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MICROBIOLOGICAL ASPECTS OF THE EFFECTIVENESS OF ANTIMICROBIAL DRUGS

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Abstract

Introduction. It is well known, that patients with deep burns belong to the category of critically ill ones. According to the data of National Nosocomial Infections Surveillance (2004), *Staphylococcus spp.* are among leading opportunistic pathogens of infectious complications in such patients. Nowadays much attention is given to the problem of antibiotic resistance of *Staphylococcus* clinical strains. More often antiseptics are used in treatment of infectious complications, caused by antibiotic resistant microorganisms. The aim of the research was to study microbiological aspects of the effectiveness of antimicrobial drugs.

Materials and methods. There were examined 372 critically ill patients with burns, having infectious complications. In all patients microbiological examinations were carried out during the first 7 days after burn trauma. There were isolated 115 clinical strains of *Staphylococcus spp.*. Their morphological, cultural, biochemical qualities and sensitivity to antibiotics, antiseptics were studied.

Rresults of the study. We found, that clinical strains of *S. aureus*, *S. epidermidis* were highly resistant to oxacillin (46,9; 59,1 % respectively); were insensitive to clavulanate and sulbactam potentiated beta-lactams; ceftriaxone; meropenem, imipenem; ciprofloxacin. Sensitivity of *Staphylococcus* to amikacin, linezolid, vancomycin was found. There was shown the sensitivity of antibiotic resistant strains of *Staphylococcus* to decamethoxin, its polymer composition, chlorhexidine digluconate. In the research there was proved the decreasing of the effectiveness of chlorhexidine digluconate against *Staphylococcus* in conditions of increasing microbial load to 10^9 CFU/ml in 6,6 times comparably to decamethoxin drugs ($p<0,001$).

Conclusions

Resistant to the majority of antibiotics strains of *Staphylococcus spp.* store their high sensitivity to antiseptic decamethoxin and its polymeric composition, chlorhexidine digluconate. Microbial load increase up to 10^9 CFU/ml decreases antimicrobial effectiveness of chlorhexidine digluconate in 4,2 – 4,8 times. Antibiotic resistant strains of *Staphylococci* do not have cross-resistance to antiseptic drugs.

Clinical strains of *S. aureus*, *S. epidermidis* cause purulent-inflammatory complications in critically ill patients with burns and have resistance to oxacillin (46,9; 59,1 % respectively), beta-lactam antibiotics with clavulanic acid and sulbactam (amoxicillin/clavulanate – 67,47±9,30 %; ampicillin/sulbactam – 58,63±8,58 %;); ceftriaxone (55,75±14,24 %); carbapenems (meropenem – 64,93 – 70,35 %; imipenem – 66,43 – 66,78 %); ciprofloxacin (65,47±9,11 %). *S. aureus*, *S. epidermidi* are sensitive to amikacin (74,62 – 80,75 %), linezolid (77,2 – 87,44 %); vancomycin (91,88 – 92,46 %).

Key words: antibiotics, antiseptics, resistance, burns, comlications, microorganisms.

Background. Patients with deep burns belong to the category of critically ill patients. Infection occupy a leading role among the life-threatening complications in critically ill patients with burn trauma. It is well known, that colonization of large in size and depth wound surfaces by opportunistic microorganisms, causing purulent-inflammatory complications, is very dangerous. Such complications happen in patients with burns in the result of violation of the integrity of local skin barrier, decreasing of non-specific factors of protection and cellular immunity [1, 2].

Bacteria of *Staphylococci* family are among prominent causative agents of opportunistic infections in critically ill patients. *Staphylococcus* are among five problematic microorganisms, monitoring of which is carried out in all developed countries of the world, first of all, because of increasing rate of antibiotic resistance (National Nosocomial Infections Surveillance, 2004). *Staphylococcus* strains, resistant to methicillin (oxacillin), are especially problematic ones. As a rule, such representatives of *Staphylococcus* are also resistant to other antibiotics. However, this situation foreshadows serious ecological problem. To date, such strains of *Staphylococci* are considered the main pathogens of nosocomial infections [3-5].

