SHST
Horticulture and Forestry Society of Transylvania

Crisan CM *et al*. (2022)
Notulae Scientia Biologicae
Volume 14, Issue 3, Article number 11344
DOI:10.15835/nsb14311344
Research Article

NSB
Notulae Scientia Biologicae

Escherichia coli infection, a negative prognostic factor on the evolution of patients with surgical diseases

Corina M. CRISAN[1,2], Stanca L. PANDREA[1,2], Manuela TOMPA[1,2], Teodora MOCAN[1,2]*, Aida PUIA[1], Lucian MOCAN[1,2]

[1]*Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca, 8 Victor Babes, 400012 Cluj-Napoca, Romania; crisan.michaela@umfcluj.ro; stanca_lucia_pandrea@yahoo.com; tompamanuela@yahoo.com; teodora.mocan@umfcluj.ro (*corresponding author); draidapuia@gmail.com; lucian.mocan@umfcluj.ro*

[2]*Prof. Dr. O Fodor Regional Institute of Gastroenterology and Hepatology, 5 Constanta, 400158 Cluj-Napoca, Romania*

Abstract

The bacterium *Escherichia coli*, one of the most studied bacteria in the world, with the greatest epidemiological impact, includes both commensal and pathogenic strains, with a genome that can be extremely varied both in size and genetic content, and it also can produce numerous diseases with specific symptoms. The vast majority of these strains can cause severe gastrointestinal diseases, hemolytic uremic syndrome, hemorrhagic colitis, renal failure and even death. Hemolytic uremic syndrome can be a consequence of the presence of *Escherichia coli* infection in gastrointestinal diseases. In this study, uremia in patients with and without the declared renal comorbidity, was negatively correlated with the response to antibiotic treatment. The increase of uremia above 92 mg/dl increases the risk of death. The highest risk categories include people with kidney disease like comorbidities starting with admission in surgical and intensive care wards in IRGH Cluj-Napoca, having as main diagnosis of hospitalization surgical digestive diseases. The occurrence of *Coli* pathogen infection was associated with increased morbidity and mortality rates in patients included in the study. In these patients, it was noticed the need to introduce therapy with increasingly complex antibiotic formulas, which lead to an increase in the duration and cost of hospitalization. In the studied group, due to E coli infection at admission, uremia had an average value of 23.99mg/dl +/-8.987(SD) in the case of patients without kidney disease, the number of patients with normal uremia values was lower than that of those with increased values of uremia. In the case of patients with confirmed kidney disease, uremia had mean values of 65.76 mg/dl +/-52.41(SD). At discharge, both in the case of patients with renal disease and in the case of those without confirmed renal disease, the number of patients with normal values of uremia was higher than those with pathological values, this proportion being reversed in the case of deceased patients where the number of patients with values pathological urea levels were significantly higher than those with normal values, proving kidney damage.

Keywords: bacterial infections; *Escherichia coli*; hemolytic uremic syndrome; multiresistant bacteria resistant to antibiotic therapy

Received: 06 Sep 2022. Received in revised form: 14 Sep 2022. Accepted: 15 Sep 2022. Published online: 29 Sep 2022.
From Volume 13, Issue 1, 2021, Notulae Scientia Biologicae journal uses article numbers in place of the traditional method of continuous pagination through the volume. The journal will continue to appear quarterly, as before, with four annual numbers.

Introduction

Resistance to classic treatments leads researchers around the world to look for new treatment methods, new types and increasingly complex formulas of antibiotics to fight against infections caused by multi-resistant bacteria. The bacterium *Escherichia coli*, was discovered in 1825 by Theodor Escherich, is found everywhere in nature, includes both commensal and pathogenic strains, with a genome that can be extremely varied both in size and in genetic content (Wassenaar, 2016). Like other bacteria that do not harm the human body, it is a commensal bacterium, obtaining its food from the human body without causing diseases under normal conditions, but in particular situations it can produce numerous diseases with specific symptoms. *Escherichia coli* is part of the Enterobacteriaceae family and the Gammaproteobacteria class (Jang *et al*., 2017). It is a Gram-negative, oxidazone-negative, lactopositive, facultatively anaerobic bacterium. The genetic information of this bacterium is in the cytoplasm and through the process of cell division the bacterium can divide every 20 minutes. The first genomic analysis of this bacterium was carried out in 1997 and since then over 4800 *E. coli* genomes have been sequenced and studied (Jang *et al*., 2017). *Escherichia coli* includes not only non-pathogenic strains but also those that cause disease. Six pathological types of *Escherichia coli* are known: Shiga toxin-producing *E. coli* (STEC), Enteropathogenic *E. coli* (EPEC), Enterotoxigenic *E. coli* (ETEC), Enteroaggregative E coli (EAEC), Diffusely adherent *E coli* and Enteroinvasive *E coli* (Jang *et al*., 2017).

The vast majority of these strains can cause severe gastrointestinal diseases, hemolytic uremic syndrome, hemorrhagic colitis, renal failure and even death (Laura *et al*., 2018). In *Escherichia coli* infections, due to the release of toxins (shigatoxins), the most common symptom is diarrhea preceding the hemolytic uremic syndrome. The risk factors in the occurrence of this syndrome are represented by hemorrhagic diarrhea, fever, vomiting, leukocytosis, advanced age, female gender and increased consumption of antisecretory drugs (Harkins *et al*., 2020; Onyenweaku *et al*., 2018). Hemolytic uremic syndrome is characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal damage (Laura *et al*., 2018; Onyenweaku *et al*., 2018; Khalid and Andreoli, 2019; Tarr *et al*., 2022).

Onyenweaku (2019) showed that over 70% of patients who develop hemolytic uremic syndrome after *E. coli* infection require transfusions, over 50% require one or more dialysis sessions and over 25% develop neurological conditions such as strokes, comas and convulsions (Onyenweaku *et al*., 2018). In the article published in Chinchilla-Lopez *et al*. (2018) it is shown that gastroenteritis is associated with hemolytic uremic syndrome and due to kidney damage, urea and creatinine have increased values (Chinchilla-López *et al*., 2018).

Travert *et al*. (2021) showed that digestive infections caused by *E. coli* - especially STEC strains, transmitted through contaminated water and food produce the most frequent diarrhea that is associated with hemolytic uremic syndrome in 5-20% of cases. In the study of Khalid *et al*. (2019), the uremic syndrome occurs in 15% of cases as well.

Materials and Methods

The present study followed the evolution of 201 patients hospitalized in the surgery and intensive care units of IRGH Cluj-Napoca between January 1, 2018 and December 31, 2019, in which the *Escherichia coli* bacterium was identified, conducting a retrospective study, approved study by the IRGH Ethical Committee. The study included data selected from patient observation sheets that were centralized in EXCELL databases, and processed with statistical functions. Both the SPSS 17.0 and Origin 7.5 programs were used for the graphic representations. Indexes of dispersion and centrality were calculated, as well as frequency tables. Normality of numerical data was assessed using the Kolmogorov-Smirnov test. According to results, selection of parametric or non-parametric was made (Mann Whitney U Test/Student T test). Chi square test was used for significance

calculation in case of cross tabular data. A significance threshold of p<=0.05 was selected. SPSS 17.0 software was used for data analyses.

The inclusion criteria in the study were represented by the presence of *Escherichia coli* bacteria in these patients during hospitalization regardless of age, associated diseases, other biological constants, treatment performed, evolution and the presence of other bacteria and fungi. Exclusion criteria were the absence of E coli bacteria, regardless of the presence of other bacteria and fungi.

The bacterium *Escherichia coli* was highlighted in the microbiology laboratory, in urine culture samples, with the help of the BACT / ALERT R3D automated microbial detection system (bioMerieux, Inc Durham NC) using calorimetric technology for the detection of microorganisms. The identification of bacteria as well as the determination of susceptibility to antibiotics was carried out with the VITEK2 COMPACT SYSTEM (bioMerieux, Inc Durham NC), with ready to use VITEK ID/AST cards.

