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PROGNOSTIC CRITERIA OF SENSITIVITY TO ANTIBIOTICS OF STAPHYLOCOCCUS CLINICAL STRAINS

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Abstract

In the article, the new data of sensitivity to antibiotics in clinical strains of *Staphylococci* are presented. For the first time, analytic dependence of dynamic prognostic criteria of the change of sensitivity of *S. aureus* clinical strains, isolated from patients, was obtained by means of mathematical prediction. There were investigated prognosticated indexes of *Staphylococcus* strains' sensitivity to beta-lactams (oxacillin, ceftriaxone, imipenem and meropenem), vancomycin and linezolid. The dynamic of sensitivity decreasing to oxacillin, ceftriaxone, carbapenems (imipenem, meropenem), vancomycin (92,5 %) and high sensitivity to linezolid in clinical strains of *S. aureus* were found out.

Key words: sensitivity, antibiotics, *Staphylococcus*, prognostic indexes.

Background. *Staphylococci* remain to be the object of the majority of scientific researches. It closely dependent on the increasing of their role in amplification of difficult infectious purulent-inflammatory complications. The specie of *Staphylococcus* occupy prominent positions among pathogens of nosocomial infectious diseases. The incidence of *Staphylococcus* infection in many countries of the world range 18,8 – 57,8 % [1–3].

Problems of prophylaxis and treatment of nosocomial infectious complications are closely connected with the resistance of *Staphylococci* to antibiotics, antiseptics. The sensitivity of clinical strains of *Staphylococcus* to widely used in clinical practice antibiotics constantly decreases.

Moreover, inadequate launching antibiotic therapy do not provide appropriate effectiveness of the management. That is why the possibility of investigation of prognostic index models of the resistance in clinical strains of *Staphylococcus* to antibiotics is of importance [3, 4].

The aim. Investigation of prognostic criteria of antibiotic sensitivity in clinical strains of *Staphylococcus*.

Materials and methods. Our research, have being held during 2011 – 2015 years. In the research, there were enrolled 380 patients, who had been treated in Vinnitsa Regional Clinical Hospital named after N. I. Pirgov. Patients were managed according to modern conventional traditional methods. Complex treatment measurements of intensive care, directed to stabilisation of critically ill patients' status, consisted of systemic and local antimicrobial therapy (antibiotics, antiseptics).

At the beginning of the treatment all patients underwent microbiological examination of their wound surfaces, with isolation of pure culture of the pathogens, their identification by their morphological, cultural, biochemical features. Generally from patients there were isolated and identified 130 strains of *S. aureus* (2011 p. – n 37; 2012 p. – n 25; 2013 p. – n 27; 2014 p. – n 24; 2015 p. – n 17).

The sensitivity of all isolated strains of *S. aureus* (n 130) to antibiotics were studied according to methodical recommendations [5]. In the research, there were studied beta-lactams (oxacillin, ceftriaxone, imipenem and meropenem), vancomycin and linezolid.

In our study there was carried out mathematical analysis of the data, characterising the sensitivity of *S. aureus* clinical strains to antibiotics of different groups. Used methods of statistics analysis gave the possibility to find out obligated link between numeric values of changing features, and probability of realization of these values for observations [6].

Mathematical prognostication belongs to the main modern research methods. Prognostication is understood as the process of the research of real system and transference of received results on the system, which is studied. The model can be defined as an object, which is some relatively common with the prototype and is mean of description, elucidation or prognostication of its demeanour. Mathematical simulation of real process is a complex of relationships (formulas), which determine characteristics of processes depending on their parameters, exterior and initial conditions and time. Reliability of designed statistical models were analyzed by the coefficient of determination (r^2). Obtained data were processed by means of computer original license programs "STATISTICA 7" та "Matlab 7.11" [7].

Every year there were calculated arithmetic average (M), error arithmetic mean (m), standard deviation (σ) for every group of patients. In the research, data approximation and interpolation were carried out and analytic dependences of dynamic prognostic indexes of antibiotic sensitivity of *S. aureus* clinical strains, isolated from patients were obtained.

