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Monitoring the antibiotic resistance in the intensive care unit of a multidisciplinary hospital

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Abstract. *Infectious complications remain a serious post-transplant problem and make a major cause of poor outcome. Given the active development of transplant services at a regional level, the problem of infectious complications becomes increasingly important and requires monitoring of the etiological structure and level of antibiotic resistance in each hospital dealing with this problem.*

The purpose *was to analyze the changes over time in the structure and antimicrobial resistance of the most common pathogens in various nosology, including in patients after organ transplantation, regardless gender and age.*

Material and methods. *The study included 37,103 patients, of whom 8,091 (21.8%) were treated in the Intensive Care Unit (ICU) of the Vitebsk Regional Clinical Hospital (VRCH) for the period from 2015 to 2017; infectious complications after organ transplantation made 3%. The clinical samples were studied for bacteriology in the Republican Scientific and Practical Center "Infection in Surgery"; 20,280 clinical isolates were investigated.*

Results. *Staphylococcus aureus (20.96%) dominated in the general structure of microorganisms cultured mainly from the wound surface in thermal burns; meanwhile, in the ICU, gram-negative microflora dominated and was presented with Acinetobacter spp. (22.75%) and Pseudomonas aeruginosa (22.74%) in the majority of cases. By 2017, there had been an increase in resistant isolates of Klebsiella spp. (22.87%) and Acinetobacter spp. (23.09%) and a reduction of P. aeruginosa (13.31%) and S. aureus (18.88%) seeding. The protocol of the antibacterial therapy initiation was set up in the ICU of Vitebsk Regional Clinical Hospital, based on the obtained results* **demonstrating that** *all S. aureus isolates were sensitive to linezolid, vancomycin and teicoplanin, while P. aeruginosa was sensitive to colistin. All isolated Acinetobacter spp. were sensitive to colistin and 80% of the isolates were sensitive to sulbactam. More than 95% of K. pneumonia isolates were sensitive to colistin and tigecycline.*

Conclusion. *The current epidemiology is characterized by the prevalence of S. aureus (20.96%) in the overall structure of microorganisms, while Acinetobacter spp. (22.25%) and P. aeruginosa (22.74%) dominate in the ICU. Based on the microbiology study results, the protocol of antibacterial therapy initiation was established in the ICU of Vitebsk Regional Clinical Hospital. It is necessary to monitor the resistance of* *common microorganisms to certain antibiotics in order to develop algorithms for rational antibacterial treatment in each hospital.*

Keywords: ICU, nosocomial infection, microbial profile, antimicrobial resistance, gram-positive and gram-negative flora

ICU, Intensive Care Unit

VRCH, Vitebsk Regional Clinical Hospital

Introduction

Infectious complications remain a serious problem of the post-transplant period and represent one of the main causes of adverse outcome. The most common entries for the infection are the postoperative wound, the central venous catheter, the airways, and the urogenital tract. A number of factors giving rise to an increased susceptibility to infection include the virulence of microorganisms, the duration and the scheme of antibacterial prevention [1].

With the active development of transplant services at the regional level, the problem of combating infectious complications is becoming increasingly important and requires the monitoring of the etiological structure and the general level of antibiotic resistance in each particular hospital dealing with this problem.

The microbial landscape of any medical institution results from a set of complex processes of interspecific micro- and macroorganism interrelationships occurring in a specific hospital environment, taking into account the influence of many aggressive environmental factors (physical and chemical disinfection methods, antibiotics). Bacteria exposed to the selective pressure of environmental factors acquire new properties: the resistance to external influences, increased virulence, resistance to antibacterial drugs, etc. [2 –4].

Examples of microorganisms that present a particular problem worldwide in terms of the growth of antibiotic resistance are the representatives of the so-called ESKAPE group (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp.) [5, 6].

The results of the long-term monitoring of nosocomial infection pathogens in the intensive care unit (ICU) have demonstrated that currently dominating microorganisms are Gram-negative non-fermenting bacteria, namely P. aeruginosa and A. baumannii; Gram-negative microorganisms of the Enterobacteriaceae family, which produce extended-spectrum β-lactamases, and methicillin-resistant S. aureus and mixed infection [7].