The interpretation of the results was carried out in compliance with EUCAST 2016-2017 standards (European Committee on Antimicrobial 2016-2017). The biological blood urea samples were performed on the COBAS PRO 503 / E 801 apparatus by the spectrophotometry method, existing in the IRGH laboratory, both at admission and at discharge.

Results and Discussion

The data obtained were presented both numerically and percentage, and the comparisons between the different groups of values obtained were expressed using procedures such as: Chi square, average, maximum, median and standard deviation. The statistical data obtained were interpreted using statistical significance, using the limit for predetermining the probability (P-value) of 0.05. Following the statistical processing of the data collected from the patients' observation sheets, we obtained the following data: 201 patients (114 men and 87 women) aged between 19 and 90 years old, 117 coming from an urban environment and 84 from the rural environment (Table 1). Of the 201 patients included in the study, one patient was under 20 years old (0.49%), 4 patients were between 21 and 30 years old (1.99%), 7 patients between 31-40 years old (3 ,48%), 23 patients between 41-50 years old (11.44%), 29 patients between 51-60 years old (14.42%), 84 patients between 61-70 years old (41.79%), 35 patients between 71-80 years old (17.41%) and 18 patients over 81 years old (8.95%). The number of days of hospitalization was between 3 and 142 days.

Table 1. Patients' characteristics

Patients' characteristics		Number of patients and percent	
Age (average +/ - SD) years)		63,3584 +/-13.8821	
Number of hospitalization days (average +/ - SD days)		20.866 +/-20.7831	
Gender	Males	114	56,7164 %
	Females	87	43,2835 %
Environment of origin:	Urban	117	58,2089 %
	Rural	84	41,7910 %
Associated diseases:	Cardiac	163	81,0945 %
	Digestive	199	99, 0049 %
	Neurological	41	20,3980 %
	Diabetes mellitus	113	56, 2189 %
	Renal	67	33,3333 %
	Pulmonary	43	21,3930 %

In the target group, digestive disease was the main disease for which patients were admitted to IRGH Cluj Napoca. The following conditions were included in the digestive disease category: gallstones, choledochal lithiasis, angiocolitis, acute and chronic pancreatitis, acute and chronic hepatitis, gastric and duodenal ulcer,

hiatal hernia, intestinal occlusion, appendicitis, organ perforation, esophageal varices, cirrhosis liver, dyslipidemia, lower and upper digestive hemorrhage, hypoproteinemia, hypoalbuminemia, benign tumors of the digestive tube, malignant tumors of the digestive tube, stenoses and digestive fistulas. Renal comorbidity was present at admission for 67 of the patients, representing 33.3% of the target group. This category included both acute and chronic renal diseases and urinary tract infections (acute and chronic renal failure, urinary infections, bladder fistulas, hydronephrosis, benign and malignant renal tumors and bladder and prostate tumors). The statistical correlation between the results of the biological samples (blood urea) recorded at admission with renal disease in comorbidity, in the patients included in the study, is statistically significant, $p < 0.01$, according to Table 2. The average value of urea at admission, in the studied group, in patients without renal disease (RBD), presenting pathogenic *E. coli*, was 37.17mg/dl +/-17.35(SD) for 66.6% patients. The number was lower than those with elevated uremia values. In the case of patients with kidney disease (RD), confirmed since admission, the average uremia value was 67.39 mg/dl +/-52.35(SD), representing 33.3% of the patients.

Table 2. Average values of blood urea in the target group for renal disease in comorbidity, at admission

Disease associated with digestive disease	Parameter	Urea value mg/dl ±SD	P value
Kidney diseases	absent	37.25±17.39	0.000
	present	65.76±52.41	

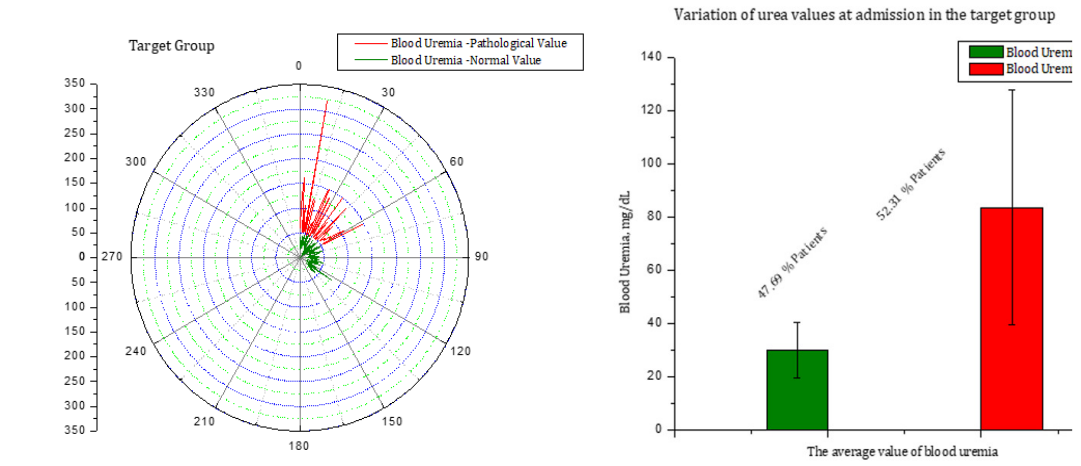
The average blood urea values in the target group were statistically significantly correlated with the urine culture sample (Table 3). The urine cultures were collected both from patients with known kidney diseases and from those without kidney diseases based only on their symptoms, which suggested presence of urinary tract infection. The main bacteria that caused the urinary infection was *Escherichia coli,* being the most frequently detected bacteria in this type of infection. The most common symptoms of urinary infections were: dysuria, pollakiuria, abdominal pain, nausea and vomiting, fever and chills. Symptoms of intestinal *Escherichia coli* infection included diarrhea, nausea and vomiting, abdominal pain, marked asthenia and fever. In serious situations, hemorrhagic diarrhea, vomiting followed by dehydration or even kidney failure may be present.

According to Popa *et al*. (2016), hemolytic uremic syndrome occurs in approximately 16% of patients with hemorrhagic colitis, being characterized by renal failure, hemolytic anemia and thrombocytopenia. In the case of urine cultures, the bacterium *E. coli* was present in all cases, sometimes being associated with other bacteria and fungi.

Table 3. The correlation between the urine culture and the average values of blood uremia, at admission

Bacteriological sample	Parameter	Urea value mg/dl ±SD	P value
Urine culture	absent	40.88± 24.68	0.020
	present	52.57±44.21	

The variation of urea values at admission in the target group is presented in Figure 1.



a)	b)

Figure 1. Variation of urea values at admission in the target group
Legend: a) Uremia value is represented for all patients in the target group; b) The average value of uremia for patients with normal values of blood uremia (<45 mg/dl) and the average value of uremia for patients with pathological values of blood uremia (>45 mg/dl) were represented.

In the case of the patients included in the study, 47.69% of them had normal values of urea at admission, with an average of 23.99mg/dl +/-8.987(SD), and 52.31% of the patients had increased values above the normal ones, the average being 72.965 mg/dl +/-14.750(SD); (urea values up to 45mg/dl being considered normal). Of the total number of patients included in the study, 67 patients were declared with kidney disease (33.33%), 134 patients (66.66%) were without kidney disease. If we make the difference, 66.66 (%FBR) -47.69 (%patients with uremia within normal limits) it turns out that another 18.91% had elevated urea values apart from those declared with kidney disease (BR), i.e., they presented hemolytic uremic syndrome since at admission. Thus, urea determinations in the target group are justified as *E. coli* infection can influence renal function. It is possible that due to the presence of *Escherichia coli* infection, the symptoms of uremic syndrome are accentuated. The correlation of urea values with the declared renal comorbidity was also achieved at the end of the hospitalization period when again statistically significant values were obtained ($p < 0.005$), Table 4.

