Gram-negative Organisms from Patients with Community-Acquired Urinary Tract Infections and Associated Risk Factors for Antimicrobial Resistance: A Single-Center Retrospective Observational Study in Japan

Naoki Kanda 1,2,*, Hideki Hashimoto 2, Tomohiro Sonoo 2, Hiromu Naraba 2, Yuji Takahashi 2,*, Kensuke Nakamura 2 and Shuji Hatakeyama 1

1 Division of General Internal Medicine, Jichi Medical University Hospital, Tochigi 329-0498, Japan; shatake-tky@umin.ac.jp
2 Department of Emergency and Critical Care Medicine, Hitachi General Hospital, Ibaraki 317-0077, Japan; hidehashimoto-tky@umin.ac.jp (H.H.); sonopy77@gmail.com (T.S.); nrbrhm@gmail.com (H.N.); yuji.mail@icloud.com (Y.T.); mamashockpapashock@yahoo.co.jp (K.N.)

* Correspondence: nakanda-tky@umin.ac.jp; Tel.: +81-285-58-7498; Fax: +81-285-40-5160

Received: 11 June 2020; Accepted: 20 July 2020; Published: 23 July 2020

Abstract: A specific antibiogram is necessary for the empiric antibiotic treatment of community-acquired urinary tract infections (UTI) because of the global spread of antimicrobial resistance. This study aimed to develop an antibiogram specific for community-acquired UTI and assess the risk factors associated with community-acquired UTI caused by antimicrobial-resistant organisms. This cross-sectional observational retrospective study included patients with community-acquired UTI caused by Gram-negative rods (GNR) who were admitted to the emergency department at a tertiary care hospital in Ibaraki, Japan, in 2017–2018. A total of 172 patients were enrolled (including 38 nursing home residents). Of the 181 GNR strains considered as causative agents, 135 (75%) were *Escherichia coli*, and 40 (22%) exhibited third-generation cephalosporin resistance. Extended-spectrum β-lactamase (ESBL)-producing *E. coli* accounted for 25/40 (63%) of resistant GNR. Overall susceptibility rate of Enterobacterales was 92%, 81%, 100%, 75%, and 89% for cefmetazole, ceftriaxone, meropenem, levofloxacin, and trimethoprim–sulfamethoxazole, respectively. Residence in a nursing home (odds ratio (OR), 2.83; 95% confidence interval (CI), 1.18–6.79) and recent antibiotic use (OR, 4.52; 95% CI, 1.02–19.97) were independent risk factors for UTI with resistant GNR. ESBL-producing *E. coli* was revealed to have a strong impact on antimicrobial resistance pattern. Therefore, an antibiotic strategy based on a disease-specific antibiogram is required.

Keywords: urinary tract infection; antibiotic resistance; antibiogram; nursing home; empiric therapy

1. Introduction

Urinary tract infection (UTI) is a common infectious disease worldwide [1–3]. Lower UTIs such as cystitis are usually treated in the outpatient setting. However, upper UTIs such as pyelonephritis or kidney abscess are often complicated by sepsis and/or bacteremia [4]; therefore, intravenous empiric antibiotic therapy and hospitalization are frequently required. UTIs are caused by several different types of bacteria, so-called uropathogens. While *Escherichia coli* is the most frequent causative agent, other Enterobacterales, enterococci, and *Pseudomonas aeruginosa* also cause UTIs.

Over the past decade, antimicrobial resistance has become a global threat [4–6]. The mechanisms of β-lactam resistance in Enterobacterales include extended-spectrum β-lactamases (ESBL), AmpC,
and carbapenemases, such as *Klebsiella pneumoniae* carbapenemase (KPC) or metallo-β-lactamase [7,8]. Enterobacterales possessing β-lactam resistance often pose resistance to other classes of antibiotics [9,10]. Although the prevalence of carbapenemase-producing Enterobacterales (CPE) is very limited in Japan so far, the prevalence of ESBL-producing Enterobacterales has been increasing in recent years. According to a report by the Japan Nosocomial Infections Surveillance (JANIS) system, the susceptibility rates to cefotaxime and levofloxacin among *E. coli* isolates were 72% and 58%, respectively, in 2017, compared to 92% and 75%, respectively, in 2007 [11].

