Infect Dis Ther (2021) 10:1479–1489
https://doi.org/10.1007/s40121-021-00469-9

ORIGINAL RESEARCH

Outcomes for Patients with Urinary Tract Infection After an Initial Intravenous Antibiotics Dose Before Emergency Department Discharge

Xue-Er Poh · Kuan-Han Wu · Chien-Chih Chen · Jyun-Bin Huang · Fu-Jen Cheng · I-Min Chiu

Received: March 18, 2021 / Accepted: May 25, 2021 / Published online: June 14, 2021

ABSTRACT

Introduction: To investigate the effect of single-dose intravenous antibiotics before emergency department (ED) discharge on the outcomes of patients with urinary tract infections (UTIs).

Methods: This is a retrospective study conducted at the EDs of three medical centers. Patients aged over 18 years who presented to the ED with UTI and were discharged without admission between January 1, 2016 and December 31, 2017 were evaluated. The study group received a single dose of effective intravenous antibiotics on the basis of urine culture during the index ED visit following oral antibiotics, while the comparison group received oral antibiotics only. The primary outcomes were ED revisit within 72 h and admission following the return visit.

Results: A total of 8168 patients were included. Of these, 20.9% received intravenous antibiotics before ED discharge. Patients who received effective intravenous antibiotics before ED discharge were associated with less than 72-h ED revisit (adjusted odds ratio [OR] 0.791, 95% confidence interval [CI] 0.640–0.979]), but not decreased admission following the return visit (adjusted OR 0.921, 95% CI [0.731–1.153]). In subgroup analysis, parenteral antibiotic use during the index ED visit was associated with decreased admission following ED revisit in patients who presented with fever (adjusted OR 0.605; 95% CI 0.443–0.932).

Conclusion: For patients with UTI and clinically well to be discharged from the ED, a single dose of effective intravenous antibiotics before ED discharge was associated with decreased 72-h ED revisit. In patients with febrile UTI, initial intravenous antibiotics were associated with decreased revisit leading to admissions.

Keywords: Urinary tract infection; Loading intravenous antibiotics; Return emergency department visit; Revisit admission

X.-E. Poh · K.-H. Wu · C.-C. Chen · J.-B. Huang · F.-J. Cheng · I.-M. Chiu (✉)
Department of Emergency Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung 833, Taiwan
e-mail: outofray@hotmail.com

Key Summary Points
Why carry out this study?
UTI were the leading cause of ED visits and accounted for approximately 2% of ED visits in the USA annually.
Optimal management of UTI in the ED is quite challenging.
To better understand the value of single-dose intravenous antibiotics for patients with presumed UTIs who were well enough to be discharged from the ED.
What was learned from the study?
Effective intravenous antibiotic use before ED discharge was associated with decreased ED revisit in patients with UTIs (adjusted OR 0.774; 95% CI 0.625–0.959).
Intravenous antibiotic use in febrile patients with UTI is associated with decreased ED readmission (adjusted OR 0.591; 95% CI 0.389–0.898) for patients who can be discharged and managed as outpatients.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14662647.

INTRODUCTION

With 11% prevalence in the general population [1], urinary tract infections (UTIs) were the leading cause of emergency department (ED) visits and accounted for approximately 2% of ED visits in the USA annually [2]. Optimal management of UTI in the ED is quite challenging because of increasing antimicrobial resistance and treatment plans are usually made in the absence of microbiologic data [3–5], making it one of the most common diagnoses made during ED revisits [6].

On the basis of the current practice guidelines, patients with acute UTI of mild to moderate illness who are able to tolerate oral intake can be treated in an outpatient setting with oral antibiotics [7]. The treatment outcomes of oral antibiotics were as effective as those of parenteral antibiotics in uncomplicated UTI [8, 9]. Decades ago, several studies suggested single-dose antibiotic treatment for UTIs, proven to be as effective as oral antibiotic regimen [10–12]. With time, increasing antibiotic resistance altered the management, and these practices were no longer recommended [13]. However, the administration of single intravenous antibiotics in addition to oral regimen before discharge from the ED remains a common practice for patients with UTIs.

To better understand the value of single-dose intravenous antibiotics for patients with presumed UTIs who were well enough to be discharged from the ED, this study investigated the data from multiple medical centers in Taiwan to evaluate the effect of intravenous antibiotics before ED discharge on outcomes in patients with UTI.