Table 4. Average values of blood urea in the target group for kidney disease in comorbidity, at discharge

Disease associated with digestive disease	Parameter	Urea value mg/dl ±SD	P value
Renal disease	absent	32.70±30.71	0,000
	present	84.32±65.11	

The variation of uremia in the target group before and after the surgical intervention is shown in Figure 2. At the same time, the average value of uremia was represented for deceased patients with and without associated kidney disease, when an increase of up to 3.84 times higher was noted.

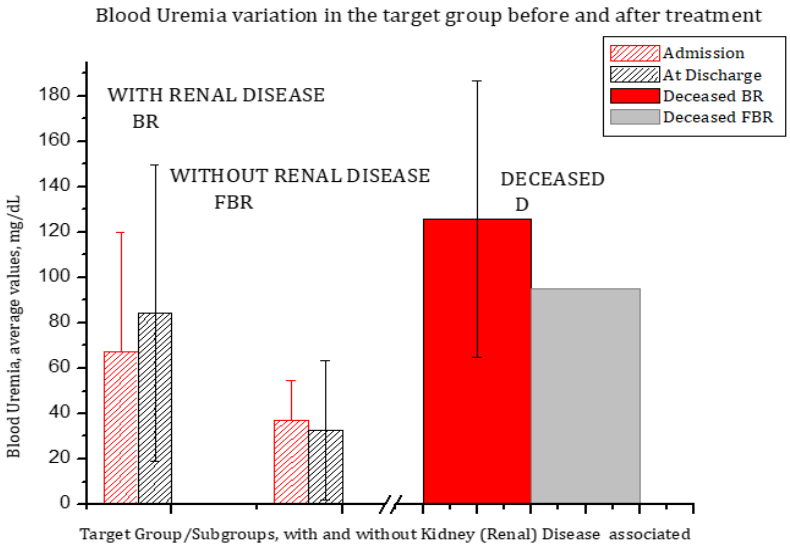


Figure 2. Uremia variation in the target group before and after antibiotic and antifungal treatment where BR= renal disease, FBR= without renal disease

The average recorded values of urea were higher at the end of the treatment period compared to the recorded values at admission both in the group of patients with renal disease and in the group of those without renal disease. At the discharge time, the recovery rate increases a lot in the case of patients without renal disease, being 5.24 times higher than those with renal comorbidity, even in the presence of infection with pathogenic *Escherichia coli* (Figure 3).

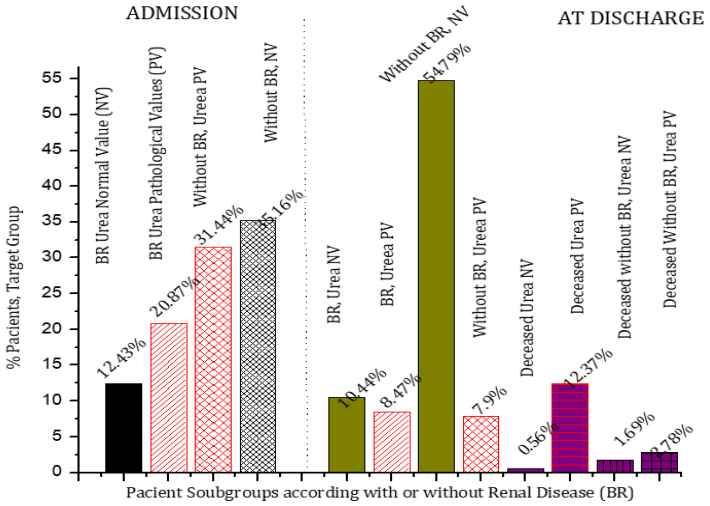


Figure 3. Comparative presentation of the number of patients (in percentages) at admission and at discharge, by subgroups: BR with uremia within normal limits, BR with uremia within pathological limits, FBR with uremia within normal limits, FBR with uremia within pathological limits and Deceased BR with uremia within normal limits, BR deceased with uremia within pathological limits, FBR deceased with uremia within normal limits, FBR deceased with uremia within pathological limits (BR = renal disease, FBR = without renal disease)

In the case of patients included in the study, several classes of antibiotics were used to carry out the antibiotic treatment (Table 5), in most cases nitroimidazole, 3rd generation cephalosporins, carbapenems and glycopeptides were administered in one or many more combinations. The antibiotic treatment considered the general condition of the patient, the associated diseases, the results of the recorded biological samples, possible allergies, age, the type of bacteria detected by laboratory tests as well as the results of the antibiogram. Antibiotic combinations were made to increase the treatment response rate, following the indications of the international treatment guidelines for each type of bacteria detected.

Table 5. Classes of antibiotics administered to patients included in the study

No	Class of antibiotic used and trade name	Number of patients to whom antibiotic was administered and percentage	
1	Nitroimidazole (Metronidazole)	162	80.5970%
2	III-generation Cephalosporins (Cefort, Ceftamil, Cefotaxime)	127	63.1840%
3	Carbapenems (Imipenem, Meronem, Invanz)	118	58.7064%
4	Glycopeptides (Vancomycin)	89	44.2786%
5	Combinations of penicillins with beta-lactamase inhibitors (Amoxicillin with clavulanic acid, Piperacillin-Tazobactam,)	45	22.3880%
6	Polypeptides (Colistin)	38	18.9054%
7	2nd generation Cephalosporins (Cefuroxime)	25	12.4378%
8	Aminoglycosides (Amikozite, Gentamicin)	25	12.4378%
9	Fluoroquinolones (Ciprofloxacin, Norfloxacin, Levofloxacin)	22	10.9452%
10	Oxazolidinones (Linezolid)	12	5.9701%
11	Sulfonamides with trimethoprim (Sumetrolim)	11	5.4726%
12	Rifamicyns(Sinerdol)	9	4.4776%
13	Tetracyclines (Tygacil)	6	2.9850%
14	Penicillins (Amoxicillin, Oxacillin, Ampicillin, Penicillin)	5	2.4875%
15	Nitrofurans (Nitrofurantoin)	4	1.990%
16	Lincosamides (Clindamicina)	3	1.4925%

The most frequently used was Metronidazole, an antibiotic from the Nitroimidazole class, which is an antibiotic with a broad spectrum of action, followed by IIIa generation Cephalosporins, Carbapenems and Glycopeptides, and only 4 patients underwent treatment with Nitrofurans and 3 patiens withLincosamides. When the response to the treatment proved ineffective for a certain antibiotic, another one was used so that the sequence of up to 4 types of antibiotics was possible. Most combinations of administered antibiotics were made between Nitroimidazole (Metronidazole) with other classes of antibiotics, namely 3rd generation Cephalosporins, Carbapanems and Glycopeptides (Vancomycin). Most patients received combinations of Nitroimidazole with III-generation Cephalosporins, followed by those with Nitroimidazole (Metronidazole), III-generation Cephalosporins, Carbapanems and Glycopeptides (Vancomycin), and the fewest patients received combinations of 3rd generation Cephalosporins, Carbapanems and Glycopeptides (Vancomycin). (Figure 4). The combination of Nitroimidazole with III-generation Cephalosporins was administered to most patients followed by the combination of Nitroimidazole with III-generation Cephalosporins, Carbapenems and Glycopeptides.