The association between antimicrobial resistance and patient risk factors has been investigated in several studies [12–15]. A retrospective multivariate analysis performed by a Chicago emergency department showed that multidrug-resistant Enterobacteriaceae infections were associated with prior fluoroquinolone use, healthcare exposure, and presence of obstructive uropathy [12]. Another study from Spain indicated that healthcare-associated UTI and antibiotic use in the previous month were independent risk factors for fluoroquinolone resistance [13].

In addition to the risk factors, local and/or regional antibiogram data should be considered before making a decision regarding initial empiric antibiotic therapy for UTI. In general, a hospital antibiogram is constructed by the clinical microbiology laboratory using hospital-wide microbiology data, including all culture results collected in the outpatient and inpatient settings, regardless of whether the isolated bacteria cause infections or not. Therefore, the surveillance of microbiology data and antibiogram of a specific infection along with patient information is desirable.

We conducted a retrospective observational study of the antimicrobial resistance pattern of Gram-negative rods (GNR) causing UTIs in recent years. Furthermore, we analyzed the association between antimicrobial resistance and patient risk factors. The aim of this study was to assess the optimal empiric antibiotic therapy for community-acquired UTI based on specific microbiology and antibiogram data.

2. Methods

2.1. Study Design

This was a cross-sectional observational study utilizing an existing database and hospital records at Hitachi General Hospital, a tertiary care 651-bed hospital in Ibaraki Prefecture, Japan. Our database included the diagnoses and clinical assessments of all patients admitted to the emergency and intensive care departments. We defined the Gram-negative bacteria resistant to ceftriaxone as resistant GNR, and analyzed the risk factors for the detection of resistant GNR in patients with community-acquired UTI. This study was approved by the Ethics Committee of the Hitachi General Hospital (Number 2017-95). The requirement for written informed consent from the enrolled patients was waived by the Ethics Committee because of the retrospective design of the study.

2.2. Study Population

The database used in this study contained the data of all patients admitted to our department from 1 January 2017 to 31 December 2018. The records of all the patients who were diagnosed with UTI, including pyelonephritis, kidney abscess, prostatitis, and prostate abscess, were collected. We also analyzed the urine and blood culture results of each patient using microbiological data from the hospital microbiology laboratory. Subsequently, we included adult patients who were diagnosed with community-acquired UTI caused by GNR in our analysis. If a patient had multiple UTI episodes in the study period, we included only the first episode.

2.3. Data Collection

Clinical information extracted from the database included patient age, sex, residence in nursing home, antibiotic use within the last three months, hospital admission within the last three months, history of isolation of resistant GNR within the last six months, bed-ridden status (unable to get off the bed
without assistance), comorbidities (including diabetes mellitus, malignancy, and immunodeficiency), and placement of a long-term urinary catheter before admission.

The automated Vitek 2 (bioMerieux) method was used for bacterial identification and antimicrobial susceptibility testing of GNRs. Susceptibility test results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints [16]. The third-generation cephalosporin used for susceptibility testing was changed from ceftriaxone to cefotaxime in our hospital during the study period. Therefore, we have presented the susceptibility results for cefotaxime instead of ceftriaxone throughout this manuscript. The ESBL confirmation tests were performed using the MicroScan Panel (Beckman Coulter). When multiple GNRs were isolated from a single patient, we regarded the patient as being in the resistant GNR group if at least one GNR was resistant to ceftriaxone.

2.4. Statistical Analysis

We analyzed the prevalence of pathogens, the rate of ESBL-producing organisms, and susceptibility rates to several antibiotics including ampicillin, ampicillin-sulbactam, piperacillin-tazobactam, cefazolin, cefmetazole, ceftriaxone, cefotaxime, cefepime, meropenem, aztreonam, amikacin, levofloxacin, trimethoprim-sulfamethoxazole (TMP-SMX), and minocycline. Univariate analysis was conducted by Pearson’s chi-square test or Fisher’s exact test, as appropriate, for categorical variables, or the Mann–Whitney U test for continuous variables. Multivariate logistic regression was performed to identify the independent risk factors for resistant GNR. Age, residence in nursing home, prior antibiotic use, and long-term urinary catheter placement were included as variables based on the evidence from previous studies [10,12,13]. The robustness of the model was confirmed by the Hosmer–Lemeshow goodness-of-fit statistic. All p-values were 2-tailed; p-values less than 0.05 were defined as statistically significant. All statistical analyses were performed using SPSS (version 22.0, SPSS Inc., Chicago, IL, USA).

