].

The complexity of the effects of urinary pH is well illustrated with nitrofurantoin. Not only is the antimicrobial activity of nitrofurantoin pH-dependent, but the tubular reabsorption of nitrofurantoin is pH-dependent, e.g., an acid urine (pH = 5–6) resulting in increased tubular reabsorption with renal, but lower, urinary concentrations. Since nitrofurantoin antimicrobial activity is optimal in an acid urine, the urinary pH may be as important as urinary concentrations in determining the efficacy of nitrofurantoin [23] (Table 3).

Table 1 Susceptibilities of "ampicillin-resistant *Escherichia coli*" tested in broth at serum pH compared to human urine at achievable urinary concentrations and urinary pH

Oral antibiotics[a]	Broth at pH 7.4		Urine[b] at pH 6.0	
	% Susceptible	% Resistant	% Susceptible	% Resistant
Ampicillin	0 % (0/25)	100 % (25/25)	64 % (16/25)	36 % (9/25)
Amoxicillin	28 % (7/25)	72 % (18/25)	100 % (25/25)	0 % (0/25)
Doxycycline	40 % (10/25)	60 % (15/25)	76 % (19/25)	24 % (6/25)

[a] Tested at urinary concentrations

[b] Human heat-treated urine to remove thermolabile antibacterial activity

Adapted from [11]

Table 2 The effects of urinary pH on antibiotic activity in urine

Urinary pH	Oral antibiotics
Antimicrobial activity increased with an acid urine (pH = 5–6)	Ampicillin Cephalosporins Nitrofurantoin Doxycycline Fosfomycin
Antimicrobial activity increased with an alkaline urine (pH > 6)	Erythromycin Quinolones TMP-SMX
Antimicrobial activity requires an acid urine (pH = 5–6)	Methenamine mandelate/hippurate (methenamine salts)
Antimicrobial activity unaffected by urinary pH	Amoxicillin

TMP-SMX trimethoprim–sulfamethoxazole

Adapted from [18, 22]

Oral antibiotic therapy of AUC due to MDR Gram-negative uropathogens

There are many antibiotics available to treat GNB uropathogens. Problematic for many practitioners is the treatment of MDR GNB uropathogens in the hospital or ambulatory setting. Ordinarily, treatment of AUC should be via the oral route [15]. Physicians often resort to intravenous (IV) therapy for MDR GNB uropathogens, if not familiar with oral antibiotics that are effective against MDR GNB uropathogens [24–27]. The most important clinical considerations in selecting therapy for MDR GNB uropathogens is evaluation of the significance of achievable urinary concentrations, i.e., urinary spectrum, and the effect of urine pH on antimicrobial activity [25, 26]. IV therapy, which is not more effective than well-selected oral therapy, is problematic, i.e., requires IV access and prolongs hospital length of stay (LOS). In the outpatient setting, IV therapy has its limitations and is less convenient for the patient than oral antibiotic therapy [27]. For susceptible uropathogens, several oral antibiotics are available, e.g., cephalosporins and quinolones [15]. Even if the uropathogen is reported as "susceptible", it is necessary to select an antibiotic that is not only susceptible against the uropathogen, but also will not induce widespread resistance in the hospital or community. Clinicians should preferentially select antibiotics with a "low resistance potential", i.e., resistance unlikely even with extensive antibiotic use, e.g., nitrofurantoin, levofloxacin, doxycycline. In contrast, "high resistance potential" antibiotics often predispose to resistance even with limited use, e.g., ciprofloxacin [12, 13, 15, 25] (Table 4). Clearly, the three most useful, "low resistance potential" oral antibiotics ideal for the treatment of MDR GNB uropathogens are nitrofurantoin, doxycycline, and fosfomycin [15, 25, 28–36]. These "low resistance potential" antibiotics are well tolerated and, properly used, have a good safety profile [15]. As with other antibiotics, optimal effectiveness is dependent on adequate renal function (CrCl > 30 ml/min), i.e., to achieve therapeutic urine levels ensuring effective urinary spectrum [15, 18, 25, 37]. Although it is commonly thought that nitrofurantoin should not be used with creatinine clearances (CrCl) <60 ml/min, nitrofurantoin is effective if renal function is adequate, i.e., CrCl ≥ 30 ml/min [15, 25, 30]. Ordinarily, CAB in normal hosts should not be treated. In compromised hosts, CAB presumptive treatment is prudent since urosepsis may result from bacteriuria, even with relatively low colony counts.