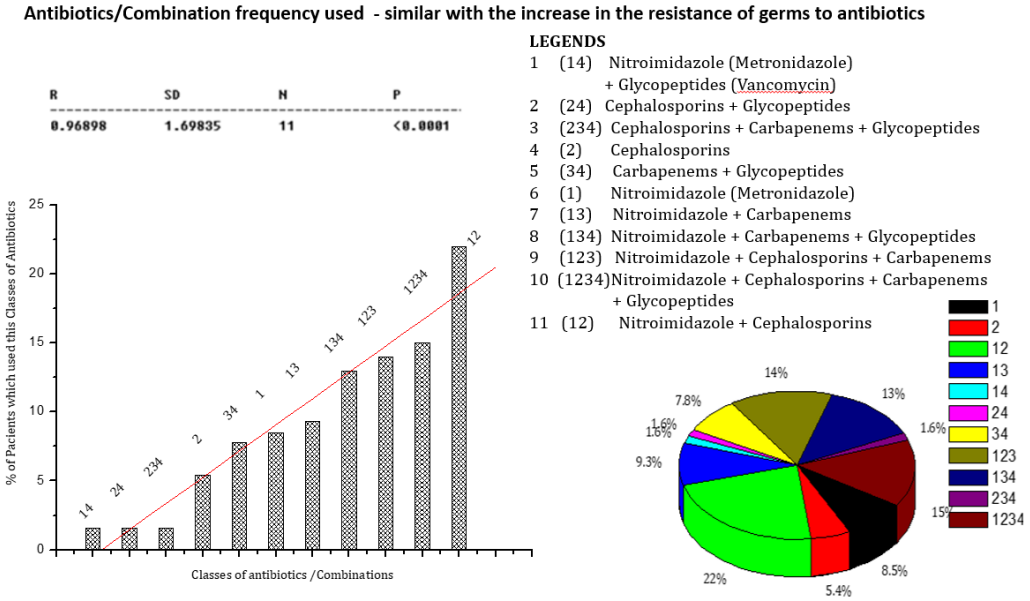


Figure 4. The increase in the resistance of germs to antibiotics compared to the number of patients who require increasingly complex combinations

Patients with renal comorbidity proved to have increased resistance of germs to antibiotic treatment, possibly due to immunosuppression, which made the need for antibiotics more complex (Figure 5)

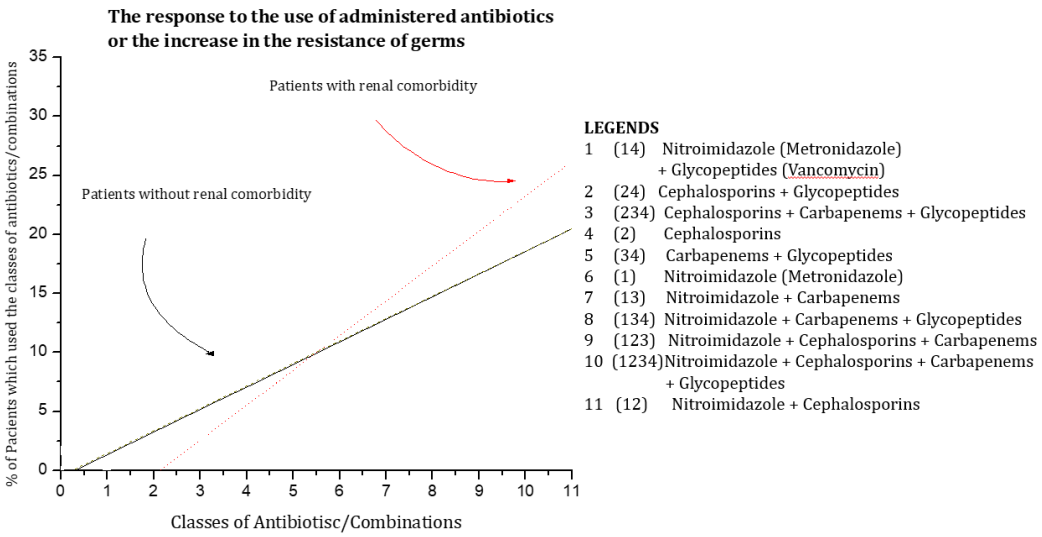


Figure 5. Graphical representation of the response to the use of administered antibiotics

Analyzing the uremia values in the different groups of patients who received treatment with the combinations of antibiotics, it was found that patients without kidney damage did not require complex combinations of antibiotics as treatment, with a good response, but patients who were administered cephalosporins + carbapenems + glycopeptides (group 3) both those with kidney disease and those without kidney disease had high urea values and in the case of deceased patients urea had increased values both in the presence of kidney disease and in its absence, the treatment proving ineffective. In group 4, where only cephalosporins were administered, we obtained high urea values both in the group of patients with kidney diseases and in the case of those without kidney diseases, and in the case of deceased patients, the values of urea were greatly increased, proving the ineffectiveness of the antibiotic treatment. In group 11, where Nitroimidazole and Cephalosporins were administered, we obtained high values of uremia in all categories, including in the case of patients who died with kidney damage, proving that even in this case the antibiotic treatment was not effective. The most effective combinations proved to be the combinations Nitroimidazole-Glycopeptides (group 1), Cephalosporins-Glycopeptides (group 2), Carbapenems-Glycopeptides (group 5), Nitroimidazole (group 6) and the combination Nitroimidazole- Cephalosporins-Carbapenems-Glycopeptides (group 10), in these groups not being registered deaths (Figure 6).

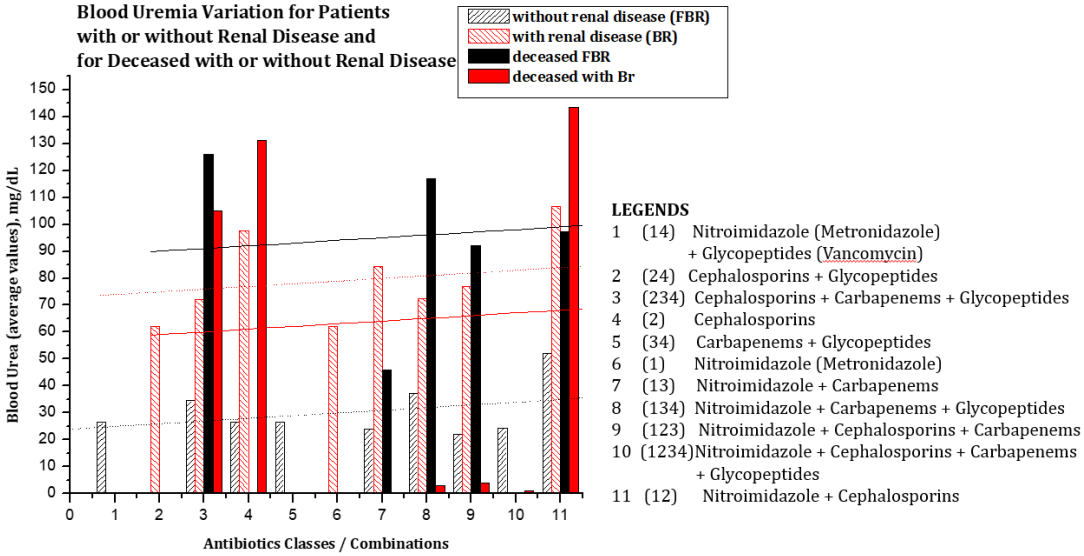


Figure 6. Variation of uremia in digestive disease with renal comorbidity and infection with pathogenic *E. coli* depending on the antibiotics/antibiotic complexes used, where BR= renal disease and FBR= without renal disease

The declared condition of the patients at discharge can be found in Table 6.

Table 6. Stated status of patients at discharge by number and sex in the entire studied group

No	Stated status of patients at discharge	Total Number of patients	Percentage Patients	Number of women	Percentage of women	Number of men	Percentage of men
1	Healed	57	28.3582%	25	12,4378%	32	15.9203%
2	Improved	99	49.2537%	46	22,8855%	53	26.3681%
3	Stationary status	8	3.98%	5	2.4875%	3	1.4925%
4	Aggravated condition	2	0.9950%	1	0.4975%	1	0.4975%
5	Deceased	35	17.4129	10	4.9751%	21	12.4378%

Correlating the value of uremia by subgroups of patients with and without renal comorbidity, with the condition declared at discharge time and with their percentage, we noticed that above a uremia of 92mg/dl, the risk of death increased greatly in patients from the target group (Figure 7).