Results and discussion. While analyzing the results of microbiological research of *S. aureus* clinical strains' sensitivity to oxacillin, there was found low level of sensitivity in 2011 year. In the research, we observed gradual increase of amount of sensitive *S. aureus* strains by 94,11 % (2014 year). However, further analysis of results, obtained in 2011-2015 years, became the basis of prognostic model of *S. aureus* sensitivity to oxacillin showed the decrease of this antibiotic in patients with burns. Mathematical formula (1) describes this regularity and represents high certainty of the incidence of methicillin-resistant strains of *S. aureus*, among pathogens of purulent-inflammatory diseases in these patients.

$$Oxacillin = a + b \cdot x^2 + c \cdot x^3 + \frac{d \cdot \ln(x)}{x}, \tag{1}$$

Where $a = -2.0750611 \cdot 10^{10}$; $b = 4636.5904$; $c = -1.1367807$; $d = 2.97293661 \cdot 10^{12}$; $r^2 = 0.9638$; error 3,62 %.
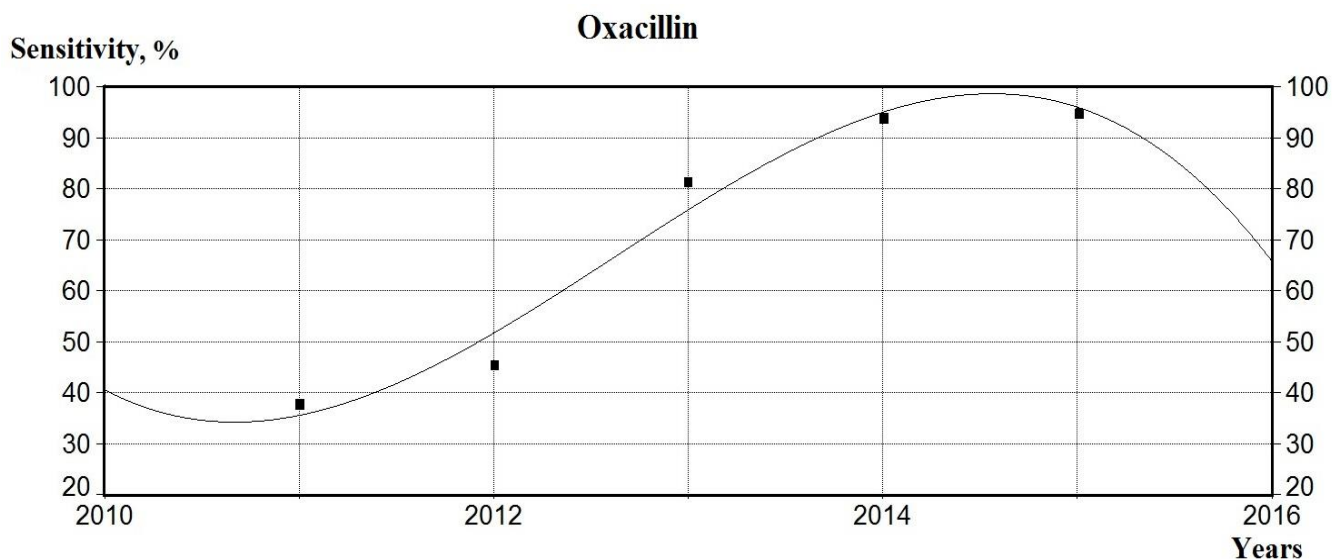
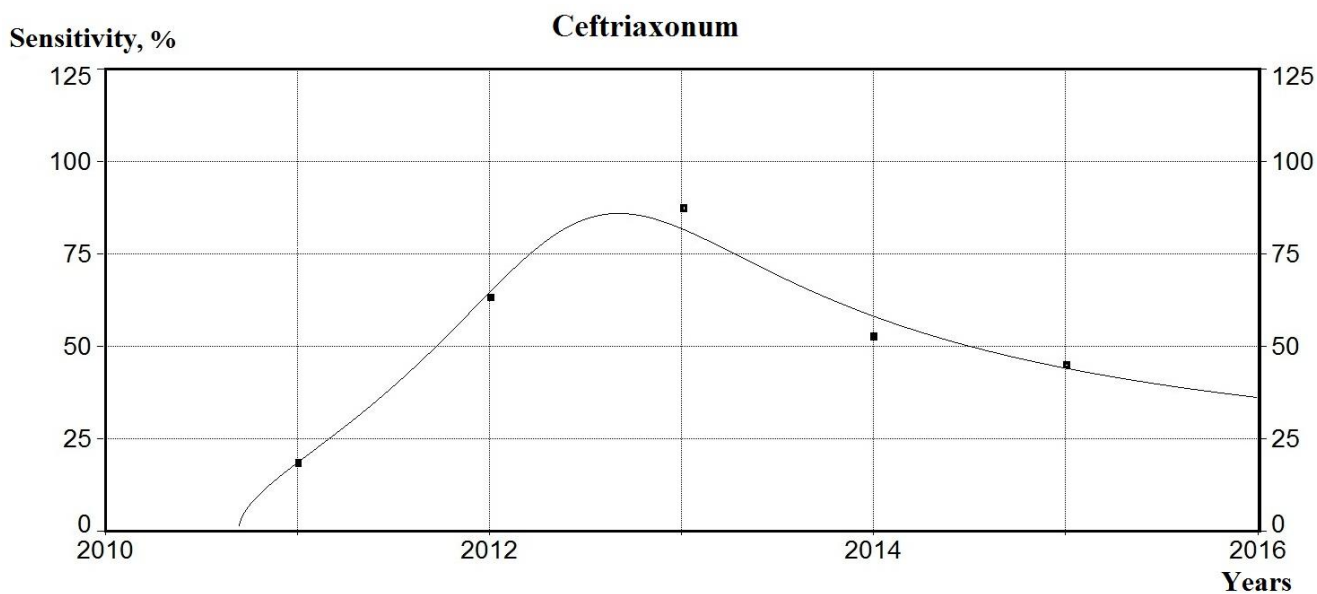**Fig. 1. Prognostic indexes of sensitivity of *S. aureus* to oxacillin**