3. Results

Among 4328 patients who were admitted to our department during the study period, 271 were diagnosed with UTI. Of these, 48 patients had hospital-associated UTI, 22 had UTI caused by non-GNR bacteria, 16 had UTI without pathogen identification, and 13 had a recurrent episode of UTI and were excluded from the study. Finally, 172 patients who had community-acquired UTI caused by GNR were included in the analyses. A total of 181 strains of GNR that were considered as causative pathogens were identified. Among them, 40 resistant GNR strains were isolated from 37 patients, and were classified as the resistant GNR group.

Patient characteristics are shown in Table 1. The median age was 80 years, 60 patients (35%) were men, and 81 (47%) cases were complicated with bacteremia. The average length of stay in the intensive care and/or high care units was 3.6 days. Pyelonephritis accounted for 96% (165/172) of the UTIs, and the rest comprised three kidney abscesses, three prostatitis cases, and one prostate abscess. Nursing home residency, preceding antibiotic use, recent hospital admission, resistant GNR colonization, bed-ridden status, and long-term urinary catheter placement were significantly more frequently observed in the resistant GNR group than in the non-resistant GNR group.

Table 2 shows the microbiology, prevalence of resistant GNR and ESBL-producing bacteria, and susceptibility rates for antibiotics. Of the 181 GNR strains, E. coli accounted for 75% (135/181), Klebsiella spp. for 12% (22/181), and P. aeruginosa for 4% (8/181). ESBL-producing GNR comprised 65% (26/40) of resistant GNR, and all but one were ESBL-producing E. coli (25/26). The overall susceptibility rate of Enterobacterales in this study was 68% for ampicillin-sulbactam, 99% for piperacillin-tazobactam, 92% for cefmetazole, 81% for ceftriaxone, 83% for cefepime, 100% for meropenem, 75% for levofloxacin, 89% for TMP-SMX, and 87% for minocycline (Table 3).
### Table 1. Patient characteristics.

| Characteristics                        | Overall (n = 172) | Resistant GNR Group (n = 37) | Non-Resistant GNR Group (n = 135) | p-value |
|----------------------------------------|-------------------|-----------------------------|----------------------------------|---------|
| Age, median (IQR), years              | 80 (72–85)        | 80 (70–85)                  | 79 (73–85)                       | 0.906   |
| Males, no. (%)                        | 60 (35)           | 18 (49)                     | 42 (31)                          | 0.047   |
| Length of ICU/HCU stay, mean (SD), days | 3.6 (2.2)         | 3.8 (2.7)                   | 3.5 (2.1)                        | 0.481   |
| Pyelonephritis, no. (%)               | 165 (96)          | 36 (97)                     | 129 (96)                         | 0.995   |
| Bacteremia, no. (%)                   | 81 (47)           | 16 (43)                     | 65 (48)                          | 0.596   |
| **Risk factors, no. (%)**             |                   |                             |                                  |         |
| Nursing home residence                | 38 (22)           | 15 (41)                     | 23 (17)                          | 0.002   |
| Antibiotic use within last 3 months   | 9 (5.2)           | 5 (14)                      | 4 (3)                            | 0.023   |
| Hospitalization within last 3 months  | 10 (5.8)          | 6 (16)                      | 4 (3)                            | 0.007   |
| Resistant GNR colonization a           | 5 (2.9)           | 3 (8.1)                     | 2 (1.5)                          | 0.071   |
| Bed-ridden status b                   | 30 (17)           | 13 (35)                     | 17 (13)                          | 0.001   |
| Diabetes                              | 47 (27)           | 8 (22)                      | 39 (29)                          | 0.415   |
| Long-term urinary catheter            | 14 (8.1)          | 7 (19)                      | 7 (5.2)                          | 0.013   |
| Immunosuppression c                   | 42 (24)           | 11 (30)                     | 31 (23)                          | 0.396   |

Abbreviations: IQR, interquartile range; GNR, Gram-negative rod; ICU, intensive care unit; HCU, high care unit; SD, standard deviation. Significant p-values are indicated in bold. 

