Article

What Doesn’t Kill Them Makes Them Stronger: The Impact of the Resistance Patterns of Urinary Enterobacterales Isolates in Patients from a Tertiary Hospital in Eastern Europe

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Abstract: (1) Background: The evolution of bacterial resistance to antibiotics is one of the factors that make infectious pathology an extremely dynamic field, also inducing a significant burden on public health systems; therefore, continuous updates on the bacterial resistance to antibiotics and their particular regional patterns is crucial for the adequate approach of various infectious diseases. (2) Methods: We retrospectively analyzed 354 patients with Enterobacterales urinary tract infections (UTIs), determined their antibiotic resistance pattern, thus aiming to correlate them with the outcome and other specific markers of poor prognosis. (3) Results: The most frequent causative agent was Escherichia coli, representing 64.6% of all UTIs. We identified 154 patients resistant to multiple antibiotic classes, of which 126 were multidrug-resistant (MDR), 17 were extensive drug-resistant (XDR) and 11 were pandrug-resistant (PDR). Moreover, 25 isolates were resistant to carbapenems (CRE), 25 were difficult-to-treat (DTR), and 84 were extended-spectrum cephalosporin-resistant (ESC), with only 95 isolates susceptible to all tested antibiotics. Mortality ranged from 1% for UTIs caused by CRE isolates, to 24% for the ones caused by DTR or CRE isolates. Other significant risk factors associated with mortality were: prolonged hospital stay (p = 0.0001), Charlson comorbidity index ≥ 3 (p = 0.02), urinary catheterization (p = 0.001), associated respiratory pathologies (p = 0.004), obesity (p = 0.047), a history of previous hospitalizations (p = 0.007), inappropriate empiric antibiotic regimen (p = 0.001), or hyper inflammatory status (p = 0.006). Basically, we observed that a multiple regression model comprising urinary catheterization, inappropriate empiric anti-biotherapy, obesity, and respiratory comorbidities exhibits the best correlation with mortality rate in patients with UTI (R = 0.347, R² = 0.12). (4) Conclusions: By focusing on the novel resistance patterns, our study provides complementary evidence concerning the resistance profiles found in an Eastern European region, as well as their prognostic implications in patients with UTI.

Keywords: Enterobacterales; carbapenem-resistance; difficult-to-treat infections; urinary tract infections

1. Introduction

Urinary tract infections (UTIs) are a common public health issue in both community and nosocomial settings, affecting ~150 million people worldwide each year [1]. UTIs are...
caused by a wide range of pathogens, both Gram-negative and Gram-positive bacteria, as well as by certain fungi, but usually by uropathogenic *Escherichia coli* [2,3]. UTI is among one of the most common bacterial infections, occurring particularly in women [4].

The development of the antimicrobial agents, which started with the discovery of penicillin by Sir Alexander Fleming in 1928, is a cardinal step in the history of medicine, allowing to prevent millions of deaths due to infectious diseases [5]. Unfortunately, shortly after their discovery, antibiotic resistance emerged, nowadays representing a significant burden to global public health [6].

Integrative approach of UTI has an important role in improving prognosis, implying that in most cases antimicrobial therapy has to be prescribed empirically. In order to provide suitable empirical therapy, it is essential to know the main bacteria typically involved in the urinary tract infection, as well as their antimicrobial resistance pattern. This approach allows limiting antimicrobial resistance and the spread of multidrug-resistant bacterial strains [7].

Numerous international experts came together through a joint initiative by the European Centre for Disease Prevention and Control (ECDC) and the United States Centers for Disease Control and Prevention (CDC), to create a standardized international definition for the description of acquired resistance profiles, as follows:

- **MDR** (Multidrug Resistance) is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories;
- **XDR** (Extensive Drug Resistance) as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories);
- **PDR** (Pandrug-resistance)—non-susceptibility to all agents in all antimicrobial categories [8].

Furthermore, McDonnell et al. [9] added to this list by proposing the notion of UDR: Usual Drug Resistance, to describe isolates that are not fully susceptible wild-type strains but that can nonetheless be readily treated with standard therapies.

More recently, Kadri et al. [10] proposed the expression of DTR: Difficult to Treat Resistance. Their point of departure is the idea that the MDR-XDR-PDR definitions make no distinction between strengths and weaknesses of the individual antibiotics: agents with higher efficacy and lower toxicity are considered in the same way as agents with lower efficacy and higher toxicity. Therefore, they define DTR as intermediate or resistant to all of the typical first-line, lower toxicity agents, defined as the beta-lactams (including carbapenems and combinations with beta-lactamase inhibitors) and the fluoroquinolones. To determine the DTR status, the susceptibility testing of at least one carbapenem, one extended-spectrum cephalosporin, and one fluoroquinolone is required.

The latest CDC report provided definitions for two other antimicrobial resistance patterns [11]:

- **ESC** (Extended-spectrum cephalosporin-resistant)—Any *E. coli, Klebsiella oxytoca* or *Klebsiella pneumoniae* that has tested Intermediate (I) or Resistant (R) to at least 1 of the following: cefepime, ceftriaxone, cefotaxime, ceftazidime, ceftolozane/tazobactam or ceftazidime/avibactam;
- **CRE** (Carbapenem-resistant Enterobacterales)—Any *E. coli, Klebsiella aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae, or Enterobacter spp.* that has tested Resistant (R) to at least 1 of the following: imipenem, meropenem, doripenem, ertapenem, meropenem/vaborbactam, or imipenem/relebactam.

The impact of multidrug-resistant Gram-negative bacteria (MDR-GNB) infections can be determined by assessing the clinical outcomes, such as length of stay in the hospital or mortality rates. Although most of the studies found significant correlations between MDR-GNB and mortality risk, other authors failed to demonstrate such an association, therefore the topic remains controversial a fertile ground for further research [12–15].
This research is a sequel of our previous observations, which focused on the characterization of UTIs caused by *K. pneumoniae*, motivated by the necessity of determining the resistance patterns for all *Enterobacterales* against common antibiotic classes in treating UTIs.

Therefore, the aim of this study was to assess the antibiotic susceptibility rates and epidemiology of UTIs caused by *Enterobacterales*. Moreover, by using the novel resistance patterns, we aim to introduce them in the clinical practice, as a useful and more accurate tool for the characterization of antibiotic resistance in UTIs, especially for the clinicians.

2. Materials and Methods

A retrospective cohort study was conducted from 30 June 2019, to 30 December 2019, at “St. Parascheva” Clinical Hospital of Infectious Diseases from Iasi, a 300 beds university setting, as it is the largest tertiary center for Infectious Diseases from North-Eastern Romania, a region with approximately 4 million inhabitants.

2.1. Study Population

In this study, we enrolled all hospitalized patients presenting a confirmed UTI, both community-acquired and hospital-acquired (i.e., >48 h after admission), with the following inclusion criteria: (i) suggestive clinical syndrome (dysuria, pollakiuria or non-specific symptoms for catheterized patients, such as fever or chills); (ii) pyuria \( \geq 10 \) white blood cell count (WBC)/mm\(^3\); (iii) isolation of GNB *Enterobacterales*, including *E. coli*, *K. pneumoniae*, and *Enterobacter* spp., *Proteus* spp., *Serratia* spp., *Providencia* spp. or *Morganella* spp. in urine culture \( \geq 10^5 \) colony forming units (CFU)/mL). We included only one isolate per patient (except for the isolates with different antibiotic susceptibility, which were considered as different isolates) and excluded those with GNB *Enterobacterales* colonization or with a urinary CFU count <10\(^5\)/mL.

