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Increasing prevalence of antimicrobial resistance in urinary tract infections of neurological patients, Seoul, South Korea, 2007–2016

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ABSTRACT

Objectives: Urinary tract infection (UTI) is a common medical complication experienced by patients with neurologic diseases. In this study, we established the microbial etiologies of UTI, and resistances to antibiotics in UTI as well as determining which appropriate empirical antibiotics should be used to treat UTI in neurological patients.
Designs and methods: We retrospectively reviewed microbial etiologies and antimicrobial resistance among patients experiencing UTI events in the neurology ward of Seoul National University Hospital from 2007 to 2016.
Results: The total number of UTI events observed was 301, and *Klebsiella pneumoniae* was the most common pathogen observed in UTIs. But in catheter-associated UTI (CAUTI), *Enterococcus* species were the most prevalent pathogens. Susceptibility to commonly-prescribed antibiotics decreased over 10 years, indicating increased antibiotic resistance in pathogens associated with UTI. ESBL-producing *K. pneumoniae* increased significantly, while increases of MDR *K. pneumoniae*, ESBL-producing *E. coli*, and VRE were not observed.
Conclusions: The worldwide trend of increasing drug-resistant pathogens should be considered, and further studies on antibiotics resistance in UTI are needed. These data will greatly assist physicians when they select antibiotics to treat UTIs in neurological patients.

Introduction

Medical complications during a hospital stay play an important role in determining the outcomes of hospitalized patients with neurologic diseases or neurological patients (Poisson et al., 2010; Stott et al., 2009). Hospital-acquired infections represent a large proportion of these complications, with urinary tract infection (UTI) as one of the most common infections affecting hospitalized patients (Poisson et al., 2010; Flores-Mireles et al., 2015). Neurological patients are increasingly vulnerable to a UTI due to the presence of a neurogenic bladder or maintenance of a urinary catheter (Poisson et al., 2010; Hufschmidt et al., 2010).

UTIs are associated with poorer outcomes during hospitalization (Rocco et al., 2007), such as death or disability at 3 months, as well as an increased length of hospital stay in stroke patients (Poisson et al., 2010; Stott et al., 2009). Proper UTI management during hospitalization is important for improving outcomes in neurological patients. We investigated the microbial etiologies of UTI in hospitalized patients with a broad spectrum of neurologic diseases in a single institution, along with observing changes in antibiotic resistance of common pathogens. Our aims were to establish the overall incidence of UTI, microbial etiologies of UTI, and resistances to antibiotics in UTI as well as to determine which appropriate empirical antibiotics should be used to treat UTI in neurological patients.

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Methods

Clinical data of patients with UTI were reviewed via an electronic medical records system for patients who were admitted to the neurology ward of the Seoul National University Hospital in Seoul, South Korea between January 2007 and December 2016. The Gram stain results, microbial cultures, antibiotic sensitivity of a urinary specimen, main diagnosis during admission to the neurology ward, and history of antibiotics administration were obtained.

We included patients who had developed a UTI during their hospital stay in the neurology ward. UTI was defined as having had at least one of the following signs and symptoms: fever, suprapubic tenderness, costovertebral angle tenderness, urinary frequency, urinary urgency, and dysuria – with at least one of the urinary cultures having at least 10^5 colony-forming units (CFU) of bacteria per mL (Ramakrishnan and Scheid, 2005; Rubin et al., 1992; Centers for Disease Control and Prevention (CDC), 2018, https://www.cdc.gov/nhsn/pdfs/pscmanual/7psccauticurrent.pdf.). Asymptomatic bacteriuria or no identified bacterium in a urinary culture were not included in this study.

UTI events were classified into two categories: community-acquired UTI and hospital-acquired UTI. Hospital-acquired UTI was defined as having occurred more than 48 h after admission (World Health Organization, 2002, http://www.who.int/csr/resources/publications/drugresist/WHO_CDS_CSR_EPH_2002_12/en/) to our hospital, and community-acquired UTI was defined as having occurred less than 48 h after admission.

Other than that, we divided UTIs into catheter-associated UTI (CAUTI) and non-catheter-associated UTI (NCAUTI). CAUTI was defined as UTI with an indwelling Foley catheter for more than 2 days after UTI onset (Centers for Disease Control and Prevention (CDC), 2018, https://www.cdc.gov/nhsn/pdfs/pscmanual/7psccauticurrent.pdf.), with the remaining events classified as NCAUTI. UTIs associated with clean intermittent catheterization (CIC) were included in the NCAUTI subgroup and were assessed separately, and was defined as a UTI that occurred after having more than two intermittent catheterizations daily over at least 2 days from the date of UTI onset.