Table 3 Nitrofurantoin: effects of urinary pH on urinary tract concentrations and antimicrobial antibiotic activity

	Renal concentration	Urine concentration	Antimicrobial activity[a]
Alkaline urine (pH > 6)	+	+++	++
Acidic urine (pH = 5–6)	+++	+	++++

[a] Against susceptible uropathogens

Adapted from [23]

Oral antibiotic therapy of CAB due to MDR Gram-negative uropathogens

Except for the urinary catheter, the principles of antibiotic treatment of CAB is the same as for AUC, i.e., inherent antibiotic activity against the uropathogen, therapeutic urinary antibiotic concentrations, adequate renal function, as well as the effect of urinary pH. The therapeutic problem presented by the indwelling urinary catheter, i.e., CAB, is related to the catheter biofilm formed by the uropathogen [2, 30]. Microorganisms become embedded in the catheter biofilm and cannot be easily eradicated by antibiotics. Antibiotics usually used for UTIs cannot penetrate the catheter biofilm to eliminate the uropathogen. Another common clinical problem is how to interpret urinalysis (UA) and urine culture (UC) in patients with indwelling catheters [2, 15, 27]. With indwelling urinary catheters, urine becomes colonized over time and pyuria is to be expected. With CAB, high-level pyuria (>50 WBCs/ml) with high urinary colony counts (bacteriuria > 100 K/hpf) are indicative of colonization, not infection. Therefore, before "treating" CAB with antibiotics, first remove/replace the urinary catheter, then repeat the UA and UC. This intervention alone is curative, in most cases, since it removes the nidus of infection, i.e., the catheter biofilm. After urinary catheter removal/replacement, if pyuria and bacteriuria persist, treat as AUC as described [15, 30].

Table 4 Antibiotic resistance potential

"High resistance potential" antibiotics (antibiotics to avoid)			
Ciprofloxacin (Organisms often resistant: *E. coli*)		Gentamicin or tobramycin (Organisms often resistant: *P. aeruginosa*)	
TMP-SMX (Organisms often resistant: *E. coli*)		Ceftazidime (Organisms often resistant: *P. aeruginosa*)	
Imipenem (Organisms often resistant: *P. aeruginosa*)		Ciprofloxacin (Organisms often resistant: *E. coli*)	
		TMP-SMX (Organisms often resistant: *E. coli*)	
"Low resistance potential" antibiotics (preferred antibiotics)			
Meropenem	Levofloxacin	Doxycycline	Nitrofurantoin
Amikacin	Aztreonam	Minocycline	Methenamine salts
Ceftriaxone	Cefepime	Levofloxacin	Fosfomycin
Piperacillin/tazobactam	Colistin		
Doxycycline	Tigecycline		

TMP-SMX trimethoprim–sulfamethoxazole

Adapted from [12, 13, 15]

Assessing antibiotic efficacy before urine culture results are reported

With AUC, an antibiotic with inherent activity against the uropathogen is used in patients with adequate renal function, i.e., CrCl > 30 ml/min, and rapid elimination of the uropathogen (<3 days) is expected [2, 38]. Early in treatment, a useful way to predict subsequent eradication of bacteriuria is to obtain a UA after 2 days of therapy. A marked decrease in intensity of pyuria is, in my experience, predictive of subsequent cure, i.e., when UC results are later reported. After 2 days of therapy, if there is no decrease in pyuria intensity and with no marked decrease in urine colony counts, discontinue therapy and select another antibiotic. If there is substantially decreased pyuria after 2 days, therapy should be completed with the selected antibiotic, i.e., 3 days in normal hosts and 3–5 days in compromised hosts. After 2 days of therapy, if pyuria intensity is less and urinary colony counts are

Table 5 Pharmacokinetic and microbiological parameters of selected oral antibiotics useful in the therapy of multidrug-resistant (MDR) uropathogens

Nitrofurantoin	Doxycycline	Fosfomycin
Usual dose = 100 mg	Usual dose = 100 mg	Usual dose = 3 g
Peak serum levels = 1 mcg/ml	Peak serum levels = 4 mcg/ml	Peak serum levels = 26 mcg/ml
Serum half life ($t_{½}$) = 0.5 h	Serum half life ($t_{½}$) = 20 h	Serum half life ($t_{½}$) = 5.7 h
Bioavailability = 80 %	Bioavailability = 93 %	Bioavailability = 37 %
PK = concentration-dependant kinetics	PK = concentration-dependant kinetics	PK = concentration-dependant kinetics
Excreted (unchanged) in the urine = 25 %	Excreted (unchanged) in the urine = 48 %	Excreted (unchanged) in the urine = 60 %
Urine levels = 100 mcg/ml[a]	**Urine levels = 300 mcg/ml**[a]	**Urine levels = 1000 mcg/ml**[a]
Optimal urinary pH = acid urine (pH = 5–6)	Optimal urinary pH = acid urine (pH = 5–6)	Optimal urinary pH = acid urine (pH = 5–6)
Urinary spectrum	**Urinary spectrum**	**Urinary spectrum**
E. coli[b]	*E. coli*[b]	*E. coli*[b]
Klebsiella sp.[c]	*Klebsiella* sp.[c]	*Klebsiella* sp.[c]
Enterobacter sp.[c]	*Enterobacter* sp.[c]	*Enterobacter* sp.[c]
	Pseudomonas aeruginosa[c]	*Serratia marcescens*[c]
		Proteus sp.
		Pseudomonas aeruginosa[c]