Antimicrobial events, aimed at the prophylaxis and treatment of purulent-inflammatory complications in burnt patients, which are critically ill, require the use of antibacterial drugs. With expanding arsenal of antibacterial drugs, it becomes difficult for clinicians to make the choice of the antibacterial. Aspects of forming the resistance to antibacterial therapy and the ways of its overcome are in the spotlight of medical community. Nowadays, in prophylaxis and treatment of purulent inflammatory complications scientists pay much attention to the use of antiseptics, which are effective against antibiotic-resistant strains of microorganisms. The study of sensitivity of *Staphylococcus*, which causes purulent-inflammatory complications in critically ill patients with burns, to antimicrobial drugs is very actual [2, 6, 7].

The aim. To study microbiological aspects of the effectiveness of antimicrobial drugs.

Materials and methods. In 2011 – 2014 years there were examined 372 patients (18 – 80 years of age) having deep burns (3^{rd} – 4^{th} rate) with 10 – 85 % of damaged area. All patients were treated in burn department of Vinnytsia Regional Clinical Hospital named after N. I. Pirogov. In all patients, microbiological examinations were carried out at first seven days after buns trauma. Microbiological study included the isolation of microorganisms from there burn wounds, their identification by morphological, cultural, biochemical qualities.

From patients there were isolated 475 strains of Gram-positive and Gram-negative microorganisms. Opportunistic microorganisms of different taxonomic groups were isolated in monoculture (58,43±2,92) % from critically ill patients with burns at the beginning of the treatment. Microbial associations also were found in patients (41,12±3,1) % during the first days after burn injury. Among pathogens of purulent-inflammatory complications, in examined patients there were isolated and identified, accordingly to Bergey's Manual, such microorganisms as *P. aeruginosa* (n=102), *A. baumannii* (n=133), *S. aureus* (n=86), *Proteus spp.* (n=35), *S. epidermidis* (n=29), *Eterobacter spp.* (n=27), *E. faecalis* (n=16), *E. coli* (n=12), *K. pneumoniae* (n=12), *Citrobacter spp.* (n=8), *C. albicans* (n=8). In some we found other microorganisms [8].

Taking into account a significant role of opportunistic coccus in causation of infectious complications in critically ill patients, in our research we colligated the results of research of pathogens' qualities, in particular *Staphylococcus spp.* (115 strains). If we observed Gram-positive

cocci, collected in “bunch” during microscopy, cultures of such bacteria were seeded on salt dense nutrient media (with 10 % of NaCl) for identification of their belonging to *Staphylococcus* family.

There were studied cultural qualities of such bacteria and 16 indicators of their biochemical activity by means of diagnostic test-system «Staphy-test 16» (PLIVA – Lachema a.s., Brno, Czech Republic). We also studied DNA-ase activity while seeding of biomaterial on DNA-medium, based on dry nutrient medium “DNAse test agar”; hyaluronidase activity – by the method of Winkle (1979). Among ethologically important *Staphylococcus*, we identified, *S. aureus* (74,8 %) and *S. epidermidis* (25,2 %), which were leading in causing purulent-inflammatory complications in such category of patients (table 1).

Isolated strains of *Staphylococci*, which did not have coagulase activity, did not split saccharose, maltose with production of acid in anaerobic conditions; recovered nitrates, utilized glucose and lactose; germinated on Hiss’ media with mannitol without producing of acid in anaerobic conditions; demonstrated sensitivity to novobiocin, were identified as *S. epidermidis*.

In the research, we studied sensitivity of 115 clinical strains *S. aureus*, *S. epidermidis* to 24 antibiotics; antiseptics (decamethoxin, decasan, chlorhexidine digluconate); antimicrobial composition of decamethoxin with carboxymethylamylum, oxyethylcellulose, polyvinylacetate (AMC) [9].