All pathogens identified from urinary cultures of UTI patients were assayed against various antimicrobial agents. The minimal inhibitory concentrations (MICs) of the antibiotics were assessed by the methods suggested by the Clinical and Laboratory Standards Institute (CLSI) (Patel et al., 2015). UTI pathogens were classified as susceptible, intermediate-resistant or resistant to certain antibiotics according to the CLSI recommendations (Patel et al., 2015; Schito et al., 2009). Multi-drug resistant (MDR) bacteria were defined as having resistance to three or more antimicrobial classes (Magiorakos et al., 2012).

Statistical analysis

Clinical patient data, UTI microbial etiologies, and antibiotics used to treat UTI were analyzed by the R Project for Statistical Computing program, manufactured by Robert Gentleman and Ross Ihaka from University of Auckland, Auckland, New Zealand. The Cochran-Mantel-Haenszel test was used to assess trends associated with the annual spectrum of microbes associated with UTI and antibiotic susceptibilities of UTI-associated pathogens. Grouped analysis of the trend of antibiotics resistance of UTI-associated pathogens was performed using logistic regression. A comparison of microbial etiologies between UTI subgroups was performed using Fischer's exact test. Two-sided p-values <0.05 were considered significant in all statistical analyses. All of the statistical analyses were supported by the Medical Research Collaborating Center (MRCC) of Seoul National University Hospital, Seoul, Korea.

Results

Clinical characteristics of neurological patients with UTI

A total of 301 symptomatic UTI events were identified among the 28,020 patients who were admitted to the neurology ward of Seoul National University Hospital from 2007 to 2016 in 202 patients, representing 0.7% of all neurological patients.

We reviewed the clinical characteristics of neurological patients with UTI (Table 1). The median age of patients at the time of UTI was 63 years (range of 15 to 93 years), with 95 patients being over 65 years old (47.0%). A total of one hundred-six patients were female (52.5%). A total of 175 immobile patients (86.6%) were identified, who had a modified Rankin score (mRS) of 4 or 5.

The primary diagnosis of patients who experienced a UTI is shown in Table 1. The most common primary diagnosis of UTI patients was stroke (72 patients, 35.6%), followed by encephalitis that was either infective or autoimmune (40 patients, 19.8%), epilepsy (32 patients, 15.8%), and various movement disorders (20 patients, 11.0%).

Of the total of 301 cases of UTI, 272 (90.4%) were hospital-acquired, while the other 29 cases were community-acquired UTI (9.6%). In hospital-acquired UTI, 233 (77.41%) cases occurred after one week or more and 42 cases (14.0%) occurred in the intensive care unit (ICU). The number of CAUTI was 142 (47.3%). Of the remaining cases of NCAUTI (159 cases, 52.8%), 45 (28.3%) occurred with regular CIC.

Microbial etiology of UTI in neurological patients

The annual microbial spectrum of UTI from a urinary culture is shown in Figure 1. The most common pathogen associated with

Table 1
Clinical characteristics of neurologic patients with symptomatic UTI and the UTI events between 2007 and 2016.

Total patients (n = 202)	
Age, years	63 (15-93)
Age ≥ 65	95 (47.0%)
Female sex	106 (52.5%)
Immobility (Initial mRS* ≥ 4)	175 (86.6%)
The main diagnosis during hospitalization	
Stroke	72 (35.6%)
Meningoencephalitis	40 (19.8%)
Epilepsy	32 (15.8%)
Movement disorder	20 (11.0%)
Demyelinating disease & myelopathy	9 (6.0%)
Neuromuscular disease	8 (4.0%)
Toxic & metabolic encephalopathy	8 (3.7%)
Others	13 (7.0%)
Total UTI events (n = 301)	
Location of acquisition	
Hospital-acquired UTI	272 (90.4%)
Hospitalization ≥ 1 week	233 (77.4% among total UTI)
ICU hospitalization	42 (14.0% among total UTI)
Community-acquired UTI	29 (9.6%)
Associated conditions	
CAUTI	142 (47.2%)
NCAUTI	159 (52.8%)
UTI with regular CIC	45 (28.3% among NCAUTI)
Common antibiotics for UTI (n = 301)	
Ciprofloxacin	124 (41.2%)
3rd generation cephalosporin	100 (33.2%)
Piperacillin/tazobactam	55 (18.3%)
Levofloxacin	23 (7.6%)
Carbapenem	22 (7.3%)
Vancomycin	21 (7.0%)

* mRS, modified Rankin scale; ICU, intensive care unit; CAUTI, catheter-associated UTI; NCAUTI, non-catheter-associated UTI; CIC, clean intermittent catheterization.