METHODS

Study Design and Setting

This retrospective cohort study was conducted at the ED of three medical centers in Taiwan. They were located diversely in northern, middle, and southern Taiwan, and were all regarded as the largest medical centers in the metropolitan area. The diverse population and broad geographic regions in this study helped to provide a good representation of the population that experienced the same condition. The study was approved by the institutional review board of the Chang Gung Medical Foundation (date of approval 19/07/2018, number 201801085B0). The patient and physician records and information were anonymized and deidentified prior to the analysis.

Selection of Participants

We included all adult patients aged over 18 years who presented to the ED with UTI and were discharged without admission between January 1, 2016 and December 31, 2017 for analysis. Data of the enrolled patients diagnosed with UTI were collected from the research database using International Classification of Disease (ICD) codes (ICD 10th version).

Patients who were discharged against medical advice, had an ED length of stay longer than 24 h, received more than one dose of intravenous antibiotics, without urine culture study, and those with sterile or contaminated culture were excluded. A positive urine culture was defined as a bacterial count greater than 10^5/mL in urine culture. Urine cultures with three or more pathogens were regarded as contaminated [14]. As a result of increasing antimicrobial resistance in UTI cases, we also excluded patients who were ineffectively treated with intravenous antibiotics in the ED on the basis of urine culture findings.

The study group included patients who received a single dose of intravenous antibiotics during the index ED visit following oral antibiotic treatment, and the comparison group received oral antibiotic treatment only. In this study, the index ED visit was defined as the first ED visit for a unique patient or visits in which the patient had no prior ED visit during the past 3 days or hospitalization during the preceding 14 days. During the index ED, clinical variables, including age, sex, vital signs at triage, underlying comorbidities, and complicated UTI were used to analyze the use of intravenous antibiotics and their associated outcomes. UTI was considered complicated in cases of advanced age (at least 65 years old), male sex, abnormal urinary tract, and immunocompromised state with conditions of active cancer, end-stage renal disease, diabetes mellitus, and liver cirrhosis.

Outcome Measurement and Statistical Analysis

The primary outcomes were ED revisit and admission following a return visit within 72 h from discharge of the index visit. An ED revisit was not counted if the diagnosis was not related to the UTI. For patients with multiple ED visits during the study period, we included the first ED visit for UTI.

We performed the Mann–Whitney *U* test and chi-square analysis to determine the clinical characteristics that were correlated with intravenous antibiotic use. Logistic regressions assessing the association of measured outcomes with intravenous antibiotic treatment were performed after adjusting for confounding factors. Statistical significance was defined as a two-sided *P* value less than 0.05. Stratified regression analyses assessing the relationship between intravenous antibiotic use and clinical outcomes at different ages, vital signs, and comorbidities were also performed. All statistical analyses were conducted using the IBM SPSS Statistics for Mac (version 26).

RESULTS

Characteristics of Study Subjects

During the study period, 15,976 patients were discharged from the ED with a diagnosis of UTI. Of them, 6392 were not subjected to a culture test or had negative urine culture results, while 201 patients who received ineffective antibiotics were excluded. Thus, a total of 8168 patients who met the inclusion criteria were included in the study. The inclusion flowchart is shown in Fig. 1. Their median age was 57 (range 39–74) years, and 79.4% were female. A total of 1704 (20.9%) patients received intravenous antibiotics during the index ED visit. Patients with intravenous antibiotics treatment were significant older (median 63 [44–78] vs 55 [38–72] years, $p < 0.001$), tachycardiac (median 94 [81–108] vs 87 [77–100] beats per minute, $p < 0.001$), and hypotensive for both systolic blood pressure (median 139 [121–159] vs 140 [121–160]

