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SENSITIVITY TO ANTIBIOTICS AMONG STRAINS OF SALMONELLA CURRENT, WHICH CIRCULATES IN THE PAST 10 YEARS IN UKRAINE

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In this article the main results of the sensitivity to antibiotics on S. Typhimurium, S. strains of Salmonella Enteritidis and rare groups that circulate in Ukraine last 10 years were described. The unifying disc-fusion method determined the sensitivity of Salmonella strains to several antibiotics. Resistance to antibiotics of strains of Salmonella was caused by the lack of effective influence of drugs on salmonellosis. The obtained results revealed antibiotics with a strong antimicrobial action and a narrow focus on strains of Salmonella.

KEY WORDS: salmonellosis, S. Typhimurium, S. Enteritidis, rare Salmonella strains, antibiotics

ЧУТЛИВІСТЬ ДО АНТИБІОТИКІВ СЕРЕД АКТУАЛЬНИХ ШТАМІВ САЛЬМОНЕЛ, ЩО ЦИРКУЛЮЮТЬ НА ТЕРИТОРІЇ УКРАЇНИ ОСТАННІ 10 РОКІВ

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У статті визначені основні результати дослідження на чутливість до антибіотиків щодо S. Typhimurium, S. enteritidis та штамів сальмонел рідких груп, що циркулюють на території України останні 10 років. За уніфікованим дискодифузійним методом була визначена чутливість штамів сальмонел до ряду антибіотиків. Резистентність штамів сальмонели до антибіотиків була викликана відсутністю ефективного впливу ліків на сальмонельоз. Отримані результати дозволили виявити антибіотики з вираженою протимікробною дією і вузькою спрямованістю на штами сальмонели.

КЛЮЧОВІ СЛОВА: сальмонельоз, S. Typhimurium, S. Enteritidis, штами сальмонел рідких груп, антибіотики

ЧУВСТВИТЕЛЬНОСТЬ К АНТИБИОТИКАМ СРЕДИ АКТУАЛЬНЫХ ШТАММОВ САЛЬМОНЕЛЛ, ЦИРКУЛИРУЮЩИХ НА ТЕРРИТОРИИ УКРАИНЫ ПОСЛЕДНИЕ 10 ЛЕТ

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В статье определены основные результаты исследования на чувствительность к антибиотикам по S. Typhimurium, S. Enteritidis и штаммов сальмонелл редких групп, циркулирующих на территории Украины последние 10 лет. Унифицированным дискодифузийним методом была определена чувствительность штаммов сальмонелл к ряду антибиотиков. Резистентность штаммов сальмонеллы к антибиотикам была вызвана отсутствием эффективного воздействия лекарств на сальмонеллез. Полученные результаты позволили выявить антибиотики с выраженной противомикробным действием и узкой направленностью на штаммы сальмонеллы.

КЛЮЧЕВЫЕ СЛОВА: сальмонеллез, S. Typhimurium, S. Enteritidis, штаммы сальмонелл редких групп, антибиотики

INTRODUCTION

The frequency of infections caused by antibiotic-resistant bacteria increases among the population of the world [1-3], causing these infections are becoming animportant health-care problem [4-6]. Incorrect use of antibiotics is developing resistance to these drugs [7-9].

Application of antibiotics in farm animals allows persistent bacteria and genes of resistance be transferred through the food chain from animals to humans [10-13]. The failured treatment leads to a rise in the mortality rate, as well as to the necessity to develop new antibiotics [14-16].

RELEVANCE

At present the problem of sensitivity to antibiotics diseases is relevant to public health: each year in the European Union, more than 25,000 people die from infections caused by resistant bacteria [17, 18]. The use of antibiotics has led to the formation and spread of resistance to these drugs, which are associated with a decrease in the effectiveness of treatment and, therefore, more difficult and long duration of disease, increased frequency of hospitalization, increase the number of deaths and an increase in economic losses to society [19-21]. Microbial resistance to antibacterial agents is characterized by retention of their ability to multiply in the presence of concentrations of these substances which are administered at therapeutic doses [22-24].

The problem of stability of Salmonella to antibiotics was exacerbated in 1972, when many countries have experienced outbreaks of infections caused by S. typhi, resistant to chloramphenicol, sulfonamide, tetracycline and streptomycin, whereas ampicillin and cotrimoxazole retain activity.

After twenty years, most of the strains were resistant and so microbial agents, wherein the allocation of multidrug resistant S. typhi has become commonplace [25-27].

