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OPPORTUNISTIC PATHOGENS

IN PATIENTS WITH URINARY TRACT INFECTION

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Abstract

Urinary tract infections (UTIs) remain one of the most important problems of modern urology and medicine. Infections bring great discomfort and significantly reduce the quality of life. UTIs rank second after respiratory tract infections in outpatients. The most common pathogen of UTI are *E.coli*. The study of the etiology of UTI has great clinical and epidemiological importance in routine practice.

Objective: To assess the etiological significance of pathogens in the occurrence of urinary tract infections in the Karaganda region of Kazakhstan.

Methods: A total of 2378 patients presenting UTIs were enrolled and each provided a urine sample. The study was carried out in the Clinical Microbiology Laboratory MediTEC-NS between 2 January and 29 December 2018. Identification of isolated microorganisms was carried out on a WalkAway 96 Plus microbiological analyzer, Microscan model manufactured by Beckman Coulter (USA). Statistical Analysis was performed using the STATISTICA-6 package.

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Results: Out of 2378 patients a total of 1177 (49,5%) urine samples tested positive by culture test. From these samples, 1356 strains of microorganisms were isolated, of which 84.79% were monoculture and 21% were of a mixed culture. Gram-positive bacteria 690 (50, 88%), Gram-negative bacteria 630 (46, 46%), and *Candida* 36 (2.65%) were identified. Gram-negative rods were represented by *Enterobacterales* 557 (88.41%) and non-fermenting bacteria 73 (11.59%). In the *Enterobacterales* group included *Escherichia coli* 371 (66.61%) of which 108 (29,1%) ESBL strains. The next etiologically significant uropathogens were *Klebsiella*- 99 (17, 77%), *Enterobacter*-36 (6,46%) and *Proteus*-32 (8,09). *K.pneumoniae* prevailed in comparison with other *Klebsiella spp.* ESBL producing was 34 (57, 6%) out of 59 *K.pneumoniae* isolates. Gram-negative non-fermenting rod were represented by *Acinetobacter spp*-34 (46.57%) and *Pseudomonas spp* 31 (42.47%). Of 34 Acinetobacter spp. isolates 22 (64.7%) were identified as *Acinetobacter lwoffii*. Among the gram-positive pathogens of UTI, *Staphylococcus spp* prevailed - 411 (59.57%), followed by *Enterococcus spp* 197 (28.55%) and *Streptococcus spp* 81 (11.73%). Coagulase-negative staphylococci 381 (92,7%) isolates out of total 411 staphylococcal isolates. *Staphylococcus epidermidis* 245 (59,61%) and *Staphylococcus haemolyticus* 81 (21,17%) were the most frequent isolated coagulase-negative staphylococci. Of 411 staphylococcal isolates, 182 (44.28%) were MRS

Conclusion: We found that UTIs among our study population were predominantly caused by ten opportunistic pathogens. The most common uropathogens with a frequency of 66.9% were *E. coli*-30.53%, *S. epidermidis* -20.16%, and *Enterococcus spp.* -16.21%. Frequently isolated pathogens included *Klebsiella, S. haemolyticus spp.,* and *Streptococcus spp*. which amounted to 21.98%. The distribution within the patient group was equable and ranged from 6,67% to 8,15%. Etiologically significant pathogens included *Enterobacter spp., Proteus spp., Acinetobacter spp., Pseudomonas spp.* These bacteria accounted for 11.11%. The distribution within the group was again equable and ranged within 2,55% to 2,96%.

Key words: Urinary tract infections (UTIs), opportunistic pathogens

Introduction

Urinary tract infections (UTIs) remain one of the most important problems of modern urology and medicine. Infections bring great discomfort and significantly reduce the quality of life. UTIs rank second after respiratory tract infections among outpatients. Every year, 150 million people around the world are diagnosed with UTI [1]; moreover, about 50% -60% of women have a UTI at least once in their lifetime [2] [3]. In the United States, about 7 million visits to a doctor with urinary tract infections are registered annually, more than 100 thousand patients are hospitalized, and annual costs exceed US $ 1.6 billion [4]. According to Qiao LD et al. [3] in China, UTIs comprise 50% of all nosocomial infections. It should be noted that about 50% of UTIs in children are not counted, suggesting a significant under-estimation of infection rates. [5]. Data analysis also showed that out of 448 216 hospital admissions in Kazakhstan (2014), 33 613 were associated with kidney and urinary tract infections [6]. According to numerous data from researchers, including Kazakhstan, the majority cases of UTI are caused by E. coli, with the bacteria accounting for over 80% and some cases nearly 90%. of uncomplicated UTIs.[7] [8] [9]. *E. faecalis, C. albicans* are also associated with hospital acquired UTIs in Kazakhstan [10, 11]. Due to the fact that the ecological niche of pathogens, including