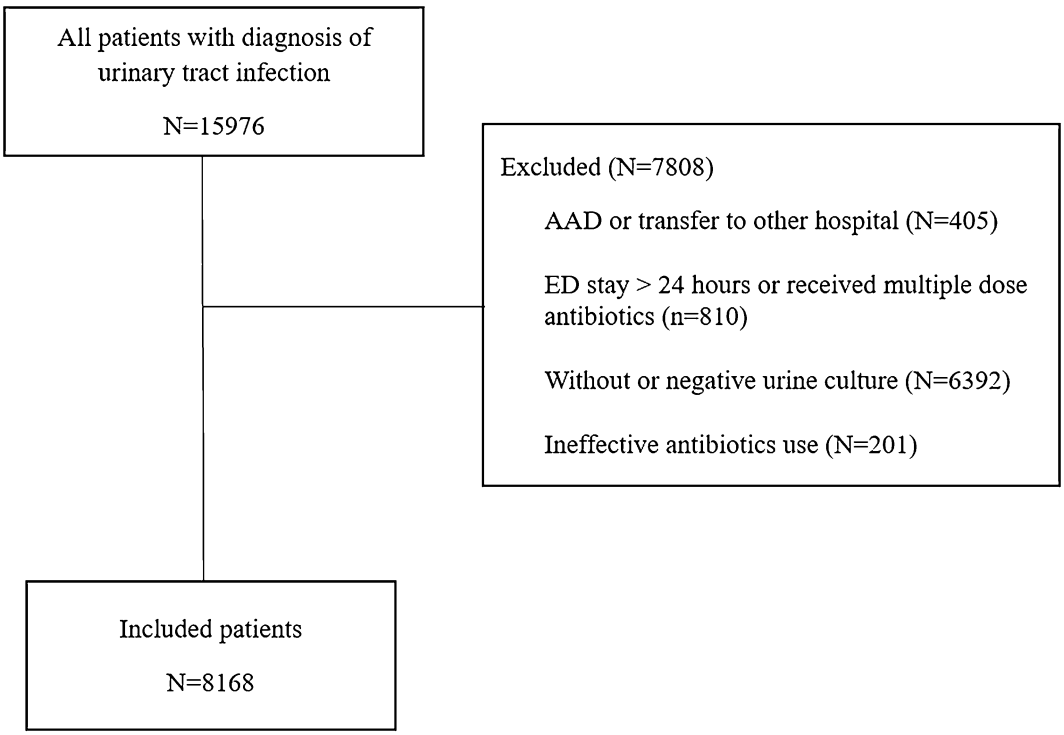

Fig. 1 Study inclusion flowchart

mmHg, $p = 0.045$) and diastolic blood pressure (median 81 (72–92) vs 84 (74–94) mmHg, $p < 0.001$) compared to those with oral antibiotic treatment only. Patients with complicated UTIs (61.6% vs 45.5%, $p < 0.001$) were also associated with intravenous antibiotic treatment during the ED visit. The other clinical variables are shown in Table 1. Regarding clinical outcomes, there was no statistical difference in return ED visits (8.4% vs 7.3%, $p = 0.135$) between the two patient groups. However, a higher percentage of patients receiving intravenous therapy had an ED revisit (6.2% vs 3.9%, $p < 0.001$).

Table 2 presents the use of intravenous antibiotics in the study patients. The most commonly prescribed antibiotics were cephalosporins (78.3%), followed by fluoroquinolones (9.4%), carbapenems (5.9%), and penicillin (1.3%). The common bacteria isolated from the urine cultures in this study are shown in Table 3. The most commonly isolated bacteria were *Escherichia coli*, accounting for 65.3% of the included patients, followed by *Klebsiella pneumoniae* (5.2%), *Enterococcus* species (4.7%), group B *Streptococcus* (4.5%), *Proteus mirabilis* (2.8%), and *Pseudomonas aeruginosa* (2.1%).

Logistic regression analysis was performed to identify the correlation between intravenous antibiotics and ED revisits. Since systolic and diastolic blood pressure were included in the regression model, we used median arterial blood pressure to replace these two variables to prevent multicollinearity. After adjustment for confounding factors, including age, sex, vital signs, and underlying diseases, receiving intravenous antibiotics during the index ED visit was associated with reduced 72-h ED revisits (adjusted OR 0.774; 95% CI 0.625–0.959]), but not with decreased admission following the return visit (adjusted OR 0.900; 95% CI 0.694–1.168), as shown by the logistic regression analysis. Other factors associated with both return ED visits and admission following return visits were older age, higher temperature, higher heart rate, and comorbidities, such as diabetes mellitus and liver cirrhosis (Table 4).