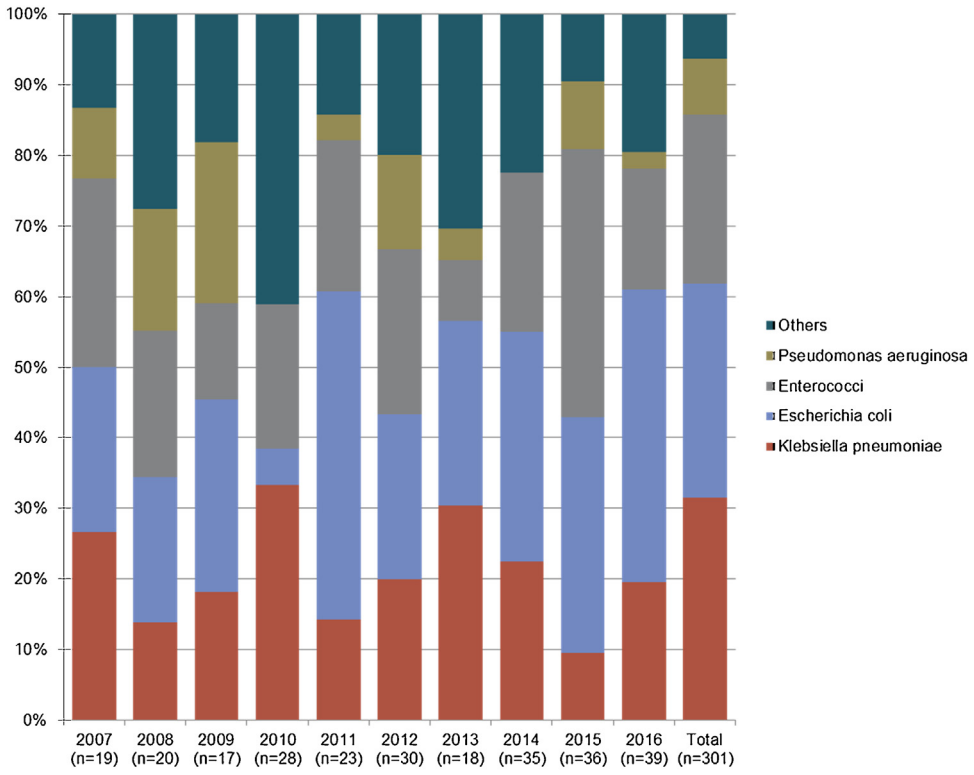

Figure 1. Number of cultured microorganism in urinary tract infection between 2007 and 2016. The microbial etiology of urinary tract infections over the last decade was reviewed. The most common pathogen was *Klebsiella pneumoniae* (95 cases, 35.9%), followed by *Escherichia coli* (91 cases, 34.3%), *Enterococcus* species (72 cases, 27.2%) and *Pseudomonas aeruginosa* (24 cases, 9.1%). However, the UTI-associated pathogen distribution did not significantly change over 10 years.

UTI was *Klebsiella pneumoniae* (95 cases, 35.9%), followed by *Escherichia coli* (91 cases, 34.3%), *Enterococcus* species (72 cases, 27.2%) and *Pseudomonas aeruginosa* (24 cases, 9.1%). During the study period, the proportion of UTI cases attributed to *E. coli* and *P. aeruginosa* varied significantly (p-value = 0.011 for *E. coli* and p-value = 0.027 for *P. aeruginosa*); however, a persistent increasing or decreasing trend was not observed, as the overall proportion of *K. pneumoniae* (p-value = 0.359) and *Enterococci* (p-value = 0.618) did not change.

We compared the microbial etiology between hospital-acquired UTI and community-acquired UTI (Figure 2A). In hospital-acquired UTI (272 cases, 90.4%), the most common pathogen was *K. pneumoniae* (89 cases, 32.7%), followed by *E. coli* (79 cases, 29.0%), *Enterococcus* species (67 cases, 24.6%) and *P. aeruginosa* (21 cases, 7.7%). However, in community-acquired UTI (29 cases, 9.6%), *E. coli* (12 cases, 41.4%) was the most common pathogen, followed by *K. pneumoniae* (6 cases, 20.7%), *Enterococcus* species (5 cases, 17.2%) and *P. aeruginosa* (3 cases, 10.3%). These results showed an observed difference in microbial etiology between hospital-acquired UTI and community-acquired UTI (p-value = 0.003).