According to the Healthcare Ministry of the Russian Federation, the number of registered nosocomial infection cases was 56,000; and according to calculated data, there should be about 2.5 million [8]. Of great concern is the constant increase in the proportion of resistant strains among the main nosocomial pathogens. Thus, in multicenter Russian studies conducted in previous years, the frequency of methicillin-resistant strains of S. aureus ranged from 33.4 in 2001–2002 to 54.4% in 2006–2008, while in the burn wards in Russia, methicillin-resistant staphylococci cultures reached 77.5%, and up to 54.8% in ICUs [9]. Pseudomonas aeruginosa is already multi-resistant in most cases [10].

Infectious complications developing during the immunosuppression administered after organ transplantation often have an atypical course, which create difficulty for making a timely diagnosis and initiating the etiotropic therapy [11].

The problem of antibiotic resistance arose as early as around the 1940s of the 20th century, but in the past few decades it became rampant [12]. The problem of bacteria antibiotic resistance in the Republic of Belarus is not new either. Over the recent 3-4 years, there has been a relative decrease in antibiotic resistance, but there is a clearly seen tendency to an increased resistance of clinically significant bacteria to III–IV generation cephalosporins, carbapenems, which consumption has increased significantly. Therefore, the issue of optimizing the rational use or limiting the use of antibacterial drugs is relevant [13].

Nosocomial infections develop in 5–15 % of in-hospital patients. The ICU patients are at the highest risk of their development, the incidence of such infections among them is 5–10 times higher compared to the patients in other hospital departments [14].

The severity of patient's condition is the cause of a greater (almost 10 times) consumption of antimicrobial drugs in the ICU compared to other hospital departments [15]. Over 60% of ICU patients usually receive antibacterial therapy with the most commonly used broad-spectrum antibiotics or a combination of several antimicrobial agents [16]. An intensive use of the broad-spectrum drugs contributes to the emergence and spread of antibiotic resistance among nosocomial pathogens [17].

The spread of the pathogenic bacteria resistant to antibiotics results in a steady growth of bacteria-associated diseases, which used to be successfully cured quite recently. Thus, the mortality rates for sepsis and pneumonia have acutely increased, since their pathogens have become resistant to the most common antibacterial drugs [18, 19].

Infectious complications after organ transplantation remain currently an unsolved problem requiring additional efforts aimed at the prevention of bacterial infections.

The study objective was to investigate the changes over time in the structure of common pathogens and their antibiotic resistance in various nosologies, including in ICU patients after organ transplantation, for the period 2015–2017.

Material and methods

The study included 37,103 patients admitted in the Vitebsk Regional Clinical Hospital (VRCH) in 2015–2017, of which 8091 (21.8%) were treated in the ICU; the infectious complication rate after organ transplantation was 3%. In case of patient's re-admission in the hospital, he/she was registered in the database as a new case. The bacteriology study of clinical samples was made on the base of the Republican Scientific and Practical Center "Infection in Surgery". The material for the study included wound discharge, blood, sputum, drain discharge, peritoneal fluid, cerebrospinal fluid, urine, etc. Material for microbiology study was taken in the ICU patients on the day of their admission before administering any antibacterial drugs, and later on several times, at an interval of 3-4 days during the entire hospital stay. The samples were collected into sterile containers from patients in fasting state in the morning from 8 to 9 hours, using the microbiology techniques as per instructions "The microbiological methods for the study of biological material" issued by the Healthcare Ministry of the Republic of Belarus [20].

Antibiotic susceptibility testing was made on Mueller–Hinton media by the disk-diffusion method using the ATB Expression semi-automatic analyzer (Bio Merieux, France). The obtained antibioticograms (antibiotic susceptibilities) of the pathogens isolated from patients were recorded in laboratory logs and used for continuous making a database. The antibiotic susceptibility of microorganisms was assessed using the WHONET computer analytical software. The isolate occurrences in VRCH for 3 years were assessed, as was the antibiotic susceptibility of the most common isolates, namely P. aeruginosa, A. baumannii, K. pneumoniae, and S. aureus. The results were statistically processed using Microsoft Excel 2007, and Statistica software (Version 10, StatSoft Inc., USA, License No. STAF999K347156W).

Student’s t-test was used to determine the difference significance. The differences were considered statistically significant at $p < 0.05$.

Results and discussion

Negative results were obtained in 16,823 cases, of which 3826 (22.7%) cases accounted for ICU. During the study period, 20,280 isolates of various locations were investigated. The highest number of isolates was obtained from urine (9791; 48.2%) and sputum (6530; 32.2%).