We further performed a subgroup regression analysis of specific age groups, sex, initial vital signs, and comorbidities (Table 5). Intravenous

Table 1 Demographic features and outcomes in patients with and without single-dose intravenous antibiotics before emergency department discharge

	With intravenous antibiotics treatment ***N* = 1704**	**Without intravenous antibiotics treatment** ***N* = 6464**	***p* value**
Age (year), median (IQR)	63 (44–78)	55 (38–72)	< 0.001
Male, *n* (%)	426 (24.7%)	1289 (19.4%)	< 0.001
Vital sign at presentation			
Temperature (°C), median (IQR)	37.2 (36.4–38.2)	36.6 (36.2–37.0)	< 0.001
Heart rate (/min) median (IQR)	94 (81–108)	87 (77–100)	< 0.001
Systolic blood pressure (mmHg), median (IQR)	139 (121–159)	140 (121–160)	0.045
Diastolic blood pressure (mmHg), median (IQR)	81 (72–92)	84 (74–94)	< 0.001
Underlying disease			
Hypertension, *n* (%)	665 (40.2%)	1779 (26.9%)	< 0.001
Diabetes mellitus, *n* (%)	485 (28.9%)	1169 (17.7%)	< 0.001
End-stage renal disease, *n* (%)	65 (4.0%)	215 (3.2%)	0.110
Liver cirrhosis, *n* (%)	280 (17.2%)	794 (12.0%)	< 0.001
Stroke, *n* (%)	97 (6.4%)	292 (4.3%)	< 0.001
Malignancy, *n* (%)	69 (4.2%)	135 (2.0%)	< 0.001
Abnormal urinary tract structure, *n* (%)	326 (19.6%)	850 (12.9%)	< 0.001
Complicated UTI, *n* (%)	1050 (62.9%)	2942 (44.8%)	< 0.001
Outcome			
Return ED visit	143 (8.4%)	473 (7.3%)	0.135
Admission following return ED visit	105 (6.2%)	255 (3.9%)	< 0.001

antibiotic use during the index ED visit was correlated with decreased 72-h ED revisit in patients aged 65 years or older (adjusted OR 0.719; 95% CI 0.536–0.905), those who presented with fever (adjusted OR 0.570; 95% CI 0.392–0.830) or tachycardia (adjusted OR 0.671; 95% CI 0.478–0.943); and those with underlying hypertension (adjusted OR 0.724; 95% CI 0.526–0.996), diabetes mellitus (adjusted OR 0.693; 95% CI 0.480–0.999), or complicated UTI (adjusted OR 0.770; 95% CI 0.598–0.991). Among them, intravenous antibiotic use was further associated with decreased admission following ED revisit in those who presented with fever (adjusted OR 0.591; 95% CI 0.389–0.898).

DISCUSSION

In this multicenter retrospective study, we found that a single dose of intravenous

Table 2 Intravenous antibiotics used in studied patients

Rank	Name	*N* (%)
	Total	1704
1st	1st generation cephalosporin	568 (33.3%)
2nd	2nd generation cephalosporin	401 (23.5%)
3rd	3rd generation cephalosporin	366 (21.5%)
4th	Fluoroquinolone	160 (9.4%)
5th	Carbapenem	100 (5.9%)
6th	Penicillin	23 (1.3%)

Table 3 Common urinary tract infection pathogens in included patients

Rank	Name	*N* (%)
	Total	8168
1st	*Escherichia coli*	5334 (65.3)
2nd	*Klebsiella pneumoniae*	423 (5.2)
3rd	*Enterococcus* species	387 (4.7)
4th	Group B *Streptococcus*	370 (4.5)
5th	*Proteus mirabilis*	232 (2.8)
6th	*Pseudomonas aeruginosa*	168 (2.1)
7th	*Staphylococcus saprophyticus*	121 (1.5)

antibiotics was administered to one out of every five patients with UTIs who could be discharged from the ED and managed as outpatients. Generally, patients with UTIs receiving intravenous antibiotics before ED discharge were associated with decreased 72-h ED revisits, but not on admission following return visits.

Prescribing intravenous antibiotics before ED discharge is a multifactorial decision. In this study, we found that patients who tended to receive a single dose of antibiotics before discharge were those with older age, male sex, worse vital signs, and more comorbidities. Previous studies have shown that UTIs account for approximately 25% of the source of sepsis in adult patients [15]. Mortality rates for patients with urosepsis range from 25% to 60%, and are especially high in the elderly, in patients with anatomical or functional abnormalities, or in immunosuppressed individuals [16–18]. This may explain why ED clinicians tend to provide more treatment in patients with immunosuppressed conditions alone than in those with worsening vital signs. Although oral antibiotics were shown to be as effective as parenteral antibiotics, the clinical severity and comorbidities of patients may affect the clinician's decision to administer parenteral antibiotics before they discharge the patient. As a result, patients who received intravenous antibiotics generally had a higher rate of return ED visits and subsequent admissions. However, we believe that this initial observational finding is biased because of significant differences in clinical characteristics between the two patient groups.

