Urinary tract infections (UTIs) are the most common bacterial infections among adults in the community setting. Pyelonephritis is the most severe manifestation of such infection. A recent population-based study noted an overall rate of pyelonephritis of 15–17 cases per 10,000 women and 3–4 cases per 10,000 men [1]. The in-hospital mortality rate for pyelonephritis varies from 7.3 cases per 1000 hospitalized women to 16.5 cases per 1000 hospitalized men [2]. Finally, the annual societal cost of treatment of acute pyelonephritis in the United States has been estimated to be >$2 billion [3]. Although numerous studies have focused on the emergence and impact of antimicrobial resistance in cystitis, surprisingly few data are available specifically for patients with pyelonephritis. Infectious Diseases Society of America guidelines for the treatment of uncomplicated cystitis and pyelonephritis were written in 1999, and some recommendations may no longer be current [4]. Data regarding the prevalence of antimicrobial resistance in pyelonephritis and the potential impact of resistance on antimicrobial treatment strategies for this disease are urgently needed.

In this issue of *Clinical Infectious Diseases*, Talan et al. [5] report their findings about the population of patients presenting to the emergency department (ED) with presumptive pyelonephritis. All adults presenting for care within a network of 11 university-affiliated urban EDs in the United States were identified. Of these patients, those for whom culture revealed a single infecting organism were included in the study cohort. For all patients, ED physicians ascertained data at the time of care on baseline demographic characteristics, comorbid conditions, presence of indwelling devices, and recent antibiotic use. Antibiotic use was assessed for both the 2 days and the 2 months before presentation.

Of the 1272 patients who presented with pyelonephritis, 977 (77%) had a urine culture performed. Of these 977 patients, 288 (29%) were excluded because either their culture result was negative or 1 organism did not grow on culture in sufficient quantity to meet inclusion criteria. *Escherichia coli* was the predominant pathogen (in 89% of isolates). Among patients with uncomplicated pyelonephritis, the prevalence of *E. coli* resistance to trimethoprim-sulfamethoxazole (TMP-SMX) was 27%. There were, however, marked differences in the prevalence of TMP-SMX resistance across the participating sites (range, 13%–45%). The proportion of *E. coli* resistant to ciprofloxacin and levofloxacin was 1% (range, 0%–5%) and 2% (range, 0%–17%), respectively. Only exposure to TMP-SMX within the 2 days before presentation and Hispanic ethnicity were associated with TMP-SMX resistance of *E. coli* in unadjusted analyses. There was no statistically significant association between antibiotic use during the 60 days before presentation and TMP-SMX resistance. Finally, among 226 women with uncomplicated pyelonephritis who were discharged after ED care and for whom data were available regarding antimicrobial treatment and drug susceptibility, 15 (6.6%) were treated with an antibiotic lacking in vitro activity, including 10 (38%) of 26 patients who received TMP-SMX therapy.

Talan et al. [5] are to be commended for providing a comprehensive prospective assessment of the epidemiology of antimicrobial resistance in pyelonephritis. Of particular interest is the marked variability in TMP-SMX resistance rates across different geographic regions. Although guidelines for UTI therapy often identify a threshold of resistance above which use of that agent should be discouraged, these guidelines depend on knowledge of local and regional resistance rates. Although UTI treatment guidelines recommend pe-
periodic reassessment of antimicrobial susceptibility at the community level [4], these data are rarely available. In this regard, the fact that 23% of patients with suspected pyelonephritis did not have a urine culture performed is troubling, particularly in light of recommendations for routine assessment by culture for patients with pyelonephritis [4]. These data are, however, consistent with recent work demonstrating low rates of culture confirmation of pyelonephritis [1]. Routine performance of cultures is important not only for informing therapeutic decisions for the patient not responding to therapy but also, perhaps more importantly, for better defining local resistance patterns to guide broader treatment recommendations.