- **a** A history of positive resistant GNR culture within the last 6 months. 
- **b** Patient unable to get off the bed without assistance. 
- **c** Patient with malignancy or immunodeficiency and history of receiving immunosuppressive agents.
### Table 2. Gram-negative rods causing urinary tract infection and their antimicrobial resistance pattern.

| Factors                  | Total | E. Coli | K. Spp. | P. Aeruginosa | P. Mirabilis | E. Cloacae | P. Retgleri | S. Marcescens | C. Spp. | Others |
|--------------------------|-------|---------|--------|--------------|--------------|------------|-------------|---------------|---------|--------|
| GNR no. (%)              | 181   | 135 (73) | 22 (12) | 8 (4.4)      | 4 (2.2)      | 3 (1.7)    | 3 (1.7)     | 2 (1.1)       | 2 (1.1) | 2 (1.1) |
| Resistant GNR, no. (%)   | 40 (22)| 29 (22)  | 0       | 8 (100)      | 1 (25)       | 0          | 1 (33)      | 1 (50)        | 0       | 0      |
| ESBL+, no. (%)           | 26 (14)| 25 (19)  | 0       | 1 (25)       | 0            | 0          | 0           | 0             | 0       | 0      |
| Susceptibility rate, %   |       |         |        |              |              |            |             |               |         |        |
| Ampicillin               | 48    | 62      | 0      | 0            | 0            | 0          | 0           | 0             | 0       | 0      |
| Ampicillin-sulbactam     | 65    | 70      | 82     | 0            | 75           | 0          | 0           | 0             | 100     | 50     |
| Cefazolin                | 62    | 70      | 73     | 0            | 25           | 0          | 0           | 0             | 0       | 50     |
| Cefmetazole              | 87    | 96      | 86     | 0            | 100          | 0          | 0           | 67            | 0       | 100    |
| Ceftriaxone              | 78    | 78      | 100    | 0            | 75           | 100        | 67          | 50            | 100     | 100    |
| Ceftazidine              | 83    | 79      | 100    | 88           | 75           | 100        | 100         | 100           | 100     | 100    |
| Meropenem                | 98    | 100     | 100    | 63           | 100          | 100        | 100         | 100           | 100     | 100    |
| Aztreonam                | 79    | 79      | 96     | 63           | 75           | 100        | 33          | 50            | 100     | 0      |
| Amikacin                 | 100   | 100     | 100    | 100          | 100          | 100        | 100         | 100           | 100     | 100    |
| Levofloxacin             | 76    | 68      | 100    | 88           | 100          | 100        | 100         | 100           | 100     | 100    |
| TMP-SMX                  | 85    | 90      | 91     | 0            | 50           | 100        | 100         | 50            | 100     | 100    |
| Minocycline              | 83    | 91      | 86     | 0            | 100          | 33          | 50          | 100           | 100     | 100    |

Abbreviations: GNR, Gram-negative rods; ESBL, extended-spectrum β-lactamase; TMP-SMX, trimethoprim-sulfamethoxazole.

### Table 3. Antibiotic susceptibility pattern of isolates from nursing home residents and community-dwelling patients.

| Antibiotics          | Enterobacterales (n = 171) | P. aeruginosa (n = 8) | Enterobacterales (n = 39) | P. aeruginosa (n = 3) | Enterobacterales (n = 132) | P. aeruginosa (n = 5) |
|----------------------|-----------------------------|-----------------------|---------------------------|-----------------------|-----------------------------|-----------------------|
|                      | Overall                     | Living in Nursing Home | Community-Dwelling Patients |
| Susceptibility rate, %|                             |                       |                           |                       |                             |                       |
| Ampicillin           | 50                          | 0                     | 36                        | 0                     | 55                          | 0                     |
| Ampicillin-sulbactam | 68                          | 0                     | 59                        | 0                     | 71                          | 0                     |
| Piperacillin-tazobactam | 99                  | 88                    | 100                       | 100                   | 99                          | 80                    |
| Cefazolin            | 66                          | 0                     | 56                        | 0                     | 69                          | 0                     |
| Cefmetazole          | 92                          | 0                     | 90                        | 0                     | 93                          | 0                     |
| Ceftriaxone          | 81                          | 0                     | 64                        | 0                     | 86                          | 0                     |
| Ceftazidine          | 83                          | 88                    | 69                        | 100                   | 87                          | 80                    |
| Meropenem            | 100                         | 63                    | 100                       | 100                   | 100                         | 40                    |
| Aztreonam            | 81                          | 63                    | 67                        | 33                    | 85                          | 80                    |
| Amikacin             | 100                         | 100                   | 100                       | 100                   | 100                         | 100                   |
| Levofloxacin         | 75                          | 88                    | 54                        | 100                   | 81                          | 80                    |
| TMP-SMX              | 89                          | 0                     | 79                        | 0                     | 92                          | 0                     |
| Minocycline          | 87                          | 0                     | 82                        | 0                     | 87                          | 0                     |