We compared the microbial etiologies of CAUTI to those of UTI without catheterization (Figure 2B). In CAUTI (142 cases, 47.2%), *Enterococcus* species (43 cases, 30.3%) were the most common pathogens, followed by *E. coli* (34 cases, 24.3%), *K. pneumoniae* (33 cases, 23.2%), *P. aeruginosa* (13 cases, 9.3%) and *Proteus mirabilis* (13 cases, 9.3%). However, in NCAUTI (159 cases, 52.8%), *K. pneumoniae* was the most common pathogen (58 cases, 36.5%), followed by *E. coli* (54 cases, 34.0%), *Enterococcus* species (26 cases, 16.4%), *P. aeruginosa* (12 cases, 7.5%) and *Proteus mirabilis* (8 cases, 5.0%). The microbial etiologies of CAUTI and NCAUTI are observed to be different (p-value = 0.003).

Trends of antibiotics susceptibility in pathogens involved in UTI

The antibiotics administered to treat UTI were reviewed (Figure 3) and are shown in Table 1. Ciprofloxacin was the most frequently prescribed antibiotic for UTI (124 cases, 41.2%), followed by 3rd generation cephalosporins (100 cases, 33.2%), piperacillin/tazobactam (55 cases, 18.3%), levofloxacin (23 cases, 7.6%), carbapenems (22 cases, 7.3%), and vancomycin (21 cases, 7.0%).

The trend of susceptibility to common antibiotics in UTI pathogens is shown in Figure 3. The ten-year overall susceptibility of UTI cases to individual antibiotics was as follows: 25.5% (26 susceptible over 102) to levofloxacin, 32.0% (127 susceptible over 397) to ciprofloxacin, 53.4% (163 susceptible over 305) to ceftazidime (one of the 3rd generation cephalosporins), 65.9% (170 susceptible over 258) to piperacillin/tazobactam, 83.2% (89 susceptible over 107) to vancomycin, and 85.0% (267 susceptible over 314) to imipenem (one of the carbapenems) (Figure 3A). Over the last 10 years, the susceptibilities to ciprofloxacin (p-value = 0.031), ceftazidime (p-value<0.001), and piperacillin/tazobactam (p-value < 0.001) have decreased in UTI-associated pathogens. However, the susceptibilities to levofloxacin (p-value = 0.311), imipenem (p-value = 0.891), and vancomycin (p-value = 0.132) were unchanged (Figure 3B).

We analyzed whether the prevalence of antibiotics-resistant pathogens in UTI had increased over the past 10 years. Trends were assessed related to the presence of extended-spectrum beta-lactamases (ESBL)-producing and MDR pathogens in *E. coli* and *K. pneumoniae*, the most common UTI-associated pathogens (Figure 4A–D). The proportion of ESBL-producing pathogens increased in UTIs associated with *K. pneumoniae* (p-value = 0.001) (Figure 4A). However, MDR in *K. pneumoniae*, ESBL-producing *E.coli*, and MDR in *E.coli* did not change over the last 10 years (p-value = 0.094,

