ORIGINAL ARTICLE

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Time courses of bacterial density in urine during antibacterial chemotherapy and influential factors in patients having positive bacteriuria with a complicated urinary tract

Abstract A series of consecutive urine cultures was performed to determine the time points of elimination of bacteria from urine and the factors influencing these time points in patients receiving antimicrobial chemotherapy for positive bacteriuria. Between 1988 and 2000, 110 patients who had positive bacteriuria and received a 5-day regimen of parenteral antibacterials were included in this study. Quantitative urine cultures were performed every 24h throughout the therapy. Bacteria were identified; minimum inhibitory concentrations of antibacterial agents for causative bacteria were determined, and the bacteria were categorized as susceptible or nonsusceptible. The complexity of the urinary tract was graded as high or low. A multivariate Cox proportional hazards model was utilized to identify the factors that determined the time course of bacterial density in urine. Two penicillins, seven cephalosporins, five carbapenems and one fluoroquinolone were administered to 110 patients. The overall bacteriurial elimination rate at the end of treatment was 73% (80/110), and the most frequent day of elimination was day 1 (54%; 43/80), followed by day 2 (20%; 16/80). The significant factors for persistence of bacteriuria after chemotherapy were the presence of an indwelling catheter, a nonsusceptible pathogen, and high complexity of the urinary tract; risk ratios were: 2.398 ($P = 0.0009$), 2.227 ($P = 0.0020$), and 2.113 ($P = 0.0455$), respectively, which also influenced the day of elimination. In conclusion, the efficacy of treatment and the time point of bacteriurial elimination were determined by the presence of a urinary catheter, drug susceptibility, and urinary complexity in patients with positive bacteriuria undergoing antibacterial chemotherapy.

Introduction

Chemotherapy for patients with positive bacteriuria and with a complicated urinary tract (see definition below) is one of the most problematic issues in urological practice. The most acceptable indication for antibacterial chemotherapy for these patients is the presence of clinical symptoms.[1] However, we often have to perform traumatic urinary procedures for asymptomatic patients. Although pretreatment is not always beneficial for all patients, antibacterial coverage must be started prior to the procedure.[2] The appropriate timing of antibacterial chemotherapy prior to an operation is crucial, because too-early attempts at sterilization frequently result in the emergence of drug-resistant microorganisms. A uniform regimen seems unacceptable, because the underlying condition of the urinary tract varies from patient to patient. In addition, the causative microorganisms are highly variable and are frequently drug-resistant. Therefore, information about the time course of bacteriuria during chemotherapy and factors influencing the course are both important to schedule treatment.[3] However, these have not been fully studied. In this study, a series of quantitative urine cultures was performed to clarify the time course of bacteriuria in patients with a complicated urinary tract during antimicrobial chemotherapy and to identify the factors that influence the bacteriological outcome and time point of elimination of bacteria from urine.

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Patients, materials, and methods

Between 1988 and 2000, a total of 110 inpatients at the Department of Urology, Sapporo Medical University Hospital who had positive bacteriuria and pyuria, were enrolled in this study. All patients satisfied the inclusion criteria: $\geq 10^4$ colony-forming units (CFU)/ml for bacteriuria and

≥10 WBCs/high-power field for pyuria. The patients received a parenteral antibacterial agent, empirically, every 12 h, given over a period of 30 to 60 min, administered for 5 days (day 0 to day 4). No antibacterial agent was added unless local or general symptoms remained on day 5 or high-grade fever was present before and during the treatment.

We defined a complicated urinary tract as one having anatomical or functional abnormalities that could potentially enhance bacterial colonization or impair the host defense mechanisms. Abnormalities of the urinary tract were classified into four main categories: (i) anatomical and (ii) functional outlet obstructions in the lower urinary tract; (iii) urothelial malignancy; and (iv) urolithiasis and others. We summed the number of categories that each patient had, and the sum represented the complexity grade of the urinary tract. The grade was classified as either low (sum ≤1) or high (sum ≥2), and was used for further analysis.