A total of 354 clinical specimens were analyzed during the study period. Bacterial identification was automated, using phenotypical characters. Based on the antibiotic resistance pattern, we classified the isolates as susceptible to all tested antibiotics (S), MDR, XDR, and PDR. We also further divided the strains according to the novel resistance pattern such as UDR, DTR, CRE, or ESC.

2.2. Data Collection

Patient information was collected from the medical records, including age, gender, type of bacteria (*E. coli*, *K. pneumoniae*, *Enterobacter* spp., *Proteus* spp., *Serratia* spp., or *Morganella* spp.), resistance pattern for each isolate, previous hospitalizations (within the past 3 months) or use of antibiotics within the past 30 days, urinary catheterization, presence of comorbid conditions (such as kidney disease, or diabetes mellitus), treatment regimen, and clinical outcome.

2.3. Microbiological Procedures

Antimicrobial susceptibility testing was performed by the Kirby Bauer disk diffusion method, using the following antimicrobial discs: ampicillin, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefixime, cefuroxime, ceftazidime, ceftriaxone, ceftoxitine, cefepime, imipenem, meropenem, ertapenem, amikacin, gentamicin, tobramycin, ciprofloxacin, norfloxacin, moxifloxacin, ofloxacin, trimethoprim/sulfamethoxazole, and nitrofurantoin. We used EUCAST clinical breakpoint table v9.0 for the interpretation of the minimal inhibitory concentrations (MIC) and zone diameters.

2.4. Carbapenemase Detection

For isolates resistant to carbapenems, NG-Test Carba 5 multiplex lateral flow immunoassay was used for the phenotypic detection and differentiation of five common carbapenemase families: *Klebsiella pneumoniae* carbapenemase (KPC), oxacillinase (OXA-48-like), Verona integron encoded metallo-\(\beta\)-lactamase (VIM), imipenemase (IMP),
and New Delhi metallo-β-lactamase (NDM). The test was performed according to the manufacturer’s instructions.

2.5. Statistical Analysis

We used Kolmogorov–Smirnov test to assess the normal distribution of parameters in the study population, normally distributed variables being presented as means ± standard deviation. Categorical variables are presented as absolute numbers or percentages. The differences between various subgroups were assessed using independent t-test or one-way ANOVA, as appropriate. For certain significant differences objectified within subgroups following the ANOVA analysis, we performed a post hoc Dunnett’s test. The correlation analysis between two or more variables was performed using either Pearson’s (for continuous variables) or Spearman’s (for categorical variables) rank (r) coefficients.

To compare the survival distribution within the resistance pattern subgroups we used the log-rank test, while Kaplan–Meier method was used for the estimation of the survival curves.

A multivariate logistic regression was also performed to identify a specific model comprising multiple risk factors as predictors associated with multidrug resistance (dependent variable), with Hosmer–Lemeshow goodness-of-fit test indicating that the model adequately describes the analyzed data.

A p-value of 0.05 was considered statistically significant. For the initial data collection, we used Microsoft Excel 2013 version (Microsoft Corporation, Redmond, WA, USA), while the data analysis was performed with SPSS version 23 (IBM, Armonk, VA, USA).

3. Results

3.1. Etiology of UTIs and the Pathogen’s Resistance Profile

The 354 specimens were analyzed during the study period. The most frequent causative agent was E. coli, representing 64.6% of all cases (229 strains), followed by Klebsiella, encountered in 21.4% cases (76 strains; 72—K. pneumoniae and 4—K. oxytoca), Proteus spp.—9.6% (34 cases; 32—Proteus mirabilis and 2 Proteus vulgaris), and Enterobacter spp.—2.8% (10 cases; 8—Enterobacter spp. and 2—Enterobacter cloacae); we also identified Providencia spp. and Serratia marcescens, in 2 cases each and Morganella morganii in only one case.

We identified a worrisome share of 43.5% isolates resistant to multiple antibiotic classes (154 patients), of which 126 were MDR, 17 were XDR, and 11 were PDR. Moreover, 25 isolates were CRE and 84 were ESC, with only 95 isolates susceptible to all antibiotics tested. Of the 25 DTR strains, 2 (8%) were MDR, 12 (48%) were XDR, and 11 (44%) were PDR, while in the UDR group, there were only 20 (16.5%) MDR strains without any PDR or XDR. In the CRE group, we found 6 (24%) MDR, 12 (48%) XDR, and 7 (28%) PDR strains, and from the ESC group, 62 (73.8%) strains were MDR, 14 (16.6%) were XDR, and 7 (8.3%) were PDR (Table 1).

Table 1. Distribution of the causative microorganisms isolated in urine culture by resistance profile in the study population.

| Bacterial Species | MDR | XDR | PDR | UDR | DTR | S | CRE | ESC |
|-------------------|-----|-----|-----|-----|-----|---|-----|-----|
| E. coli           | 76  | 3   | 0   | 92  | 0   | 74| 2   | 44  |
| (60.3%)           | (4.8%) | (17.6%) | (34.1%) | (7%) | (26.8%) | (7%) | (23.7%) |
| Klebsiella spp.   | 23  | 11  | 7   | 20  | 18  | 14| 20  | 40  |
| (18.2%)           | (64.7%) | (63.6%) | (16.5%) | (72%) | (14.7%) | (80%) | (47.6%) |
| Proteus spp.      | 20  | 0   | 1   | 7   | 1   | 6 | N/A | N/A |
| (15.8%)           | (9%) | (5.7%) | (4%) | (6.3%) | N/A | N/A |
Table 1. Cont.

| Bacterial Species       | MDR | XDR | PDR | UDR | DTR | S   | CRE | ESC |
|-------------------------|-----|-----|-----|-----|-----|-----|-----|-----|
|                         | 126 | 17  | 11  | 121 | 25  | 95  | 25  | 84  |
|                         | (35.5%) | (4.8%) | (3.1%) | (34.1%) | (7%) | (26.8%) | (7%) | (23.7%) |
| Enterobacter spp.       | 5 (3.9%) | 3 (17.6%) | 0 | 2 (1.6%) | 3 (12%) | 1 (1%) | 3 (12%) | N/A |
| Serratia spp.           | 1 (0.7%) | 0 | 1 (9%) | 0 | 1 (4%) | 0 | N/A | N/A |
| Providencia spp.        | 0 | 0 | 2 (18%) | 0 | 2 (8%) | 0 | N/A | N/A |
| Morganella spp.         | 1 (0.7%) | 0 | 0 | 0 | 0 | 0 | N/A | N/A |

MDR—Multi-drug Resistant, XDR—Extensive Drug Resistant, PDR—PDR-resistant, UDR—Usual Drug Resistance, DTR—Difficult to Treat Resistance, S—Susceptible to all the tested antibiotics, ESC—Extended-spectrum cephalosporin-resistant), CRE—Carbapenem-resistant Enterobacterales. N/A—Not Applicable.