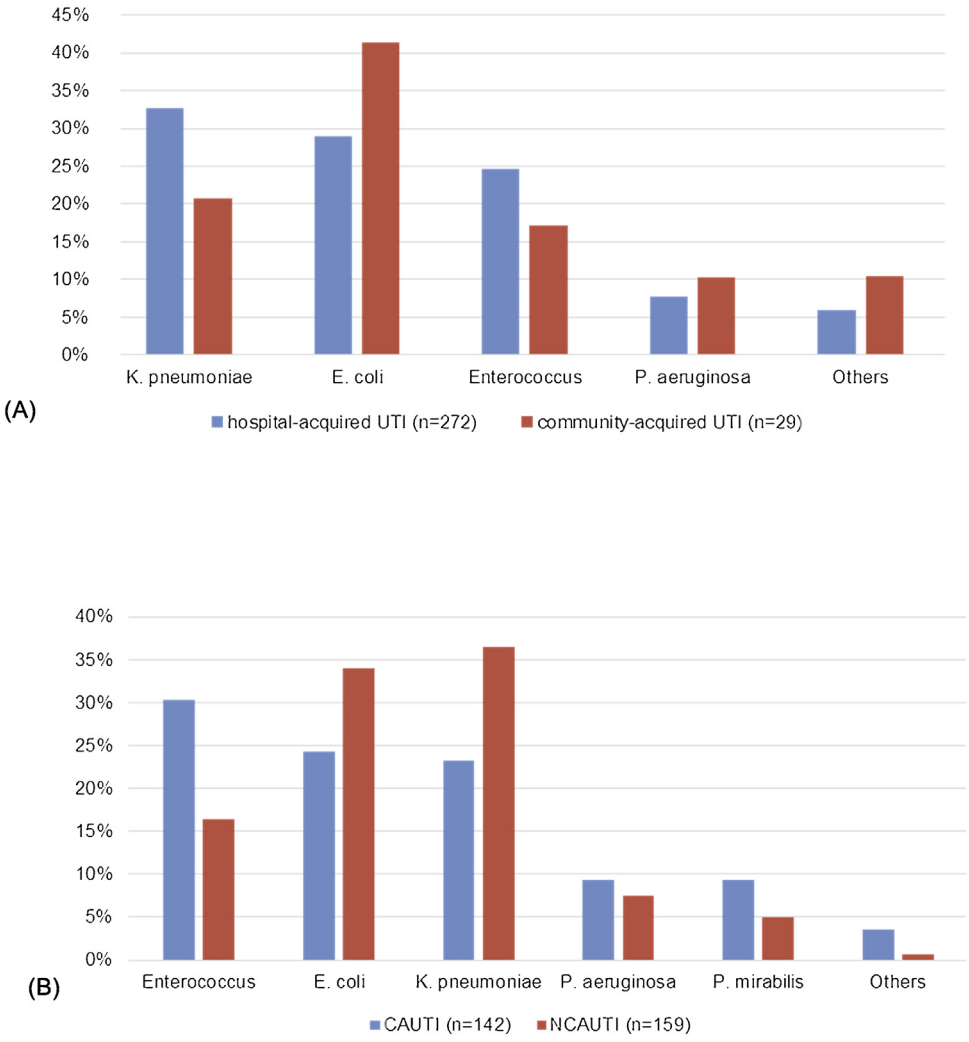

Figure 2. Comparison of microbial etiologies between UTI subgroups. We compared microbial etiologies by specific groups in UTI. (A), (B) In hospital-acquired UTI, *K. pneumoniae* was the most common pathogen, but in community-acquired UTI, *E. coli* was the most common. Differences were observed between pathogens of hospital-acquired UTI and community-acquired UTI (p-value = 0.003) (C), (D) Classified by urinary catheterization, *Enterococcus* species were the most common pathogens in catheter-associated UTI (CAUTI) and *K. pneumoniae* was the most common in UTI without urinary catheterization. A difference was observed between pathogens of CAUTI and NCAUTI (p-value = 0.003).

p-value = 0.056, p-value = 0.078 each) (Figure 4B–D). We also analyzed the trend comparing the proportion of vancomycin-resistant *Enterococcus* (VRE) to Enterococcal UTI (Figure 4E), and it was unchanged (p-value = 0.335).

Then we analyzed the proportion of ESBL-producing and MDR *E. coli* and *K. pneumoniae* pathogens present in three groups (2007 to 2009, 2010 to 2012, 2013 to 2016) (Supplementary Table S1, Supplementary Figure S1). In these three groups, an increasing trend was suggested comparing ESBL-producing and MDR bacteria compared to the total numbers of *E. coli* and *K. pneumoniae* (Supplementary Table S1, Supplementary Figure S1). However the increments were not stastically significant, except the comparison between 2007 to 2009 and 2013 to 2016 in ESBL-producing *K. pneumoniae*.

Discussion

This study describes trends in the microbial etiology of and antimicrobial resistance in UTI during 2007–2016 in the neurology ward in the Seoul National University Hospital. The most common microbial etiology of UTI was associated with *K. pneumoniae*, while *Enterococcus* species were the most common microbial etiology in CAUTI. UTI pathogens' susceptibility to commonly-prescribed antibiotics decreased over 10 years, while the proportion of ESBL-producing *K. pneumoniae* increased. The decreasing susceptibility of pathogens to empirical antibiotics and increasing trend of antibiotics-resistant pathogens should be noted in managing symptomatic UTIs in neurological patients.

In total, *K. pneumoniae* was the most common pathogen associated with total UTI, while *Enterococcus* species were most commonly associated with CAUTI. Previous studies show that *E.coli* is the most common pathogen associated with UTI (Flores-Mireles et al., 2015; Ramakrishnan and Scheid, 2005; Rubin et al., 1992); however, *K. pneumoniae* was more prevalent than *E. coli* in the UTIs described in our study. This difference may be because most UTIs in this study were hospital-acquired (272 cases, 90.4%). In hospital-acquired UTI, *K. pneumoniae* was the most common pathogen-associated UTI, whereas in community-acquired UTI, *E. coli* was the most common pathogen. *Enterococcus* species were the most common pathogens associated with CAUTI, which is in accordance with previous reports that Enterococcal UTIs are frequently related to CAUTI (Flores-Mireles et al., 2015; Swaminathan and Alangaden, 2010; Arias and Murray, 2012; Guiton et al., 2013). The adhesion factors of *Enterococcus* species, especially endocarditis- and