Abbreviations: TMP-SMX, trimethoprim-sulfamethoxazole.
Multivariate logistic analysis revealed that nursing home residence (odds ratio (OR), 2.83; 95% confidence interval (CI), 1.18–6.79) and antibiotic use within the last three months (OR, 4.52; 95% CI, 1.02–19.97) were independent risk factors for community-acquired UTI caused by resistant GNRs (Table 4). The susceptibility rate of Enterobacterales among patients living in nursing homes was 100% for piperacillin-tazobactam, 90% for cefmetazole, 64% for ceftriaxone, 69% for cefepime, 54% for levofloxacin, 79% for TMP-SMX, and 82% for minocycline (Table 3).

### Table 4. Multivariate analysis for resistant Gram-negative rods.

| Risk Factors                  | Odds Ratio (95% CI) | p-Value |
|-------------------------------|---------------------|---------|
| Age                           | 1.00 (0.96–1.03)    | 0.900   |
| Nursing home residence        | 2.83 (1.18–6.79)    | 0.020   |
| Antibiotic use within 3 months| 4.52 (1.02–19.97)   | 0.047   |
| Long-term urinary catheter placement | 2.77 (0.81–9.45) | 0.103   |

Abbreviation: CI, confidence interval. Significant values are indicated in bold.

### 4. Discussion

Our study investigated the etiology, risk factors, and antibiotic resistance pattern of GNRs causing community-acquired UTI. The most frequently isolated species from community-acquired UTI was *E. coli*, which comprised the majority of antibiotic resistant GNRs. There have been several studies regarding the increasing rate of resistant GNRs globally [9,10,17–19]. The ESBL-producing rate among *E. coli* isolated from patients with UTI increased from 10.4% to 13.0% in Canada, and from 7.8% to 18.3% in the US between 2010 and 2014 [10]. Although CPE are not prevalent in Japan yet, they have become an increasing threat worldwide [20,21]. CPE are mainly isolated from nosocomial specimens, but in one report, about 15% of the specimens that tested positive for CPE were from nursing home residents [22].

According to the JANIS system, the susceptibility rates for cefotaxime and levofloxacin among *E. coli* in 2017 were 72% and 58%, respectively, in Japan, and 73% and 62%, respectively, in Ibaraki Prefecture. As the JANIS system predominantly covers the isolates from hospitalized patients, the antibiotic susceptibility rates were considered to be lower than those from community-acquired specimens. In our study, the *E. coli* susceptibility rates for third generation cephalosporins (i.e., ceftriaxone and cefotaxime) and levofloxacin were 78% and 68%, respectively, suggesting that the susceptibility pattern of *E. coli* strains from patients with community-acquired UTI were similar to, or only 5–10% better than those from hospital-acquired infections.

We identified nursing home residence and prior antibiotic use within the last three months as independent risk factors associated with resistant GNR. These findings were consistent with those of previous studies in other countries [12,13,23]. In our study, long-term urinary catheter placement showed only a modest association (OR 2.77, *p* = 0.103) with the risk of resistant GNRs, which was not statistically significant. This may be partly attributed to the sample size of this study, which was insufficient for detecting a significant difference.

Several guidelines have emphasized the importance of taking an antibiogram into account when determining empiric treatment of UTIs [24–27]. In this study, the majority (95%) of the isolates from community-acquired UTI were Enterobacterales, and their overall susceptibility rates for ceftriaxone/cefotaxime and levofloxacin were almost 70–80%. Moreover, in terms of isolates from patients living in nursing homes, the susceptibility rate decreased to approximately 40%, mainly due to the prevalence of ESBL-producing *E. coli* strains. Optimal empiric antibiotic treatment options are limited; only piperacillin-tazobactam, cefmetazole, meropenem, and amikacin had a susceptibility rate of more than 90% to Enterobacterales in community-acquired UTI in this study.

Piperacillin-tazobactam and meropenem might be the reasonable choices for empiric antibiotic treatment in this setting. However, routine use of such broad-spectrum agents for community-acquired
UTI may lead to further increases in antimicrobial resistance. A prospective study has demonstrated that piperacillin-tazobactam was inferior to carbapenems for the initial empiric treatment of bacteremia due to ESBL-producing Enterobacterales [28]. Cefmetazole may be an alternative option for the treatment of UTIs caused by ESBL-producing organisms, although only limited data is currently available [29,30].

