



Healthcare-Associated Urinary Tract Infection: Multi Drug Resistance and Risk Factors

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A new category of infections called healthcare-associated (HCA) infections was created due to increased procedures performed in outpatient clinics of hospitals. The risk of HCA infections is on the rise as the use of long-term care facilities (LTCFs) is increasing. HCA-urinary tract infection (UTI) is one of the most frequently occurring bacterial infections. In clinical and microbiological analyses, HCA-UTI is similar to hospital-acquired-UTI. The prevalence of multidrug-resistant (MDR) organisms in HCA-UTI has increased and is varied according to the type of LTCFs and regions. Finally, prior investigations reported the association between several risk factors and MDR acquisition, which vary considerably according to study design. Therefore, additional research is needed to develop a more accurate methodology.

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INTRODUCTION

Infections have been classified into hospital-acquired (HA) or community-acquired (CA) categories, depending on the place of acquisition [1]. However, procedures performed in hospitals are generally performed on an outpatient basis. Such infections cannot be classified into the traditional sense of HA or CA. Therefore, a new category of infection called healthcare-associated (HCA) infections was recently created.

The risk of HCA infections is increasing due to the increased use of long-term care facilities (LTCFs) [2]. LTCFs play an important role in the modern healthcare system, especially with an aging population. Elderly patients living in LTCFs are an important reservoir of multidrug-resistant (MDR) organisms, which can be transmitted to acute care hospitals through inter-hospital transfer [3,4].

Urinary tract infections (UTI) represent one of the most frequently occurring bacterial infections. HCA-UTI is also the most frequent bacterial infection among all HCA infections [5,6]. In particular, when acute pyelonephritis occurs in elderly people, bacteremia and septic shock are more frequent than in young people [7,8]. Therefore, it is critical to understand the characteristics of HCA-UTI and risk factors of MDR in elderly people.

DEFINITION OF HEALTHCARE-ASSOCIATED

HA-UTI is commonly defined as an infection that has been detected after the initial 48 hours of hospital admission. CA-UTI has been defined as an infection detected at or within 48 hours of hospital admission. However, in recent healthcare delivery system, CA-UTI should satisfy additional

conditions without fulfilling any criteria for HCA-UTI. HCA-UTI is defined as an infection detected at or within 48 hours of hospital admission based on specific criteria.

The criteria of HCA infection vary according to study design. Cardoso et al. [9] conducted a systematic review of HCA infection defined in clinical studies for ten years. Of the 52 studies, 30 studies used the definition proposed by Friedman et al. [2]. Among the 30 studies, a majority showed a low risk of bias and evidence of good quality. Additional criteria not included in the initial Friedman definition were: transfer from other LTCFs, immunosuppression, active or metastatic cancer, contact with family member infected with MDR microorganism, elderly or physical disabled patients, surgery in the last six months, and patients treated with radiation therapy. Based on this systemic review, we suggest that the Friedman criteria are widely accepted with quality results.

CHARACTERISTICS OF HEALTHCARE-ASSOCIATED-URINARY TRACT INFECTIONS

A comparative analysis of CA-UTI and HA-UTI is needed to determine the characteristics of HCA-UTI. Several studies showing HCA infections were more likely to resemble HA infections than CA infections. Friedman et al. [2] reported that HCA-bloodstream infections are similar to HA-bloodstream infections. In a prospective cohort study, 504 patients with 143 CA-bloodstream infections, 175 with HA-bloodstream infections, and 186 with HCA-bloodstream infections were enrolled. Methicillin-resistant *Staphylococcus aureus* (MRSA) was detected in patients with HCA and HA infections, and rarely in patients with CA infection. The mortality rate was higher in patients with HCA or HA infection ($p < 0.05$) than in those with CA infection. Other factors including comorbidity and pathogens also showed similar patterns. Valles et al. [10] reported the characteristics of 1,157 bloodstream infections. They reported that HCA-bloodstream infections differed considerably from CA-bloodstream infections and suggested an empirical antibiotic therapy similar to that indicated for HA-bloodstream infections.

