Urinary Tract Infections: Resistance Is Futile

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We read with interest the recent article by Cole et al. (1). As the authors report, despite the mean MIC90 of 128 mg/liter of aminopenicillins for vancomycin-resistant Enterococcus faecium (VRE), a single dose of amoxicillin results in peak urinary drug concentrations of 306 to 856 mg/liter after a 250-mg oral dose (2, 3). Therefore, in theory, the urinary amoxicillin concentrations after oral administration are high enough to have adequate antibacterial efficacy against ampicillin-resistant VRE urinary tract infections (UTIs). Despite the plausibility of this theory, it has never been validated in a clinical setting. Cole et al. found no difference in the rates of clinical cure for the 31 patients with VRE UTIs who received an aminopenicillin and the 30 who received a non-β-lactam antibiotic (primarily linezolid) (83.9% versus 73.3%; P = 0.315). We anticipate that this treatment regimen will be adopted by many institutions that have not already implemented this practice in response to this paper. We find it curious that administering an antibiotic for an infection caused by a pathogen that is extremely likely or known to be resistant to that agent is widely accepted in the case of aminopenicillins and VRE UTIs but has not been adopted elsewhere. We wish to add our perspective on this issue.

As informed clinicians, we must begin to place more trust in our knowledge of antibiotic pharmacokinetics/pharmacodynamics (PK/PD) and how this applies to patient care. Antibiotic use should no longer be based solely on in vitro bug-drug combinations; instead, we should rely upon an integrated approach utilizing microbiology susceptibility reports, PK/PD relationships, host factors, and knowledge of collateral damage and costs to society (4, 5). It is imperative that we interpret data from our clinical microbiology laboratories in light of the site of infection and the myriad of patient-specific factors involved, as opposed to simply the susceptible-intermediate-resistant (S-I-R) interpretations provided in the antibiogram. It is far too easy to impetuously reach for a broader-spectrum agent when one sees an R next to an Escherichia coli isolate cultured from a patient’s urine, which is, in part, why we now find ourselves in the midst of the postantibiotic era. The limited ability of in vitro susceptibility testing to predict clinical efficacy has been previously recognized (6, 7). Unfortunately, these limitations are easily forgotten in exchange for an easy-to-understand rule of thumb in the form of the S-I-R antibiogram. We must not forget the 90–60 rule; which observes that infections due to susceptible isolates respond to appropriate therapy ~90% of the time, whereas infections due to resistant isolates or those treated with inappropriate antibiotics still respond ~60% of the time (8). In fact, in the study by Cole et al., this was actually the “75–85 rule” in favor of resistant pathogens.

It is well understood that effective antimicrobial therapy requires adequate drug concentrations at the target site of infection (9, 10). Currently, clinical microbiology labs use the same breakpoints for all isolates, regardless of the site of infection, with few exceptions. In response to this, the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing have recently introduced site-specific breakpoints for cephalmorins against Enterobacteriaceae in urine (11, 12). Unfortunately, the lack of flexibility in FDA-approved automated broth microdilution panels inhibits many institutions from adopting these new breakpoints. Until more clinically useful breakpoints are established by these organizations and widely adopted by health care institutions, we must move our understanding of antimicrobial PK/PD relationships from the bench to the bedside and verify the clinical efficacy of these theories as done by Cole et al.

The role and adequacy of site-specific concentrations as they relate to UTIs were established long ago. Early studies suggested that urinary drug concentrations are far more reliable than serum drug concentrations in predicting outcomes of therapy when treating UTIs (13, 14). This concept has also been observed in a randomized controlled trial of uncomplicated UTIs in which there was no difference in cure rates when the infecting pathogen was not susceptible to the agent administered (15). Importantly, patients with complicated and/or bacteremic UTIs have demonstrated worse outcomes when receiving inappropriate empirical therapy (16, 17). Therefore, these concepts should only be applied to uncomplicated cystitis until further clinical data are available.

As the rate of community-acquired multidrug-resistant Gram-negative infections, particularly UTIs, continues to increase, we are in desperate need of a way to treat these patients without admitting them and administering intravenous antibiotics in the hospital or as outpatient infusion therapy. Following the lead of Cole et al., we believe other commonly used oral antibiotics could and should be reliable agents for the treatment of uncomplicated UTIs, regardless of reported in vitro susceptibility. Most Gram-negative pathogens achieve an asymptote of resistance far below the achievable urinary drug concentrations of commonly used antibiotics for genitourinary infections. Even after multistep selection of resistance to fluoroquinolones at physiologically achievable concentrations, E. coli and Klebsiella pneumoniae rarely produce MICs above 16 mg/liter (18). Although this MIC is several-fold above the CLSI resistance breakpoints of 1 and 2 mg/liter for ciprofloxacin and levofloxacin, respectively, these concentrations could easily be overcome by the urinary drug concentrations achieved after oral doses of these agents, as shown in Table 1. In fact, the peak-to-MIC ratio would be several-fold higher than the aminopenicillin/VRE MIC ratio suggested by Cole et al.

We advocate for the setting of urine-specific susceptibility breakpoints for all relevant antimicrobials. Until this occurs, we

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suggest that clinicians begin to adopt the strategy reported by Cole et al. and expand this to other bug-drug combinations in uncomplicated UTIs, specifically, Gram-negative Enterobacteriaceae and previously discarded first-line agents such as the fluoroquinolones. In order to protect our remaining antibiotic armamentarium, we must find a way to utilize our in-depth knowledge of antimicrobial PK/PD and move this understanding from bench to bedside in order to maximize the efficacy and life span of our existing antimicrobials while we still can.

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REFERENCES

TABLE 1 Urinary concentrations of selected fluoroquinolones after oral administrationa

<table>
<thead>
<tr>
<th>Antibiotic and dose (mg)</th>
<th>Urinary Cmax b (mg/liter)</th>
<th>Urinary trough concn (mg/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>268 (130–967)</td>
<td>13 (5.1–37)</td>
</tr>
<tr>
<td>1,000c</td>
<td>892.52 ± 476.4</td>
<td>32.80 ± 22.01</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td></td>
<td></td>
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<tr>
<td>500</td>
<td>498.89 ± 246.93</td>
<td>112.49 ± 52.5</td>
</tr>
<tr>
<td>500</td>
<td>406 (202–1,002)</td>
<td>84 (41–299)</td>
</tr>
</tbody>
</table>

a Data are from references 19 and 20 and are mean values ± standard deviations or medians and ranges.

b Cmax, maximum concentration.
c Ciprofloxin XR.