Table 1

Enzymatic qualities of clinical strains of *Staphylococcus*

Tests	Microorganisms	
	S. aureus (n 86)	*S. epidermidis* (n 29)
Arginine	+	+/-
Urease	+/-	+
Phosphatase	+	+/-
Galactose	+	+/-
Saccharose	+	+/-
Trehalose	+	-
Mannitol	+	-
Xylose	-	-
Maltose	+	+/-
Mannose	+	+/-
lactose	+	+/-
haemolysis	+	-
Coagulase	+	-
Hyaluronidase	+	-
β-galactosidase	-	+/-
Resistance to novobiocin	-	-
DNA-ase	+	-

Footnote: «+» - positive value; «–» - negative value; «±» - variable value

Sensitivity of strains of *Staphylococcus spp.* to antibiotics were determined by means of disc-diffusion method on dense nutrient media. For estimation of antimicrobial activity of antiseptics and AMC, we studied *in vitro* minimal inhibitory (MIC) and minimal bactericidal concentrations (MBcC) of decamethoxin (control samples), decasan (DS), chlorhexidine digluconate (CH) and antimicrobial composition of decamethoxin against isolated clinical strains *S. aureus*, *S. epidermidis*. We used dilution test of antiseptics in conditions of different microbial load of *Staphylococcus spp.* (10^6, 10^9 CFU/ml) [10, 11]. For statistical analysis of research data descriptive and comparative analysis with determining Student criterion of authenticity we used software package of Microsoft Office Excel 2010, BIOSTAT 4.03 by Stanton A. Glantz for Windows.

Results and discussion. From critically ill patients there were isolated strains of bacteria belonging to family of *Staphylococcus*, which caused purulent-inflammatory complications at the first days after burn injury. The research has shown low antibiotic sensitivity of *S. aureus* strains. It was found, that only 64,67 % of clinical isolates of *S. aureus*, had being caused purulent-inflammatory complications in critically ill patients with burns, were sensitive to oxacillin (table 2).

Table 2

The sensitivity of *Staphylococci* strains, isolated from critically ill patients with burns, to antibiotics (%)

Antibiotics	(M ± m)					
	sensitive		indifferent		resistant	
	S. aureus	*S. epidermidis*	*S. aureus*	*S. epidermidis*	*S. aureus*	*S. epidermidis*
Ampicillin	41,86±8,87	37,75±10,66	9,23 ± 4,03	13,4±7,77	48,91±6,14	45,3±6,06
Oxacillin	64,67±13,64	41,3±13,15	0	3,56±3,58	35,33±13,64	55,12±11,02
Ampicillin/sulbactam	58,63±8,58	62,25±6,79	5,15±3,11	3,56±3,58	24,45±3,007	34,17±6,83
Amoxicillin/clavulanate	67,47±9,30	80,75±4,55	3,59±2,12	9,83±6,08	30,49±7,246	9,425±3,37
Ceftriaxone	55,75±14,24	70,35±6,31	13,76±10,94	2,23±2,28	32,90±10,75	27,38±5,90
Imipenem	66,43±11,43	66,78±4,01	0,68±0,68	8,13±4,76	32,13±10,34	25,1±2,45
Meropenem	64,93±10,5	70,35±2,41	2,94±2,94	10,8±6,39	41,13±13,54	18,85±6,75
Erythromycin	55,03±13,88	43,95±5,28	3,835±2,29	7,15±4,13	37,39±13,1	47,55±6,48
Clarithromycin	58,19±13,94	34,12±8,73	4,42±1,97	22,8±7,48	37,39±13,1	41,75±4,62
Azithromycin	58,19±13,94	37,7±6,46	4,42±1,97	15,65±3,36	27,63±13,19	45,3±6,06
Clindamycin	66,97±12,34	69,05±4,05	5,40±3,19	0	27,17±10,8	30,95±4,05
Lincomycin	66,05±11,73	69,05±4,05	6,79±4,01	0	34,41±11,02	30,95±4,05
Chloramphenicol	59,49±11,38	42,62±10,58	6,11±4,28	2,25±2,25	28,66±8,19	55,12±11,02
Doxycycline	60,17±7,88	78,47±3,23	11,17±2,71	0	28,66±8,19	21,52±3,23
Gentamicin	57,92±10,76	61,93±7,49	9,69±1,60	14,3±10,11	32,39±12,22	23,8±8,87
Tobramycin	64,67±10,3	52,12±7,06	3,38±3,38	10,73±6,846	31,95±7,95	37,2±5,54
Amikacin	74,62±4,68	80,75±4,55	2,24±1,48	0	23,14±5,04	19,25±4,55
Linezolid	87,44±5,03	77,2±12,55	2,822±1,63	20,52±13,54	7,46±3,84	2,275±2,28
Vancomycin	92,46±4,48	91,88±4,76	2,94±2,94	0	4,60±2,98	8,125±4,76
Ciprofloxacin	65,47±9,11	49,82±7,6	5,98±1,31	2,26±2,28	28,55±9,89	44,33±10,42
Levofloxacin	73,47±10,55	48,12±13,32	4,265±2,63	13,4±7,77	22,26±9,39	34,93±7,13
Gatifloxacin	85,66±5,11	67,35±9,02	5,23±4,37	6,25±6,25	9,11±5,27	22,82±4,65
Moxifloxacin	75,94±5,47	67,35±9,02	3,85±2,29	9,83±6,08	20,23±5,34	19,25±4,55
Rifampicin	64,23±3,75	80,75±9,425	4,42±1,97	9,42±6,74	31,35±3,09	9,825±6,08

