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Original Article

Antimicrobial susceptibility of pathogens in acute uncomplicated cystitis cases in the urology department of a community hospital in Japan: Comparison with treatment outcome and hospital-wide antibiogram

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ABSTRACT

We hypothesized that cases of uncomplicated cystitis treated in a Urology Department would display higher antimicrobial susceptibility than those reported by the hospital antibiogram. This would suggest narrow spectrum antibiotics could still be an effective treatment for uncomplicated cystitis despite this era of antimicrobial resistance. The objective of this study was thus to evaluate the rates of antimicrobial susceptibility of isolates cultured from uncomplicated cystitis cases that presented to the Urology Department of a community hospital in Japan. We evaluated the efficacy of cefaclor, a narrow spectrum antibiotic, for uncomplicated cystitis. We further compared the rates of antimicrobial susceptibility of isolates from uncomplicated cystitis cases to those reported in a hospital-wide antibiogram.

A retrospective chart review was performed of patients diagnosed with uncomplicated cystitis in the Urology Department. The patients were mainly treated orally by cefaclor at 750 mg/day for seven days.

Significantly greater susceptibilities to ceftazidime (87.0% vs 65.7%), trimethoprim-sulfamethoxazole (89.4% vs 79.1%) and levofloxacin (84.6% vs 66.9%) were observed in a cystitis antibiogram for *Escherichia coli* compared with a hospital-wide antibiogram. The clinical efficacy of cefaclor for acute cystitis was also demonstrated.

The greater susceptibility of *Escherichia coli* to antimicrobials observed in this study supports the hypothesis that antimicrobial susceptibility rates in uncomplicated cystitis cases that present to the Urology Department would be greater than those reported in the hospital antibiogram. Therefore, uncomplicated acute cystitis can be treated by narrow spectrum antibiotics such as cefaclor even in this “antimicrobial resistance era”.

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Abbreviations: ABPC, ampicillin; PIPC, piperacillin; CEZ, ceftazidime; CPDX-PR, cefpodoxime proxetil; CAZ, ceftazidime; IPM/CS, imipenem cilastatin; MEPM, meropenem; AMK, amikacin; GM, gentamicin; MINO, minocycline; ABPC/SBT, ampicillin sulbactam; TAZ/PIPC, tazobactam piperacillin; CXM, cefixime; CFDN, cefdinir; CMZ, cefmetazole; CTX, cefotaxime; CFPM, cefepime; LMOX, latamoxef; AZM, aztreonam; LVFX, levofloxacin; CPRO, ciprofloxacin; ST, trimethoprim-sulfamethoxazole; CVA, clavulanic acid; *E. coli*, *Escherichia coli*; UTI, urinary tract infection; UD, urology department; MIC, minimum inhibitory concentration.

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1. Introduction

Acute cystitis, an infection of the lower urinary tract, is the most frequent infection encountered by urologists in community hospitals in Japan. *Escherichia coli* (*E. coli*) is the most common pathogen associated with acute cystitis [1–3]. Common antimicrobial agents, such as fluoroquinolones, trimethoprim-sulfamethoxazole (ST), and cephalosporins, are used to treat this disease, although variable local patterns of resistance to these agents exist [4–6].

In Japan, fluoroquinolones have been widely prescribed as empirical therapy for acute cystitis. However, *E. coli* resistance to fluoroquinolones has been increasing in recent years. A 2011 Japanese surveillance program showed that in cultures obtained from complicated urinary tract infection (UTI) samples, the resistance of *E. coli* to fluoroquinolones was 30% [7]. As a comparison, *E. coli* resistance to fluoroquinolones was under 20% in uncomplicated cystitis patients [3]. However, in 2016, the U.S. Food and Drug Administration advised that serious adverse events associated with fluoroquinolones generally outweigh the benefit for patients with uncomplicated UTIs, acute bronchitis and acute sinusitis who have other treatment options [8]. Thus, fluoroquinolones have been henceforth deemed unsuitable as empirical therapy for acute uncomplicated cystitis.

ST is also prescribed worldwide for acute cystitis. However, *E. coli* resistance to ST is also increasing. Recent epidemiological studies have found that the rate of ST resistance in isolates from uncomplicated UTI samples is from 3.4% [9] to over 15% [3] in Japan, 15.7% in 16 European countries, including 34.8% in Portugal and Spain [10], and 18% in USA [11]. In Japan, even the manufacturer of ST advises physicians to prescribe this drug only when other options are not available because of the serious adverse event of anxiety.

In Japan, third-generation oral cephalosporins, such as cefepime pivoxil, cefditoren pivoxil, and ceftoram pivoxil, are also often prescribed to treat acute cystitis. However, the bioavailability of third-generation oral cephalosporins is low [12,13]; the allowed dose is also low in Japan. Further, medical cautions have recently been issued with regard to the pivoxil group causing hypocarnitinemia [14].