uropathogens, cannot be the same for many years, and also taking into account modern diagnostic capabilities, it was interesting for us, from a scientific and practical point of view, to study the etiological significance of various opportunistic microorganisms in the occurrence of UTIs within our region.

Material and methods

Study area

The study was carried out in the Karaganda Clinical Microbiology Laboratory MediTEC-NS from January to December 2018.

Study design

A total of 2378 patients were enrolled and provided a urine sample. Inpatients and outpatients with clinical symptoms of UTI were included. The age range of the selected patients was from 15 to 80 years. The study participants were majorly females 1586 (66, 69%).

Sample collection and Processing

A total of 2378 patients were enrolled and provided a urine sample. Inpatients and outpatients with clinical symptoms of UTI were included. The age of the selected patients was from 15 to 80 years. The study participants were majorly females 1586 (66,69%). For each patient, midstream urine samples for bacterial culture were collected before treatment. Urine samples were collected in sterile containers with a urine needle and transported to the laboratory within two hours for culturing. The culture media were prepared on an automated ProfiClave system (Switzerland). The following (HiMedia, India) culture media - nutrient agar, Columbia blood agar, MacConkey agar, Sabouraud agar with chloramphenicol, mannitol saline agar with yolk emulsion - were used for cultivation. Bacteria were incubated at T-37 C, fungi at T-20-22 C. Colonies were counted, and microscopic examination of their morphological tinctorial properties were observed. According to the classic definition, bacteriuria is caused by 10^5colony-forming units in 1 mL [12] HootonTM et al [13] believe that true infection may occur in patients with lower colony-forming units in 1 mL in the presence of symptoms and urinary leukocytes. In this context, more than 10^3 colony-forming units in 1 mL of urine is associated with infection [14]. In our case, in the presence of leukocytes more than 7 per high power field, colony counts higher or equal to 10^3 (colony-forming units in 1 mL) were considered as positive culture test. Identification of the isolated microorganisms was carried out on a WalkAway 96 Plus microbiological analyzer, Microcsan model manufactured by Beckman Coulter (USA). The results of identification and sensitivity to antimicrobial drugs after 17-24 hours were taken into account on the analyzer display and were automatically transferred to the information system of the laboratory. Identification of bacteria of the genus *Acinetobacter* was carried out on the MicroScan® panels: Gram-negative bacteria on the NEG MIC 44 B1016-175 and Neg/Urine Combo 61 B1017-414; non-fermenting bacteria- on the NEG MIC 44 B1016-175; Gram-positive bacteria - on POS Combo 33 B1017-211, streptococci - on MICroSTREP 6 plus. These panels are designed to determine the sensitivity of aerobic and facultative anaerobic Gram-negative rod-shaped bacteria to antibacterial drugs and their identification to the species. The fungi were indicated on Sabouraud's agar medium with chloramphenicol. Presumptive identification on chromogenic Sabouraud's agar by colony color.

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Statistical Analysis

A total of 2378 patients were enrolled and provided a urine sample. Inpatients and outpatients with clinical symptoms of UTI were included. The age of the selected patients ranged from 15 to 80 years. The study participants were majorly females 1586 (66, 69%). Statistical analysis was performed using the STATISTICA-6 package. The relative frequency (p) of the occurrence of an attribute was determined as follows:

$$p = \frac{k}{n},$$

k – Number of cases with the attribute of interest

n – Sample size

The attribute is defined as a specific characteristic or feature of a given subject p is calculated by sample, it reflects the population with some error:

$$m_o = \sqrt{\frac{p \times (1-p)}{n}}$$

The confidence interval for the *p* is located within:

$$p - t_\alpha \times \sqrt{\frac{p(1-p)}{n}}$$

and tα- is the critical value of the bilateral t-criterion of the Student for a given α and (n-1) degrees of freedom.