Gram-negative flora prevailed in the general structure, making up 56.2% of isolates, mainly, K. pneumoniae (1758 isolates; 8.67%), P. aeruginosa (2896; 14.28%), A. baumannii (1449; 7.14%), E. coli (2287; 11.28%), P. mirabilis (267 isolates; 1.32%), E. faecium (829; 4.09%), and E. faecalis (1804; 8.9 %). Of gram-positive microflora, S. aureus prevailed (4251 isolates; 20.96%). Candida fungi made a significant part (2602 isolates; 12.83 %). Data on the dynamics of isolated microorganism occurrences in VRCH in the period 2015–2017 are presented in Table 1.

Table 1. Prevalence of isolated microorganisms (n = 20,280) in patients of VRCH for the period from 2015–2017

Isolate	2015		2016		2017		2015–2017	
	n	%	n	%	n	%	n	%
A. baumannii	327	5.10	463	7	659	9.08	1449	7.15
K. pneumoniae	378	5.89	393	5.95	987	13.60	1758	8.67
K. oxytoca	8	0.12	2	0.03	2	0.03	12	0.06
P. aeruginosa	927	14.46	1003	15.17	966	13.31	2896	14.28
S. aureus	1498	23.36	1383	20.92	1370	18.88	4251	20.96
S. epidermidis	520	8.11	515	7.79	448	6.17	1483	7.31
S. saprophyticus	31	0.48	15	0.23	16	0.22	62	0.31
E. coli	681	10.62	798	12.07	808	11.13	2287	11.28
P. mirabilis	63	0.98	73	1.10	131	1.81	267	1.32
P. vulgaris	5	0.08	1	0.02	2	0.03	8	0.04
E. faecium	188	2.93	340	5.14	301	4.15	829	4.09
E. faecalis	418	6.52	711	10.76	675	9.30	1804	8.90
Enterococcus spp.	6	0.09	-	-	-	-	6	0.03
S. haemolyticus	-	-	2	0.03	-	-	2	0.01
Streptococcus spp.	222	3.46	143	2.16	70	0.96	435	2.14
Candida spp.	1118	17.43	744	11.26	740	10.20	2602	12.83
Aspergillus spp.	11	0.17	14	0.21	13	0.18	38	0.19
Bacteroides spp.	1	0.02	-	-	-	-	1	0.00
Citrobacter spp.	2	0.03	2	0.03	28	0.39	32	0.16
Enterobacter spp.	7	0.11	6	0.09	40	0.55	53	0.26
Propionibacterium spp.	1	0.02	-	-	-	-	1	0.00
S. liquefaciens	1	0.02	-	-	-	-	1	0.00
M. morganii	-	-	1	0.02	1	0.01	2	0.01
S. maltophilia	-	-	1	0.02	-	-	1	0.00
Total number	6413	100.0	6610	100	7257	100.0	20280	100.0
No isolates found	4813	-	5629	-	6381	-	16823	-

S. aureus took a leading position in the overall structure among the studied isolates for the latest 3 years. Worthwhile to note the growth in K. pneumoniae, which amounted to 5.89% in 2015, 5.95% in 2016, and 13.6% in 2017 ($p < 0.05$).

Total 4265 clinical isolates (21.0%) from ICU patients were studied; negative results were obtained in 3826 cases (22.7%). The largest number of isolates were obtained from sputum (2701; 33%), blood (2294; 28%), urine (1526; 19%), and wound discharge (894; 11%).

Gram-negative flora also prevailed among the isolates obtained from ICU patients; it was mainly represented by P. aeruginosa (970; 22.74%), A. baumannii (949; 22.25%), K. pneumoniae (687 isolates; 16.11%), E. coli (73; 1.71%), P. mirabilis (40 isolates; 0.94%), E. faecium (162; 3.8%), and E. faecalis (91; 2.13 %). Of gram-positive microflora, S. aureus prevailed; 658 isolates were obtained (15.43 %). The dynamics of the isolate occurrences among the ICU patients is presented in Table 2.

