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Original Article

Influence of inadequate antimicrobial therapy on prognosis in elderly patients with severe urinary tract infections

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ABSTRACT

Background: Inadequate empirical antimicrobial therapy (IEAT) in intensive care unit (ICU) is associated with adverse outcomes. However, the influence of IEAT on prognosis for elderly patients with urinary tract infection (UTI) in non-ICU settings is unknown.
Methods: A retrospective cross-sectional study of elderly patients admitted to a non-ICU ward in a university hospital with a primary diagnosis of UTI over a 3-year period was done. Data relating to age, sex, background comorbidities, severity of infection, bacteremia, microorganisms isolated in urine, treatment given, length of stay and prognosis were obtained using chart review. Cases were segregated according to the adequacy of empirical antimicrobial therapy. In-hospital mortality rate was the main outcome variable evaluated.
Results: A total of 270 patients with a mean age of 83.7 years were studied. Sixty-eight percent were health-care associated infections. Seventy-nine (29.3%) cases received IEAT. IEAT was associated with previous hospitalization, urinary catheter and previous antibiotic. A Gram stain of urine with a gram-positive cocci was predictive of IEAT by multivariate analysis (OR, 6.29; 95% CI, 1.05–37.49). In-hospital mortality rate was 8.9%. IEAT (OR, 3.47; 95% CI, 1.42–8.48) was an independent risk factor for mortality along with APACHE II $\geq$15 (OR, 3.14; 95% CI, 1.24–7.90), dementia (OR, 3.10; 95% CI, 1.19–8.07) and neoplasia (OR, 3.49; 95% CI, 1.13–10.77). IEAT was not associated with length of stay in hospital.
Conclusion: IEAT is associated with mortality in elderly patients with UTI admitted to a non-ICU ward, suggesting that improving empirical antimicrobial therapy could have a favorable impact on prognosis.
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1. Introduction

Urinary tract infection (UTI) is the most common infection in elderly patients [1]. The high incidence of UTI in this population is due to the declining immunity and to the physiological and anatomical changes related to aging. Most bacteriurias in elderly patients are asymptomatic and do not require treatment. Symptomatic infections frequently have atypical and nonspecific presentations, these being in some cases acute confusion and rapid functional deterioration [2].

Elderly patients with UTI admitted to hospital usually have a high number of comorbidities, a history of admissions to hospital, chronic carriers of urinary catheters and previous use of antibiotics. All these factors are related to infections caused by drug resistant microorganisms and to inadequate empirical antimicrobial therapy (IEAT) [3,4]. IEAT is associated with poor prognosis in severe infections such as pneumonia, meningitis, bacteremia and peritonitis in the general population [5,6]. Studies on IEAT mainly include critical patients with blood stream infections from several focuses of infection, including a small proportion of cases of urinary origin [7–10]. Mortality rate in urosepsis is lower than mortality in other focuses, 44.8% versus 6.2%. However, in elderly patients with bacteremic UTI the mortality rate varies from 4.7% to 33.0% [10–13].

The influence of IEAT on prognosis of UTI in elderly patients admitted to hospital in non-intensive care units (ICU) is unknown. Therefore, we design this study with the aim of gaining knowledge on the influence of IEAT on in-hospital mortality in elderly patients in this setting.

Abbreviations: UTI, urinary tract infection; IEAT, inadequate empirical antimicrobial therapy; AEAT, adequate empirical antimicrobial therapy; ICU, intensive care unit; APACHE II classification system, acute physiology and chronic health evaluation classification system; CA-UTI, community acquired urinary tract infection; HA-UTI, community-onset healthcare-associated urinary tract infection; OR, odds ratio; CI, confidence interval.

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2. Methods

2.1. Design, setting and patients

Retrospective cross-sectional study of patients admitted to a teaching tertiary hospital with community acquired urinary tract infection (CA-UTI) or community-onset healthcare-associated urinary tract infection (HA-UTI) as the primary diagnosis at discharge from the hospital.

This study was carried out in the Department of Internal Medicine of the University Hospital Dr. Peset in Valencia, Spain. The hospital has 549 beds with 50 for internal medicine.

All patients 75 years old or older hospitalized between September 2009 and September 2012 with a primary diagnosis of UTI at discharge were included. Patients with hospital-acquired UTI were excluded.

2.2. Data collection

Epidemiological, clinical and laboratory data were collected from the medical records of each patient. Cases were segregated according to the adequacy of empirical antimicrobial therapy. In-hospital mortality rate was the main outcome variable evaluated. The other independent variables were: age, sex, comorbidities, McCabe and Jackson index, APACHE II score, severe sepsis, septic shock, health-care associated infection, IEAT, bacteremia, Gram stain and microorganisms isolated in urine.

2.3. Definitions

Severe UTI was defined when a patient admitted to the hospital had at least one of the following signs or symptoms with no other recognized causes: fever (>38 °C), urgency, frequency, dysuria, or suprapubic tenderness and the patient had a positive urine culture that was $>10^5$ microorganisms per cc of urine with no more than 2 species of microorganisms [12]. We included two types of UTI: CA-UTI and HA-UTI. HA-UTI was considered when UTI occurred in patients with any of the adapted criteria for healthcare-associated pneumonia and bloodstream infections: 1) to have been admitted to an acute care hospital 48 h or more within 90 days prior to the new hospital admission; 2) to have received treatment at home by qualified health care workers in the 30 days before hospital admission; 3) to have attended a day hospital, hemodialysis clinics or have received intravenous chemotherapy in the 30 days prior to hospital admission and/or 4) resided in a nursing home or long-term facility. CA-UTI was defined when a case of UTI did not met HA-UTI criteria [14].