Results

Positive and Negative Urine Culture test

Table 1 shows the ratio of positive and negative urine culture test among investigated patients.

Table 1. The Ratio of Positive and Negative Urine Culture

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№	Culture tests	N (samples)	%	95%CI	
1.	Positive	1177	49,5	47,5	51,5
2.	Negative	1201	50,5	48,5	52,5
3.	Total	2378	100		

From the subject total, 1177 patients tested positive for culture test and out of that 803 (68%) were females while 374 (32%) were males. 1201 tested as negative urine samples and out of that 398 (33,3%) cases the clinical pathogens were identified 10^1 or 10^2(colony-forming units in 1 mL) and in 803 (66,7%) could not be detected**.**

Distribution of Isolated microorganisms in patients with UTIs

Out of 1177 urine samples, 1356 strains of microorganisms were isolated, of which 998 (84.79%) were monoculture and 177 (15, 21%) in mixculture. Table 2 shows the distribution of the Isolated microorganisms from the urine samples

Table 2. Microorganisms Isolated from the Urine in Patients with UTIs

№	Isolated microorganisms	n	%	95%CI	
1	Gram-negative rods	630	46,46	43,81	49,11
2	Gram-positive cocci	690	50,88	48,22	53,54
3	Fungi	36	2,65	1,80	3,50
	Total	1356	100		

A total of 1356 strains with identified clinical pathogens were included in the final analysis: 690 (50, 88%) Gram-positive bacteria, 630 (46, 46%) Gram-negative bacteria, and 36 (2.65%) Candida.

Distribution of Isolated Gram-Negative Rods in patients with UTIs

Table 3 shows that among the gram-negative rods the *Enterobacterales* 557 (88.41%) prevailed over non-fermenting bacteria 73 (11.59%).

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Table 3. Gram-Negative Rods Isolated from the Urine in Patients with UTIs

№	Gram-negative rods	n	%	95%CI	
1	*Enterobacterales* group	557	88,41	85,91	90,91
2	Nonfermenting gram-negative bacteria	73	11,59	9,09	14,09
	Total	630	100		

Distribution of the *Enterobacterales* in patients with UTIs

Table 4 shows that *Escherichia* was the most common uropathogen 371 (66,61%).

It should be noted that 108 of Escherichia strains were ESBL, which accounted for 29,1% of all Escherichia. The next etiologically significant uropathogens were *Klebsiella*- 99 (17, 77%), *Enterobacter*-36 (6,46%) and *Proteus*-32 (8,09%). *K.pneumoniae* prevailed in comparison with other *Klebsiella spp.* ESBL producing were 34 (57, 6%) out of 59 *K. pneumoniae* isolates.

Table 4. Enterobacterales Isolated from the Urine in Patients with UTIs

№	Genus	n	%	95%CI		Species	n
1	*Escherichia coli*	371	66,61	62,69	70,53	*Escherichia coli*	263
						*Escherichia coli ESBL**	108
2	*Enterobacter spp.*	36	6,46	4,42	8,50	*Enterobacter aerogenes*	10
						Enterobacter agglomerans group	5
						Enterobacter cancerogenous	2
						Enterobacter cloacae	14
						Enterobacter intermedius	1
						Enterobacter species	4
3.	*Citrobacter*	6	1,08	0,22	1,94	*Citrobacter amalonaticus*	2

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№	Genus	n	%	95%CI		Species	n
	spp.					*Citrobacter freundii complex*	2
						Citrobacter koseri	1
						Citrobacter species	1
4	*Klebsiella spp.*	99	17,77	14,60	20,94	*Klebsiella oxytoca*	5
						Klebsiella ozaenae	1
						Klebsiella pneumoniae	59
						Klebsiella pneumoniae ESBL	34
5	*Proteus spp.*	34	6,10	4,11	8,09	*Proteus mirabilis*	28
						Proteus mirabilis ESBL	4
						Proteus vulgaris	2
6	*Morganella spp.*	8	1,44	0,45	2,43	*Morganella morganii*	8
7	*Serratia spp.*	1	0,18	0	0,53	*Serratia marcescens*	1
8	*Providencia spp.*	2	0,36	0	0,86	*Providencia stuartii*	2
9	Total	557	100			Total	557

*ESBL-Extended-spect*extended spectrum β-lactamase producing

The most frequently identified Gram-positive uropathogens were: *Staphylococcus spp.* (in 411 isolates (59,57%)), *Enterococcus spp* (in 197 isolates (28,55%)) and *Streptococcus spp* (in 81 isolates (11,73%).