Table 2. Prevalence of isolated microorganisms (n = 4265) in ICU patients for the period from 2015–2017

Isolate	2015		2016		2017		2015–2017	
	n	%	n	%	n	%	n	%
A.baumannii	227	20.18	291	22.86	431	23.09	949	22.25
K. pneumoniae	92	8.18	168	13.20	427	22.87	687	16.11
P.aeruginosa	285	25.33	315	24.74	370	19.82	970	22.74
S. aureus	208	18.49	187	14,69	263	14.09	658	15.43
S. epidermidis	13	1.16	31	2.4	8	0.43	52	1.23
S. saprophyticus	1	0.09	1	0.08	-	-	2	0.05
E. coli	21	1.87	24	1.89	28	1.50	73	1.71
P. mirabilis	7	0.62	16	1.26	17	0.91	40	0.94
E.faecium	43	3.82	57	4.48	62	3.32	162	3.80
E. faecalis	27	2.40	30	2.36	34	1.82	91	2.13
Enterococcus spp.	3	0.27	-	-	-	-	3	0.07
S. haemolyticus	-	-	2	0.16	2	0.11	4	0.09
S. pyogenes	1	0.09	3	0.24	1	0.05	5	0.12
S. pneumoniae	1	0.09	-	—-	-	-	1	0.02
S. equi	-	-	-	-	1	0.05	1	0.02
S. salivarius	2	0.18	-	-	-	-	2	0.05
Enterobacter spp.	1	0.09	-	-	-	-	1	0.02
Citrobacter spp.	-	-	1	0.08	-	-	1	0.02
Candida spp.	192	17.07	141	11.08	222	11.89	555	13.01
Aspergillus spp.	1	0.09	3	0.24	1	0.05	5	0.12

S. maltophilia	-	-	1	0.08	-	-	1	0.02
S. viridans	-	-	2	0.16	-	-	2	0.05
Total number	1125	100.00	1273	100.00	1867	100.00	4265	100.00
No isolates found	1020	-	1081	-	1725	-	3826	-

The analysis of the changes in the bacteriological landscape shows that among the studied isolates, the proportion of gram-negative microflora remains consistently high. The number of K. pneumoniae isolates increased dramatically from 8.18 in 2015 to 13.2% in 2016, and 22.87% in 2017; and that of A. baumannii increased slightly less: from 20.18 % in 2015 up to 22.86 % in 2016, and 23.09% in 2017 (statistically significant in all cases, $p<0.05$). The share of P. aeruginosa isolates was 25.33% in 2015, slightly decreased to 24.74% in 2016, and made 19.82% in 2017 (statistically significant in all cases, $p<0.05$). The share of S. aureus decreased from 18.49% in 2015 to 14.69% in 2016 and remained at the same level in 2017, reaching 14.09% (statistically significant in both cases, $p <0.05$).

A. baumannii was the predominant gram-negative pathogen for respiratory tract infections in the ICU, making up 656 isolates (24.3%), of which 642 isolates were derived from sputum (23.8%). In addition to Acinetobacter, the comparatively commonly isolated pathogens in respiratory tract infections were P. aeruginosa (547 isolates; 20.3%) and K. pneumoniae (388; 14.4%), while S. aureus was found in 420 cases (15.5 %). Candida fungi accounted for 342 isolates (12.7%). The changes over time in the pattern of microorganisms cultured from the lower respiratory tract of the ICU patients for the period 2015–2016 are summarized in the Figure.