Patients with UTIs due to resistant strains were more likely men, aged over 65 years, with recent hospitalizations (within the past three months) and previous antibiotic intake (within the last month). In addition, they were more likely to have an indwelling urinary catheter, an increased inflammatory status (expressed as a high C-reactive protein-CRP), with a significantly longer length of hospital stay. In addition, we observed a gradient of the mean values of Charlson comorbidity index (CCI) following the susceptibility patterns’ spectrum; the overall mean value was 3.4, the lowest (2.6) was encountered in the S group, while the highest values were observed in PDR group (5.6), CRE, DTR (5 each), and XDR (4.9), respectively. In this regard, as components of CCI, we noted that chronic kidney disease (CKD) was more prevalent among patients with resistant strains, while diabetes mellitus (DM) was affecting a roughly similar share of patients, irrespective of their resistance profile (Table 2).

Table 2. Baseline characteristics of the study population according to the resistance profile.

| Parameter                        | MDR | XDR | PDR | UDR | DTR | S   | CRE | ESC |
|----------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|
|                                  | N = 126 | N = 17 | N = 11 | N = 121 | N = 25 | N = 95 | N = 25 | N = 84 |
| Female gender                    | 69 (54.7%) | 8 (47%) | 5 (45.4%) | 93 (76.8%) | 10 (40%) | 81 (85.2%) | 9 (36%) | 45 (53.5%) |
| Previous hospitalizations        | 41 (32.5%) | 10 (58.8%) | 8 (71.7%) | 20 (16.5%) | 16 (64%) | 8 (8.4%) | 14 (56%) | 33 (39.2%) |
| Previous antibiotic use          | 19 (15%) | 7 (41.1%) | 3 (27.2%) | 14 (11.5%) | 8 (32%) | 12 (12.6%) | 8 (32%) | 19 (22.6%) |
| Mean age (years)                 | 65.1 ± 15.2 | 67.3 ± 17.3 | 74.3 ± 19.2 | 60.1 ± 21.8 | 71.4 ± 9.9 | 57.4 ± 20.5 | 71.4 ± 10.9 | 65.5 ± 16.4 |
| Length of stay (days)            | 11.2 ± 7.2 | 12.6 ± 7.5 | 15.6 ± 9.4 | 9.1 ± 5.0 | 14.8 ± 8.7 | 9.2 ± 7.2 | 14.2 ± 8.8 | 11.4 ± 7.1 |
| CRP (mg/dL)                      | 9.1 ± 9.7 | 6.9 ± 7.8 | 9.4 ± 8.2 | 8.1 ± 9.5 | 8.8 ± 7.8 | 7.6 ± 9.5 | 6.6 ± 7.3 | 8.4 ± 8.9 |
| Urinary catheterization          | 38 (30.1%) | 8 (47%) | 9 (81.8%) | 14 (11.5%) | 18 (72%) | 10 (10.5%) | 14 (56%) | 31 (36.9%) |
| Appropriate empirical antibiotic therapy | 51 (40.4%) | 6 (35.2%) | 5 (45.4%) | 78 (64.4%) | 9 (36%) | 76 (80%) | 6 (24%) | 32 (38%) |
| Diabetes mellitus                | 32 (26.2%) | 4 (23.5%) | 3 (27.2%) | 32 (26.4%) | 7 (28%) | 20 (21%) | 6 (24%) | 23 (27.3%) |
| Charlson comorbidity index       | 3.8 ± 2.3 | 4.9 ± 2.6 | 5.6 ± 2.4 | 3 ± 2.3 | 5 ± 2.3 | 2.6 ± 2.2 | 5 ± 2.5 | 4.1 ± 2.6 |
| Chronic kidney disease           | 17 (13.5%) | 7 (41.1%) | 2 (18.1%) | 8 (6.6%) | 7 (28%) | 8 (3.4%) | 6 (24%) | 15 (17.8%) |
Table 2. Cont.

| Parameter | MDR | XDR | PDR | UDR | DTR | S | CRE | ESC |
|-----------|-----|-----|-----|-----|-----|---|-----|-----|
| N = 126   |     |     | N = 11 |     | N = 25 | N = 95 | N = 25 | N = 84 |
| rUTIs     | 22 (17.4%) | 5 (29.4%) | 0 | 15 (12.3%) | 3 (12%) | 10 (10.5%) | 3 (12%) | 16 (19%) |
| ESBL production | 75 (59.5%) | 13 (76.4%) | 8 (72.7%) | 5 (4.1%) | 17 (68%) | 0 | 6 (24%) | 71 (84.5%) |
| Mortality | 16 (12.6%) | 3 (17.6%) | 2 (18.1%) | 5 (4.1%) | 6 (24%) | 1 (1%) | 6 (24%) | 12 (14.2%) |

MDR—Multi-drug Resistant, XDR—Extensive Drug Resistant, PDR—Pandrug-resistant, UDR—Usual Drug Resistance, DTR—Difficult to Treat Resistance, S—Susceptible to all the tested antibiotics, ESC (Extended-spectrum cephalosporin-resistant), CRE—(Carbapenem-resistant Enterobacterales), CRP—C-reactive protein. rUTIs—Recurrent urinary tract infections, ESBL—Extended spectrum β-lactamases.

3.2. Particular Aspects of the Antibiotic Resistance and Antibiotherapy

Enterobacterales species showed different resistance patterns to certain antibiotics, as presented in Table 3. Except for E. coli, all isolates showed low susceptibility rate (below 70% or 80%) to all beta-lactams, the carbapenems being the only notable exception. A severe susceptibility pattern was found in Klebsiella isolates, with significant resistance to beta-lactams (except for imipenem and meropenem), fluoroquinolones, and all aminoglycosides.

Table 3. Rates of susceptibility (%) for the most common pathogens isolated.

| Type of Bacteria | Tested Antibiotic |
|-----------------|-------------------|
|                 | AMP | AMC | SAM | TMT-SMX | CXM | CAZ | CTX | FEP | GM | TOB | AK | CIP | TZP | IMI | MEM | ETP | COL |
| E. coli         | IR  | 80.1 | 65.0 | 71.1 | 62.8 | 80.3 | 80.7 | 81.2 | 80.7 | 86.9 | 84.2 | 94.2 | 71.1 | 89.9 | 100 | 100 | 99.1 | 99.5 |
| Klebsiella spp. | IR  | 32.8 | 36.8 | 60.5 | 47.5 | 58.6 | 52.6 | 52.6 | 56.5 | 50.0 | 59.9 | 44.7 | 82.8 | 82.8 | 68.9 | 85.5 |
| Proteus spp.    | IR  | 55.8 | 52.9 | 52.4 | 50 | 52.9 | 53.8 | 73.5 | 64.7 | 44.1 | 54.1 | 32.5 | 86.2 | 91.1 | 97 | 94.1 | IR  |

AMP = ampicillin; AMC = amoxiclav; SAM = ampicillin + sulbactam; TMT-SMX = sulfamethoxazole-trimethoprim; CXM = cefuroxime; CAZ = ceftazidime; CTX = cefotaxime; FEP = cefepime; GM = gentamicin; TOB = tobramycin; AK = amikacin; CIP = ciprofloxacin; TZP = piperacillin-tazobactam; IMI = imipenem; MEM = meropenem; ETP = ertapenem; COL = colistin; IR = intrinsic resistance. Green: ≥90% susceptibility rates; Yellow: susceptibility rate ≥80% but <90%; Red: susceptibility <80%; these antibiotics should not be prescribed empirically in any kind of infection; Grey: Not applicable.