Cephalosporins were the most commonly chosen intravenous antibiotics, accounting for 78.3% of all intravenous antibiotic therapies. According to a recent study, first-generation cephalosporins had 72.1–83.4% drug susceptibility for lower UTI cases and 77% for upper UTI cases, making them not the first choice to cover possible resistance pathogens in UTI cases [19–21]. While one-third of patients received first-generation cephalosporins, 45% of patients received second-generation or newer cephalosporin antibiotics. On the other hand, fluoroquinolone and carbapenem were also chosen as suggested by recent practice guidelines [22].

Common pathogens that caused UTIs in the included population were comparable to those in previous studies; *E. coli*, *K. pneumoniae*, *Enterococcus* spp., and group B *Streptococcus* accounted for the majority of uropathogens [23]. On the other hand, *P. aeruginosa,* as previously reported to be more common in complicated UTIs, was found to constitute approximately 2% of the patients who could be discharged directly from the ED in this study [24].

In the early 1990s, an unscheduled ED revisit within 72 h after being discharged from a previous ED visit became a widely reviewed medical quality assessment tool [25, 26]. Return visits to the ED are resource consuming and can add strain to the already overburdened ED [27]. As

Table 4 Logistic regression analysis of confounding factors for return emergency department (ED) visit and admission following the return visit

	Return ED visit		Return ED visit with admission	
	Adjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
With intravenous antibiotics	0.774 (0.625–0.959)	0.019	0.900 (0.694–1.168)	0.428
Age	1.003 (0.997–1.476)	0.360	1.005 (0.998–1.012)	0.161
Temperature	1.346 (1.227–1.476)	< 0.001	1.575 (1.407–1.763)	< 0.001
Heart rate	1.007 (1.002–1.013)	0.005	1.010 (1.003–1.017)	0.004
Mean arterial pressure	1.000 (0.997–1.003)	0.931	0.997 (0.992–1.002)	0.231
Hypertension	1.225 (0.984–1.526)	0.069	1.211 (0.913–1.606)	0.184
Diabetes mellitus	1.536 (1.235–1.910)	< 0.001	1.506 (1.139–1.990)	0.004
End-stage renal disease	0.865 (0.563–1.329)	0.508	0.628 (0.334–1.181)	0.149
Liver cirrhosis	1.401 (1.116–1.758)	0.004	1.416 (1.061–1.889)	0.018
Stroke	0.943 (0.654–1.360)	0.754	1.014 (0.638–1.611)	0.953
Malignancy	0.927 (0.570–1.509)	0.761	1.021 (0.563–1.852)	0.945
Abnormal urinary tract structure	1.030 (0.814–1.303)	0.805	1.032 (0.764–1.393)	0.837

one of the most common diagnoses associated with ED revisit, one recent study showed that UTI-associated return visits were significantly higher in patients with advanced age, obstructive uropathy, fever, and tachycardia [3]. We found similar results in our study: older age, higher temperature, tachycardia, Foley indwelling, and comorbidities, such as hypertension, diabetes, and liver cirrhosis were associated with return ED visits after regression analysis. On regression analysis, the patients with comorbidities who received parenteral antibiotics and were then shifted to oral antibiotics had a lower likelihood of an ED revisit.

A recent study evaluated the effect of single-dose intravenous antibiotics for UTIs in children and found that it had no benefit in both ED revisit and readmission [28]. Our study showed that intravenous antibiotics before discharge were associated with decreased ED revisit, but not with admission following a return visit. To further investigate the effect of single-dose intravenous antibiotics for UTIs, we performed a subgroup analysis based on the patient's age, sex, vital signs, comorbidity, and complicated UTI. Single-dose intravenous antibiotics were still associated with decreased ED revisit in several subgroups, such as the elderly (age greater than 65 years), those presenting with fever, tachycardia, comorbid hypertension, diabetes mellitus, and complicated UTI.

