Antibiotic Resistance and Pyelonephritis

Betsy Foxman,[1] Moran Ki,[3] and Patricia Brown[2]

[1]Department of Epidemiology, University of Michigan, Ann Arbor, and [2]Division of Infectious Diseases, Department of Internal Medicine, Wayne State University, School of Medicine, Detroit, Michigan; and [3]Department of Preventive Medicine, Eulji University, School of Medicine, Daejeon, South Korea

(See the article by Czaja et al. on pages 273–80)

Increasing antibiotic resistance threatens our ability to effectively treat bacterial infections. Antibiotic therapy enhances the growth of existing drug-resistant bacteria and the exchange of resistance mechanisms between bacteria (and even between species) and selects for resistance mutations. The effect on levels of drug-resistant infection in the population of treating 1000 people with antibiotics for 1 day is roughly equivalent to treating 1 person with antibiotics for 1000 days. Furthermore, antibiotic therapy selects for drug resistance, not only in the pathogen, but in commensal bacteria that are present in the patient, thereby creating a resistance reservoir. Thus, it is important to monitor drug resistance patterns among pathogens causing common bacterial infections, such as urinary tract infection (UTI).

Every year, 12% of women and 3% of men in the United States experience a UTI [1]. UTI is the most common bacterial infection among adults in the community, and it is the most common health care–associated infection. Because UTI is usually easily treated with antibiotics, it is easy to forget that UTI is often a source of bacteremia and sepsis and can be fatal. Among men hospitalized for pyelonephritis, the mortality rate is 16.5 deaths per 1000 hospitalizations; for women, the figure is lower but is still substantial: 7.3 deaths per 1000 hospitalizations [2]. Uropathogens in the community and in hospitals are increasingly resistant to antibiotics; furthermore, because the infection is so common, it is likely that antibiotic therapy for UTI is an important selective factor for antibiotic resistance at the population level.

Pyelonephritis is the most severe manifestation of UTI. There are surprisingly few studies of therapy for this disease or of the epidemiology and risk factors for pyelonephritis; therefore, it is welcome to see the study of the epidemiology of pyelonephritis by Czaja et al. [3] in this issue of *Clinical Infectious Diseases*. Using computerized records of the Group Health Cooperative in Seattle, Washington, Czaja et al. [3] estimate the outpatient and inpatient incidence rates of pyelonephritis from 1997 through 2001 and document trends in infecting organisms and antibiotic resistance. The study moves the literature forward by providing population-based estimates of the incidence of pyelonephritis among individuals treated either as inpatients or as outpatients and, when available, providing microbiologic and antimicrobial treatment data.

The authors choose to limit their analysis to individuals who were identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* code as having pyelonephritis. All persons treated as inpatients were included. Only those outpatients who had a positive urine culture result within 7 days before or 2 days after the date of diagnosis were treated. Because culture data were not available for all inpatients, only 40% had culture confirmation of infection. Any patients who were initially seen as an outpatient and were later hospitalized were considered to be inpatients. Only the first recorded episode was included in the analysis. There were 10,330 episodes among 4887 patients; only 828 patients (17%) were treated in the hospital. Culture confirmation was available for only 2408 (59%) of 4059 individuals who received a diagnosis of pyelonephritis and were treated as outpatients; thus, 41% were excluded from the analysis. Because the analysis is limited to the first recorded episode, the results underestimate the incidence of pyelonephritis, which perhaps explains why the incidence rates reported in this study are considerably lower than those in previous reports [4]. Furthermore, by using more-stringent inclusion criteria for outpatients than for inpatients, the study may overestimate the proportion of pyelonephritis cases treated in the hospital.

In a previous study, the authors found a similar case definition for outpatients to be 98% accurate among young adult

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Reprints or correspondence: Dr. Betsy Foxman, Dept. of Epidemiology, University of Michigan School of Public Health, 109 Observatory St., Ann Arbor, MI 48109-2029 (bfoxman@umich.edu).

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women treated at Group Health Cooperative [5]. Although apparently quite specific, it is probably not very sensitive, because 41% of outpatients were excluded. What is unclear from the presentation is whether culture results were unavailable or were ordered and were negative. Treating UTI empirically results in considerable cost savings, at least in the short term. A urine culture, followed by determination of antibiotic sensitivities, takes at least 3 days, which is much too long to wait before initiating therapy in the ill patient. Thus, the culture results only have immediate utility when treatment fails. Localization studies, now quite old, suggest that as many as 50% of all UTIs include some kidney involvement [6]. However, localization studies are not standard practice, and the determination that a UTI involves the kidney is generally based solely on signs and symptoms such as fever, flank pain, and costovertebral angle tenderness, with or without lower urinary tract symptoms, such as dysuria, urgent urination, and frequent urination, although gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, are common and may be the presenting complaint [7].