Out of 354 isolates, 25 (7%) were CRE, with 19 isolates being carbapenemase producers, as determined by the NG-Test Carba 5 multiplex immunoassay. Of these, 17 isolates were K. pneumoniae, one was E. coli (NDM), and one was Enterobacter cloacae (OXA-48). The most commonly identified carbapenemase was OXA-48 (8 isolates), followed by NDM (7 isolates), KPC (3 isolates), and VIM (1 isolate).

Given the high prevalence of resistant strains, the most commonly used antibiotic classes were carbapenems, followed by third generation cephalosporins and aminoglycosides. Beta-lactams (+/-beta-lactamase inhibitors) and fluoroquinolones were used mostly for UDR and S infections, while colistin was predominantly administered in patient with PDR or DTR (Figure 1).

3.3. Resistance Profile and the Prognosis Assessment

Mortality rate amongst patients with resistant strains was significantly higher compared to their S counterparts (1.05% vs. 8.9%, p = 0.009) (Table 4).

Table 4. Mortality rates according to the resistance profile.

| Resistance Profile | N | Fatalities | p     |
|--------------------|---|------------|-------|
| Mortality rate     | S | 95         | 1 (1.05%) | 0.009 |
|                    | R | 259        | 23 (8.9%) |       |
Log-rank test revealed the increased risk of death amongst patients with resistant strains compared to S ones ($p = 0.002$). The subsequent detailed Kaplan–Meier survival curves confirmed the high mortality risk associated with resistant strains, but failed to draw a specific prognosis pattern concerning different types of antibiotic resistance (Figure 2).

Figure 1. Antibiotic treatment. BL+/−BLI—Beta-lactam+/− Beta-lactamase inhibitor; C3G—3rd generation cephalosporin; AG—aminoglycosides; FQ—fluoroquinolones; MDR—Multi-drug Resistant, XDR—Extensive Drug Resistant, PDR—Pandrug-resistant, UDR—Usual Drug Resistance, DTR—Difficult to Treat Resistance, S—Susceptible to all the tested antibiotics, ESC—Extended-spectrum cephalosporin-resistant, CRE—Carbapenem-resistant Enterobacterales.

Consequently, an additional ANOVA test revealed a significant difference concerning mortality rate within resistance groups. By performing a detailed Dunnnett post hoc analysis, we observed that MDR and XDR profiles were associated with a significant excess of mortality compared to susceptible strains. Although PDR and UDR also showed higher mortality rates, they did not reach the threshold of statistical significance, while DTR group was slightly above it (Table 5).

Table 5. Influence on the mortality rate of various resistance patterns, compared to S strains.

| ANOVA (Dunnett 2-Sided) | Mean Difference in Mortality | $p$ |
|--------------------------|-------------------------------|-----|
| MDR−S                    | 0.109                         | 0.006 |
| XDR−S                    | 0.166                         | 0.05 |
| PDR−S                    | 0.080                         | 0.817 |
| UDR−S                    | 0.019                         | 0.895 |
| DTR−S                    | 0.198                         | 0.065 |

Abbreviations: MDR—Multi-drug Resistant, XDR—Extensive Drug Resistant, PDR—Pandrug-resistant, UDR—Usual Drug Resistance, DTR—Difficult to Treat Resistance, S—Susceptible to all the tested antibiotics.
Concerning the recently introduced CDC resistance patterns, we found that both CRE and ESC were positively and significantly correlated with mortality, but also with other markers of severity, such as length of stay, indwelling urinary catheter and Charlson comorbidity index. Moreover, the two resistance patterns were significantly correlated with each other ($r=0.387$, $p<0.001$). The same trend was also observed for DTR, which presented significant positive correlations with the above-mentioned factors of poor outcome (Table 6).

Table 6. Correlations between novel resistance patterns and mortality rates or other markers of severity.

| Variable                  | CRE     | ESC     | DTR     |
|---------------------------|---------|---------|---------|
|                           | $R$     | $p$     | $R$     | $p$     | $R$     | $p$     |
| Mortality rate            | 0.145   | 0.006   | 0.138   | 0.009   | 0.156   | 0.003   |
| Length of stay            | 0.142   | 0.007   | 0.122   | 0.02    | 0.176   | 0.001   |
| Urinary catheterization   | 0.229   | 0.001   | 0.201   | 0.001   | 0.326   | 0.0001  |
| Charlson comorbidity index| 0.187   | 0.001   | 0.158   | 0.003   | 0.185   | 0.001   |

Abbreviations: DTR—Difficult to Treat Resistance, ESC—Extended-spectrum cephalosporin-resistant, CRE—Carbapenem-resistant Enterobacterales.

However, we did not identify any notable differences between the types of carbapenemases concerning the vital prognosis or the presence of other markers of severity. Neither OXA, NDM, KPC, or VIM were not significantly associated with an excess of mortality ($p>0.05$ for all paired comparisons).
3.4. Additional Poor Prognosis Factors in UTIs

Further, we aimed to analyze the correlation between mortality rate and certain risk factors commonly associated with UTIs. We found that comorbidities play a major role in the outcome of these patients, as Charlson comorbidity index, respiratory pathologies and obesity presented significant direct correlations with the mortality risk (Table 7). On the other hand, female sex was significantly associated with an improved survival rate \( (r = -0.106, p = 0.045) \). Very importantly, a history of previous hospitalizations or urinary catheterization, as well as an inappropriate empiric antibiotic regimen or hyper inflammatory status (expressed as high levels of C-reactive protein) also exhibited strong correlations with mortality rates in our study group. On the other hand, some traditionally incriminated UTI risk factors, such as smoking, diabetes mellitus, or cardiovascular diseases were not significantly correlated with a poor outcome.

Table 7. Correlations between mortality and specific risk factors for UTI.

| Variable                        | Deceased |   |
|---------------------------------|----------|---|
| Age >65 years                   | 0.085    | 0.109 |
| Length of hospital stay (days)  | 0.311    | 0.0001 |
| Charlson comorbidity index ≥ 3 | 0.164    | 0.02 |
| Urinary catheterization         | 0.266    | 0.001 |
| Female sex                      | -0.106   | 0.045 |
| C-reactive protein              | 0.148    | 0.006 |
| Rural area                      | -0.071   | 0.186 |
| Pregnancy                       | -0.044   | 0.416 |
| Smoking                         | 0.020    | 0.710 |
| Alcohol abuse                   | 0.013    | 0.810 |
| Respiratory comorbidities       | 0.154    | 0.004 |
| Cardiovascular comorbidities    | 0.034    | 0.522 |
| Diabetes mellitus               | -0.05    | 0.929 |
| Obesity                         | 0.105    | 0.047 |
| Previous hospitalizations       | 0.142    | 0.007 |
| Previous antibiotic therapy     | 0.101    | 0.051 |
| Inappropriate antibiotic empiric therapy | 0.193 | 0.001 |