Among these subgroups, patients with UTI who presented with fever may benefit from single-dose intravenous antibiotics before discharge, resulting in a decreased rate of admission following ED revisit. In infected individuals, fever represents a systemic host response to a microbial infection. Febrile UTI cases usually involve tissue invasion and systemic inflammation resulting from an upper UTI, such as pyelonephritis, which may be accompanied by sepsis syndrome progressing to life-threatening circulation failure [22]. For patients with an upper UTI who do not require hospitalization, current expert opinions suggest loading intravenous antibiotics followed by an oral regimen until results are obtained from the culture test [7]. Although it was difficult to distinguish upper UTI and lower UTI in ED most of

Table 5 Subgroup regression analysis of single-dose intravenous antibiotics use before emergency department (ED) discharge to outcomes

Specified subgroup	Return ED visit		Return ED visit with admission	
	Adjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Sex				
Female	0.815 (0.656–1.011)	0.063	0.959 (0.730–1.257)	0.756
Male	0.735 (0.534–1.013)	0.06	0.872 (0.567–1.337)	0.530
Age				
Age ≥ 65 years old	0.719 (0.536–0.905)	0.037	1.095 (0.789–1.520)	0.588
Age < 65 years old	0.805 (0.598–1.085)	0.155	0.757 (0.523–1.097)	0.141
Initial fever				
Yes	0.570 (0.392–0.830)	0.003	0.591 (0.389–0.898)	0.014
No	0.883 (0.684–1.140)	0.340	1.159 (0.846–1.589)	0.358
Initial tachycardia				
Yes	0.671 (0.478–0.943)	0.022	0.755 (0.512–1.114)	0.156
No	0.841 (0.639–1.107)	0.217	1.021 (0.724–1.442)	0.904
With underlying disease				
Hypertension	0.724 (0.526–0.996)	0.047	0.850 (0.575–1.258)	0.418
Diabetes mellitus	0.693 (0.480–0.999)	0.049	0.872 (0.589–1.274)	0.551
Liver cirrhosis	0.730 (0.463–1.150)	0.175	0.933 (0.542–1.605)	0.802
Stroke	1.071 (0.494–2.501)	0.862	1.057 (0.394–2.835)	0.912
Malignancy	0.817 (0.273–2.446)	0.718	1.014 (0.277–3.903)	0.953
Complicated UTI	0.770 (0.598–0.991)	0.042	0.999 (0.706–1.362)	0.996
Noncomplicated UTI	0.911 (0.641–1.296)	0.605	0.793 (0.510–1.235)	0.305

the time, the results of our study accord with this idea. From the perspective of pharmokinetics, there was a clear gap in bioavailability between intravenous and oral antibiotics for treating bacterial infections, especially in the early phase [29]. While most oral antibiotics require days to catch up from their initial 50–90% bioavailability, early intravenous antibiotics are recommended for treating patients with sepsis [30, 31]. In addition, intravenous antibiotics were more rapidly absorbed and enhanced the time to peak serum concentrations, particularly cephalosporins and penicillin [32]. It is therefore reasonable that intravenous antibiotic use in febrile patients with UTI is associated with decreased ED readmission for patients who can be discharged and managed as outpatients.

There are several important limitations to our study. First, this was a retrospective multihospital database study, and we were unable to review individual medical records to collect other clinical confounding factors that may influence the cause of the ED revisits. It was difficult to distinguish UTI type (upper vs lower) using the retrospective data. This may have

limited the detailed analysis of the effect of intravenous antibiotic use by UTI type. In addition, the decision to administer a single dose of intravenous antibiotics before discharge can be multifactorial. Patients' social education status, medication compliance, and family support may change clinicians' minds about whether to administer extra antibiotics. This unstructured information may not be present in a retrospective database review. Second, we included patients on the basis of ICD codes documented in the electronic health record system, which may have limited the number of UTI-related visits identified in the study. Third, we tracked the ED visits of included patients longitudinally in the same medical hospitals, and we do not know if the patients visited different hospitals for follow-up. This may have underestimated the general revisit rate in this study.

CONCLUSION

Administration of an initial single-dose intravenous antibiotic for patients with UTIs before ED discharge was associated with a decrease in ED revisit within 72 h of discharge. For patients with febrile UTIs, initial intravenous antibiotics were further associated with decreased admission following ED revisit within 72 h.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article. The Rapid Service Fee was funded by the authors.