Nonetheless, authoritative reviews of acute pyelonephritis recommend urine culture, even when the infection is treated on an outpatient basis. Assuming urine cultures were ordered, why would a patient with a clinical presentation consistent with pyelonephritis have a negative urine culture result? One possibility is that the patients were already taking antibiotics (if, for example, treatment had been initiated after consultation over the telephone). Excluding outpatients without a positive urine culture result undoubtedly reduces misclassification of those without pyelonephritis as having infection, but it also leads to an overall underestimation of disease burden. Furthermore, the extent of this bias is probably not uniform across patient groups. Thus, it would be informative to know whether those excluded had a urine culture ordered and to characterize that group. Similarly, it would be informative to characterize the group with a negative urine culture result. Understanding the potential effects of a history of UTI, underlying conditions, the age and sex of the patient, and the medical specialty of the treating physician on whether a urine culture was ordered and, if ordered, on whether the result was negative, is crucial for interpreting the presented trends in antibiotic resistance and in the infecting agent.

The proportion of inpatients without culture data was also very high. If culture data had been available for the 60% of patients with missing data, it is quite possible that a different distribution of organisms might have been observed. Missing data might also explain the apparent decrease in trimethoprim-sulfamethoxazole resistance. Some estimate of the rate of patients with positive culture results, the number of positive culture results compared with the number of cultures ordered, and whether these vary according to UTI history, underlying conditions, age or sex of the patient, and the medical specialty of the treating physician would aid in interpreting the validity of the inclusion criteria for inpatients.

From a public health perspective, culture results are essential for understanding trends in antibiotic resistance and infecting organisms. Because we do not understand the indications for culture, and because these might have changed over the course of the study, it is difficult to accurately interpret many of the findings of Czaja et al. [3]. For example, the authors note that the distribution of causative uropathogens did not differ greatly between inpatients and outpatients. However, the authors did not assess the effects of age, sex, or pregnancy status on patients with a positive urine culture result treated as inpatients, compared with outpatients. Trends in prescribing might also be misrepresented by not including prescription information for the 41% of patients who were treated as outpatients without a positive urine culture result. One can imagine that these patients might have less severe cases and, thus, may possibly be treated with trimethoprim-sulfamethoxazole.

For all UTIs, including pyelonephritis, the recurrence rates are high. In a South Korean study using national insurance claims and covering 99% of the population, the 1-year risk of a second episode of pyelonephritis was 9.2% for females and 5.7% for males; following a fourth episode, the 1-year risk of a fifth episode was 50% for females and 53% for males. Although Czaja et al. [3] limited their analysis to the first reported episode, future studies should address the determinants of recurring pyelonephritis.

Another gap in understanding is in the determinants of health care–associated and community-acquired pyelonephritis. Czaja et al. [3] did not distinguish between primary and secondary diagnoses or attempt to analyze their data to compare health care–associated and community-acquired pyelonephritis. It should be possible to distinguish in their data between (1) community-acquired pyelonephritis treated on an outpatient basis, (2) community-acquired pyelonephritis treated on an inpatient basis either immediately or following treatment failure, and (3) hospital-acquired pyelonephritis. The microbiology and antibiotic resistance of these groups might vary in important ways. In addition, excluding hospital-acquired cases would give a better estimate of the proportion of community-acquired pyelonephritis treated on an inpatient basis. It also would have been useful to examine cases of pyelonephritis among pregnant women separately, because therapeutic choices are more limited during pregnancy, and hospitalization for initial therapy continues to be recommended for this group [8]. Finally, these data might be used to gain some insight into the most cost-effective treatment strategies.

Some of the limitations of the Czaja et al. [3] study could be addressed with a more comprehensive analysis and the addition of data from medical records. Other limitations are more problematic, particularly for monitoring microbiologic and

antibiotic resistance trends. Urine culture rates appear to be quite low among both inpatients and outpatients who receive a diagnosis of pyelonephritis. Although examining the determinants of whether a culture is ordered will give some insight into whether some biases might have occurred, as well as the possible direction of those biases, these analyses cannot make up for missing data. In the absence of culture results, therapy is chosen on the basis of a combination of individual profile and physician preference, which may or may not be optimal for limiting the spread of antibiotic resistance. Furthermore, without more-representative data on drug resistance, it is difficult to advise physicians on local resistance trends. Finally, without representative trend data, it is difficult to increase our understanding of the determinants of resistance and, thus, to develop accurate models predicting the emergence and spread of antibiotic resistance.

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