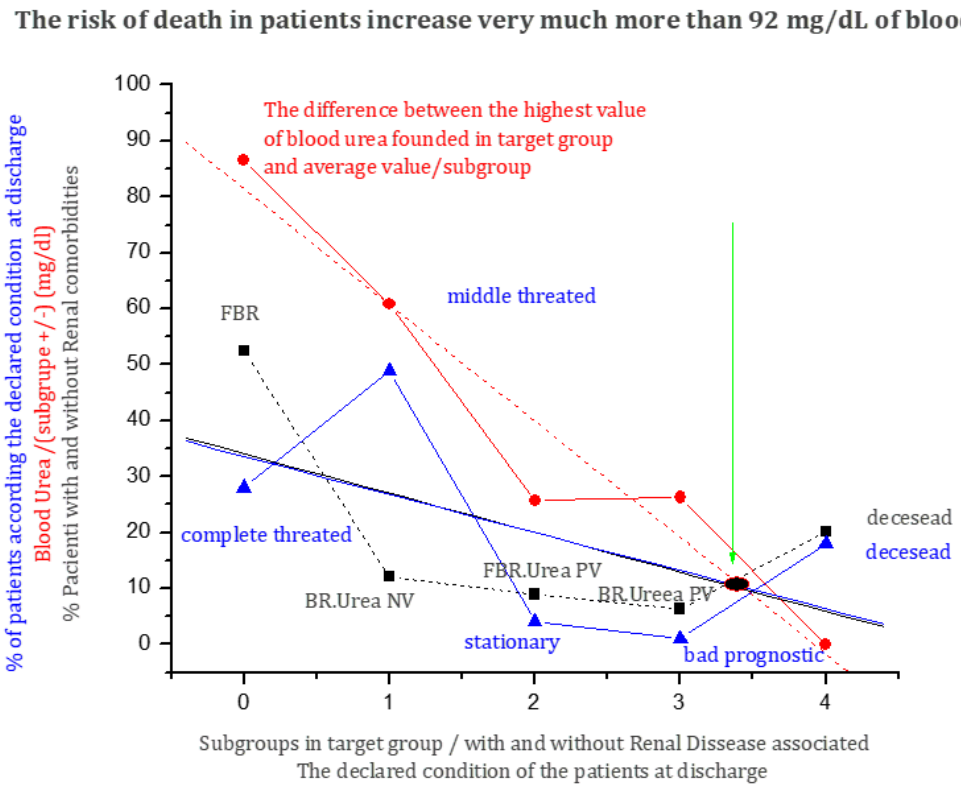


Figure 7. The increase in the risk of death in patients from the target group above the uremia value of 92 mg/dl

Legend: FBR=patients without kidney disease, BR urea VN=patients with kidney disease with normal uremia values, FBR urea VP=patients without kidney disease but with pathological values of uremia, BR urea VP=patients with kidney disease with pathological values of uremia.

In the case of patients who had pathological values of uremia, we had an increase in the number of days of hospitalization directly proportional to the number of combinations of antibiotics represented in Figure 9. In the case of patients without kidney disease and normal values of uremia, the number of days of hospitalization have decreased in direct proportion to the increase in the number of antibiotic combinations. In the case of antibiotic group 11 where we had combinations of Nitroimidazole with III-generation Cephalosporins, Carbapenems and Glycopeptides, we had the highest values of the number of days of hospitalization, the most deaths both in the case of patients with associated kidney disease and in the case of those without associated kidney disease. We also had a large number of deaths with an increased number of days of hospitalization in group 3 of antibiotics in patients with kidney disease who received 3rd generation Cephalosporins, Carbapenems and Glycopeptides (Figure 8).

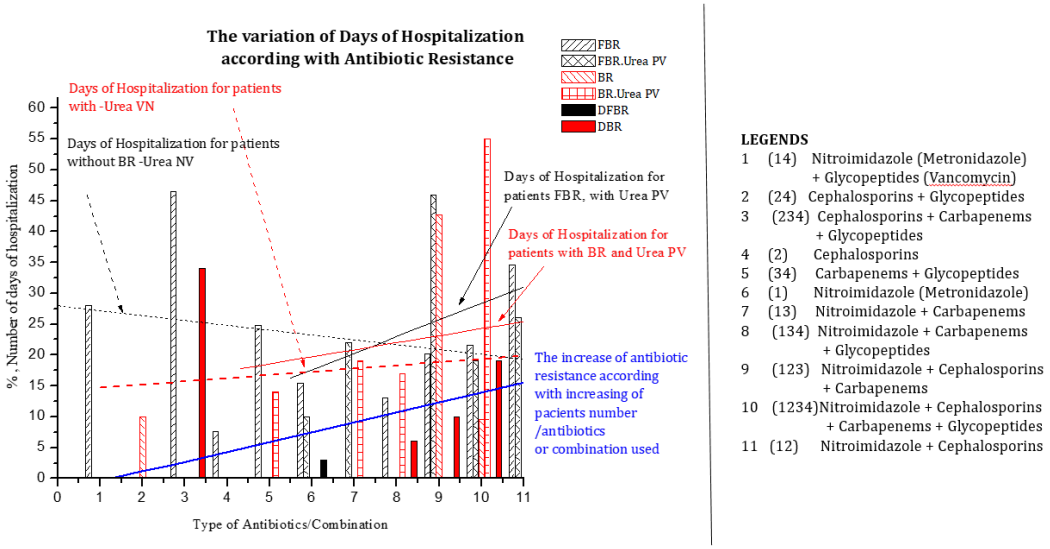


Figure 8. The variation of the number of days of hospitalization according to antibiotic resistance, where BR = kidney disease, FBR = without kidney disease, FBR nitrogen VP = without kidney disease with pathological values of urea, BR nitrogen VP = kidney disease with pathological values of urea, DFBR = deceased without renal disease, DBR= deceased with renal disease

The average number of days of hospitalization in the studied group was 20,866 +/-20,7831 days. By correlating the combinations of antibiotics administered with the number of patients and the duration of hospitalization, we obtained the lowest average number in the case of combination 13 (Nitroimidazole with Carbapenem), of 6 days, and the highest average number of days of hospitalization in the case of patients who were administered combination 1234 (Nitroimidazole, Cephalosporins, Carbapenems, Glycopeptides) of 57.2 days (Table 7).

Table 7. The average number of days of hospitalization correlated with the antibiotic combination administered

Antibiotic combination	Average number days of hospitalization		Average number days of hospitalization		Average number days of hospitalization	
Combination of antibiotics	Renal disease with normal uremia	Renal disease with pathologic uremia	Withoutrenal disease with normal uremia	Withoutrenal disease with pathologic uremia	Deaths with renal disease	Deaths without renal disease
1		19 days/1 P		22 days/1 P		
2			7.57zile/7P			
12	11.5days /2P	7.33 days/3P	13.5 days/20P		13.66 days/3P	10.6days/5 P
13		17days/2 P	13days/13P		6 days/1 P	
14			28days/2 P			
24	10 days/1P					
34			15.5days/2P	10days /1 P		3days/1P
123	9.5days/2P	55days/1P	21.64days/ 17 P	19 days/2P	19 days/2P	
134	42.75days/ 4 P		20 days/14P	46days/2P	10 days/2P	
234			46.5days/2P		34days/1P	
1234			34.66 days/12P	26 days/1 P	57.2 days/ 10P	50.25 days/4P

Legend: 1 Nitroimidazole, 2 Cephalosporins, 12 Nitroimidazole-Cephalosporins, 13 Nitroimidazole-Carbapenems, 14 Nitroimidazole-Glycopeptides, 24 Cephalosporins-Glycopeptides, 34 Carbapenems-Glycopeptides, 123 Nitroimidazole Cephalosporins-Carbapenems, 124 Nitroimidazole-Cephalosporins-Glycopeptides, 134 Nitroimidazole- Carbapenems Glycopeptides, 234 Cephalosporins-Carbapenems -Glycopeptides, 1234 Nitroimidazole -Cephalosporins -Carbapenems Glycopeptides, P=patient(s)

Correlating the number of days of hospitalization with the combinations of antibiotics administered, we obtained the best values in the case of patients without kidney disease with normal uremia and combination 12 an index of 0.675, with combination 13 of 1, with combination 123 an index of 1.27 and with the combination 134 an index of 1.43. (Table 8). I considered significant values obtained ≤1.