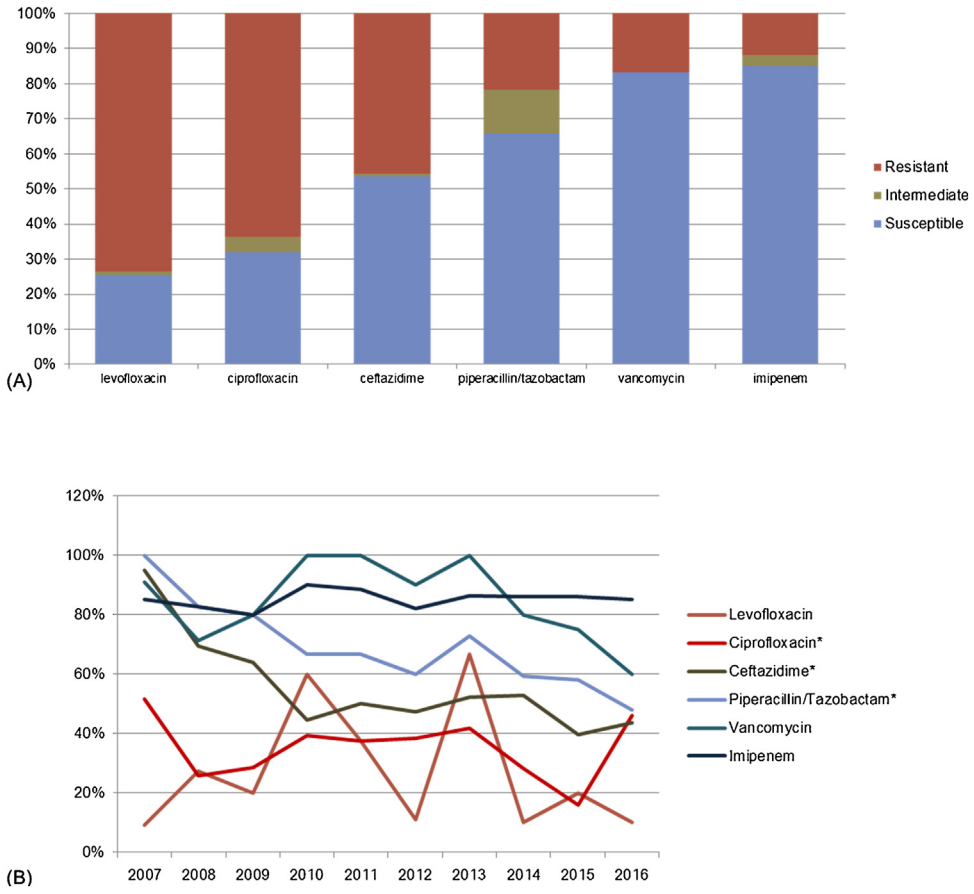

Figure 3. Susceptibility and resistance trends of commonly-prescribed antibiotics for UTI. The overall susceptibility and trend of susceptibility to commonly-prescribed antibiotics were reviewed. (A) The overall susceptibility was relatively high to imipenem (85.0%) and vancomycin (83.2%) and relatively low to ciprofloxacin (32.0%) and levofloxacin (25.5%). (B) We analyzed the trend of susceptibility to commonly-prescribed antibiotics for UTI in the neurology ward between 2007 and 2016. The susceptibility of ciprofloxacin (p-value = 0.031), ceftazidime (p-value < 0.001), and piperacillin/tazobactam (p-value < 0.001) declined over the last 10 years. However, the susceptibility to levofloxacin (p-value = 0.311), imipenem (p-value = 0.891), and vancomycin (p-value = 0.132) did not have a significant trend over the last 10 years.

biofilm-associated pili, are thought to be contribute to UTI pathogenesis after the mechanical stress induced by urinary catheterization (Flores-Mireles et al., 2015; Arias and Murray, 2012). Likewise, *P. mirabilis* produces adhesion factors, such as mannose-resistant *Proteus*-like pili and *P. mirabilis*-like fimbriae, which play an important role in biofilm formation and colonization and can cause UTIs in catheterized patients (Flores-Mireles et al., 2015; Jacobsen et al., 2008).

The most remarkable finding of this study is that we found a decreasing susceptibility of commonly-administered antibiotics in UTI pathogens, including ciprofloxacin, ceftazidime - the 3rd generation cephalosporin, and piperacillin/tazobactam. Since ciprofloxacin and 3rd generation cephalosporins are suggested as the first line of empirical antibiotics in UTI (Ramakrishnan and Scheid, 2005), we should recognize the increasing drug resistance in UTI-associated pathogens. Increasing resistance to 3rd generation cephalosporin and piperacillin/tazobactam is probably due to a rise in ESBL- producing bacteria (Meyer et al., 2010) because ESBLs can hydrolyze beta-lactam antibiotics, including penicillins, cephalosporins and monobactams (Rupp and Fey, 2003).