Previous studies also showed similarities between HCA and HA infections in pneumonia and native valve endocarditis. Carratala et al. [11] analyzed a prospective cohort of 727 immunosuppressed hospitalized patients with 126

HCA-pneumonia and 601 CA-pneumonia. HCA-pneumonia patients were older and more commonly classified as a high-risk class. Drug-resistant *pneumococci* were more frequently detected along with a higher mortality rate in patients with HCA pneumonia. Benito et al. [12] reported that the clinical characteristics and outcomes of outpatients with HCA-naive valve endocarditis were similar to those with HA infection according to the International Collaboration on Endocarditis Prospective Cohort Study.

Therefore, it is necessary to investigate whether the characteristics of HCA-UTI were similar to those of other HCA infections. Horcajada et al. [13] compared HCA-UTI with CA-UTI and HA-UTI, involving 667 subjects (246 HCA-UTI, 279 CA-UTI, and 142 HA-UTI patients), in a prospective multi-center cohort study conducted in Spain. Compared with CA-UTI, patients with HCA-UTI were predominantly male (60% vs. 31%, $p < 0.001$) with a history of increased urinary tract obstruction, urological neoplasm, and structural or functional urinary tract abnormalities. Patients with HCA-UTI and HA-UTI showed fewer specific urinary tract symptoms ($p = 0.001$), albeit showing higher Pitt scores than those with CA-UTI. The all-cause 1-month mortality rate was higher in HCA-UTI and HA-UTI (11.4% and 20.4%) than in CA-UTI (3.9%). In microbiological studies, the isolation of extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* was less frequent in CA-UTI (5%) than in HCA-UTI and HA-UTI (13% and 12%). *Enterobacteriaceae* resistant to quinolones, amoxicillin-clavulanate, and piperacillin-tazobactam were more frequently detected in HCA-UTI and HA-UTI than in CA-UTI.

Smithson et al. [14], in a cross-sectional study, analyzed the characteristics of HCA-febrile UTI compared with CA-febrile UTI in men. HCA-febrile UTI patients were generally older, had higher Charlson comorbidity index, and received more frequent empirical antibiotics compared with CA-febrile UTI patients. Resistance to antibiotics, such as ceftriaxone, gentamicin, quinolone, cotrimoxazole, and fosfomycin, was higher in HCA-febrile UTI patients. The mortality rate was also higher in HCA-febrile UTI patients. Overall, patients diagnosed with HCA-UTI differed clinically and microbiologically from patients with CA-UTI, showing similarities with patients diagnosed with HA-UTI.

PREVALENCE OF MULTIDRUG-RESISTANT IN HEALTHCARE-ASSOCIATED-URINARY TRACT INFECTIONS

The prevalence of MDR organisms in LTCFs was approximately 20% to 50% with increasing trends, as reported in previous studies [3,15-17]. Lim et al. [18] conducted a nested case-control study involving four LTCFs in Australia using nasal and rectal swabs. Of the 136 participants, 41 (30%) carried at least one MDR organism. The prevalence was 16% MRSA, 6% vancomycin-resistant *enterococci* (VRE), and 21% MDR Gram-negative *bacilli* (GNB), including ESBL-producing *Escherichia coli* and *Acinetobacter baumannii*. Denkinger et al. [15] analyzed the prevalence of MRSA, VRE, and MDR GNB in a tertiary healthcare center for over 12 years. During the study period, MRSA was detected in 2,636 patients (56.8% of *S. aureus*), and 11% of MRSA was detected in urine. VRE was detected in 471 patients (17.6% of *enterococcal* isolates) and 49% of VRE were detected in urine. MDR GNB was detected in 1,060 patients (10.4% of Gram-negative isolates) and 61% of MDR GNB were detected in urine. All the MDR organisms showed an increasing prevalence from 1998 to 2009.

However, limited data exist for MDR in HCA-UTI, especially in patients of LTCFs. Lautenbach et al. [19] conducted a cross-sectional study that included 63 LTCFs located across three states in the US; they identified 1,805 Gram-negative organisms in patients admitted to LTCFs for ten months. The most common Gram-negative organism was *E. coli*. The prevalence of fluoroquinolone resistance was founded in 51% of *E. coli* and 29% of *Klebsiella* species. The prevalence of ceftazidime resistance was reported at 26% of *Klebsiella* species and 12% of *E. coli*. Even imipenem resistance was noted in 6% of *Klebsiella* species and 37% of *Pseudomonas aeruginosa*. The prevalence of MDR organisms varied significantly according to the type of LTCFs and regions.