Table 8. Efficiency of the treatment carried out according to the number of combinations of antibiotics administered

Antibiotic combination treatment	Effectiveness index treatment		Effectiveness index treatment		Effectiveness index treatment	
Antibiotic Combination Treatment	Renal disease with normal uremia	Renal disease with pathologic uremia	Without Renal disease with normal uremia	Without Renal disease with pathologic uremia	Deaths with renal disease	Deaths without renal disease
1		19		22		
2			1.08			
12	5.75	2.44	0.675		4.55	2.12
13		8.5	1		6	
14			14			
24	10					
34			7.75	10		3
123	4.75	55	1.27	9.5	9.5	
134	10.68		1.43	23	5	
234			23.25		34	
1234			2.88	26	5.7	12.56

Legend: 1 Nitroimidazole, 2 Cephalosporins, 12 Nitroimidazole-Cephalosporins, 13 Nitroimidazole-Carbapenems, 14 Nitroimidazole-Glycopeptides, 24 Cephalosporins-Glycopeptides, 34 Carbapenems-Glycopeptides, 123 Nitroimidazole Cephalosporins-Carbapenems, 124 Nitroimidazole-Cephalosporins-Glycopeptides, 134 Nitroimidazole- Carbapenems Glycopeptides, 234 Cephalosporins-Carbapenems -Glycopeptides, 1234 Nitroimidazole -Cephalosporins -Carbapenems Glycopeptides

In the case of patients with kidney disease, we obtained an average of 10.94 days of hospitalization/patient, in the case of patients without kidney disease, we obtained an average of 3.41 days/patient, and in the case of deceased patients, we obtained an average of 7, 27 days / patient (Table 9).

Table 9. The average number of days of hospitalization after association with the presence or absence of kidney disease

Number of days of hospitalization	Renal disease with normal uremia	Renal disease with pathologic uremia	Without renal disease with normal uremia	Without renal disease with pathologic uremia	Deaths with renal disease	Deaths without renal disease
Number of days	73.75days/9P	112.33days /8 P	225.34days/ 95 P	23 days/ 7 P	139.86days/19P	63.85days/9P
Total	186.08 days/17 P		348.34 days/102 P		203.71 days /28 P	
Average	10.94days/ P		3.41days/ P		7.27 days/ P	

Legend: P= patient (s)

From the target group, 30 patients without kidney disease and with normal uremia received the combinations of antibiotics considered the least effective, another 4 patients from the group without known kidney disease but with increased uremia received the same combinations (Table 10).

Table 10. Correlation between the average number of days of hospitalization and combinations of antibiotics considered inappropriate

Number of	Average number of days of hospitalization		Average number of days of hospitalization		Average number days of hospitalization	
Antibiotic combination	Renal disease with normal uremia	Renal disease with pathologic uremia	Without renal disease with normal uremia	Without renal disease with pathologic uremia	Deaths with renal disease	Deaths without renal disease
34			15.5/2 P	10/1P		3/1P
134	42.75/4P		20.14/14 P	46/2P	10/2P	
234			46.5/2P		34/1P	
1234			34.66/12P	26/1P	57.2/10P	50.25/4P

Legend: P= patient (s)

The most common digestive diseases were neoplasias of the colon, stomach, pancreas, liver and bile ducts. Among the benign digestive conditions that led to the death of patients were organ perforations, intestinal occlusions and peritonitis. In all cases, the antibiotic treatment was correlated with the age and condition of the patient, the existing comorbidities, the results of the laboratory tests and the antibiogram, and the bacterial and fungal infections required additional antibiotic and antifungal treatment and for this reason the period of hospitalization was extended.

In the case of deceased patients, the antibiotic treatment was carried out in 31 patients with carbapenems, in 29 patients with nitroimidazoles, in 25 patients with III-generation cephalosporins, in 24 patients with glycopeptides, in 17 patients with polypeptides, in 10 patients with combinations of penicillins with beta-lactamase inhibitors, in 5 patients with sulfonamides with trimethoprim, in 4 patients with aminoglycosides, in 3 patients with respective oxazolidinones and tetracyclines and in 2 patients each fluoroquinolones, lincosamides and penicillins were administered. From the group of deceased patients, only one patient received a single class of antibiotic, i.e., fluoroquinolones, for urinary infection, the rest received combinations of several classes of antibiotics throughout hospitalization, and one patient received 12 classes of antibiotics during 97 days of hospitalization. The number of days of hospitalization in the case of deceased patients was between 3 and 142 days. Of the 35 deceased patients, in addition to the infections confirmed by bacteriological tests, 9 patients had digestive, cardiac, renal, pulmonary, neurological and diabetes disorders, 34 also had heart diseases, 21 patients had diabetes and 26 patients had kidney disease.

As early as 2010, international treatment guidelines have recommended for uncomplicated urinary infections the treatment with fluoroquinolones and the administration of an initial dose of cephalosporins or aminoglycosides if the rate of resistance to fluoroquinolones was higher than 10% (Talan *et al*., 2016). *Escherichia coli*, frequently encountered in urinary infections, has developed resistance to most of the usual treatments with beta-lactams, Ciprofloxacin, Nalidixic acid, Co-trimoxazole and tetracyclines precisely because of the excessive, unjustified use of antibiotic therapy by administration without a medical prescription and by increasing the consumption of treated animal products in excess of antibiotic (Karam *et al*., 2019).

Urinary tract infections caused by E coli occur in 1-2.5% of hospitalized patients and these infections represent 30-40% of all nosocomial infections (Golli *et al*., 2019).

As the data from the specialized literature also show, diabetes decreases urinary cytokines and leukocytes, as a result of the increased incidence of infections in these patients, and the treatment of diabetic patients is identical to that administered to patients without this disease and is determined according to the clinical data and laboratory, considering the initial infection complicated. Recurrences occur more frequently in diabetic patients, but not all studies can confirm this (Geerlings, 2008).

Studies in the specialized literature have shown that the administration of nitrofurantoin and fosfomycin in the case of uncomplicated urinary tract infections has proven to be the optimal treatment modality, with the lowest rates of antimicrobial resistance (Ny *et al*., 2019). The highest rates of antimicrobial resistance were detected in patients treated with ampicillin, trimethoprim, trimethoprim sulfamethoxazole,

amoxicillin with clavulanic acid and ciprofloxacin as shown by Ny *et al*. (2018), tracking antimicrobial resistance of E coli bacteria in urinary tract infections in several European countries. In the Netherlands, the use of nitrofurantoin as the first choice of treatment and fosfomycin as the second choice followed the indications of the international treatment guidelines for uncomplicated urinary tract infection caused by *E. coli* (van Driel *et al*., 2019)

Lee Dong Sup *et al*. (2018) show in his article that the two antibiotics (nitrofurantoin and fosfomycin) showed a sensitivity of over 90% in most countries of the world, compared to other antibiotics Lee *et al*. (2018).

Kot *et al*. (2019), shows the same treatment behavior in the case of urinary infection caused by *E. coli*. Although trimethoprim sulfamethoxazole was frequently used as the first treatment intention for the same condition, it demonstrated an increase in antimicrobial resistance as in the case of fluoroquinolones – ciprofloxacin (Kot, 2019) and so did Tenney *et al*. (2018). In the case of infections with ESBL producing E coli (extended spectrum betalactamases E coli), fosfomycin and nitrofurantoin remain the drugs of choice, but also piperacillin-tazobactam has proven good results in treatment. Carbapenems and second-generation cephalosporins have not shown satisfactory results in this case (Fournier *et al*., 2013).