According to WHO, the use of fluoroquinolones in animal's food has led to the emergence of an appropriate antibiotic resistance of Campylobacter in Salmonella that cause infectious disease in humans. In diseases, caused by multi-drug resistant strains of Salmonella Typhimurium phage type specific (DT) 104 resistance to quinolones, observed treatment failure, a higher rate of hospitalization and higher risk of death [28].

Thus, resistance to antibiotics in infections has become a growing international public health problem that requires urgent attention [29-31].

The aim is to determine the sensitivity to antibiotics of current Salmonella strains circulating in Ukraine last 10 years.

MATERIALS AND METHODS

To investigate the biological properties of Salmonella used 136 strains during the period 1996-2012 years, obtained from the Museum of pathogenic microbial organism «L.V. Gromashevskiy Institute of Epidemiology and Infectious Diseases of Academy of Medical Sciences of Ukraine».

Of the 62 strains of Salmonella period 1996-2006, 24 (38 %) belonged to S. typhimurium, 38 (62 %) - to S. enteritidis, with 57 of museum culture period 2006-2012 7 (12 %) belonged to S. typhimurium, 50 (88 %) - to S. enteritidis, also for better comparison Sal-monella sampling of rare groups was formed which were isolated from the external environment in the S. java - 7 strains, S. derby - 1 strain, S. colorado - 1 strain, S. infantis - 1 strain, S. blegdam - 2 strain, S. montevideo - 1 strain, S. senftenberg -1 strain of S. haifa - 2 strain.

The study of antibiotic sensitivity was performed using a standardized Kirby Bauer Disk Diffusion Method. Getting results of diffusion in Mueller-Hinton agar was performed using paper discs and a special measuring stick that served to account for the fields of growth retardation [32]. The results are interpreted on the basis of criteria of CLSI (2010) growth inhibition zone diameter in millimeters of culture (tab. 1) and the disc manufacturer.

Depending on the diameter of growth inhibition zones around the disks were classified as resistant strains (resistant), moderately sensitive and stable. Strain of E. Coli ATCC 25922 was used as a reference and for the control; it was obtained from the Museum of pathogenic microbial organism SI «L.V. Gromashevskiy Institute of Epidemiology and Infectious Diseases of Academy of Medical Sciences of Ukraine».

Received results were treated by quantitative methods of mathematical statistics including standard deviation of sample values (M) and the mean error (m). The significance

Table 1

Standard interpretation of the results (limiting values of diameters of zones of growth delay)

Antibiotic name	Content antibiotic in disk, mcg	The diameters of zones of growth inhibition, mm		
		stable	moderately resistant	sensitive
Ampicillin	10	13	14-16	17
Gentamicin	10	12	13-14	15
Kanamycin	30	13	14-17	18
Co-trimoxazole	1,25/23,75	10	11-15	16
Nitrofurantoin	300	14	15	17
Polymyxin-B	300	11	-	12
Streptomycin	10	11	12-14	15
Sulfamethizole	300	11	12-14	15
Tetracycline	30	14	15-18	19
Ticarcillin	75	14	15-19	20
Chloramphenicol	30	12	13-17	18
Cefazolin	30	14	15-17	18
Cefoxitin	30	14	15-17	18
Cefotaxime	30	14	15-22	23
Ceftriaxone	30	13	14-20	21
Cefuroxime	30	14	15-17	18
Ciprofloxacin	5	15	16-20	21

of differences was determined using indicators Student t-test, which is defined by a table of critical points of distribution. The correlation coefficient was considered with the error probability $p < 0.05$, which was determined by comparison with the critical value from the table depending on the size of the study group, the correlation coefficients and the likelihood of errors. The data were processed using a personal computer and software for processing and analysis of statistical information «Excel 2003», included in the package «Microsoft Office 2003».

RESULTS AND DISCUSSION

Evaluation of the distribution of sensitivity to antibiotics showed that in 1996-2005, strains of S. Typhimurium were highly sensitive to polymyxin-B (100 %), cefoxitin (87,5 %), ciprofloxacin (83,33 %), cefotaxime and gentamicin (at 70,83 %), cefazolin (66,67 %), and ampicillin cefotaxime (by 62,5 %), nitrofurantoin and streptomycin (58,33 %). The most resistant strains were to sulfamethizole (83,33 %), cotrimoxazole (75,0 %), kanamycin (58,33 %), tetracycline (50,0 %).