In Korea, a retrospective case control study performed in 2016 [20] involved 196 patients diagnosed with a UTI during the study period, of which 52 patients were referred to Seoul Medical Center for UTI from LTCFs. MDR UTI was found in 54%, which showed an increasing trend compared with previous studies conducted at this center.

In patients with MDR UTI, *E. coli* was the most common organism (n=22); most isolates were resistant to ampicillin-sulbactam, ceftriaxone, ceftazidime, cefepime, ciprofloxacin, and levofloxacin. The higher prevalence of MDR UTI compared with previous studies from other countries was attributed to the regional and economic characteristics of LTCFs in this study. In brief, the prevalence of MDR in HCA-UTI showed an increasing trend and varied with the type of LTCFs and region.

RISK FACTORS FOR MULTIDRUG-RESISTANT URINARY TRACT INFECTIONS IN LONG-TERM CARE FACILITIES

The associated risk factors for MDR UTI in LTCFs include the following: length of stay, diabetes, pressure sores, medical device in situ, malignancy, recent hospitalization, neurogenic bladder, advanced dementia, and antibiotic exposure, some of which have been proven to be risk factors, while others remain controversial.

Advanced dementia has been associated with MDR, GNB, and MRSA colonization [21,22]. Patients with advanced dementia usually require greater support from healthcare workers and are more frequently exposed to antibiotics than those without dementia [22,23]. However, there are also studies showing opposite results. Hwang et al. [20] reported that advanced dementia prevented MDR UTI (odds ratio=0.088; 95% confidence interval, 0.014-0.531), unlike some previous studies. They asserted that in the absence of symptoms, tests or treatments for UTI are generally not performed. Therefore, patients with mild UTI—non-visible symptoms—may not be exposed to antibiotics, manifesting limited antibiotic resistance. Additionally, the definition of dementia used in this study was an important confounding factor. Patients with dementia may be categorized according to the International Classification of Diseases, or categorized based on the Diagnostic and Statistical Manual of Mental Disorders criteria via chart review and history taking.

Second, according to Shaffer et al. [24], who reviewed several studies examining the association between antibiotic exposure and MDR in long-term care populations, they found that while many studies reported positive association between antibiotic exposure and MDR, a few studies failed to identify such a significant relationship. They argued that

this discrepancy may likely be due to the variation of methodological approaches. To date, no standardized approach to antimicrobial exposure thresholds or durations has been established. Defining acquisition itself remains an important challenge; this is because the precise moment of MDR acquisition is impossible to establish. Therefore, future investigations are required to determine a more accurate methodology.

CONCLUSIONS

HCA-UTI is characterized by clinical and microbiological differences from CA-UTI, and similarities with HA-UTI. The prevalence of MDR in HCA-UTI increased and varied depending on the type of LTCFs and region. Prior investigations reported the association between several risk factors and MDR acquisition, which varied considerably according to study design. Therefore, further studies are needed to develop a more accurate methodology.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

- Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988;16:128-40.
- Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health care--associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med* 2002;137:791-7.
- Ben-Ami R, Schwaber MJ, Navon-Venezia S, Schwartz D, Giladi M, Chmelnitsky I, et al. Influx of extended-spectrum beta-lactamase-producing enterobacteriaceae into the hospital. *Clin Infect Dis* 2006;42:925-34.
- Pop-Vicas A, Tacconelli E, Gravenstein S, Lu B, D'Agata EM. Influx of multidrug-resistant, gram-negative bacteria in the hospital setting and the role of elderly patients with bacterial bloodstream infection. *Infect Control Hosp Epidemiol* 2009;30: 325-31.
- Rosenthal VD, Bijie H, Maki DG, Mehta Y, Apisarnthanarak A, Medeiros EA, et al. International Nosocomial Infection Control Consortium (INICC) report, data summary of 36 countries, for 2004-2009. *Am J Infect Control* 2012;40:396-407.
- Laupland KB, Ross T, Pitout JD, Church DL, Gregson DB. Community-onset urinary tract infections: a population-based assessment. *Infection* 2007;35:150-3.
- Nicolle LE. Urinary tract infections in the elderly. *Clin Geriatr Med* 2009;25:423-36.
- Gleckman R, Blagg N, Hibert D, Hall A, Crowley M, Pritchard A, et al. Community-acquired bacteremic urosepsis in the elderly patients: a prospective study of 34 consecutive episodes. *J Urol* 1982;128:79-81.
- Cardoso T, Almeida M, Friedman ND, Aragao I, Costa-Pereira A, Sarmiento AE, et al. Classification of healthcare-associated infection: a systematic review 10 years after the first proposal. *BMC Med* 2014;12:40.
- Valles J, Calbo E, Anoro E, Fontanals D, Xercavins M, Espejo E, et al. Bloodstream infections in adults: importance of healthcare-associated infections. *J Infect* 2008;56:27-34.
- Carratala J, Mykietiuik A, Fernandez-Sabe N, Suarez C, Dorca J, Verdaguier R, et al. Health care-associated pneumonia requiring hospital admission: epidemiology, antibiotic therapy, and clinical outcomes. *Arch Intern Med* 2007;167:1393-9.
- Benito N, Miro JM, de Lazzari E, Cabell CH, del Rio A, Altclas J, et al. Health care-associated native valve endocarditis: importance of non-nosocomial acquisition. *Ann Intern Med* 2009;150:586-94.
- Horcajada JP, Shaw E, Padilla B, Pintado V, Calbo E, Benito N, et al. Healthcare-associated, community-acquired and hospital-acquired bacteraemic urinary tract infections in hospitalized patients: a prospective multicentre cohort study in the era of antimicrobial resistance. *Clin Microbiol Infect* 2013;19:962-8.
- Smithson A, Ramos J, Bastida MT, Bernal S, Jove N, Nino E, et al. Differential characteristics of healthcare-associated compared to community-acquired febrile urinary tract infections in males. *Eur J Clin Microbiol Infect Dis* 2015;34:2395-402.
- Denkinger CM, Grant AD, Denkinger M, Gautam S, D'Agata EM. Increased multi-drug resistance among the elderly on admission to the hospital--a 12-year surveillance study. *Arch Gerontol Geriatr* 2013;56:227-30.
- Lautenbach E, Synnestvedt M, Weiner MG, Bilker WB, Vo L, Schein J, et al. Epidemiology and impact of imipenem resistance in *Acinetobacter baumannii*. *Infect Control Hosp Epidemiol* 2009;30:1186-92.
- Gagliotti C, Balode A, Baquero F, Degener J, Grundmann H, Gur D, et al. *Escherichia coli* and *Staphylococcus aureus*: bad news and good news from the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS), 2002 to 2009. *Euro Surveill* 2011;16. pii: 19819.
- Lim CJ, Cheng AC, Kennon J, Spelman D, Hale D, Melican G, et al. Prevalence of multidrug-resistant organisms and risk factors for carriage in long-term care facilities: a nested case-control study. *J Antimicrob Chemother* 2014;69:1972-80.
- Lautenbach E, Marsicano R, Tolomeo P, Heard M, Serrano S, Stieritz DD. Epidemiology of antimicrobial resistance among gram-negative organisms recovered from patients in a multistate

- network of long-term care facilities. *Infect Control Hosp Epidemiol* 2009;30:790-3.
20. Hwang I, Kim H, Son Y, Jeong H, Kim M, Lee S, et al. Rate of antimicrobial resistant urinary pathogens and associated risk factor in older adults living in long-term care facilities in Seoul. *Korean J Fam Pract* 2017;7:864-9.
 21. Snyder GM, O'Fallon E, D'Agata EM. Co-colonization with multiple different species of multidrug-resistant gram-negative bacteria. *Am J Infect Control* 2011;39:506-10.
 22. Lasseter G, Charlett A, Lewis D, Donald I, Howell-Jones R, McNulty CA. *Staphylococcus aureus* carriage in care homes: identification of risk factors, including the role of dementia. *Epidemiol Infect* 2010;138:686-96.
 23. D'Agata E, Mitchell SL. Patterns of antimicrobial use among nursing home residents with advanced dementia. *Arch Intern Med* 2008;168:357-62.
 24. Shaffer ML, D'Agata EM, Habtemariam D, Mitchell SL. Examining the relationship between multidrug-resistant organism acquisition and exposure to antimicrobials in long-term care populations: a review. *Ann Epidemiol* 2016;26: 810-5.