Distribution of the Gram-Negative Nonfermenting Rods in patients with UTIs

Table 5 shows that *Acinetobacter spp*-34 (46.57%) and *Pseudomonas spp* 31 (42.47%) were the most commonly detected gram-negative non-fermenting rods. Of 34 *Acinetobacter spp*. isolates 22 (64.7%) were identified as *Acinetobacter lwoffii*.

Table 5. Gram-Negative Nonfermenting Rods Isolated from the Urine in Patients with UTIs

№	Genus	n	%	95%CI	Species	n

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Distribution of the Gram-positive cocci in patients with UTIs

Table 6 shows that The most frequently identified Gram-positive uropathogens were: *Staphylococcus spp* (in 411 isolates (59,57%)), *Enterococcus spp* (in 197 isolates (28,55%)) and *Streptococcus spp* (in 81 isolates (11,73%).

Table 6. Gram-positive cocci Isolated from the Urine in Patients with UTIs

№	Genus	n	%	95%CI		Species	n
1	*Acinetobacter spp.*	34	46,57	35,13	58,01	*Acinetobacter baumannii/haemolyticus*	10
						Acinetobacter haemolyticus	1
						Acinetobacter lwoffii	22
						Acinetobacter species	1
2	*Pseudomonas spp.*	31	42,47	31,13	53,81	*Pseudomonas aeruginosa*	21
						Pseudomonas species	10
3	*Others spp.*	8	10,96	3,79	18,13	*Burkholderia (P.) cepacia*	**3**
						Ochrobactrum anthropi	**1**
						Achromobacter xylosoxidans subsp xylosoxidans	**1**
						Chryseobacterium (F.) indologenes	**1**
						Stenotrophomonas (X.) maltophilia	**2**
Total		73	100				73

№	Gram-positive cocci	n	%	95%CI	
1	*Staphylococcus spp.*	411	59,57	55,91	63,23
2	*Enterococcus spp.*	197	28,55	25,18	31,92
3	*Streptococcus spp.*	81	11,73	9,33	14,13
4	*Aerococcus urinae*	1	0,15	0	0,44
5	Total	690	100		

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Distribution of the of the Staphylococcus in patients with UTIs

Table 7 shows species identification of staphylococcal isolates in patients with UTIs. It should be noted coagulase-negative staphylococci 381 (92,7%) isolates out of total 411 staphylococcal isolates. *Staphylococcus epidermidis* 245 (59,61%) and *Staphylococcus haemolyticus* 81 (21,17%) were the most frequent isolated coagulase-negative staphylococci.

Table 7. Gram-positive cocci Isolated from the Urine in Patients with UTIs

Species	**n**	**%**	**95%CI**	
Staphylococcus aureus	30	7,3	2,18	12,42
Staphylococcus auricularis	3	0,73	-0,95	2,41
Staphylococcus capitis subsp. ureolyticus	1	0,24	-0,72	1,20
Staphylococcus epidermidis	245	59,61	49,94	69,28
Staphylococcus haemolyticus	87	21,17	13,12	29,22
Staphylococcus hominis	10	2,44	0	5,48
Staphylococcus hyicus	3	0,73	0	2,41
Staphylococcus intermedius	2	0,48	0	1,84
Staphylococcus lugdunensis	8	1,95	0	4,67
Staphylococcus saprophyticus	6	1,46	0	3,82
Staphylococcus simulans	11	2,68	0	5,86
Staphylococcus warneri	5	1,22	0	3,38

Analysis of MRS isolated is presented in table 8. Of 411 staphylococcal isolates, 182 (44.28%) were methicillin-resistant staphylococci. Out of 182 MRS isolates *Staphylococcus epidermidis* 126 (51,43%) and *Staphylococcus haemolyticus* 42 (48,28%).