Given that all these aspects associated with a poor prognosis may coexist in varying proportions in the same patient, through a multiple regression we aimed to create a model for more accurate prediction mortality. We observed that a model comprising urinary catheterization, inappropriate empiric antibiotics, obesity, and respiratory comorbidities has the best correlation with mortality \( (R = 0.347) \). Basically, the \( R^2 \) of 0.12 express that 12% of mortality variance may be explained by this composed model. Very interestingly, when included in multiple regression, CCI was no longer a significant predictor of poor outcome and, therefore, cannot be added in the above-mentioned model (Table 8).
Table 8. Multiple regression model for predicting in-hospital mortality.

| Model | R     | R Square | Adjusted R Square | Std. Error of the Estimate | p   |
|-------|-------|----------|-------------------|---------------------------|-----|
| 1     | 0.277 | 0.077    | 0.074             | 0.238                     | 0.001|
| 2     | 0.309 | 0.095    | 0.090             | 0.236                     | 0.001|
| 3     | 0.331 | 0.109    | 0.102             | 0.235                     | 0.001|
| 4     | 0.347 | 0.120    | 0.110             | 0.234                     | 0.001|

a. Predictors: (Constant), Urinary catheterization. b. Predictors: (Constant), Urinary catheterization, Inappropriate antibiotic. c. Predictors: (Constant), Urinary catheterization, Inappropriate antibiotic, obesity. d. Predictors: (Constant), Urinary catheterization, Inappropriate antibiotic, obesity, respiratory comorbidities. e. Dependent Variable: Mortality.

4. Discussions

This study focused on the widespread prevalence of various drug-resistance patterns among Enterobacterales UTIs in North-Eastern Romania and their impact on the patients’ outcome. This is one of the first studies that specifically addressed DTR as a novel resistance pattern in UTIs, the other currently available data referring mainly to bloodstream infections.

As expected, the most commonly identified uropathogen was *E. coli*, responsible for almost two-thirds of the recorded cases of UTI. This finding is in accordance with multiple recent studies [16–19], which found it to be the main etiological agent in up to 95% of the UTIs. The second most isolated bacteria were *Klebsiella* spp., encountered in 76 cases (21.4%), of which *K. pneumoniae* was by far the most common species, an aspect in accordance with the results reported by several recent studies [4,17,18,20], even though a recent study conducted in another region of Romania reported *K. pneumoniae* as the leading etiology in some settings [21].

Regarding the antibiotic resistance pattern, we identified that 43.5% of isolates were resistant to multiple antibiotic classes. Of those, the majority was MDR (35.5%), followed by XDR (4.8%) and PDR (3.1%). The identification of PDR strains represents a major concern; multiple studies that analyzed the resistance profile of Gram-negative pathogens have failed to identify such a pattern [13,22], while others have reported negligible amounts [23,24].

Another goal of the study was to turn the spotlight on the novel resistance classification, aiming to outline a local epidemiological profile, since Romania constantly top ranks in terms of antibiotic resistance [25]. The DTR pattern can be described as a subcategory within MDR/XDR/PDR strains, being resistant to all first-line agents: entire range of β-lactams (including carbapenems), various combinations with β-lactamase inhibitors, as well as to fluoroquinolones. A plethora of studies has tried so far to assess the prognostic utility of this novel resistance pattern, but were focusing mainly on bloodstream infections. Benkő et al. analyzed the prevalence of DTR strains among the ESKAPE pathogens and found only 23 isolates (0.46%), mostly *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, with only one *Klebsiella* spp. and one *Proteus* spp. [26]. Similarly, Gianella et al. conducted a research in the region of Emilia-Romagna, Italy, and identified higher numbers of DTR patterns, representing 11% of all isolates, with *K. pneumoniae* accounting for all but one strains [23], while reports from France [27], Hungary [28] or United States [10] highlighted a much lower prevalence of DTR, constantly reported as maximum 1%. Interestingly, there is a wide spectrum of DTR variance among bacterial species, the highest shares of DTR being found among UTIs caused by *A. baumannii* [10]. In our study, we found that out of the 25 DTR strains (7% of all cases, of which two were MDR, 12 were XDR, and 11 were PDR), most of the isolates were K. pneumoniae, followed by *Enterobacter* spp., *Providencia* spp., *Proteus* spp. and *Serratia* spp.

The already established risk factors for the acquisition of an UTI caused by a drug-resistant pathogen, as reported in numerous studies conducted worldwide [29–31] are age,
male gender, previous hospitalizations, previous antibiotic use, and urinary catheterization, all of them being also significantly higher among patients with resistant isolates from our study, especially in the PDR and DTR groups. Furthermore, Faine et al. identified some other risk factors, such as chronic hemodialysis and nursing home residence [32], while Ben Ayed et al. found a correlation between the presence of diabetes mellitus or a history of urinary tract surgery in the last 12 months, with the acquisition of a MDR community-acquired UTI [33].

Moreover, Tenney et al. [34] performed a systematic review including more than 30,000 patients, aiming to stratify the risk factors for MDR UTIs, according to their prevalence; in this regard, they classified the risk factors as probable (urinary catheterization, previous hospitalization, or antibiotic intake and nursing home residence), possible (age, history of UTI and male gender) and unlikely (diabetes mellitus, recent travel, ethnicity, immunosuppression, and female gender). This classification is consistent with our findings; all the noteworthy risk factors we identified fit in the “probable” and “possible” categories, while those categorized as “unlikely” did not reach the statistical significance; worth mentioning, female gender was a protective factor, being strongly associated with S isolates and, consequently, with a favorable outcome.

When assessing individual antibiotic susceptibility, we identified a great rate of isolates resistant to all aminopenicillins (+/− IBL) and fluoroquinolones, given the fact that these antibiotics usually represent the empiric treatment for UTIs in the north east region of Romania. We also identified a high resistance rate to aminoglycosides, particularly to gentamicin and tobramycin, while amikacin remains active for most isolates of *E. coli* and *Proteus* spp. Carbapenems continue to be a viable option for most Gram-negative UTIs, even though we identified a total of 25 strains, mostly *K. pneumoniae*, resistant to carbapenems (of which 19 were carbapenemase-producers).

Our results are more dramatic than those reported in most of the studies [35–38], even though we have found some others with higher resistance rates [19,24,39]. For example, Kot et al. identified all *E. coli* and *P. mirabilis* isolates as susceptible to carbapenems (vs. 99.1% and 91.1%, respectively, in our study), and an 84.4% susceptibility for *K. pneumoniae* isolates (vs. 68.4% sensitivity to ertapenem in ours) [17]. Even though *Proteus* spp. is usually associated with hospital-acquired UTIs [21], with higher resistance rates to carbapenems [40,41], we identified up to 97% susceptibility to meropenem, similar to other Romanian research [16]; however, we must interpret these results with caution, due to the relatively small number of *Proteus* spp. isolates. Interestingly, a recent study that included isolates from other regions of Romania, reported a significantly lower resistance rates for both *E. coli* and *K. pneumoniae* UTIs in females, with 85.3% of *E. coli* and 73.9% of *K. pneumoniae* isolates being susceptible to amoxicillin-clavulanic acid (vs. 65% and 32.8%, respectively, in our study), 91.2% and 81.8% presenting sensitivity to cefazidime (vs. 80.7% and 48.6% in ours), 96% and 88.4% to amikacin (vs. 71.1% and 44.7%) and 98.16% and 93.9% sensitivity to Imipenem (vs. 100% and 82.8%) [42]. However, Sokhn et al., while investigating the resistance pattern of Gram-negative uropathogens in Lebanon, found similar or even lower sensitivity to some of the antibiotics tested; they reported only 42.4% and 35.8% sensitivity to amoxicillin-clavulanic acid for *E. coli* and *K. pneumoniae*, respectively, 69.4% and 65.7% to ciprofloxacin (vs. 71.1% and 44.7% in our study), 77.6% and 77.8% to amikacin, while 100% of their isolates were susceptible to all tested carbapenems (imipenem and meropenem) [19].