The results of sensitivity to antibiotic resistant strains of S. Typhimurium 2006-2012 years showed significantly decreased sensitivity of cefoxitin and ceftriaxone, respectively, 73,21 and 42,26 %, tetracycline - by 31,54 %. It should be noted that strains of S. Typhimurium remained absolute sensitivity (100 %) to polymyxin-B during the whole investigated period – 1996–2012. It was found that a semisynthetic broad-spectrum penicillin - ampicillin increased its activity on 23,21 %, with a simultaneous decrease of the same level of stability during the study during the period from 1996-2005, 2006-2012 years. Among the newest synthetic antibiotic quinolones ciprofloxacin stands, the sensitivity of which was in 1996-2005, 83.33 %, and in 2006-2012 declined slightly - by 11.9 %.

Summarizing the results for the group of cephalosporins, it should be noted that almost all the members of this class, except cefazolin, lowered resistance at 2005-2012 with 1996-2005 years moderately resistant (tab. 2).

The obtained result of the distribution of sensitivity to antibiotics revealed that in 1996-2005 strains of S. Enteritidis were 100 % sensitive to polymyxin-B throughout the study from 1996 to 2012. High sensitivity was found in ampicillin (94,74 %). In 1996-2005, strains of S. enteritidis in the majority had a high

Table 2

Resistance to antibiotics of S. typhimurium strains

Antibiotic name	Distribution of sensitivity to antibiotics (M ± m), %					
	Strains 1996-2005 years (n = 24)			Strains 2006-2012 years (n = 7)		
	stable	moderately	sensitive	stable	moderately resistant	sensitive
Ampicillin	37,50 ± 9,88	0	62,50 ± 9,88	14,29 ± 13,23	0	85,71 ± 13,23
Gentamicin	4,17 ± 4,08	25,00 ± 8,84	70,83 ± 9,28	0	42,86 ± 18,70	57,14 ± 18,70
Kanamycin	58,33 ± 10,06	8,33 ± 5,64	33,33 ± 9,62	28,57 ± 17,07	0	71,43 ± 17,07
Co-trimoxazole	75,00 ± 8,84***	0	25,00 ± 8,84*	28,57 ± 17,07***	0	71,43 ± 17,07*
Nitrofurantoin	12,50 ± 6,75	29,17 ± 9,28	58,33 ± 10,06	28,57 ± 17,07	14,29 ± 13,23	57,14 ± 18,70
Polymyxin-B	0	0	100	0	0	100
Streptomycin	16,67 ± 7,61	25,00 ± 8,84	58,33 ± 10,06	14,29 ± 13,23	28,57 ± 17,07	57,14 ± 18,70
Sulfamethizole	83,33 ± 7,61***	0	16,67 ± 7,61*	28,57 ± 17,07***	0	71,43 ± 17,07*
Tetracycline	50,00 ± 10,21***	4,17 ± 4,08**	45,83 ± 10,17	14,29 ± 13,23***	71,43 ± 17,07**	14,29 ± 13,23
Ticarcillin	41,67 ± 10,06	37,50 ± 9,88	20,83 ± 8,29	14,29 ± 13,23	42,86 ± 18,70	42,86 ± 18,70
Chloramphenicol	37,50± 9,88	8,33 ± 5,64	54,17 ± 10,17	14,29 ± 13,23	0	85,71 ± 13,23
Cefazolin	12,50 ± 6,75	20,83 ± 8,29**	66,67 ± 9,62	14,29 ± 13,23	0	85,71 ± 13,23
Cefoxitin	0	12,50 ± 6,75**	87,50 ± 6,75*	0	85,71 ± 13,23**	14,29 ± 13,23*
Cefotaxime	12,50 ± 6,75	16,67 ± 7,61**	70,83 ± 9,28*	14,29 ± 13,23	57,14 ± 18,70**	28,57 ± 17,07*
Ceftriaxone	20,83 ± 8,29	16,67 ± 7,61	62,50 ± 9,88	14,29 ± 13,23	28,57 ± 17,07	57,14 ± 18,70
Cefuroxime	29,17 ± 9,28	37,50 ± 9,88	33,33 ± 9,62	14,29 ± 13,23	71,43 ± 17,07	14,29 ± 13,23
Ciprofloxacin	0	16,67 ± 7,61	83,33 ± 7,61	0	28,57 ± 17,07	71,43 ± 17,07