Absolute resistance of *S. aureus* to oxacillin was determined in (35,33±13,64)% of cases. Taking into account the received data, we can say that, ponderable deal of *S. aureus* clinical isolates, determined as pathogens of purulent-inflammatory complications in critically ill patient with burn injuries, had their resistance to methicillin. The presence of resistant *S. aureus* strains (24,45 %) to ampicillin/sulbactam testified inefficiency of penicillin-derived antibiotics, combined with sulbactam, when purulent-inflammatory processes, caused by this pathogen, took place (table 2).

Similar low sensitivity of *S. aureus*, isolated from critically ill patients with burns (67,47±9,30) % has been established to amoxicillin with clavulanate. The resistance of *S. aureus* (30,49 %) indicated insufficient effectiveness of amoxicillin, containing inhibitor of bacterial beta-lactamase (potassium clavulanate). We also found the resistance to ceftriaxone (32,9 %) in clinical strains of *S. aureus*, isolated from burn surfaces in the first days after the injury.

Low sensitivity to oxacillin was also appropriate for clinical strains of *S. epidermidis* (41,3±13,15 %). The research of antimicrobial qualities of Cephalosporins against clinical isolated of *S. epidermidis* have demonstrated low activity of ceftriaxone (70,35±6,31 %). There were 27,38 % of *S. epidermidis* strains, isolated from critically ill patients with burns, resistant to ceftriaxone (table 2).

High ability of *Staphylococci* to form the resistance to Carbapenems is a troubling phenomenon. There were sensitive to meropenem only (64,93 ± 10,5) % of clinical strains of *S. aureus*, isolated from critically ill patients with burns in the early period of the illness. A little bit better sensitivity to meropenem was found in *S. epidermidis* (70,35±2,41 %). We did not find the difference of antimicrobial activity of Imipenem against *S. aureus* and *S. epidermidis*.