Those regional differences in terms of antibiotic resistance can be based also on the socioeconomic status of the countries where the studies were conducted. Although the resistance mechanisms are triggered by certain microbiological and molecular particularities, those phenomena may be enhanced by specific socioeconomic and behavioral factors. There is a growing body of evidence that antibiotic resistance is positively correlated with a poor economic status, with higher rates of resistance found in less developed countries [43–45]. Some socio-governmental determinants that may induce the selection of resistant strain are the limited acknowledge of the standardized protocols concerning
the antibiotic prescription by the medical staff, the non-judicious use of broad-spectrum antibiotics in several medical departments, or even the abusive prescriptions by general practitioner irrespective of the involved germ or local epidemiology recommendations. Of course, at individual level, a poor educational status can be the source for frequent, empirical antibiotic self-administration or, conversely, for incomplete adherence to a prescribed antibiotic regimen, resulting in an increased antibiotic resistance [46], as confirmed by the results of our study. Last but not least, an impaired socioeconomic status can be the trigger for various comorbidities that can alter the natural immunity against infections or can even be associated with some precarious housing issues vastly incriminated in the apparition of UTIs (e.g., lack of running water or indoor sanitation facilities) [47]. The region of Romania where this study was conducted can be considered a borderline region, exhibiting characteristics from both the developed and the developing countries, therefore the reported resistance profiles from this area could emerge as relevant epidemiological benchmarks.

The prognosis of patients with UTIs may be significantly influenced by the resistance pattern. Therefore, we noted that the overall in-hospital mortality in our study was 6.7%, ranging from 1% in the S group to 24% in CRE and DTR groups. Risk factors strongly associated with a negative outcome were urinary catheterization, previous recent antibiotic treatment or hospitalizations within the past 3 months, respiratory comorbidities, obesity, longer hospital stay, and inappropriate empirical therapy. Clearly, multiple associated pathologies, as well as older age, all summed in the CCI, have a negative impact on the survival rate. A CCI value $\geq 3$ was positively correlated with a higher mortality risk in our study, a similar cut-off value being reported also by Hoxha et al. [48], while Hussein et al. [49] claimed that a value $\geq 5$ is more appropriate in the mortality risk assessment in patients with carbapenem-resistant \textit{K. pneumoniae} infections. We also observed that a high inflammatory state was correlated with increased risk of death. Even if this biomarker is not specific for UTIs, the baseline and dynamics of CRP’s serum levels represent an adequate tool for risk stratification and prognosis assessment of every admitted patient, regardless the etiology of infection or the resistance pattern [50].

5. Conclusions

Our study provides complementary evidence concerning DTR’s regional epidemiological pattern, as Romania and, in general, the whole of Eastern Europe present significant bacterial resistance to various antibiotic classes. The high prevalence of resistant strains and the extensive use of broad-spectrum antibiotics highlighted in our study define not only the alarmingly increasing severity of UTIs in this area, but also the need for prompt strategies concerning their prophylaxis and therapeutic approach. We noted that novel resistance patterns such as DTR, ESC, and CRE are both significantly correlated with a poor outcome in patients with UTI. Therefore, the knowledge of these resistance patterns may represent a cornerstone for a more appropriate antibiotic selection or initial empiric therapy, with a subsequent positive impact on patients’ prognosis and the healthcare-associated burden.

6. Limitations

The main limitations of the study were its unicentric design and the relatively small number of cases, due to the fact that, starting with January 2020, the hospital was designated as a COVID-19 support facility, hence the addressability of patients with UTIs significantly decreased.

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**Informed Consent Statement:** Patient consent was waived due to the retrospective nature of the study. However, all the patients signed a standard consent at admission in an university clinic, all the data being anonymously processed.