A study from Saudi Arabia published in 2018 shows that in the case of *E. coli* bacteria, nitrofurantoin proved to be the most effective, followed by Ciprofloxacin, Augmentin and Cefazolin. Increased resistance has been reported to ampicillin and co-trimoxazole (Alanazi *et al*., 2018).

Multi-resistant bacteria can survive for a long time on surfaces and medical equipment, their survival being determined by temperature, humidity and the incorrect application of chemical and physical disinfection measures. Contamination is prevented if appropriate disinfectants are used, especially in intensive care units, by reducing biofilm formation (Russotto *et al*., 2017).

Antimicrobial resistance is one of the most important public health problems worldwide, involving additional treatment costs, increasing morbidity and mortality in patients infected with multidrug-resistant bacteria (Zhen *et al*., 2019). This resistance is due to the inadequate consumption of antibiotics both in humans and birds and animals (Roth *et al*., 2019; Ahmed *et al*., 2021), poor hygiene, ineffective measures to prevent and control bacterial infections. Antimicrobial resistance in Europe and the US is lower compared to Asia and other regions of the world (Pormohammad *et al*., 2019). In order to prevent the occurrence of urinary tract infections, frequently encountered in the elderly and in those with repeated admissions or frequent catheterization, compliance with the hygiene measures imposed by the fitting and changing of the urinary probe and the proper hydration of the patient can prevent relapse (Jones *et al*., 2019). Unjustified use of antibiotics leads to the emergence of antimicrobial resistance (Dhingra *et al*., 2020). *E. coli* resistance to many classes of antibiotics can lead to increased treatment costs in the case of nosocomial infections. Powels *et al*. (2019) shows that in Great Britain the vast majority of antibiotics was prescribed by primary medicine, most frequently for viral and respiratory tract conditions but in many overestimated doses.

And other classes of antibiotics, such as cefuroxime (2nd generation cephalosporin) through unjustified administration, did not demonstrate the expected effects due to the emergence of antimicrobial resistance (Li *et al*., 2019).

E. coli infection is transmitted from animals to humans through non-compliance with hygiene measures, the most frequently reported symptom being diarrhea (Valilis *et al*., 2018). Resistance to Ampicillin, Gentamicin, Kanamycin, Sulfamides, Streptomycin, Tetracycline and Trimethoprim has been demonstrated in the Netherlands and in Australia neither Colistin, Streptomycin, Spectinomycin, Ampicillin, Trimethoprim-Sulfamethoxazole are effective. In both humans and animals, E coli infections can cause increased morbidity and mortality and raise treatment costs (Hartadi *et al*., 2020).

American treatment guidelines indicate the administration of combinations of penicillin, cephalosporins and carbapenems with aminoglycosides or fluoroquinolones for a longer period (4-6 weeks) in

patients with endocarditis, with risk factors, immunosuppressants, alcohol users, with dialysis, neoplastic diseases, renal diseases and diabetes (Akuzawa and Kurabayashi, 2018).

Conclusions

Escherichia coli is one of the bacteria that includes both commensal and pathogenic strains, the most frequently encountered and studied, with an enormous epidemiological impact on the population of the entire world. In the case of bacterial infections caused by *Escherichia coli,* the risk factors are the patient's age, sex, associated comorbidities, recurrent infections, prolonged hospitalization especially in intensive care units, repeated and long-term treatment with antibiotics, but also invasive medical procedures with a risk of nosocomial infections. The most common locations of this type of infection are in the urinary and digestive system and required antibiotic treatments with one or more classes of antibiotics to eradicate the infection, prolonging the period of hospitalization. Bacterial infections produced by *Escherichia coli,* together with the other bacteria highlighted in the patients taken into the study, affected their evolution during hospitalization, increased morbidity and mortality, increased the duration and costs of hospitalization. Mortality of patients in the studied group was 17.5%, higher in men compared to women (25 men and 10 women), it was caused by the comorbidities of the patients to which infections caused by *Escherichia coli* and other bacteria and fungi.

Authors' Contributions

CMC has collected data, contributed to systematization of results, and manuscript writing. SLP and TM contributed to all hematological and biochemical, as well as bacteriological tests in all included patients. MT and AP were involved in statistical analyzes of data. ML structured the study design, manuscript review and correction, data interpretation.

All authors read and approved the final manuscript.

Ethical approval (for researches involving animals or humans)

The procedures performed involving human participants were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. Consequently, the study obtained the approval from The Ethical Commission of our institutions (5025/12.04.2021, and 116/15.04.2021, respectively).

Acknowledgements

The authors wish to acknowledge financial support from the "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania, grant contract no. 1529/16/18.01.2019. This work was also supported by the Romanian National Authority for Scientific Research and Innovation, CNCS-UEFISCDI project number PN-III-P2-2.1-PED-2019-0997, PN-III-P2-2.1-PED-2021-0073

Conflict of Interests

The authors declare that there are no conflicts of interest related to this article.

References

Ahmed S, Hansen C, Dahlkilde AL, Herrero-Fresno A, Pedersen KS, Nielsen JP, Olsen JE (2021). The effect of colistin treatment on the selection of colistin-resistant *Escherichia coli* in Weaner pigs. Antibiotics 10:465. *https://doi.org/10.3390/antibiotics10040465*

Akuzawa N, Kurabayashi M (2018). Native valve endocarditis due to *Escherichia coli* infection: a case report and review of the literature. BMC Cardiovascular Disorders 18:1-9. *https://doi.org/10.1186/s12872-018-0929-7*

Alanazi MQ, Alqahtani FY, Aleanizy FS (2018). An evaluation of *E. coli* in urinary tract infection in emergency department at KAMC in Riyadh, Saudi Arabia: retrospective study. Annals of Clinical Microbiology and Antimicrobials 17:1-7. *https://doi.org/10.1186/s12941-018-0255-z*

Chinchilla-López P, Cruz-Ramón V, Ramírez-Pérez O, Méndez-Sánchez N (2018). Gastroenteritis in an adult female revealing hemolytic uremic syndrome: case report. World Journal of Gastroenterology 24:763. *https://doi.org/10.3748/wjg.v24.i6.763*

Dhingra S, Rahman NA, Peile E, Rahman M, Sartelli M, Hassali MA, . . . Haque M (2020). Microbial resistance movements: an overview of global public health threats posed by antimicrobial resistance, and how best to counter. Frontiers in Public Health 8:535668. *https://doi.org/10.3389/fpubh.2020.535668*

Fournier D, Chirouze C, Leroy J, Cholley P, Talon D, Plesiat P, Bertrand X (2013). Alternatives to carbapenems in ESBL-producing *Escherichia coli* infections. Médecine et Maladies Infectieuses 43:62-66. *https://doi.org/10.1016/j.medmal.2013.01.006*

Geerlings SE (2008). Urinary tract infections in patients with diabetes mellitus: epidemiology, pathogenesis and treatment. International Journal of Antimicrobial Agents 31:54-57. *https://doi.org/10.1016/j.ijantimicag.2007.07.042*

Golli AN-L, Nițu FM, Bălășoiu MA, Rascu S, Lungu MA, Dinescu SN, . . . Olteanu M (2019). Microbiological profile and antibiotic resistance pattern of bacterial uropathogens among hospitalized patients. Farmacia 67:167-173.

Harkins VJ, McAllister DA, Reynolds BC (2020). Shiga-toxin *E. coli* hemolytic uremic syndrome: review of management and long-term outcome. Current Pediatrics Reports 8:16-25. *https://doi.org/10.1007/s40124-020-00208-7*

Hartadi EB, Effendi MH, Plumeriastuti H, Sofiana ED, Wibisono FM, Hidayatullah AR (2020). A review of enterotoxigenic *Escherichia coli* infection in piglets: Public health importance. Systematic Reviews in Pharmacy 11:687-698.