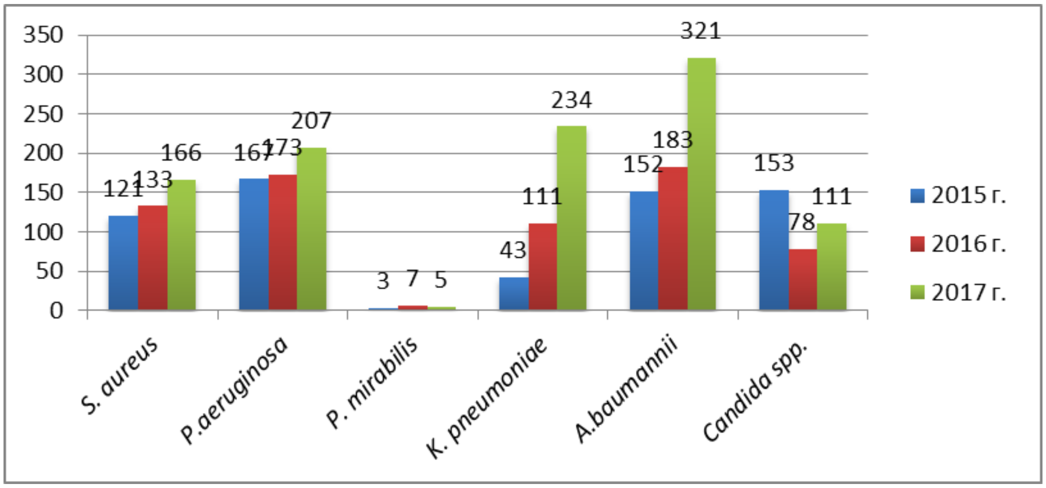

Figure. The changes in the number of isolates (n = 2,368) cultured from lower respiratory tract in ICU patients for the period 2015–2017

Note: the ordinate axis indicates the absolute number of isolates.

In 2015, when studying the etiology structure of the material obtained from the lower respiratory tract of ICU patients, we found that P. aeruginosa prevailed, reaching 167 isolates (26.13%), but giving way to A. baumannii in the following years that accounted to 183 isolates (26.71%) in 2016, and 321 isolates (30.7%) in 2017.

Antibiotic susceptibility of A. baumannii (n = 949) in the ICU patients for the period 2015–2017 is presented in table 3.

Table 3. Sensitivity of A. baumannii (n = 949) in ICU patients for the period from 2015–2017

Antibiotic	2015			2016			2017		
	% R	**% I**	**% S**	**% R**	**% I**	**% S**	**% R**	**% I**	**% S**
Penicillins (semisynthetic):									
Ampicillin / Sulbactam	27.2	39.3	33.5	9.3	8.9	81.8	0	13.5	86.5
Cephalosporins:									
Cefoperazone / Sulbactam	0.4	38.1	61.5	0	7.2	92.8	0	16.9	83.1
Cefoperazone	99.6	0	0.4	100	0	0	99	1	0
Ceftazidime	97.1	0	2.9	100	0	0	99.4	0	0.6

Ceftriaxone	100	0	0	100	0	0	96.6	0	3.4
Cefotaxime	100	0	0	-	-	-	-	-	-
Cefepim	96.5	2.2	1.3	96.2	3.8	0	99.1	0.9	0
Carbapenems:									
Imipenem	100	0	0	96.2	2.4	1.4	75.2	14.2	10.7
Meropenem	100	0	0	97.6	1.7	0.7	90.7	3.2	6
Aminoglycosides:									
Amikacin	93.4	3.5	3.1	86.6	6.5	6.9	89.8	7.7	2.6
Fluoroquinolones:									
Ciprofloxacin	100	0	0	100	0	0	99.3	0.5	0.2
Levofloxacin	92.4	6.1	1.5	88.7	6.7	4.6	89.1	9.3	1.6
Ofloxacin	100	0	0	100	0	0	-	-	-
Polymyxin:									
Colistin	0	0	100	0	0	100	0	0	100

Note: R, resistant, I, moderately resistant, S, sensitive.

Isolates of A. baumannii were highly resistant to all classes of antibiotics with the exception of cefoperazone in combination with sulbactam, and ampicillin with sulbactam, to which were susceptible 61.5% and 33.5% of isolates in 2015, 92.8% and 81.8% in 2016, 83.1% and 86.5% of isolates in 2017, respectively, due to the specific antimicrobial activity of this β-lactamase inhibitor. Noteworthy is the retained 100% sensitivity of A. baumannii to the colistat action. Carbapenems had a low activity against A. baumannii: only 10.7% of the isolates were sensitive to imipenem, 6% of the isolates were sensitive to meropenem in 2017. Almost all isolates found in the study period were resistant to cephalosporins and fluoroquinolones. Only 2.6% of Acinetobacter isolates were susceptible to amikacin.

Isolates of P. aeruginosa studied in 2015–2017 manifested a high resistance rate to all classes of antibiotics.

The dynamics of P. aeruginosa (n=970) sensitivity to the antibacterial drugs used in the ICU in the period 2015–2017 is presented in Table 4.