There are several limitations to this study. First, this was a single-center retrospective study. Our sample size was relatively small; thus, the susceptibility pattern observed might not accurately represent the local epidemiology, particularly for organisms with less than 10 isolates. We collected patient information by performing a chart review, which may result in an information bias and some factors might be underestimated. In addition, selection bias could not be ruled out because this study was conducted at an emergency department. Therefore, more severely ill patients were likely to be included. Second, patients with false-negative urine cultures due to preceding antibiotic use were excluded from this study, although there were only a small number of such cases.

5. Conclusions

In conclusion, this observational study developed an antibiogram specific for GNRs from community-acquired UTIs and demonstrated that the patients who live in nursing homes and have a recent history of antibiotic use are at significant risk of community-acquired UTI caused by resistant GNRs. As ESBL-producing E. coli accounted for the majority of resistant GNRs, cefmetazole, piperacillin-tazobactam, and carbapenems may be reasonable options for empiric treatment, particularly among nursing home residents.

Author Contributions: Conceptualization, N.K.; data curation, N.K., T.S.; formal analysis, N.K., H.H., S.H.; writing—original draft preparation, N.K., writing—review and editing, H.H., S.H.; investigation, H.N., Y.T., K.N. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported in part by the Foundation for Development of the Community.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Czaja, C.A.; Scholes, D.; Hooton, T.M.; Stamm, W.E. Population-based epidemiologic analysis of acute pyelonephritis. Clin. Infect. Dis. 2007, 45, 273–280. [CrossRef] [PubMed]
2. Foxman, B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect. Dis. Clin. N. Am. 2014, 28, 1–13. [CrossRef] [PubMed]
3. Tandogdu, Z.; Wagenlehner, F.M. Global epidemiology of urinary tract infections. Curr. Opin. Infect. Dis. 2016, 29, 73–79. [CrossRef]
4. Johnson, J.R.; Russo, T.A. Acute Pyelonephritis in Adults. N. Engl. J. Med. 2018, 378, 48–59. [CrossRef] [PubMed]
5. Walker, E.; Lyman, A.; Gupta, K.; Mahoney, M.V.; Snyder, G.M.; Hirsch, E.B. Clinical Management of an Increasing Threat: Outpatient Urinary Tract Infections Due to Multidrug-Resistant Uropathogens. Clin. Infect. Dis. 2016, 63, 960–965. [CrossRef]
6. Lob, S.H.; Nicolle, L.E.; Hoban, D.J.; Kazmierczak, K.M.; Badal, R.E.; Sahm, D.F. 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, 459–465. [CrossRef]
11. Ministry of Health, Labour and Welfare. Japan Nosocomial Infections Surveillance (JANIS). About JANIS. Available online: https://jantis.mhlw.go.jp/english/report/index.html (accessed on 7 June 2020).

12. Khawcharoenporn, T.; Vasoo, S.; Singh, K. Urinary Tract Infections due to Multidrug-Resistant Enterobacteriaceae: Prevalence and Risk Factors in a Chicago Emergency Department. Emerg. Med. Int. 2013, 2013, 258517. [CrossRef] [PubMed]

13. Smithson, A.; Chico, C.; Ramos, J.; Netto, C.; Sanchez, M.; Ruiz, J.; Porron, R.; Bastida, M.T. Prevalence and risk factors for quinolone resistance among Escherichia coli strains isolated from males with community febrile urinary tract infection. Eur. J. Clin. Microbiol. Infect. Dis. 2012, 31, 423–430. [CrossRef] [PubMed]

14. Fagan, M.; Lindbaek, M.; Grude, N.; Reiso, H.; Romore, M.; Skaare, D.; Berild, D. Antibiotic resistance patterns of bacteria causing urinary tract infections in the elderly living in nursing homes versus the elderly living at home: an observational study. BMC Geriatr. 2015, 15, 98. [CrossRef] [PubMed]

15. Bischoff, S.; Walter, T.; Gerigk, M.; Ebert, M.; Vogelmann, R. Empiric antibiotic therapy in urinary tract infection in patients with risk factors for antibiotic resistance in a German emergency department. BMC Infect. Dis. 2018, 18, 56. [CrossRef] [PubMed]

16. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Sixth Informational Supplement M100-S26; CLSI: Wayne, PA, USA, 2016.