Infectious Diseases Society of America guidelines for treatment of uncomplicated pyelonephritis recommend a fluoroquinolone (FQ) as first-line therapy [4]. Given the high rates of TMP-SMX resistance demonstrated by Talan et al. [5], this would seem to be a reasonable recommendation. However, how long such an approach will remain viable is questionable. There is ample recent evidence, particularly in the hospital setting, of significant increases in FQ resistance and of a strong association between FQ use and FQ resistance [6, 7]. There is no reason to expect that similar trends will not continue to emerge in the outpatient setting. Indeed, a recent study noted that, from 1997 through 2001, the frequency of use of FQs for treatment of outpatient pyelonephritis increased from 35% to 61%, and the percentage of prescriptions for TMP-SMX decreased from 53% to 32% [1]. During this same period, FQ resistance in E. coli increased significantly, from 0.2% to 1.5%. In the study by Talan et al. [5], 10% of TMP-SMX–resistant E. coli were also resistant to FQs. Thus, although routine use of FQs as first-line therapy for pyelonephritis may be a reasonable approach now, history suggests that broader use of these agents will result in further increases in FQ resistance. Emerging FQ resistance will almost certainly limit the role of FQs in the treatment of pyelonephritis in future years. When (not if) that occurs, the next best option for outpatient oral therapy of pyelonephritis is less clear.

Given these considerations, is there a way that physicians can better preserve FQs for the future? Can TMP-SMX still be first-line therapy for patients who, on the basis of certain risk factors, are deemed to be at very low risk of a TMP-SMX–resistant infection? By investigating the association between numerous risk factors and TMP-SMX resistance, Talan et al. [5] provided the groundwork for such a patient-specific approach to selecting empirical antibiotic therapy for pyelonephritis. The authors note an association between use of TMP-SMX during the 2 days before presentation and TMP-SMX–resistant infection. The most likely explanation for this association is that TMP-SMX use during the 2 days before presentation represents failed treatment of UTI symptoms that ultimately resulted in presentation to the ED. Indeed, patients who initiated outpatient TMP-SMX therapy for pyelonephritis due to TMP-SMX–susceptible E. coli would presumably be likely to respond clinically and, thus, would never present to the ED.

The lack of an association between antibiotic use during the 60 days before presentation and TMP-SMX resistance is surprising, because numerous previous studies of cystitis have found such a relationship even after controlling for other confounders [8–10]. One possible explanation is that TMP-SMX–resistant E. coli is largely spread from person to person, as has been suggested by the emergence of clonal group A as a cause of TMP-SMX–resistant E. coli UTIs [11, 12]. Another possible explanation is exposure to TMP-SMX–resistant E. coli through recent travel [12]. Assessment of these variables would shed further light on the complex epidemiology of TMP-SMX resistance.

An alternative explanation for the lack of association between antibiotic use during the 60 days before presentation and TMP-SMX resistance is misclassification of antibiotic exposure. Obtaining an accurate history of outpatient antibiotic use can be challenging. In 1 study [13], open-ended questions of recent antibiotic use failed to identify nearly 50% of antibiotic exposures identified in a pharmacy database. Even with use of a comprehensive 3-step survey approach, only 73% of all antibiotic exposures were identified [13].

Regardless of the interpretation of the risk factor analysis, Talan et al. [5] demonstrate a clear role for such work in better informing therapeutic decision-making. Individual risk factors for TMP-SMX resistance should be taken into account when selecting empirical therapy for pyelonephritis [14, 15]. Development and validation of a clinical prediction rule to accurately identify patients at low risk of TMP-SMX–resistant infection would permit TMP-SMX to remain a viable first-line therapy for many patients. Of note, nearly 75% of the study population was infected with TMP-SMX–susceptible E. coli [5]. This approach would help to optimize therapy while still preserving FQs.

In women with pyelonephritis, in vitro resistance to TMP-SMX is strongly associated with bacteriologic and clinical failure [16]. As such, any prediction rule must be able to accurately discriminate between TMP-SMX–susceptible and TMP-SMX–resistant infections. Indeed, in a recent study [17], likelihood of treatment failure was shown to be a primary factor in a clinician’s decision-making process when selecting antibiotics for pyelonephritis. In that study [17], even theoretical antibiotic failure rates of 5% resulted in decreases in the likelihood of using that drug.

Pyelonephritis has a substantial clinical and economic impact, and its treatment is increasingly complicated by antimicrobial resistance. Talan et al. [5] provide an important framework for identifying approaches designed to better target antimicrobial therapy at the patient level. Although such a course does not represent the path of least resistance, it may confer...
the best chance of least antimicrobial resistance.

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References