Table 4. Sensitivity of P. aeruginosa (n = 970) in ICU patients for the period from 2015-2017

Antibiotic	2015			2016			2017		
	% R	% I	% S	% R	% I	% S	% R	% I	% S
Penicillins (natural and semisynthetic):									
Piperacillin / Tazobactam	67.9	0	32.1	37.6	37.6	24.8	24.9	40.3	34.8
Cephalosporins:									
Cefoperazone	95.5	3	1.5	87.3	9.8	2.9	87.1	10.8	2.2
Ceftazidime	77.9	15.9	6.2	79.7	11	9.3	70.1	16.9	13.1
Ceftriaxone	100	0	0	82.8	17.2	0	88.9	0	11.1
Cefotaxime	100	0	0	95.8	4.2	0	85.7	14.3	0
Cefepim	87.1	9	3.8	82.5	9.1	8.4	75.9	15.7	8.4
Carbapenems:									
Imipenem	87.4	7.5	5	91.7	3.5	4.8	67.3	14.6	18.1
Meropenem	87.1	10	2.9	93.5	1.9	4.5	87.9	4.7	7.4
Doripenem	-	-	-	100	0	0	85.3	8.8	5.9
Aminoglycosides:									
Amikacin	91	4.3	4.8	65.6	11.8	22.6	55.7	13.5	30.8
Fluoroquinolones:									
Ciprofloxacin	98.6	0	1.4	96.6	0.7	2.7	94.5	2.2	3.3
Levofloxacin	66.7	0	33.3	92.6	1.3	6	95.5	0.9	3.6
Norfloxacin	100	0	0	94.1	0	5.9	100	0	0
Ofloxacin	100	0	0	94.7	0.8	4.6	89.9	7.2	2.9
Polymyxin:									
Colistin	0.5	0	99.5	0.3	0	99.7	0	0	100

Note: R, resistant, I, moderately resistant, S, sensitive.

With respect to P. aeruginosa, it was colistin that proved itself best of all, to which almost 100% of the studied isolates showed susceptibility. The most active antibiotics against P. aeruginosa were Piperacillin in combination with tazobactam (67.9% of isolates were resistant in 2015, 37.6% in 2016, and only 24.9% of isolates were resistant in 2017), and amikacin (91% of isolates were resistant in 2015, 65.6% in 2016, and 55.7% of isolates were resistant in 2017). Perhaps, that was due to some reduction in the use of aminoglycosides: amikacin purchases amounted to 68 and 59 packs in 2015 and 2016, respectively, and 55 packs in 2017. Pseudomonas aeruginosa was characterized by a very high resistance rate to carbapenems: susceptibility to imipenem was noted only in 5% of isolates in 2015, 4.8% of isolates in 2016, and 18.1% of isolates in 2017; 2.9%, 4.5%, and 7.4% of isolated were susceptible to meropenem in 2015, 2016, and 2017, respectively; and only 5.6% of isolates were susceptible to doripenem in 2017. Fluoroquinolones were also characterized by a low activity against Pseudomonas aeruginosa. Resistance to ciprofloxacin was seen in 98.6% of isolates in 2015, 96.6% in 2016, and 94.5% in 2017; 66.7%, 92.6%, and 95.5% of isolates were resistant to levofloxacin in 2015, 2016, and 2017, respectively.

A serious problem for ICU in 2017 was the prevalence of K. pneumoniae isolates serving as producers of extended-spectrum beta-lactamase and resistant to natural and semi-synthetic penicillins, cephalosporins of I–IV generation, and also to carbapenems, the resistance to which could be explained by the presence of the bla_{NDM} and $bla_{oxa\text{-}48}$ genes. It is important that the part of the gene encoding the extended-spectrum beta-lactamase synthesis is responsible for the mechanisms of resistance not only to cephalosporins, but also to other classes of antibiotics, primarily, to aminoglycosides and fluoroquinolones [21]. Sensitivity of K.

pneumoniae (n = 687) in the ICU patients in the period 2015–2017 is presented in Table 5.