Low antibiotic sensitivity has been found to Aminoglycosides. As follows, low sensitivity of *S. aureus* was determined to gentamicin (57,92±10,76 %), tobramycin (64,67±10,3 %). Antimicrobial efficacy of amikacin was found against 75 % of *S. aureus* strains, and their resistance took place in 23,14 % of cases. In the research, low antimicrobial activity of macrolide antibiotics against *S. aureus* strains, isolated from patients with purulent-inflammatory complications after burn injuries, has been proven. The sensitivity of *S. aureus* to erythromycin did not exceed (55,03 ± 13,88) %. Low sensitivity of *S. aureus* was also determined to such semi-synthetic derivative of erythromycin as clarithromycin (58,19±13,94 %). We found low effectiveness of azithromycin, sensitivity to which had only 58 % strains of *S. aureus*. There was high resistance of *Staphylococcus spp.*to azithromycin (*S. aureus* – 27,63 %; *S. epidermidis* – 45,3 %) and clarithromycin (*S. aureus* – 37,39 %; *S. epidermidis* – 41,75 %). As for erythromycin, it had low efficacy against clinical strains of *S. epidermidis* (43,95 %).

We have found low sensitivity of *S. aureus* to lincomycin (66,05±11,73 %) and clindamycin (66,97±12,34 %). Alike sensitivity to lincomycin was discovered for *S. epidermidis* (69,05±4,05

%). The evidence of *S. epidermidis* resistance to clindamycin and lincomycin have been revealed in 30,95 % of cases. The sensitivity of *Staphylococci* has been found to be insufficient to doxycycline (*S. aureus* – 60,17 %; chloramphenicol (*S. aureus* – 9,49 %; *S. epidermidis* – 42,62 %); rifampicin (*S. aureus* – 64,23 %). Doxycycline (78,47 %), rifampicin (80,75 %) demonstrated some superior antimicrobial activity against *S. epidermidis*.

In the research of sensitivity of clinical strains of *S. aureus, S. epidermidis*, which colonized burn wounds in critically ill patients, to fluoroquinolone antibacterials, there have been proved low effectiveness of ciprofloxacin. Sensitivity rate among *S. aureus* was (65,47±9,11) %; among *S. epidermidis* was (49,82±7,6) %. *S. aureus, S. epidermidis* demonstrated higher sensitivity to moxifloxacin (75,94±5,47) % and (67,35±9,02) % respectively. Gatifloxacin was effective against (85,66±5,11) % of *S. aureus* clinical strains and (67,35±9,02) % in the case of *S. epidermidis,* which had been isolated from patients with burns in early period after the trauma.

It is well known, that forecasting of drugs' effectiveness is carried out by such indicator as minimal bactericidal concentration (MBcC), which value shows the sensitivity of a strain of microorganism to the main active ingredient of antibacterial drug. In clinics, activity of antiseptic decreases, because of the change of concentration of CFU of a pathogen, and some other factors. Such conditions require using effective concentration of antibacterial in its finished dosage forms, in comparison with MBcC. Physicians should take into account this dependency, while administering antibacterial drugs to their patients. Bactericidal qualities of antiseptics against *Staphylococci* have been proved to have essential differences in clinical strains of *S. aureus, S. epidermidis,* isolated from critically ill patients.

For better understanding of antimicrobial activity of modern antiseptics, their action was studied in conditions of different microbial load of *S. aureus, S. epidermidis*. While changing microbial load (10^3 – 10^9 CFU/ml), we have found that decasan, AMC were highly active against these bacteria. There was defined that clinical strains of *S. aureus, S. epidermidis* had sensitivity to studied antiseptics (table 3).

There was proved high antimicrobial activity of decamethoxin against *S. aureus,* when different concentrations of this pathogen took place. Strains of *S. epidermidis* were sensitive to such MBcC of DCM as (2,13±0,18 mkg/ml) in presence 10^6 CFU/ml. In presence of 10^9 CFU/ml of *S. epidermidis* clinical strains, MBcC of decamethoxin were no more than (2,86±0,27) mkg/ml. We found high antimicrobial activity against *Staphylococci* while using AMC. We discovered potentiating of antimicrobial activity of decamethoxin in composition in 1,5 – 2 times, even when the increase of *S. aureus* concentration to the level of 10^9 CFU/ml happened. High antimicrobial activity of AMC against *S. epidermidis* was also determined. Decasan demonstrated the expressed bactericidal action against clinical strains of *Staphylococcus spp.*, which caused purulent-inflammatory complications in critically ill patients with burns. In conditions of increased microbial

load of *S. aureus, S. epidermidis* we did not found changes of antimicrobial activity of decasan. Its MBcC against *S. aureus* ranged from (0,78±0,06) to (3,12±0,25) mkg/ml and *S. epidermidis* were sensitive to (1,32±0,16) – (3,52±0,44) mkg/ml of decasan.