We identified that the proportion of ESBL-producing *K. pneumoniae* is increasing in neurological patients with UTI. Previous studies show antibiotics-resistant bacteria are increasing worldwide and are a serious problem in infection control (Schito et al., 2009; Magiorakos et al., 2012; Rupp and Fey, 2003; Fair and Tor, 2014; Ventola, 2015; Karam et al., 2016). ESBL-producing pathogens are spreading worldwide, and their prevalence is increasing (Rupp and Fey, 2003; Fair and Tor, 2014; Thaden et al., 2016; Chong et al., 2013). ESBL-producing *Enterobacteriaceae*, such as *E. coli* and *K. pneumoniae*, are particularly responsible for numerous infections, including UTI, and the increasing prevalence of ESBL-producing bacteria importantly affects patients' clinical outcomes and management (Rupp and Fey, 2003; Fair and Tor, 2014; Thaden et al., 2016). MDR prevalence in bacteria has also been found to be increasing worldwide (Fair and Tor, 2014; Ventola, 2015; Karam et al., 2016). Likewise, vancomycin-resistant *Enterococcus* (VRE) are increasing steadily worldwide and commonly cause UTI (Zhanel et al., 2003; Heintz et al., 2010). In this study, the levels of ESBL-producing *K. pneumoniae* increased. We did not find a statistically significant increase in MDR *K. pnuemoniae*, ESBL-producing *E. coli*, MDR E. coli and VRE, but the increasing trend was suggested when we analyzed the proportion of ESBL-producing and MDR *E. coli* and *K. pneumoniae* pathogens in three groups (2007 to 2009, 2010 to 2012, 2013 to 2016). We should follow up the further trend of drug-resistant pathogens of UTI.

Clinicians should be fully aware of the decreasing susceptibility of UTI-associated pathogens to commonly-prescribed antibiotics and the increasing amount of drug-resistant pathogens when selecting empirical antibiotics in UTI. Drug-resistant pathogens are increasing worldwide (Rupp and Fey, 2003; Fair and Tor, 2014; Ventola, 2015), and we found the increment in resistance to common antibiotics in UTI. Therefore, we should consider broad-spectrum or newer antibiotics as an empirical therapy in UTI.