Table 8. Prevalence of MRS isolates from the Urine in Patients with UTIs

Microorganisms	**n**	**n MRS***	**% MRS***	**95%CI**	
Staphylococcus aureus	30	2	6,67	0	15,60

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Microorganisms	n	n MRS*	% MRS*	95%CI	
Staphylococcus capitis subsp. ureolyticus	1	1	100		
Staphylococcus epidermidis	245	126	51,43	45,17	57,69
Staphylococcus haemolyticus	87	42	48,28	37,78	58,78
Staphylococcus hominis	10	2	20	0	44,79
Staphylococcus intermedius	2	1	50	0	119,30
Staphylococcus lugdunensis	8	2	25	0	55,01
Staphylococcus simulans	11	6	54.55	25,12	83,98
Staphylococcus warneri	5	0	0		
Staphylococcus saprophyticus	6	0	0		
Staphylococcus auricularis	3	0	0		
Staphylococcus hyicus	3	0	0		

MMRS*-*MRS-Methicillin-Resistant *Staphylococcus;** MRSA-Methicillin-Resistant *Staphylococcus aureus*

Distribution of the Streptococcaceae in patients with UTIs

Table 9 shows that *Enterococcus* was identified in 197 (70,86%) out of 279 isolates *Streptococcaceae*. Among enterococci, *E.faecalis* 192 (97.5%) prevailed. Streptococci were identified in 81 samples with a predominance of *S.agalactiae*, 45,7%.

Table 9. *Streptococcaceae* Isolated from the Urine in Patients with UTIs

genus	n	%	95%CI		species	n	%	95%CI	
Enterococcus spp.	197	70,86	65,5	76,2	*E. faecalis*	192	97,5	95,4	99,8
					E. faecium	2	1,02	0	2,42
					E. gallinarum	1	0,51	0	1,5

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genus	n	%	95%CI		species	n	%	95%CI	
					E. spp.	2	1,02	0	2,4
					Total	197	100		
Streptococcus spp.	81	29,14	23,8	34,4	*S. agalactiae* (Group B)	37	45,7	34,8	56,5
					S. pyogenes (Group A)	2	2,47	0	5,85
					Other streptococci	42	51,8	41,0	62,7
					Total	81	100		
Aerococcus urinae	1								
Total	279	100							

Etiologically significant bacterial pathogens isolated from patients with UTIs

Of the 1356 isolated opportunistic pathogens 1215 account for 90% of cases were of epidemic significance and 141 were considered as sporadic cases.

Table 10 shows that the ten most common bacterial pathogens in patients with UTIs were ranked in 3 groups according to the frequency of occurrence.

Table 10. Frequency of occurrence of the ten etiologically significant opportunistic bacterial pathogens isolated from patients with UTI-s

Pathogen's detection rate	Bacteria	n	%	95%CI	
The most common uropathogens	*E.coli*	371	30,53	27,94	33,12
	S.epidermidis	245	20,16	17,90	22,42
	Enterococcus spp.	197	16,21	13,68	18,74
Total		813	66,9	63,67	70,13
Frequently	*Klebsiella*	99	8,15	6,61	9,69

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Pathogens detection rate	Bacteria	n	%	95%CI	
isolated have divided uropat	*S. haemolyticus spp.*	87	7,16	5,71	8,61
	Streptococcus spp.	81	6,67	5,27	8,07
Total		267	21,98	19,65	24,31
Etiologically significant	*Enterobacter spp.*	36	2,96	2,01	3,91
	Proteus spp.	34	2,8	1,87	3,73
	Acinetobacter spp.	34	2,8	1,87	3,73
	Pseudomonas spp.	31	2,55	1,66	3,44
Total		135	11,11	9,34	12,88
All together		1215	100		

We have divided uropathogens into 3 categories according to the frequency of detection. Common uropathogens were *E.coli*- 30,53% are followed by *S.epidermidis* -20,16% and *Enterococcus spp.*-16,21%. According to the results of our study, these microorganisms were included in category 1 with a high incidence rate 66,9%. The share of isolated pathogens in this group ranged from 16.9% to 30,53%.

The second category was frequently isolated including *Klebsiella, S. haemolyticus spp.*, and *Streptococcus spp*. These bacteria amounted to 21.98%. The distribution within the group was equable and ranged from 6,67% to 8,15%.