Table 5. Sensitivity of K. pneumoniae (n = 687) in ICU patients for the period from 2015–2017

Antibiotic	2015			2016			2017		
	% R	% I	% S	% R	% I	% S	% R	% I	% S
Penicillins (natural and semisynthetic):									
Amoxicillin / Clavulanate	82	11.2	6.7	99.2	0.8	0	98.8	0	1.2
Cephalosporins:									
Cefoperazone	100	0	0	90.9	6.1	3	100	0	0
Ceftazidime	92.7	6.1	1.2	96.5	0	3.5	96.1	3.9	0
Ceftriaxone	100	0	0	100	0	0	94.5	3.4	2.1
Cefotaxime	97.3	1.4	1.4	99.2	0.8	0	98.4	1	0.5
Cefepim	93.2	2.3	4.5	97.6	1.2	1.2	95.8	0.9	3.3
Carbapenems:									
Imipenem	9.9	2.2	87.9	63.9	10.2	25.9	58.3	19.4	22.2
Meropenem	11.7	3.3	85	67.1	8.7	24.2	78.7	8	13.3
Doripenem	-	-	-	100	0	0	96.2	0	3.8
Aminoglycosides:									
Amikacin	33	6.6	60.4	18	4.8	77.2	66.7	6.6	26.7
Fluoroquinolones:									
Ciprofloxacin	96.7	2.2	1.1	96.5	1.8	1.8	98.8	0.5	0.7
Levofloxacin	96.8	0	3.2	96.5	0	3.5	97.2	2	0.8
Norfloxacin	100	0	0	100	0	0	100	0	0
Ofloxacin	100	0	0	90	2.5	7.5	98.3	0.6	1.1
Polymyxin:									
Colistin	-	-	-	0	0	100	0	0	100
Tetracyclines:									
Tigecycline	-	-	-	-	-	-	0	4.2	95.8

Note: R, resistant, I, moderately resistant, S, sensitive.

Tigecycline and colistin proved themselves well, no isolate was resistant to them. Resistance to imipenem and meropenem was manifested by 9.9% and 11.7% of isolates in 2015, 63.9% and 67.1% in 2016, and 58.5% and 78.7% of isolated strains in 2017, respectively. The purchases of carbapenems decreased in 2016 and 2017, reaching 200 and 240 imipenem packs and 2534 and 1770 meropenem packs, respectively, as compared to 2015 when 901 imipenem packs were purchased, and to 1998 with meropenem purchases. When analyzing the activity of aminoglycosides, noteworthy was a relatively low activity of amikacin: there were 33% of resistant isolates in 2015, 18% in 2016, and 66.7% in 2017. Almost all isolates were resistant to fluoroquinolones and cephalosporins.

The problems associated with the increase in the share of gram-negative pathogens and the growth of their antibiotic resistance do not diminish the importance of controlling the spread of resistant gram-positive cocci, as well as the issues of restricting their resistance. A serious problem is the MRSA strains of S. aureus. Dynamics of S. aureus (n = 658) sensitivity to the antibacterial drugs used in the ICU patients for the period 2015–2017 is presented in Table 6.

Table 6. Sensitivity of S. aureus (n = 658) in ICU patients for the period from 2015–2017

	2015			2016			2017		
Antibiotic	**% R**	**% I**	**% S**	**% R**	**% I**	**% S**	**% R**	**% I**	**% S**
Penicillins:									
Oxacillin	84.2	0	15.8	100	0	0	-	-	-
Cephalosporins:									
Cefoxytin	-	-	-	-	-	-	88.6	0	11.4
Cefazolin	74.2	0	25.8	90.7	0.5	8.7	89	0	11

Cefuroxime	91.7	0	8.3	93.6	0	6.4	88.9	0	11.1
Ceftriaxone	74.6	0	25.4	92.3	0	7.7	87.5	0	12.5
Cefotaxime	88.9	1.4	9.7	100	0	0	88.6	0	11.4
Carbapenems:									
Meropenem	100	0	0	-	-	-	-	-	-
Aminoglycosides:									
Amikacin	50.2	16.9	32.9	41.2	24.1	34.8	39.5	21.3	39.2
Gentamicin	29.2	14.6	56.2	-	-	-	-	-	-
Fluoroquinolones:									
Ciprofloxacin	74.8	4.9	20.4	87.1	5	7.9	84.4	3	12.7
Levofloxacin	79.3	1.7	19	85.9	2.8	11.3	84.7	7.3	8
Norfloxacin	100	0	0	-	-	-	-	-	-
Ofloxacin	58.3	18.1	23.5	-	-	-	80.6	6.8	12.5
Lincosamides:									
Clindamycin	63.1	9.6	27.3	62.9	4.4	32.7	72.4	2.7	24.9
Oxazolidinones:									
Linezolid	0	0	100	0	0	100	0	0	100
Glycopeptides:									
Vancomycin	0	0	100	0	0	100	0	0	100
Teicoplanin	-	-	-	0	0	100	0	0	100
Glycylcyclines:									
Tigecycline	15.7	2	82.4	0	2.9	97.1	-	-	-

Note: R, resistant, I, moderately resistant, S, sensitive.