[a] With adequate renal function

[b] Including ESBL-positive strains

[c] Including MDR strains

Table 6 Clinical approach to the therapy of MDR Gram-negative acute uncomplicated cystitis (AUC) based on the intensity of pyuria as a predictor of clinical response

Marked decrease in intensity of pyuria is predictive of eradication of bacteriuria (TTNC < 2 days)
• Complete therapy with antibiotic selected
• Normal hosts: 3 days
• Compromised hosts: 3–5 days
No decrease in intensity of pyuria after 2 days is predictive of treatment failure
• Discontinue antibiotic
• Retreat with another antibiotic with inherent activity against the uropathogen that achieves high urinary concentrations
Mild to moderate decrease in intensity of pyuria is predictive of delayed eradication of bacteriuria (TTNC > 2 days)
• If the antibiotic being used has optimal activity in an *alkaline urine* (pH > 6) but the urinary pH is acid (pH = 5–6), retreat with an antibiotic with optimal activity in an *alkaline urine* or alkalinize the urine (sodium bicarbonate)
• If the antibiotic has optimal activity in an *acid urine* (pH = 5–6) but the urinary pH is alkaline (pH > 6), retreat with an antibiotic with optimal activity in an *acid urine* or acidify the urine (ascorbic acid)

TTNC time to negative culture

decreasing, but bacteriuria persists, i.e., increased TTNC, then the clinician should consider the potential effect of urinary pH on antibiotic activity in urine. With effective antibiotic therapy for AUC, bacteriuria (TTNC = 1–2 days) rapidly clears. CAB due to MDR GNB uropathogens resistant to fosfomycin, at urinary concentrations and acid urinary pH, after catheter replacement, therapy with methenamine salts are reliably effective if an acid pH is maintained [15, 18, 37, 39].

Summary

In conclusion, in normal hosts, AUC is easily treated using antibiotics to which the uropathogen is susceptible if renal function is adequate. Preferentially, use oral antibiotics with a "low resistance potential". For AUC due to MDR GNB, carefully select oral therapy, e.g., nitrofurantoin, doxycycline, or fosfomycin is as effective as IV therapy. The urinary spectrum of nitrofurantoin includes MDR GNB uropathogens (except *Proteus* sp., *S. marcescens*, *P. aeruginosa*) as well as vancomycin-susceptible enterococci (VSE) and vancomycin-resistant enterococci (VRE). At urinary concentrations, doxycycline is active against most MDR GNBs, including *P. aeruginosa*. Fosfomycin has the same urinary spectrum as nitrofurantoin, but, in addition, is also active against *Proteus* sp., *S. marcescens*, and *P. aeruginosa* [15, 40] (Table 5). An effective clinical response may be assessed by repeat UA and UC after 2 days of therapy. Decreased intensity of pyuria is an early predictor of subsequent elimination of bacteriuria, i.e., negative urine culture. Unchanged pyuria intensity predicts therapeutic failure. The antibiotic should be stopped. After re-assessing the factors that determine therapeutic efficacy, i.e., achievable urinary concentrations and urinary pH, the patient should be treated with another antibiotic. If there is a partial response to therapy, i.e., somewhat decreased pyuria and somewhat decreased urine colony counts, it is often the effect of an unfavorable urine pH on antibiotic activity and may be manifested by a prolonged TTNC. In such cases, there is delayed but eventual resolution of bacteriuria [39] (Table 6). Delayed or lack of response should prompt the clinician to re-assess renal function, antibiotic urinary concentrations, and urinary pH. Careful antibiotic selection, preferentially using "low resistance potential" antibiotics with an effective urinary spectrum, is critical to assure cure and to prevent resistance.

Compliance with ethical standards

Conflict of interest All authors declare there is no conflict of interest in the publication of this article.

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