**Data Availability Statement:** The data presented in this study are available in this article.

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

**References**

1. Stamm, W.E.; Norrby, S.R. Urinary Tract Infections: Disease Panorama and Challenges. *J. Infect. Dis.* 2001, 183, S1–S4. [CrossRef]
2. Klein, R.D.; Hultgren, S.J. Urinary tract infections: Microbial pathogenesis, host-pathogen interactions and new treatment strategies. *Nat. Rev. Microbiol.* 2020, 18, 211–226. [CrossRef] [PubMed]
3. Flores-Mireles, A.L.; Walker, J.N.; Caparon, M.; Hultgren, S.J. Urinary tract infections: Epidemiology, mechanisms of infection and treatment options. *Nat. Rev. Microbiol.* 2015, 13, 269–284. [CrossRef] [PubMed]
4. Ahmed, S.S.; Shariq, A.; Alsulloom, A.A.; Babikir, I.H.; Alhomoud, B.N. Uropathogens and their antimicrobial resistance patterns: Relationship with urinary tract infections. *Int. J. Health Sci.* 2019, 13, 48–55.
5. Ventola, C.L. The Antibiotic Resistance Crisis: Part 1: Causes and threats. *Pharm. Ther.* 2015, 40, 277–283.
6. Abdeta, A.; Bitew, A.; Fentaw, S.; Tsige, E.; Assefa, D.; Lejisa, T.; Kefyalew, Y.; Tigabu, E.; Evans, M. Phenotypic characterization of carbapenem non-susceptible gram-negative bacilli isolated from clinical specimens. *PLoS ONE* 2021, 16, e0256556. [CrossRef] [PubMed]
7. Linares, I.; Raposo, T.; Rodrigues, A.; Almeida, A. Frequency and antimicrobial resistance patterns of bacteria implicated in community urinary tract infections: A ten-year surveillance study (2000–2009). *BMC Infect. Dis.* 2013, 13, 19. [CrossRef] [PubMed]
8. Magiorakos, A.P.A.; Srinivasan, R.B.; Carey, Y.; Carmeli, M.E.; Falagas, C.G.; Giske, S.; Harbarth, J.F.; Hindler, G.; Kahlmeter, B.; Olsson-Liljequist, D.L.; et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. *Clin. Microbiol. Infect.* 2012, 18, 268–281. [CrossRef]
9. McDonnell, A.; Rex, J.H.; Goossens, H.; Bonten, M.; Fowler, V.G., Jr.; Dane, A. Efficient Delivery of Investigational Antibacterial Agents via Sustainable Clinical Trial Networks. *Clin. Infect. Dis.* 2016, 63, S57–S59. [CrossRef]
10. Kadri, S.S.; Adjemian, J.; Lai, Y.L.; Spaulding, A.B.; Ricotta, E.; Prevots, D.R.; Palmore, T.N.; Rhee, C.; Klompas, M.; Dekker, J.P.; et al. Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents. *Clin. Infect. Dis.* 2018, 67, 1803–1814. [CrossRef]
11. CDC. Antimicrobial-Resistant Phenotype Definitions Analysis of Antimicrobial-Resistant Organisms in NHSN. Available online: [https://www.cdc.gov/nhsn/pdfs/ps-analysis-resources/phenotype_definitions.pdf](https://www.cdc.gov/nhsn/pdfs/ps-analysis-resources/phenotype_definitions.pdf) (accessed on 10 February 2022).
12. Cosgrove, S.E. The Relationship between Antibiotic Resistance and Patient Outcomes: Mortality, Length of Hospital Stay, and Health Care Costs. *Clin. Infect. Dis.* 2006, 42, S82–S89. [CrossRef]
13. Alkofide, H.; Alhammad, A.M.; Alruwaili, A.; Aldemerdash, A.; Almangour, T.A.; Alsuwayegh, A.; Almoqbel, D.; Alsaud, A.; Enani, M. Multidrug-Resistant and Extensively Drug-Resistant Enterobacteriaceae: Prevalence, Treatments, and Outcomes—A Retrospective Cohort Study. *Infect. Drug Resist.* 2020, 13, 4653–4662. [CrossRef]
14. Magira, E.E.; Islam, S.; Niederman, M.S. Multi-drug resistant organism infections in a medical ICU: Association to clinical features and impact upon outcome. *Med. Intensiva* 2018, 42, 225–234. [CrossRef]
15. Lye, D.C.; Earnest, A.; Ling, M.L.; Lee, T-E.; Yong, H-C.; Fisher, D.A.; Krishnan, P.; Hsu, L.-Y. The impact of multidrug resistance in healthcare-associated and nosocomial Gram-negative bacteraemia on mortality and length of stay: Cohort study. *Clin. Microbiol. Infect.* 2012, 18, 502–508. [CrossRef]
16. Chibelean, C.B.; Petca, R.-C.; Mares, C.; Popescu, R.-I.; Enikő, B.; Mehedintu, C.; Petca, A. A Clinical Perspective on the Antimicrobial Resistance Spectrum of Uropathogens in a Romanian Male Population. *Microorganisms* 2020, 8, 848. [CrossRef]
17. Kot, B.; Gruzewska, A.; Szveda, P.; Wicha, J.; Parulski, U. Antibiotic Resistance of Uropathogens Isolated from Patients Hospitalized in District Hospital in Central Poland in 2020. *Antibiotics* 2021, 10, 447. [CrossRef]
18. Esposito, S.; Maglietta, G.; Di Costanzo, M.; Ceccoli, M.; Vergine, G.; La Scola, C.; Malaventura, C.; Falcioni, A.; Iacono, A.; Crisafi, A.; et al. Retrospective 8-Year Study on the Antibiotic Resistance of Uropathogens in Children Hospitalised for Urinary Tract Infection in the Emilia-Romagna Region, Italy. *Antibiotics* 2021, 10, 1207. [CrossRef]
19. Sokhn, E.S.; Salami, A.; El Roz, A.; Salloum, L.; Bahmad, H.F.; Ghsein, G. Antimicrobial Susceptibilities and Laboratory Profiles of Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis Isolates as Agents of Urinary Tract Infection in Lebanon: Paving the Way for Better Diagnostics. *Med. Sci.* 2020, 8, 32. [CrossRef]
20. Mițode, I.-L.; Nastase, E.V.; Mițode, R.; Mițode, E.G.; Iancu, L.S.; Lunci, C.; Pâdaru, D.-T.A.; Costache, I.-L.; Stafie, C.-S.; Doneanu, O.-S. Insights into multidrug-resistant *K. pneumoniae* urinary tract infections: From susceptibility to mortality. *Exp. Ther. Med.* 2021, 22, 1086. [CrossRef]  
21. Petca, R.-C.; Negoiță, S.; Mares, C.; Petca, A.; Popescu, R.-I.; Chibelean, C.B. Heterogeneity of Antibiotics Multidrug-Resistance Profile of Uropathogens in Romanian Population. *Antibiotics* 2021, 10, 523. [CrossRef]  
22. Basak, S.; Singh, P.; Rajurkar, M. Multidrug Resistant and Extensively Drug Resistant Bacteria: A Study. *J. Pathog.* 2016, 2016, 4065603. [CrossRef] [PubMed]  
23. Giannella, M.; Bussini, L.; Pascale, R.; Bartoletti, M.; Malagrinò, M.; Pancaldi, L.; Toschi, A.; Ferraro, G.; Marconi, L.; Ambretti, S.; et al. Prognostic Utility of the New Definition of Difficult-to-Treat Resistance Among Patients with Gram-Negative Bloodstream Infections. *Open Forum Infect. Dis.* 2019, 6, ofz505. [CrossRef] [PubMed]  
24. Majeed, H.Y.; Aljanaby, A.A.J. Antibiotic Susceptibility Patterns and Prevalence of Some Extended Spectrum Beta-Lactamases Genes in Gram-Negative Bacteria Isolated from Patients Infected with Urinary Tract Infections in Al-Najaf City, Iraq. *Avicenna J. Med. Biotechnol.* 2019, 11, 192–201.  
25. Machowska, A.; Lundborg, C.S. Drivers of Irrational Use of Antibiotics in Europe. *Int. J. Environ. Res. Public Health* 2018, 16, 27. [CrossRef] [PubMed]  
26. Benkó, R.; Gajdács, M.; Matuz, M.; Bodó, G.; Lázár, A.; Hajdú, E.; Papfalvi, E.; Hannauer, P.; Erdélyi, P.; Pető, Z. Prevalence and Antibiotic Resistance of ESRAPE Pathogens Isolated in the Emergency Department of a Single-Center Teaching Hospital in Hungary: A 5-Year Retrospective Survey. *Antibiotics* 2020, 9, 624. [CrossRef]  
27. Diallo, O.O.; Baron, S.A.; Dubourg, G.; Chaudet, H.; Halfon, P.; Camiade, S.; Comte, B.; Joubert, S.; François, A.; Seyral, P.; et al. Major discrepancy between factual antibiotic resistance and consumption in South of France: Analysis of 539,037 bacterial strains. *Sci. Rep.* 2020, 10, 18262. [CrossRef]  
28. Gajdács, M.; Bátori, Z.; Ábrók, M.; Lázár, A.; Burián, K. Characterization of Resistance in Gram-Negative Urinary Isolates Using Existing and Novel Indicators of Clinical Relevance: A 10-Year Data Analysis. *Life* 2020, 10, 16. [CrossRef]  
29. Benaissa, E.; Belouad, E.; Mechal, Y.; Benlahlou, Y.; Chadli, M.; Maleb, A.; Elouennass, M. Multidrug-resistant community-acquired urinary tract infections in a northern region of Morocco: Epidemiology and risk factors. *Germis* 2021, 11, 562–569. [CrossRef]  
30. Malcolm, W.; Fletcher, E.; Kavanagh, K.; Deshpande, A.; Wiuff, C.; Marwick, C.; Bennie, M. Risk factors for resistance and MDR in community isolates: Population-level analysis using the NHS Scotland Infection Intelligence Platform. *J. Antimicrob. Chemother.* 2018, 73, 223–230. [CrossRef]  
31. Wright, S.W.; Wrenn, K.D.; Haynes, M.; Haas, D.W. Prevalence and risk factors for multidrug resistant uropathogens in ED patients. *Am. J. Emerg. Med.* 2000, 18, 143–146. [CrossRef]  
32. Faine, B.A.; Harland, K.K.; Porter, B.; Liang, S.Y.; Mohr, N. A Clinical Decision Rule Identifies Risk Factors Associated with Antimicrobial-Resistant Urinary Pathogens in the Emergency Department: A Retrospective Validation Study. *Ann. Pharm.* 2015, 49, 649–655. [CrossRef]  
33. Ben Ayed, H.; Koubaa, M.; Hammami, F.; Marrakchi, C.; Rekik, K.; Ben Jemaa, T.; Maaroul, I.; Yaich, S.; Damak, J.; Ben Jemaa, M. Performance of an Easy and Simple New Scoring Model in Predicting Multidrug-Resistant Enterobacteriaceae in Community-Acquired Urinary Tract Infections. *Open Forum Infect. Dis.* 2019, 6, ofz103. [CrossRef]  
34. Tenney, J.; Hudson, N.; Alnifaidy, H.; Li, J.T.C.; Fung, K.H. Risk factors for acquiring multidrug-resistant organisms in urinary tract infections: A systematic literature review. *Saudi Pharm. J.* 2018, 26, 678–684. [CrossRef]  
35. Folliero, V.; Caputo, P.; Della Rocca, M.T.; Chianese, A.; Galdiero, M.; Ivone, M.R.; Hay, C.; Franci, G.; Galdiero, M. Prevalence and Antimicrobial Susceptibility Patterns of Bacterial Pathogens in Urinary Tract Infections in University Hospital of Campania “Luigi Vanvitelli” between 2017 and 2018. *Antibiotics* 2020, 9, 215. [CrossRef]  
36. Kanda, N.; Hashimoto, H.; Sonoo, T.; Naraba, H.; Takahashi, Y.; Nakamura, K.; Hatakeyama, S. 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. *Antibiotics* 2020, 9, 438. [CrossRef]  
37. Delcaru, C.; Podgreanu, P.; Alexandru, I.; Popescu, N.; Mărutescu, L.; Bleotu, C.; Mogosanu, G.D.; Chifiriuc, M.C.; Gluck, M.; Lázár, V. Antibiotic Resistance and Virulence Phenotypes of Recent Bacterial Strains Isolated from Urinary Tract Infections in Elderly Patients with Prostatic Disease. *Pathogens* 2017, 6, 22. [CrossRef]  
38. Gajdács, M.; Ábrók, M.; Lázár, A.; Burián, K. Comparative Epidemiology and Resistance Trends of Common Urinary Pathogens in a Tertiary-Care Hospital: A 10-Year Surveillance Study. *Medicina* 2019, 55, 356. [CrossRef]  
39. Said, K.B.; Alsolami, A.; Khalîfa, A.M.; Khalîl, N.A.; Moursi, S.; Osman, A.; Fahad, D.; Rakha, E.; Rashidi, M.; Moussa, S.; et al. A Multi-Point Surveillance for Antimicrobial Resistance Profiles among Clinical Isolates of Gram-Negative Bacteria Recovered from Major Ha’il Hospitals, Saudi Arabia. *Microorganisms* 2021, 9, 2024. [CrossRef]  
40. Gajdács, M.; Ábrók, M.; Lázár, A.; Burián, K. Urinary Tract Infections in Elderly Patients: A 10-Year Study on Their Epidemiology and Antibiotic Resistance Based on the WHO Access, Watch, Reserve (AWaRe) Classification. *Antibiotics* 2021, 10, 1098. [CrossRef]  
41. Gajdács, M.; Urbán, E. Comparative Epidemiology and Resistance Trends of Proteae in Urinary Tract Infections of Inpatients and Outpatients: A 10-Year Retrospective Study. *Antibiotics* 2019, 8, 91. [CrossRef]  
42. Petca, R.-C.; Mares, C.; Petca, A.; Negoiţă, S.; Popescu, R.-I.; Bot, M.; Barabás, E.; Chibelean, C.B. Spectrum and Antibiotic Resistance of Uropathogens in Romanian Females. *Antibiotics* 2020, 9, 472. [CrossRef] [PubMed]
43. Riaño-Moreno, J.; Romero-Leiton, J.P.; Prieto, K. Contribution of Governance and Socioeconomic Factors to the \textit{P. aeruginosa} MDR in Europe. \textit{Antibiotics} \textbf{2022}, 11, 212. [CrossRef] [PubMed]