In 2015, 84.2% of isolates were resistant to oxacillin, reaching 100% in 2016; in 2017, 88.6% of the isolates were resistant to cefoxitin. Increased resistance rates manifested in varying degrees to III–IV generation cephalosporins were seen, with the sensitivity to them ranging from 6.4 % to 25.8%. As for fluoroquinolones, ciprofloxacin was slightly more active than levofloxacin, and the percentages of susceptible isolates were 12.7% vs. 8% in 2017, respectively. A high resistance percentage was noted with respect to amikacin and clindamycin, making 39.2% and 24.9% in 2017, respectively. During the reported period, the studied isolates of S. aureus retained 100% sensitivity to linezolid, vancomycin, and teicoplanin.

According to literature reports, the rational use of antibiotics should be based on a clear understanding of the etiological structure of pyo-inflammatory diseases and complications, the resistance of pathogens to antimicrobial drugs; this understanding can be achieved by using the properly standardized methods for identifying bacteria and determining their susceptibility to chemical agents in bacteriological laboratories. In this regard, the Republican Healthcare is tasked with creating a reliable system for monitoring the use of antibiotics, organizing a network for monitoring the antibiotic resistance, systematically collecting data on antibiotic susceptibility test results (antibioticograms) and exercising control over the spread of multi-resistant strains and the clinical outcomes of bacterial complications. A systematic interdisciplinary approach and active measures at the national level are necessary to overcome the problem of bacterial resistance to antibiotics [22].

Knowledge of the most common microflora and antibiotic susceptibility levels directs physicians to prescribe a rational empirical antibiotic therapy to severely ill patients prior to receiving antibiotic susceptibility test results (antibioticogram) and forms the basis for developing algorithms for an optimal antibacterial treatment in each hospital.

The limitations of this study include its retrospective nature in analyzing the occurrence of the most common isolated microorganisms and their antibiotic susceptibility within one hospital, so the results can be extrapolated to other institutions very conditionally. Nevertheless, the obtained results correspond to the global microbiology situation. Thus, according to EPIC multicentre study conducted on a single day in 1417 ICUs in 17 countries of Europe with the coverage of more than 10,000 patients, revealed infection in 44.8% of the patients. Pneumonia (46.9%) and lower respiratory tract infections (17.8%) were the most frequently detected infections in ICUs. Gram-negative bacteria of the Enterobacteriaceae family (34.4%), S. aureus (30.1%), and P. aeruginosa (28.7%) dominated in the etiological structure. In many etiologically significant microorganisms, the resistance to traditional antibiotics was identified, specifically, the prevalence of methicillin-resistant staphylococci increased [23]. Despite a 100% sensitivity of P. aeruginosa and A. baumannii to colistin in the VRCH, the *Marathon* study conducted in various clinics of Russia in 2011–2012 reveled 3.2% of P. aeruginosa isolates and 1.6% of A. baumannii isolates resistant to polymyxins, namely, to colistin. [24, 25].

Conclusions

1. Currently, a typical epidemiological feature is the predominance of S. aureus (20.96%) in the general microorganism structure in hospital; in patients after organ transplantation, the most common were the representatives of gram-positive flora, while in intensive care units, gram-negative microflora dominated and was represented by Acinetobacter spp. (22.25%) and P. aeruginosa (22.74%) in most cases.

2. In the Intensive Care Unit of Vitebsk Regional Clinical Hospital, we have developed the Protocol of the antibacterial therapy initiation, based on the obtained results, according to which all S. aureus isolates were susceptible to linezolid, vancomycin, and teicoplanin, while P. aeruginosa was susceptible to colistin. All isolates of Acinetobacter spp. were susceptible to colistin and 80% of isolates were susceptible to sulbactam. Over 95% of K. pneumonia isolates were susceptible to tigecycline and colistin.

3. Due to an active development of transplant programs in our country, the use of immunosuppressive therapy, and the growth of infectious complications in recent times, there is a need to monitor the etiological structure and overall level of antibiotic resistance in medico-prophylactic institutions that perform organ transplantation.

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