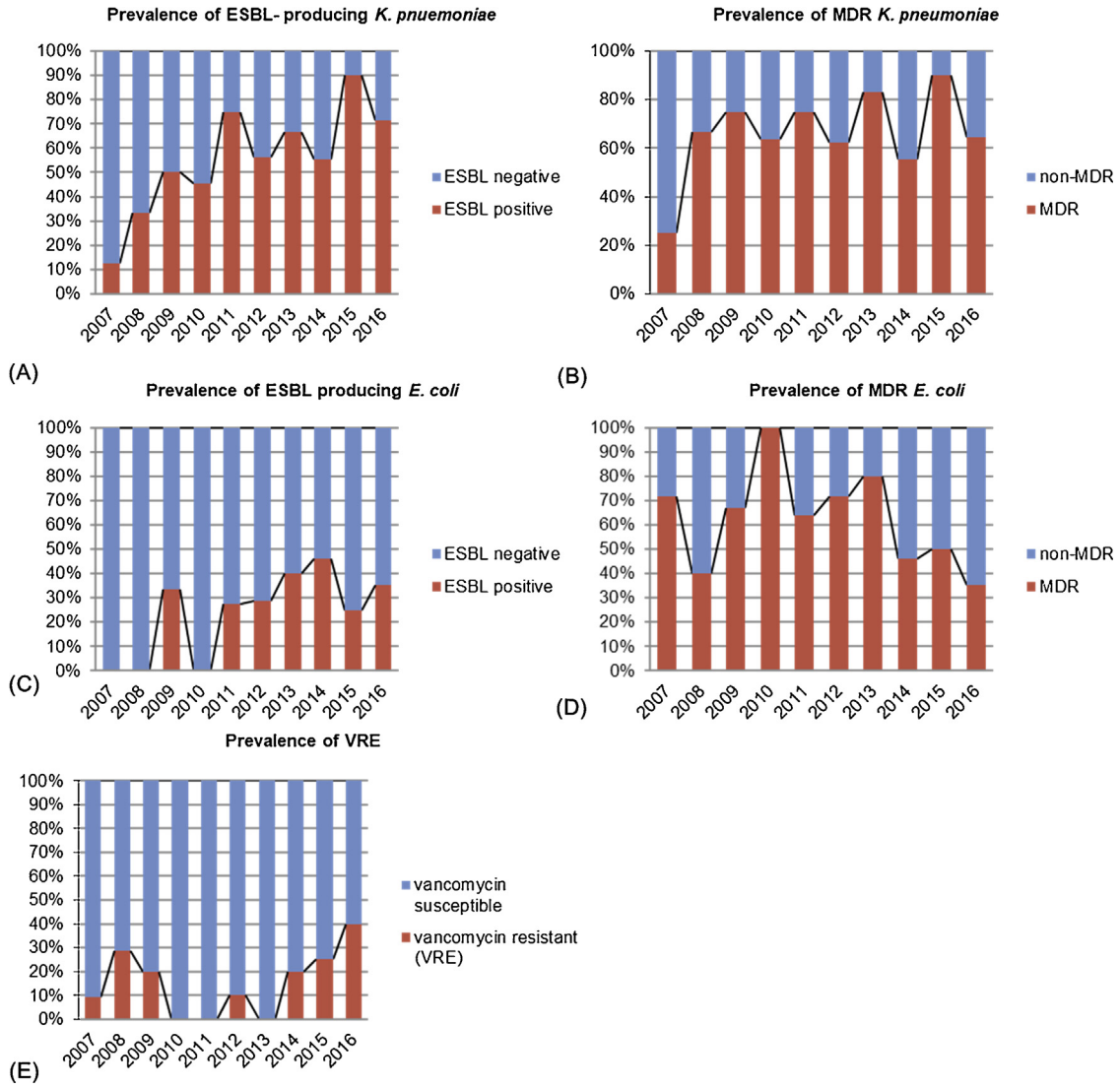

Figure 4. Trend of antibiotics resistance in UTI between 2007 and 2016. We assessed the changing trends of extended-spectrum beta-lactamase (ESBL)-producing and MDR pathogens in *E. coli* and *K. pneumoniae*, which are the most common pathogens in UTI. (A), (B) Among *K. pneumoniae* UTI, there was an observed increase in the proportion of ESBL producing pathogens (p-value = 0.001), but MDR did not increase (p-value = 0.094) (C), (D) Among the UTIs exhibiting a microbial etiology attributed to *E. coli*, the proportion of ESBL-producing pathogens and MDR in pathogens did not increase (p-value = 0.06, p-value 0.078 for each). (E) For Enterococcal UTI, the proportion of VRE did not change (p-value = 0.335).

Previous studies have shown that patients with urinary catheterization who are hospitalized in the ICU or have had previous hospitalization within past 30 days experience an increased risk of UTIs by ESBL-producing bacteria and VRE (Rupp and Fey, 2003; Karam et al., 2016; Zhanel et al., 2003). Thus, we should consider broad-spectrum antibiotics, including carbapenems, as empirical antibiotics for UTI, considering the clinical severity and risk factors, such as urinary catheterization and ICU hospitalization.

This study has some limitations. First, we reviewed limited data collected from a single medical center, so it may not reflect the national status of microbial etiology of and antibiotics resistance in UTI. However, this study is important as there are no previous studies characterizing long-term surveillance data for UTIs in all neurological patients in a tertiary referral hospital in South Korea. And since this was a retrospective study and depended on medical records, some UTI events may have been missed due to insufficient medical records. Otherwise, the antibiotics susceptibility test for levofloxacin and vancomycin was performed in only 102 and 107 cases, respectively, among a total of 412 UTI pathogens. Therefore, the reliability of levofloxacin and vancomycin sensitivity might be relatively low, and it was difficult to analyze the annual trend of susceptibility to these antibiotics. So, the nationwide surveillance program of microbial etiology and antibiotics resistance in infectious diseases is needed. We have not shown an increasing trend of drug-resistant pathogens other than ESBL-producing *K. pneumoniae*, but additional findings could be obtained by a nationwide study.

Treatment choices targeting UTIs in neurologic patients should change over time, reflecting the local distribution of possible pathogens and their resistances to antibiotics. Our investigation of the microbial landscape of UTI over 10 years represents important data for making decisions regarding the empirical antibiotics used in neurologic patients. Finally, choosing the best empirical antibiotics for UTIs will improve outcomes in patients in the neurological department.

Contributions

Study design: HR S, J M, K C; Data collection: HR S, J M, HS L; Data analysis: HR S, HS L; Writing first draft: HR S, Writing

subsequent drafts: all authors; Contributed intellectually: all authors.

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Ethical approval

All of the authors read and complied with the policy of the journal on ethical consent and the standards of animal care.

Conflicts of interest

The author claims no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.05.002.

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