Jang J, Hur H-G, Sadowsky MJ, Byappanahalli MN, Yan T, Ishii S (2017). Environmental *Escherichia coli*: ecology and public health implications—a review. Journal of Applied Microbiology 123:570-581. *https://doi.org/10.1111/jam.13468*

Jones LF, Meyrick J, Bath J, Dunham O, McNulty CA (2019). Effectiveness of behavioural interventions to reduce urinary tract infections and *Escherichia coli* bacteraemia for older adults across all care settings: a systematic review. Journal of Hospital Infection 102:200-218. *https://doi.org/10.1016/j.jhin.2018.10.013*

Karam MR, Habibi M, Bouzarz S (2019). Urinary tract infection: Pathogenicity, antibiotic resistance and development of effective vaccines against uropathogenic *Escherichia coli*. Molecular Immunology 108:56-67. *https://doi.org/10.1016/j.molimm.2019.02.007*

Khalid M, Andreoli S (2019). Extrarenal manifestations of the hemolytic uremic syndrome associated with Shiga toxin-producing *Escherichia coli* (STEC HUS). Pediatric Nephrology 34:2495-2507. *https://doi.org/10.1007/s00467-018-4105-1*

Kot B (2019). Antibiotic resistance among uropathogenic. Polish Journal of Microbiology 68:403-415.

Laura B, Federica G, Francesca V, Stefano K, Gioacchino L, Gian LDA, Claudio R (2018). Hemolytic uremic syndrome: differential diagnosis with the onset of inflammatory bowel diseases. Acta Bio Medica: Atenei Parmensis 89(Suppl 9):153. *https://doi.org/10.23750/abm.v89i9-S.7911*

Lee DS, Lee S-J, Choe H-S (2018). Community-acquired urinary tract infection by *Escherichia coli* in the era of antibiotic resistance. BioMed Research International. *https://doi.org/10.1155/2018/7656752*

Li J, Rettedal EA, van der Helm E, Ellabaan M, Panagiotou G, Sommer MO (2019). Antibiotic treatment drives the diversification of the human gut resistome. Genomics, Proteomics & Bioinformatics 17:39-51.

Ny S, Edquist P, Dumpis U, Gröndahl-Yli-Hannuksela K, Hermes J, Kling AM, ... Group NU (2019). Antimicrobial resistance of *Escherichia coli* isolates from outpatient urinary tract infections in women in six European countries including Russia. Journal of Global Antimicrobial Resistance 17:25-34. *https://doi.org/10.1016/j.jgar.2018.11.004*

Onyenweaku Florence C, Ifeanyi OE, Nwandikor Uzoije U (2018). A review on heamolytic uremic syndrome. International Journal of Current Research in Medical Sciences 4(3):80-92.

Popa GL, Preda M, Gheorghe S-A, Popa M-I (2016). Infectii intestinale ale epocii moderne: diareea calatorului prin ochiul clinicianului/Intestinal infections of the modern era: travelers' diarrhea through the clinician's eye. Infectio 46:5.

Pormohammad A, Nasiri MJ, Azimi T (2019). Prevalence of antibiotic resistance in *Escherichia coli* strains simultaneously isolated from humans, animals, food, and the environment: a systematic review and meta-analysis. Infection and Drug Resistance 12:1181. *https://doi.org/10.2147/IDR.S201324*

Pouwels KB, Muller-Pebody B, Smieszek T, Hopkins S, Robotham JV (2019). Selection and co-selection of antibiotic resistances among *Escherichia coli* by antibiotic use in primary care: an ecological analysis. PLoS One 14:e0218134. *https://doi.org/10.1371/journal.pone.0218134*

Roth N, Käsbohrer A, Mayrhofer S, Zitz U, Hofacre C, Domig KJ (2019). The application of antibiotics in broiler production and the resulting antibiotic resistance in *Escherichia coli*: A global overview. Poultry Science 98:1791-1804. *https://doi.org/10.3382/ps/pey539*

Russotto V, Cortegiani A, Fasciana T, Iozzo P, Raineri SM, Gregoretti C, . . . Giarratano A (2017). What healthcare workers should know about environmental bacterial contamination in the intensive care unit. BioMed Research International. *https://doi.org/10.1155/2017/6905450*

Talan DA, Takhar SS, Krishnadasan A, Abrahamian FM, Mower WR, Moran GJ, . . . EMERGEncy ID Net Study Group (2016). Fluoroquinolone-resistant and extended-spectrum β-lactamase–producing Escherichia coli infections in patients with pyelonephritis, United States. Emerging Infectious Diseases 22:1594. *https://doi.org/10.3201/eid2209.160148*

Tarr GA, Downey E, Pang X-L, Zhuo R, Strickland AJ, Ali S, . . . Freedman SB (2022). Clinical profiles of childhood astrovirus-, sapovirus-, and norovirus-associated acute gastroenteritis in pediatric emergency departments in Alberta, 2014–2018. The Journal of Infectious Diseases 225:723-732. *https://doi.org/10.1093/infdis/jiab429*

Tenney J, Hudson N, Alnifaidy H, Li JT, Fung KH (2018). Risk factors for aquiring multidrug-resistant organisms in urinary tract infections: a systematic literature review. Saudi Pharmaceutical Journal 26:678-684. *https://doi.org/10.1016/j.jsps.2018.02.023*

Travert B, Dossier A, Jamme M, Cointe A, Delmas Y, Malot S, ... des Microangiopathies Thrombotiques CDR (2021). Shiga toxin–associated hemolytic uremic syndrome in adults, France, 2009–2017. Emerging Infectious Diseases 27(7):1876. *https://doi.org/10.3201/eid2707.204638*

Valilis E, Ramsey A, Sidiq S, DuPont HL (2018). Non-O157 Shiga toxin-producing *Escherichia coli*—A poorly appreciated enteric pathogen: Systematic review. International Journal of Infectious Diseases 76:82-87. *https://doi.org/10.1016/j.ijid.2018.09.002*

van Driel AA, Notermans DW, Meima A, Mulder M, Donker GA, Stobberingh EE, Verbon A (2019). Antibiotic resistance of *Escherichia coli* isolated from uncomplicated UTI in general practice patients over a 10-year period. European Journal of Clinical Microbiology & Infectious Diseases 38:2151-2158. *https://doi.org/10.1007/s10096-019-03655-3*

Wassenaar TM (2016). Insights from 100 years of research with probiotic *E. coli*. European Journal of Microbiology and Immunology 6:147-161. *https://doi.org/10.1556/1886.2016.00029*

Zhen X, Lundborg CS, Sun X, Hu X, Dong H (2019). Economic burden of antibiotic resistance in ESKAPE organisms: a systematic review. Antimicrobial Resistance & Infection Control 8:1-23. *https://doi.org/10.1186/s13756-019-0590-7*

The journal offers free, immediate, and unrestricted access to peer-reviewed research and scholarly work. Users are allowed to read, download, copy, distribute, print, search, or link to the full texts of the articles, or use them for any other lawful purpose, without asking prior permission from the publisher or the author.

License - Articles published in ***Notulae Scientia Biologicae*** are Open-Access, distributed under the terms and conditions of the Creative Commons Attribution (CC BY 4.0) License.

© Articles by the authors; Licensee SMTCT, Cluj-Napoca, Romania. The journal allows the author(s) to hold the copyright/to retain publishing rights without restriction.

Notes:

- Material disclaimer: The authors are fully responsible for their work and they hold sole responsibility for the articles published in the journal.
- Maps and affiliations: The publisher stay neutral with regard to jurisdictional claims in published maps and institutional affiliations.
- Responsibilities: The editors, editorial board and publisher do not assume any responsibility for the article's contents and for the authors' views expressed in their contributions. The statements and opinions published represent the views of the authors or persons to whom they are credited. Publication of research information does not constitute a recommendation or endorsement of products involved.