To classify the patients according to their underlying diseases we used a modified McCabe and Jackson's classification, with the following categories: 1, non-fatal; 2, rapidly fatal; and 3, ultimately fatal [15]. To evaluate the severity of the patient's infection at admission we used acute physiology and chronic health evaluation classification system (APACHE II) score [16]. Sepsis, severe sepsis and septic shock were defined following the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [17]. Inappropriate empirical antimicrobial therapy (IEAT) was considered as the occurrence of infection that was not effectively treated at the time when the causative microorganism and its antibiotic susceptibility were known. This included the absence of antimicrobial agents directed at a specific class of microorganisms and the administration of an antimicrobial agent to which the microorganism responsible for the infection was resistant [8,9].

2.4. Statistical analysis

Categorical variables were compared using the chi-squared test or Fisher's exact test when appropriate. Continuous variables were expressed as means ± SD, and Student's t-test was used for comparing means. Two-tailed tests were used to determine statistical significance; a P value of <0.05 was considered significant. Logistic regression analysis was used to determine independent predictors of in-hospital mortality. All statistical analyses were performed by using the statistical pack SPSS 18.0.

3. Results

A total of 270 patients were included during the study period. One hundred and sixty-two patients (60.0%) were women and the average age was 83.7 ± 5.4 years. There were 85 (31.5%) CA-UTI and 185 (68.5%) HA-UTI. One hundred and ninety-one patients (70.7%) received adequate empirical antimicrobial therapy (AEAT) and 79 (29.3%) patients received IEAT. The antibiotics empirically used and the proportion in which every one of them were considered IEAT were: ceftriaxone (used 35.5%, IEAT 34.3%), levofloxacin (used 27.4%, IEAT 36.4%), meropenem (used 16.3%, IEAT 0.0%), amoxicillin-clavulanate (used 13.3%, IEAT 16.6%), gentamicin (used 10.7%, IEAT 3.4%), imipenem (used 4.4%, IEAT 0.0%), ciprofloxacin (used 4.0%, IEAT 54.0%), cefuroxime (used 1.4%, IEAT 75.0%) and others (used 4.0%, IEAT 15.3%).

The epidemiological, clinical and microbiological characteristics of the patients on admission according to the adequacy of the antimicrobial therapy are shown in Table 1. No patient received home intravenous therapy, home health care or hemodialysis. Hospitalization within the 90 days prior to admission, urinary catheter, recurrent urinary infection, prior antibiotic use and a Gram stain with either gram-positive cocci or both gram-negative and gram-positive microorganisms were more common in the IEAT group. Only a Gram stain with gram-positive cocci was statistically associated with IEAT by multivariate analysis (Table 2). Following exclusion of 13 (5.2%) cases with missing Gram stain a second regression analysis showed that prior hospital admission was the only factor associated with IEAT (OR 2.15, 95% CI 1.10–4.18, $p = 0.024$).

Two hundred and fifty-four UTI cases were monomicrobial (90.4%), and 26 cases were polymicrobial (9.6%) in which two microorganisms were isolated. The microorganisms isolated were *Escherichia coli* 196 (66.2%), *Enterococcus faecalis* 33 (11.2%), *Klebsiella pneumoniae* 31 (10.5%), *Pseudomonas aeruginosa* 17 (5.7%), *Proteus* spp. 11 (3.6%) and others 8 (2.7%). The antibiotic resistance pattern of the 196 cases due to *E. coli* was: ampicillin (76.5%), amoxicillin-clavulanate (7.6%), cefazolin (30.0%), cefotaxime (20.4%), ciprofloxacin (42.6%), gentamicin (13.7%), imipenem (0.0%), piperacillin-tazobactam (4.6%) and trimethoprim-sulfamethoxazole (33.5%). In 33 (16.8%) cases of UTI due to *E. coli* extended spectrum beta-lactamases (ESBL) containing strains were detected. No case of *E. coli* infection was resistant to carbapenems. Thirty-three (18.5%) cases of *E. coli* infection received IEAT. Antibiotics that were inadequate to *E. coli* infection were the following: 21 (63.6%) cases with quinolones, 8 (24.2%) cases with cephalosporins, 3 (9.1%) cases with amoxicillin-clavulanate and 2 (6.1%) cases with gentamicin. Twenty-five (75.5%) cases of *E. faecalis* infection received IEAT: 17 (68.0%) cases with cephalosporins and 8 cases (32.0%) with quinolones. Ten (32.2%) cases of *K. pneumoniae* infection received IEAT: 7 (70.0%) cases with cephalosporins, 2 cases (20.0%) with quinolones and 1 (10.0%) with amoxicillin-clavulanate. In 10 (32.2%) cases of UTI due to *K. pneumoniae* ESBL containing strains were detected. Ten (58.8%) cases of *P. aeruginosa* infection received IEAT: 6 (60.0%) cases with cephalosporins, 3 cases (30.0%) with quinolones and 1 (10.0%) case with amoxicillin-clavulanate. Three (17.6%) case of *P. aeruginosa* were due to multidrug-resistant strains. Four (44.4%) cases of *Proteus mirabilis* infection received IEAT: 2 (50.0%) cases with quinolones, 1 (25.0%) case with cephalosporins and 1 (25.0%) case with amoxicillin-clavulanate. No case of *P. mirabilis* infection was due to ESBL-producing *P. mirabilis*.

The proportion of IEAT and AEAT of the more common microorganisms is shown in Fig. 1. IEAT was more common in *E. faecalis* and polymicrobial infection ($p \leq 0.001$). AEAT was more common in *E. coli* ($p < 0.001$) whereas *K. pneumoniae* ($p = 0.342$), *P. aeruginosa*

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