44. Laxminarayan, R.; Sridhar, D.; Blaser, M.; Wang, M.; Woolhouse, M. Achieving global targets for antimicrobial resistance. \textit{Science} \textbf{2016}, 353, 874–875. [CrossRef]

45. Collignon, P.; Beggs, J.J.; Walsh, T.; Gandria, S.; Laxminarayan, R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: A univariate and multivariable analysis. \textit{Lancet Planet. Health} \textbf{2018}, 2, e398–e405. [CrossRef]

46. El-Sokkary, R.; Uysal, S.; Erdem, H.; Kullar, R.; Pekok, A.U.; Amer, F.; Grgić, S.; Carevic, B.; El-Kholy, A.; Liskova, A.; et al. Profiles of multidrug-resistant organisms among patients with bacteremia in intensive care units: An international ID-IRI survey. \textit{Eur. J. Clin. Microbiol. Infect. Dis.} \textbf{2018}, 2, e398–e405. [CrossRef] [PubMed]

47. Miftode, R.-S.; Costache, I.-I.; Cianga, P.; Petris, A.O.; Cianga, C.-M.; Maranduca, M.-A.; Miftode, I.-L.; Constantinescu, D.; Timpau, A.-S.; Crisan, A.; et al. The Influence of Socioeconomic Status on the Prognosis and Profile of Patients Admitted for Acute Heart Failure during COVID-19 Pandemic: Overestimated Aspects or a Multifaceted Hydra of Cardiovascular Risk Factors? \textit{Healthcare} \textbf{2021}, 9, 1700. [CrossRef]

48. Hoxha, A.; Kärki, T.; Giambi, C.; Montano, C.; Sisto, A.; Bella, A.; D’Ancona, F.; Tura, G.; Rossi, A.; Pedna, M.; et al. Attributable mortality of carbapenem-resistant \textit{Klebsiella pneumoniae} infections in a prospective matched cohort study in Italy, 2012–2013. \textit{J. Hosp. Infect.} \textbf{2016}, 92, 61–66. [CrossRef] [PubMed]

49. Hussein, K.; Raz-Pasteur, A.; Finkelstein, R.; Neuberger, A.; Shachor-Meyouhas, Y.; Oren, I.; Kassis, I. Impact of carbapenem resistance on the outcome of patients’ hospital-acquired bacteraemia caused by \textit{Klebsiella pneumoniae}. \textit{J. Hosp. Infect.} \textbf{2013}, 83, 307–313. [CrossRef]

50. Timpau, A.-S.; Miftode, R.-S.; Petris, A.O.; Costache, I.-I.; Miftode, I.-L.; Rosu, F.M.; Anton-Paduraru, D.-T.; Leca, D.; Miftode, E.G. Mortality Predictors in Severe COVID-19 Patients from an East European Tertiary Center: A Never-Ending Challenge for a No Happy Ending Pandemic. \textit{J. Clin. Med.} \textbf{2022}, 11, 58. [CrossRef]