Urine specimens were obtained for culture every 24 h immediately prior to the first administration of antibacterial agents on each day, from day 0 through day 5 for a total of six consecutive times. Quantitative urine cultures were performed by the dip-slide method (Uricult or Uricult-E; Orion Diagnostica, Espoo, Finland). This method has acceptable accuracy, reliability, and cost-effectiveness as a method for quantitative urine culture.[4] Bacteria were identified and the minimum inhibitory concentrations (MICs) of the antibacterial agent used for the bacteria were measured using the broth microdilution method.[5] The overall bacteriological outcomes at the end of treatment, assessed on day 5 (12 h after the last administration of the antibacterial agent), were judged as *eliminated* or *persistent*, as described in the evaluation criteria of the Japanese Society of Chemotherapy, with minor amendments.[5] *Eliminated* was defined as bacterial density of less than 1000 CFU/ml, and *persistent* as bacterial density equal to or greater than 1000 CFU/ml. If the species of isolate from a patient with the result of *persistent* on day 5 was identical to that on day 0, it was categorized as *unchanged*; otherwise it was categorized as *replaced*. If the outcome was judged to be *eliminated*, the day of bacteriurial elimination was determined. The day was determined as the first day from which a negative urine culture was observed consecutively through day 5. For example, in a patient with bacterial cultures showing day 1 positive, day 2 negative, day 3 positive, day 4 negative, and day 5 negative, day 4 is the day of bacteriurial elimination. Posttreatment urinary culture was performed for 5 to 14 days after the end of treatment in those patients whose bacteriological outcome was *eliminated*. We defined *recurrence* as a positive urine culture (≥10 000 CFU/ml), and divided the recurrent bacteria into two types according to the species isolated. If the species of recurrent bacterium was identical to that on day 0, it was categorized as *relapse*; if different, then the category was *new infection*.

The multivariate Cox proportional hazards model was used to identify independent risk factors for persistence of bacteriuria after chemotheraphy. The factors included in the stepwise regression analysis were as follows: the demographic parameters listed in Table 1, the presence or absence of medical conditions that would probably affect the outcome (e.g., diabetes mellitus), class of antibacterial agents used, the score for grade of urinary complexity (low or high), bacterial density in urine as a common logarithm of CFU/ml, and the number of causative bacterial species and their drug susceptibility. The MICs of antibacterial agents for causative bacteria were determined, and bacteria were categorized as susceptible or nonsusceptible (intermediate and resistant) according to the National Committee for Clinical Laboratory Standards (NCCLS) interpretive standards.[6] When a patient received an antibacterial agent not listed in the NCCLS standards, our own standards (listed in Appendix 1) were applied. If any nonsusceptible bacterium was isolated, the overall susceptibility was regarded as nonsusceptible. We then categorized the patients into risk groups according to the number of significant risk factors for each patient. The Kaplan-Meier method was utilized to show the time-course of bacteriuria, stratified by the determined risk factor(s). The median day of bacteriurial elimination was calculated, and the Kruskal-Wallis test was performed to evaluate differences among the risk groups.

Table 1. Clinical demographics of 110 patients

Parameters	Measures
Number of patients	110
Age, years, median (range)	69 (19–86)
Sex	Male 83, Female 27
Symptoms	
Asymptomatic	84 (76.4)
Symptomatic	26 (23.6)
Indwelling urinary catheter	
With	38 (34.5)
Without	72 (65.5)
Serum creatinine, mg/dl, median (range)	0.9 (0.3–2.7)
Blood urea nitrogen, mg/ml, median (range)	15 (5–35)
Antibacterial agents used	
Penicillins[a]	22
Cephalosporins[b]	39
Carbapenems[c]	40
Fluoroquinolones[d]	9

Values are expressed as numbers (percentages) unless otherwise indicated
[a] Piperacillin, 5; piperacillin/tazobactam, 17
[b] Ceftazidime, 8; cefoselis, 13; cefepime, 6; cefozopran, 9; miscellaneous, 3
[c] Biapenem, 15; meropenem, 19; panipenem/betamipron, 4; miscellaneous, 2, [d] Pazufloxacin, 9

Results

Demographics and clinical characteristics of the 110 patients are summarized in Table 1. More than 75% of the patients were asymptomatic. Acute exacerbation of chronic infection, manifested as fever or upper urinary tract infection (UTI), was diagnosed in the remainder. Thirty-eight patients had indwelling urinary catheters. Impairment of renal function (serum creatinine level, ≥2.0 mg/ml) was observed in 2 patients. Diabetes mellitus had been diagnosed in 7 patients. No other discernible medical condition was