Authorship. All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for the publication of this version.

Author Contributions. XEP, KHW, and IMC conceived the study and designed the trial. IMC and CCC supervised the trial and data collection. CCC and JBH recruited the participating centers and patients, managed the data, and ensured quality control. KHW and FJC provided statistical advice on the study design and analyzed the data. XEP drafted the manuscript, and all authors contributed substantially to its revision. IMC takes responsibility for the paper as a whole.

Disclosures. Xue-Er Poh, Kuan-Han Wu, Chien-Chih Chen, Jyun-Bin Huang, Fu-Jen Cheng and I-Min Chiu have nothing to disclose.

Compliance with Ethics Guidelines. The study was approved by the institutional review board of the Chang Gung Medical Foundation (date of approval 19/07/2018, number 201801085B0). The patient and physician records and information were anonymized and deidentified prior to the analysis.

Data Availability. Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

REFERENCES

1. Chu CM, Lowder JL. Diagnosis and treatment of urinary tract infections across age groups. Am J Obstet Gynecol. 2018;219:40–51.

2. Rui P, Kang K. National Hospital Ambulatory Medical Care Survey: 2017 emergency department summary tables. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2017_ed_web_tables-508.pdf. Accessed 16 Oct 2020

3. Jorgensen S, Zurayk M, Yeung S, et al. Risk factors for early return visits to the emergency department in patients with urinary tract infection. Am J Emerg Med. 2018;36:12–7. https://doi.org/10.1016/j.ajem.2017.06.041.

4. Lob SH, Nicolle LE, Hoban DJ, Kazmierczak KM, Badal RE, Sahm DF. Susceptibility patterns and ESBL rates of *Escherichia coli* from urinary tract infections in Canada and the United States, SMART 2010–2014. Diagn Microbiol Infect Dis. 2016;85:459–65. https://doi.org/10.1016/j.diagmicrobio.2016.04.022.

5. Asadi Karam MR, Habibi M, Bouzari S. Urinary tract infection: pathogenicity, antibiotic resistance and development of effective vaccines against uropathogenic *Escherichia coli*. Mol Immunol. 2019;108:56–67. https://doi.org/10.1016/j.molimm.2019.02.007.

6. Sabbatini AK, Kocher KE, Basu A, Hsia RY. In-hospital outcomes and costs among patients hospitalized during a return visit to the emergency department. JAMA. 2016;315:663–71. https://doi.org/10.1001/jama.2016.0649.

7. Gupta K, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52:e103-120. https://doi.org/10.1093/cid/ciq257.

8. G. Bonkat, Bartoletti R, Bruyère F, et al. EAU guidelines. Presented at the EAU Annual Congress Amsterdam the Netherlands. (2020). ISBN 978-94-92671-07-3.

9. Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. Clin Infect Dis. 2019;68:e83–110. https://doi.org/10.1093/cid/ciy1121.

10. Raz R, Rottensterich E, Hefter H, Kennes Y, Potasman I. Single-dose ciprofloxacin in the treatment of uncomplicated urinary tract infection in women. Eur J Clin Microbiol Infect Dis. 1989;8:1040–2. https://doi.org/10.1007/bf01975166.

11. Richard GA, Mathew CP, Kirstein JM, Orchard D, Yang JY. Single-dose fluoroquinolone therapy of acute uncomplicated urinary tract infection in women: results from a randomized, double-blind, multicenter trial comparing single-dose to 3-day fluoroquinolone regimens. Urology. 2002;59:334–9. https://doi.org/10.1016/s0090-4295(01)01562-x.

12. Ward G, Jorden RC, Severance HW. Treatment of pyelonephritis in an observation unit. Ann Emerg Med. 1991;20:258–61. https://doi.org/10.1016/s0196-0644(05)80935-7.

13. Huttner A, Kowalczyk A, Turjeman A, et al. Effect of 5-day nitrofurantoin vs single-dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection in women: a randomized clinical trial. JAMA. 2018;319:1781–9. https://doi.org/10.1001/jama.2018.3627.

14. Hay AD, Birnie K, Busby J, et al. Chapter 7: determinants of urinary contamination. In: The Diagnosis of Urinary Tract infection in Young children (DUTY): a diagnostic prospective observational study to derive and validate a clinical algorithm for the diagnosis of urinary tract infection in children presenting to primary care with an acute illness. Health Technol Assess. 2016;20(51). https://doi.org/10.3310/hta20510.