A hospital antibiogram is a tool designed to guide clinical decisions in the face of growing bacterial resistance to drug therapy. It is generally created from data collected from a hospital-wide repertoire of cultured isolates. Thus, it can be a good resource to consult when treating a variety of pathogens, such as those that cause acute cystitis for which antimicrobials are usually selected empirically in Japan. However, it is not known whether the antimicrobial resistance of isolates from acute cystitis patients, who are mostly treated at outpatient clinics, and those from all patients, which are used to create hospital antibiograms, are similar. It has been shown that the average hospitalized patient, with risk factors for antimicrobial resistance, differs substantially from women with acute cystitis who present to the Urology Department [4,15]. Further, culture results for *E. coli* may include samples cultured from nonurine sources, which are more likely to include drug-resistant isolates [5].

In a Japanese nationwide survey, *E. coli* was found to be the most common pathogen of uncomplicated cystitis; the reported antimicrobial susceptibility of pathogens of uncomplicated cystitis was relatively high [3]. Furthermore, according to the Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy (JAID/JSC) guidelines used in Japan, cefaclor is recommended in the treatment of pre-menopausal women with uncomplicated cystitis as second-line therapy, and post-menopausal women with uncomplicated cystitis as first-line therapy [16]. We hypothesized a hospital antibiogram created from hospital-wide *E. coli* isolates

overestimates the resistance profile of this bacterium in acute uncomplicated cystitis cases. In this study, we evaluated the rates of antimicrobial susceptibility of isolates cultured from uncomplicated cystitis cases that presented to the Urology Department of a community hospital in Japan, as well as the efficacy of cefaclor, a narrow spectrum antibiotic, for uncomplicated cystitis. The existence of regional differences in antimicrobial susceptibilities means these susceptibilities need to be evaluated in various medical treatment zones of our hospital. We therefore compared the rates of antimicrobial susceptibility of isolates from uncomplicated cystitis cases to those reported in the hospital-wide antibiogram.

2. Patients and methods

This was a retrospective study that took place at the Komono Kosei Hospital, a suburban community hospital with 230 inpatient beds. This hospital provides medical services for a population of 80,000 inhabitants; other urology clinics are lacking in this area.

The patients who were included in the study: 1) were treated between August 1, 2015 and May 19, 2017; 2) received a diagnosis of acute uncomplicated cystitis; and 3) had their urine sent for culture. They were treated orally with cefaclor at 750 mg per day, which is the standard dosage in Japan, for seven days if a contraindication did not exist for this drug. If contraindications were present for cefaclor, patients were treated orally with levofloxacin at 500 mg per day for 3 days, or with trimethoprim at 320 mg and sulfamethoxazole at 1600 mg per day for 3 days. Urine culture data were analyzed and the “Urology Department (UD) cystitis antibiogram” was created.

To be enrolled in the study, patients were required to have acute uncomplicated cystitis and to be female, aged 16 years or older and under 90 years of age, with a bladder irritation, to lack underlying urinary tract disease and/or factors contributing to the onset, worsening, or prolongation of urinary tract infection, and to not have diabetes mellitus, a malignancy under treatment, cerebrovascular disease requiring assistance, or be on corticosteroid or immunosuppressant therapy. One or more of following was also required: pyuria confirmed by a reagent strip; ≥ 5 white blood cells (WBCs) per high-power field (hpf) on microscopy of urine sediment, and bacteriuria $\geq 10^3$ colony-forming units (cfu)/mL (for midstream urine, $\geq 10^4$ cfu/mL). We excluded cases that: were febrile, were pregnant, had an in-dwelling catheter, had a separate pelvic infection, had undergone recent surgery, had a negative urine culture result, or had failed a previous course of treatment, were admitted to hospital, or had asymptomatic pyuria, which may not represent true infectious cystitis. In order to exclude complicated cystitis patients, we performed abdominal and pelvic ultrasound sonography and we excluded cases that had: a urinary tract stone, residual urine, a bladder diverticulum or hydronephrosis. Successfully treated patients were defined as those that showed the elimination of a bladder irritation, bacteriuria, and of pyuria as confirmed by the negative test result of a reagent strip or having under four WBCs per hpf, on microscopy, of urinary sediment at a follow-up examination. Any adverse events of the antibiotics were recorded using the Common Terminology Criteria for Adverse Event (CTCAE) ver4.0. We reviewed 165 patient records. The antimicrobial susceptibility of each cultured isolate was recorded and the data reviewed by a single reviewer to ensure consistency.

The published hospital antibiogram that was used in this study was made from the antimicrobial susceptibility analysis of 454 cultured urine isolates collected from both outpatients and inpatients, between August 1, 2015 and May 19, 2017, who were suspected of having a urinary tract infection. Isolates were counted by one infectious episode per patient and plural isolates were

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