The third category was etiologically significant including *Enterobacter spp., Proteus spp., Acinetobacter spp., Pseudomonas spp.* These organisms accounted for 11.11%. The distribution within the group was equable and ranged within 2,55% to 2,96%.

Discussion

UTIs, a topical problem in urology and medicine in general, rank second after infections of the respiratory tract [15] [16]. The study of etiology UTIs in a particular region is of great diagnostic, prognostic and epidemiological significance. Out of 2378 urine samples, the pathogen was detected in 1177 (49, 5%) cases, and we considered 1201 (50,5%) as negative. According to our research, the sensitivity of the culture investigation is 49,5%. In fact, there are symptoms of the UTIs and leukocytes of more than 7 per high power field, hence urine cannot be sterile. Viable (or active) but nonculturable bacteria may also cause false-negative culture [17]. Numerous studies show that Gram-negative bacteria predominate in the UTIs [18] [19] [20]. Our results generally showed no clear difference in Gram-negative, at 690 (50,88%) and Gram-positive, at 630 (46,46%), recovery rates. Detailed information on the isolated pathogens is presented in tables 2-9. It should also be noted that the relatively small number of fungal isolates -36 (2,65%) in comparison with the bacteria, were isolated. We cannot conclude with confidence that these are regional features, since identification and indication of fungi was carried out by routine methods, while an automated modern system was used to identify bacteria. Many authors noted the dominant role of *E.coli* in UTIs; researchers believe that

more than 80% of UTIs is caused by *E.coli*. [5] [8] [9]. According to the results of our studies, *E.coli* also dominated but the proportion did not exceed 31%. A detailed analysis of the etiological significance of UTI pathogens allowed us to rank the frequently encountered pathogens into 3 groups (tab.10). The group with a high degree of distribution consisted of *E.coli* 371 (30,53%), *S.epidermidis* (20,16%), *Enterococcus spp.* (16,21%). It should be noted coagulase-negative staphylococci 381 (92,7%) isolates out of total 411 staphylococcal isolates. Among coagulase-negative staphylococci prevailed *S.epidermidis* and *S.haemolyticus spp*., MRS strains prevailed among *S.epidermidis* (51.43%), *S.haemolyticus spp*. (48.28%) and *S.simulans* (54.55%). Other coagulase-negative staphylococci were not included in 10 etiologically significant UTIs pathogens. According to the literature date[21] [22] [23], 5-10% of UTIs in women is associated with *S.saprophyticus*, our results were different. The results of studies carried out in Astana indicate that the nosocomial UTIs predominantly caused by gram-negative pathogens, including *P.aeruginosa, K.pneumoniae, and E.coli* [10]. According to our results, the role of gram-negative rods and of gram-negative non-fermenting bacteria in the occurrence of UTI is obvious and practically equivalent, we do not see a dominant microorganism in this group. The frequency of occurrence of *Enterobacter spp. Proteus spp. Acinetobacter spp. Pseudomonas spp*. did not differ significantly and varied from 2.55% to 2.96% (confidence interval 1.66 ; 3.91). It should also be noted that the frequency of occurrence of *Acinetobacter* slightly exceeds *Pseudomonads*, and *Acinetobacter lwoffii* prevails over other species of *Acinetobacter*.

Conclusion

We found that UTIs among our study population were predominantly caused by ten opportunistic pathogens. Widespread uropathogens were *E.coli*- 30,53%, *S.epidermidis* -20,16%, *Enterococcus spp*.-16,21%. Frequently isolated pathogens included *Klebsiella*, *S.haemolyticus spp.*, and *Streptococcus spp*. they amounted to 21.98%. The distribution within the group was equable and ranged from 6,67% to 8,15%. Etiologically significant pathogens included *Enterobacter spp., Proteus spp.,Acinetobacter spp., Pseudomonas spp.*

They accounted for 11.11%. The distribution within the group was equable and ranged within 2,55% to 2,96%.

Author Contributions:

Conceptualization, A.M. and G.A.; methodology, A.K.; software, G.B.; validation, G.A.; formal analysis, A.C.; investigation, A.M; resources, A.M.; data curation, G.A.; writing—original draft preparation, A.C., T.S; writing—review and editing, A.C., D.M; visualization, G.A.;

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