Note:
* - the difference in the percentage of resistant strains is likely,
** - the difference in the percentage of resistant strains conditionally probable,
*** - the difference in the percentage of susceptible strains is likely

sensitivity to the representatives of the cephalosporin group: ciprofloxacin – 94,74 %, cefoxitin – 89,47 %, cefotaxime – 78,95 %, ceftriaxone – 73,68 %, cefazolin – 68,42 %. The less sensitivity strains to cefuroxime (50,0 %) had. Low sensitivity, also, was noted in the combined antibiotic co-trimoxazole (52,63 %). High sensitivity was observed in a number of aminoglycosides - gentamicin (84,21 %), kanamycin (78,95 %), streptomycin (94,74 %). Different sensitivity was noted in the representatives of penicillin: in ampicillin – 94,74 % and ticarcillin – 39,47 %. The results of the period 2006-2012 years showed that from 18 tested antibiotics, strains S. enteritidis increased 100 % susceptibility to 11 antibiotics. Special attention deserves a slight increase in sensitivity to the cephalosporin group of strains (tab. 3). Sensitivity of the antibiotic-resistant strains of Salmonella rare groups compared with S. enteritidis 2006-2012 showed that 100 % of the sensitivity of the strains had 61,11 % of the investigated antibiotics. The most sensitive antibiotics for the period 1996-2012 years were: ampicillin, aminoglycosides (gentamicin, kanamycin, streptomycin), combined antibiotics (cotrimoxazole, polymyxin-B),

a synthetic broad-spectrum antibiotic - chloramphenicol, an antibiotic synthesized new quinolones - ciprofloxacin. Cefazolin had the absolute sensitivity from the number of cephalosporins (tab. 4).

Table 3

Resistance to antibiotics of S. Enteritidis strains

Antibiotic name	Distribution of sensitivity to antibiotics (M ± m), %					
	Strains 1996-2005 years (n = 24)			Strains 2006-2012 years (n = 7)		
	stable	moderately resistant	sensitive	stable	moderately resistant	sensitive
Ampicillin	0	5,26 ± 3,62	94,74 ± 3,62	0	0	100,00
Gentamicin	0	15,79 ± 5,92**	84,21 ± 5,92***	0	0**	100,00***
Kanamycin	10,53 ± 4,98*	10,53 ± 4,98**	78,95 ± 6,61***	0*	0**	100,00***
Co-trimoxazole	39,47 ± 7,93*	7,89 ± 4,37	52,63 ± 8,10***	0*	0	100,00***
Nitrofurantoin	0*	21,05 ± 6,61**	78,95 ± 6,61***	10,00 ± 4,87*	44,00 ± 8,05**	46,00 ± 8,09***
Polymyxin-B	0	0	100,00	0	0	100,00
Streptomycin	0	5,26 ± 3,62	94,74 ± 3,62	0	0	100,00
Sulfamethizole	55,26 ± 8,07*	2,63 ± 2,60	42,11 ± 8,01***	0*	0	100,00***
Tetracycline	2,63 ± 2,60	28,95 ± 7,36**	68,42 ± 7,54***	0	54,00 ± 8,09**	46,00 ± 8,09***
Ticarcillin	2,63 ± 2,60	57,89 ± 8,01	39,47 ± 7,93	0	46,00 ± 8,09	54,00 ± 8,09
Chloramphenicol	7,89 ± 4,37	15,79 ± 5,92**	76,32 ± 6,90***	0	0**	100,00***
Cefazolin	10,53 ± 4,98*	21,05 ± 6,61**	68,42 ± 7,54***	0*	0**	100,00***
Cefoxitin	0	10,53 ± 4,98	89,47 ± 4,98	0	22,00 ± 6,72	78,00 ± 6,72
Cefotaxime	0	21,05 ± 6,61	78,95 ± 6,61	0	16,00 ± 5,95	84,00 ± 5,95
Ceftriaxone	5,26 ± 3,62	21,05 ± 6,61	73,68 ± 7,14***	0	8,00 ± 4,40	92,00 ± 4,40***
Cefuroxime	13,16 ± 5,48*	36,84 ± 7,83	50,00 ± 8,11	0*	44,00 ± 8,05	56,00 ± 8,05
Ciprofloxacin	5,26 ± 3,62	0	94,74 ± 3,62	0	0	100,00

Note:
* - the difference in the percentage of resistant strains is likely,
** - the difference in the percentage of resistant strains conditionally probable,
*** - the difference in the percentage of susceptible strains is likely

For the treatment of Salmonella strains of S. typhimurium chloramphenicol, cotrimoxazole, and - ticarcillin, ampicillin, aminoglycosides, cefazolin, kanamycin, sulfamethizole are the broad-spectrum antibiotics. The resistant strains of S. typhimurium resistant to cephalosporins II and III generation, which are representatives of penicillin antibiotics group, can prevent that these strains produce betalactamase extended spectrum that can lead to future failure treating such patients by penicillins, cephalosporins I-IV and other generations of antibacterial drugs.

