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ORIGINAL ARTICLE

Risk factors and clinical impact of levofloxacin or cefazolin nonsusceptibility or ESBL production among uropathogens in adults with community-onset urinary tract infections

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Background: Gram-negative bacilli causing community-onset urinary tract infections (CoUTIs) are getting increasingly resistant to antimicrobial agents. Clinical significance and risk factors of the acquisition of antimicrobial-nonsusceptible pathogens are still under investigation.
Methods: A prospective study was performed in the medical wards of two hospitals in southern Taiwan between August 2009 and January 2012. Patients were enrolled if they were aged >18, admitted through the emergency department, and had CoUTI due to *Enterobacteriaceae* isolates.
Results: Overall 136 adults with CoUTI were enrolled. Their mean age was 67 years and females were predominant (68.4%). Comorbidities, such as diabetes mellitus (30.1%) and hypertension (54.4%), were common. *Escherichia coli* (111, 81.6%) was the predominant species, followed by *Klebsiella pneumoniae* (11, 8.1%), and *Proteus mirabilis* (7, 5.1%). Nine (8.0%) of *E. coli* isolates and 5 (45%) of *K. pneumoniae* isolates had extended-spectrum β-lactamase (ESBL) production. Out of 122 non-ESBL producing isolates, 35 (28.7%) and 31 (25.4%) were nonsusceptible to levofloxacin and cefazolin, respectively. In the multivariate analysis, several clinical characters were

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found to be independently associated with CoUTIs due to levofloxacin-nonsusceptible (i.e. males, recent hospitalization, underlying old stroke, diabetes mellitus, and altered consciousness, or absence of chills, pyuria, or tachycardia), cefazolin-nonsusceptible (i.e. males, recent hospitalization, underlying old stroke, absence of fever or chills), or ESBL-producing isolates (i.e. recent hospitalization or antimicrobial therapy). All patients survived and discharged. However, the patients with CoUTIs due to levofloxacin-nonsusceptible (16.1 vs. 7.5 days, $p < 0.01$), cefazolin-nonsusceptible (15.4 vs. 8.4 days, $p < 0.01$) or ESBL-producing (16.7 vs. 9.6 days; $p < 0.01$) pathogens had a longer hospitalization stay than those due to their susceptible comparators.
Conclusion: Several host factors were recognized to be independently associated with the acquisition of UTIs due to levofloxacin- or cefazolin- nonsusceptible, or ESBL-producing Gram-negative bacilli. The clinical impact of UTIs due to nonsusceptible uropathogens is that they result in the prolongation of hospital stays.
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Introduction

Urinary tract infection (UTI) is the most common bacterial infection encountered in the ambulatory care settling in the United States, and is associated with significant morbidity and mortality.[1,2] The global surveillance study called SMART revealed, that among *Enterobacteriaceae* isolates from complicated UTIs, there was significant antimicrobial resistance to levofloxacin/ciprofloxacin (33%) and extended spectrum cephalosporins (>30%) in the Asia-Pacific region.[2] In addition, high prevalence rate of extended-spectrum β-lactamase (ESBL) production among uropathogenic *Escherichia coli* isolates was seen. Increasing fluoroquinolone resistance is another critical issue since fluoroquinolones (FQs) have been recommended as the drugs of choice for empirical treatment of uncomplicated and complicated UTIs caused by trimethoprim-sulfamethoxazole-resistant uropathogens.[3]

The resistance issue among uropathogens has become a global problem, necessitating consensus on revising the guidelines of empirical treatment of UTIs.[4,5] There are many articles discussing the risk factors of fluoroquinolone resistance among *E. coli* isolates from UTI.[6,7] In this study, we conducted a prospective study to identify host-related risk factors for community-onset UTI (CoUTI) due to levofloxacin- or cefazolin-nonsusceptible isolates or uropathogens with ESBL production in adults admitted to medical wards. Also clinical impact of UTIs due to antimicrobial-nonsusceptible pathogens was investigated.

Materials and methods

A prospective study was conducted at medical wards of National Cheng-Kung University Hospital, Douliu branch of NCKUH, and Tainan Hospital, Department of Health, Executive Yuan, at southern Taiwan between August 2009 and January 2012. Hospitalized patients were enrolled if they met the following criteria: they were older than 18 years, admitted through the emergency department and diagnosed as having CoUTI due to one species of *Enterobacteriaceae*. There were 164 cases enrolled into the study, and 28 were excluded because of polymicrobial infections or no available causative isolates for antibiotic susceptibility tests. Clinical information including age, gender, residence in nursing home, recent hospitalization within 6 months, recent antibiotic exposure within 60 days, underlying diseases (including end-stage renal disease, old stroke, diabetes mellitus, hypertension, chronic kidney disease, renal stone, or chronic hepatitis), and the use of indwelling urinary catheter, were retrieved from chart reviews or electronic databases, or by interviewing with their care-givers. The primary end-point for clinical impact was the duration of hospitalization, since there were no fatalities until discharge.

Recurrent UTI was defined if the individual had at least one episode of UTI within 1 year. Complicated UTI was defined as the occurrence of UTI in individuals with functional or structural abnormalities of the genitourinary tract. Concurrent bacteremia was defined as the presence of the identical uropathogen with the same antibiogram in blood cultures. Abnormal liver function was defined as elevated serum levels of aspartate transaminase (>39 U/L) or alanine aminotransferase (>54 U/L). Acute kidney injury was referred to if there at least was a 2-fold increase in serum creatinine level.

This study was supported by the National Cheng Kung University Hospital Research Committee and approved by the institutional review board of National Cheng Kung University Hospital and Tainan hospital, Department of Health, Executive Yuan. Informed consents were obtained from participating patients.

Bacterial cultures and antimicrobial susceptibility tests

Fresh urine samples were delivered to the laboratory and were processed as per standard procedure. Blood cultures were processed using the automated blood culture system (VITEK 2 complete ID/AST Automation system; bioMérieux, Mercy l'Etoile, France). Urine samples were plated on the eosin methylene blue agar and the isolated microorganisms were categorized by Gram staining. Antibiotic susceptibility testing was determined using the disk diffusion method in accordance with the criteria from the Clinical and Laboratory Standards Institute, M100-S21.[8] Drug disks tested for the

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