17. Omigie, O.; Okoror, L.; Umolu, P.; Ikubu, G. Increasing resistance to quinolones: A four-year prospective study of urinary tract infection pathogens. Int. J. Gen. Med. 2009, 2, 171–175. [CrossRef] [PubMed]

18. Karanika, S.; Karantanos, T.; Arvanitis, M.; Grigoras, C.; Mylonakis, E. Fecal Colonization With Extended-spectrum Beta-lactamase-Producing Enterobacteriaceae and Risk Factors Among Healthy Individuals: A Systematic Review and Metaanalysis. Clin. Infect. Dis. 2016, 63, 310–318. [CrossRef]

19. Thaden, J.T.; Fowler, V.G.; Sexton, D.J.; Anderson, D.J. Increasing Incidence of Extended-Spectrum beta-Lactamase-Producing Escherichia coli in Community Hospitals throughout the Southeastern United States. Infect. Control. Hosp. Epidemiol. 2016, 37, 49–54. [CrossRef]

20. Bratu, S.; Landman, D.; Haag, R.; Recco, R.; Eramo, A.; Alam, M.; Quale, J. Rapid spread of carbapenem-resistant Klebsiella pneumoniae in New York City: a new threat to our antibiotic armamentarium. Arch. Intern. Med. 2005, 165, 1430–1435. [CrossRef]

21. Logan, L.K.; Weinstein, R.A. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace. J. Infect. Dis. 2017, 215, S28–S36. [CrossRef]

22. Palacios-Baena, Z.R.; Oteo, J.; Conejo, C.; Larrosa, M.N.; Bou, G.; Fernandez-Martinez, M.; Gonzalez-Lopez, J.J.; Pintado, V.; Martinez-Martinez, L.; Merino, M.; et al. Comprehensive clinical and epidemiological assessment of colonisation and infection due to carbapenemase-producing Enterobacteriaceae in Spain. J. Infect. Dis. 2016, 72, 152–160. [CrossRef]

23. Killgore, K.M.; March, K.L.; Guglielmo, B.J. Risk factors for community-acquired ciprofloxacin-resistant Escherichia coli urinary tract infection. Ann. Pharmacother. 2004, 38, 1148–1152. [CrossRef] [PubMed]

24. Gupta, K.; Hooton, T.M.; Naber, K.G.; Wullt, B.; Colgan, R.; Miller, L.G.; Moran, G.J.; Nicolle, L.E.; Raz, R.; Schaeffer, A.J.; 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, 103–120. [CrossRef] [PubMed]

25. The Japanese Association for Infectious Disease/Japanese Society of Chemotherapy; The JAIM/JSC Guide/Guidelines to Clinical Management of Infectious Disease Preparing Committee; Urinary tract infection/male genital infection working group. JAIM/JSC Guidelines for Clinical Management of Infectious Disease 2015 - Urinary tract infection/male genital infection. J. Infect. Chemother. 2017, 23, 733–751. [CrossRef] [PubMed]

26. European Association of Urology (EAU): Guidelines on urological infections. Available online: https://uroweb.org/guideline/urological-infections/#3 (accessed on 7 June 2020).

27. National Institute for Health and Care Excellence (NICE). Pyelonephritis (acute): antimicrobial prescribing. 2018. Available online: https://www.nice.org.uk/guidance/ng111 (accessed on 18 July 2020).

28. Tamma, P.D.; Han, J.H.; Rock, C.; Harris, A.D.; Lautenbach, E.; Hsu, A.J.; Avdic, E.; Cosgrove, S.E.; Antibacterial Resistance Leadership Group. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum beta-lactamase bacteremia. Clin. Infect. Dis. 2015, 60, 1319–1325. [CrossRef] [PubMed]
29. Doi, A.; Shimada, T.; Harada, S.; Iwata, K.; Kamiya, T. The efficacy of cefmetazole against pyelonephritis caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae. *Int. J. Infect. Dis.* 2013, 17, 159–163. [CrossRef] [PubMed]

30. Mawatari, M.; Hayakawa, K.; Fujiya, Y.; Yamamoto, K.; Kutsuna, S.; Takeshita, N.; Ohmagari, N. Bacteraemic urinary tract infections in a tertiary hospital in Japan: the epidemiology of community-acquired infections and the role of non-carbapenem therapy. *BMC Res. Notes* 2017, 10, 336. [CrossRef]