In this noteworthy that strains of S. typhimurium and S. enteritidis are mostly sensitive to cephalosporins, quinolones, fluoroquinolone and polymyxin. The drug nitrofuran series (nitrofurantoin), penicillin (tetracycline, ticarcillin) and cephalosporin antibiotic II generation - cefuroxime lost their effectiveness against S. typhimurium, S. enteritidis and Salmonella strains of rare groups. In most cases, antibiotic sensitivity was higher in rare strains of groups.

A characteristic feature of the use of antibiotics in patients with salmonellosis is that during the study period 1996-2005, regardless

of the type strain, the only 100% efficiency has been achieved in the treatment of polymyxin B, due, apparently, to its specific mechanism of influence on the integrity of the cytoplasmic membrane of microbial cells and its high toxicity to it.

Table 4

Antibiotic susceptibility of Salmonella strains of rare groups

Antibiotic name	Distribution of sensitivity to antibiotics (M ± m), %					
	Strains 1996-2005 years (n = 17)			Strains 2006-2012 years (n = 50)		
	stable	moderately resistant	sensitive	stable	moderately resistant	sensitive
Ampicillin	0	0	100,00	0	0	100,00
Gentamicin	0	0	100,00	0	0	100,00
Kanamycin	0	17,65 ± 9,25	82,35 ± 9,25	0	0	100,00
Co-trimoxazole	0	0	100,00	0	0	100,00
Nitrofurantoin	52,94 ± 12,11	11,76 ± 7,81	35,29 ± 11,59	10,00 ± 4,87	44,00 ± 8,05	46,00 ± 8,09
Polymyxin-B	0	0	100,00	0	0	100,00
Streptomycin	0	0	100,00	0	0	100,00
Sulfamethizole	0	0	100,00	0	0	100,00
Tetracycline	52,94 ± 12,11	47,06 ± 12,11	0	0	54,00 ± 8,09	46,00 ± 8,09
Ticarcillin	17,65 ± 9,25	35,29 ± 11,59	47,06 ± 12,11	0	46,00 ± 8,09	54,00 ± 8,09
Chloramphenicol	0	0	100,00	0	0	100,00
Cefazolin	0	0	100,00	0	0	100,00
Cefoxitin	0	29,41 ± 11,05	70,59 ± 11,05	0	22,00 ± 6,72	78,00 ± 6,72
Cefotaxime	0	17,65 ± 9,25	82,35 ± 9,25	0	16,005,95	84,00 ± 5,95
Ceftriaxone	0	0	100,00	0	8,00 ± 4,40	92,00 ± 4,40
Cefuroxime	0	52,94 ± 12,11	47,06 ± 12,11	0	44,00 ± 8,05	56,00 ± 8,05
Ciprofloxacin	0	0	100,00	0	0	100,00

CONCLUSIONS

The problem of rational use of antibiotics in the treatment of salmonellosis is among the most urgent in medicine. Strains of S. typhimurium, S. enteritidis react to cephalosporins, quinolones, fluoroquinolones. Nitrofurans, most penicillins and cefuroxime reduced their activity against S. typhimurium, S. enteritidis and Salmonella strains of rare groups. Strains of rare groups were more susceptible to antibiotics. The only current effective drug in all tested strains of Salmonella was polymyxin B.

The increase in resistance of Salmonella strains against a background of resistance to the formation of new genes produced by the microbial cells that neutralize the effect of antibiotics on their cell system. The development of resistant strains of microorganisms greatly reduces the effectiveness of antibiotic therapy.

PERSPECTIVES OF FURTHER INVESTIGAT

The development of resistance strains of Salmonella bacteria is a natural reaction, which can be controlled through the proper use of antibiotics. Advanced developments overcome resistance to antibiotics salmonellosis is to introduce the practice of rational antibiotic regimens, obtaining new types of antibiotics on the basis of known, the use of antibiotics with different mechanisms of action. For the final

solution of this problem it is expedient further research aimed at clarifying the strengths of a number of modern antibiotics against different strains of salmonella in the current economic and social terms.

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