15. Wagenlehner FM, Weidner W, Naber KG. Optimal management of urosepsis from the urological perspective. Int J Antimicrob Agents. 2007;30:390–7. https://doi.org/10.1016/j.ijantimicag.2007.06.027.

16. Rosser CJ, Bare RL, Meredith JW. Urinary tract infections in the critically ill patient with a urinary catheter. Am J Surg. 1999;177:287–90. https://doi.org/10.1016/s0002-9610(99)00048-3.

17. Kalra OP, Raizada A. Approach to a patient with urosepsis. J Glob Infect Dis. 2009;1:57–63. https://doi.org/10.4103/0974-777x.52984.

18. Ackermann RJ, Monroe PW. Bacteremic urinary tract infection in older people. J Am Geriatr Soc. 1996;44:927–33. https://doi.org/10.1111/j.1532-5415.1996.tb01862.x.

19. Kim HY, Lee S-J, Lee DS, Yoo JM, Choe H-S. Microbiological characteristics of unresolved acute uncomplicated cystitis. Microb Drug Resist. 2016;22:387–91.

20. Kim WB, et al. Recent antimicrobial susceptibilities for uropathogenic *Escherichia coli* in patients with community acquired urinary tract infections: a

multicenter study. Urogenital Tract Infection. 2017;12:28–34.

21. Wie SH, Ki M, Kim J,et al. Clinical characteristics predicting early clinical failure after 72 h of antibiotic treatment in women with community-onset acute pyelonephritis: a prospective multicentre study. Clin Microbiol Infect. 2014;20:O721-729. https://doi.org/10.1111/1469-0691.12500.

22. Kang CI, Kim J, Park DW, et al. Clinical practice guidelines for the antibiotic treatment of community-acquired urinary tract infections. Infect Chemother. 2018;50:67–100. https://doi.org/10.3947/ic.2018.50.1.67.

23. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015;13:269–84. https://doi.org/10.1038/nrmicro3432.

24. Gomila A, Carratalà J, Eliakim-Raz N, et al. Risk factors and prognosis of complicated urinary tract infections caused by *Pseudomonas aeruginosa* in hospitalized patients: a retrospective multicenter cohort study. Infect Drug Resist. 2018;11:2571–81. https://doi.org/10.2147/idr.S185753.

25. Lerman B, Kobernick MS. Return visits to the emergency department. J Emerg Med. 1987;5:359–62. https://doi.org/10.1016/0736-4679(87)90138-7.

26. Nunez S, Hexdall A, Aguirre-Jaime A. Unscheduled returns to the emergency department: an outcome of medical errors? Qual Saf Health Care. 2006;15:102–8. https://doi.org/10.1136/qshc.2005.016618.

27. Duseja R, Bardach NS, Lin GA, et al. Revisit rates and associated costs after an emergency department encounter: a multistate analysis. Ann Intern Med. 2015;162:750–6.

28. Chaudhari PP, Monuteaux MC, Bachur RG. Emergency department revisits after an initial parenteral antibiotic dose for UTI. Pediatrics. 2018. https://doi.org/10.1542/peds.2018-0900.

29. van den Broek AK, Prins JM, Visser CE, van Hest RM. Systematic review: the bioavailability of orally administered antibiotics during the initial phase of a systemic infection in non-ICU patients. BMC Infect Dis. 2021;21:285–285. https://doi.org/10.1186/s12879-021-05919-w.

30. Liu VX, Fielding-Singh V, Greene JD, et al. The timing of early antibiotics and hospital mortality in sepsis. Am J Respir Crit Care Med. 2017;196:856–63.

31. Huang Y-H, Yan J-H, Kuo K-C, Wu W-T, Su C-M, Chiu I-M. Early antibiotics use in young infants with invasive bacterial infection visiting emergency department, a single medical center's experience. Pediatr Neonatol. 2020;61:155–9. https://doi.org/10.1016/j.pedneo.2019.08.003.

32. Ahmed TA. Pharmacokinetics of drugs following IV bolus, IV infusion, and oral administration. Basic Pharmacokinet Concepts Some Clin Appl. 2015. https://doi.org/10.5772/61573.