Table 3

Antimicrobial activity of antiseptic drugs against clinical strains *Staphylococcus spp*. in conditions of different concentrations of CFU

Antiseptics	***CFU/ml****	***S. aureus* (n 86)**	***S. epidermidis* (n 29)**
		MBcC, mkg/ml**	
Decamethoxin	10^3	0,78±0,06	1,07±0,1
	10^6	1,51±0,14	2,13±0,18
	10^9	3,12±0,25	2,86±0,27
p*		<0,001	<0,001
Decasan	10^3	0,8±0,05	1,32±0,16
	10^6	1,45±0,11	2,83±0,38
	10^9	2,83±0,18	3,52±0,44
p*		<0,001	<0,001
Antimicrobial composition of decamethoxin	10^3	0,52±0,02	0,8±0,06
	10^6	1,09±0,12	2,13±0,24
	10^9	2,02±0,17	3,29±0,23
p*		<0,001	<0,001
Chlorhexidine digluconate	10^3	4,91±0,44	4,4±0,55
	10^6	12,47±1,39	16,7±2,7
	10^9	20,6±1,66	19,01±2,25
p*		<0,001	<0,001

***** – concentration of CFU of bacteria per 1 ml; ** – minimal bactericidal concentration of antiseptics; ***– comparison criteria of MBcC values of antiseptics in conditions when *Staphylococci* concentrations 10^3 and 10^9 CFU/ml were used.

High antimicrobial qualities against *Staphylococci* were found in antimicrobial composition of decamethoxin. With the increase of microbial load of *S. aureus* from 10^3 CFU/ml to 10^9 CFU/ml there was proved bactericidal action of AMC in presence of its MBcC 0,8±0,05 mkg/ml and 2,83±0,18 mkg/ml respectively.

Effective antimicrobial qualities of chlorhexidine digluconate were determined against clinical strains of *Staphylococcus spp.*. But with the increase of microbial load to 10^9 CFU/ml bactericidal action of chlorhexidine digluconate against *S.aureus, S. epidermidis* was in 6 – 6,6

times lower than decamethoxin antimicrobial composition's activity ($p<0,001$). These data proved considerable advantages of AMC comparably with chlorhexidine digluconate.

Conclusions

1. Resistant to the majority of antibiotics strains of *Staphylococcus spp.* store their high sensitivity to antiseptic, containing decamethoxin, its polymeric composition, chlorhexidine digluconate. The increase of microbial load up to 10^9 CFU/ml decreases antimicrobial effectiveness of chlorhexidine digluconate in 4,2 – 4,8 times. Antibiotic resistant strains of *Staphylococci* do not have cross-resistance to antiseptic drugs.

2. Clinical strains of *S. aureus*, *S. epidermidis* cause purulent-inflammatory complications in critically ill patients with burns and have high resistance to oxacillin (46,9; 59,1 % respectively).

3. Clinical strains of *Staphylococci* have their sensitivity to amikacin (74,62 – 80,75 %), linezolid (77,2 – 87,44 %); vancomycin (91,88 – 92,46 %). *Staphylococcus spp.*, which colonize burn surfaces of the body, demonstrate resistance to beta-lactam antibiotics with clavulanic acid and sulbactam (amoxicillin/clavulanate – 67,47±9,30 %; ampicillin/sulbactam – 58,63±8,58 %;); ceftriaxone (55,75±14,24 %); carbapenems (meropenem – 64,93 – 70,35 %; imipenem – 66,43 – 66,78 %); ciprofloxacin (65,47±9,11 %).

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