Prognostication a sensitivity level of *S. aureus*, vegetating on burn surfaces, indicated unswerving tendency of its lowering. It seemed inefficiency of the use of elemental and semi-synthetic antibiotics of penicillin for prophylaxis and treatment of Staphylococcus infection in patients (fig. 1).

While studying the resistance to cephalosporins we used antibiotic of the 3rd generation ceftriaxone, widely used in medical practice, for prophylaxis and treatment of purulent-inflammatory diseases. Analysis of sensitivity of clinical strains of *S. aureus*, isolated from patients (in 2011 − 2015 years), showed varying amount of sensitive strains to ceftriaxone from 18,91 % to 87,5 %. The curve of sensitivity of *S. aureus* clinical strains to ceftriaxone have shown uncertain sensitivity of this pathogen in dynamics. Distinctive tendency of sensitivity decreasing in *S. aureus* have been found

since 2014 p. (52,94 %). The use of mathematical model showed the decrease of sensitivity of *S. aureus* to ceftriaxone in patients (formula 2; fig. 2).

$$Ceftriaxonum = \sqrt{(a + cx) / (1 + bx + dx^2)}, \tag{2}$$

Were $a = -1.6561296$; $\qquad b = -0.00099381276$; $\qquad c = 0.00082365918$;

$d = 2.46916 \cdot 10^{-7}$ $r^2 = 0.9753$; error 2,6 %.

**Sensitivity, %**   **Ceftriaxonum**

Fig. 2. Prognostic indexes of sensitivity of *S. aureus* to ceftriaxone

In the research, we obtained similar results of sensitivity of isolated *S. aureus* strains for both carbapenem antibiotics (imipenem, moropenem), which belong to reserve antibiotics. In 2011 year the quantity of *S. aureus* strains, sensitive to imipenem, was 32,43 %, to meropenem 37,83 %. During further research, gradual increase of sensitive to imipenem (81,8 %; 2012 year) strains of *S. aureus* was found. However, later direct tendency of decreasing of sensitive quantity of *S. aureus* strains (75 % - 2013 year; 70,5 % - 2014 year was found (formula 3; fig. 3).

$$Imipenem = ((a + cx) / (1 + bx + dx^2))^2, \tag{3}$$

Where $\quad a = -0.058184821$; $\qquad b = -0.00099714612$; $\qquad c = 2.8936065 \cdot 10^{-5}$;

$d = 2.485736 \cdot 10^{-7}$;

$r^2 = 0.9959$; error 0,41 %.
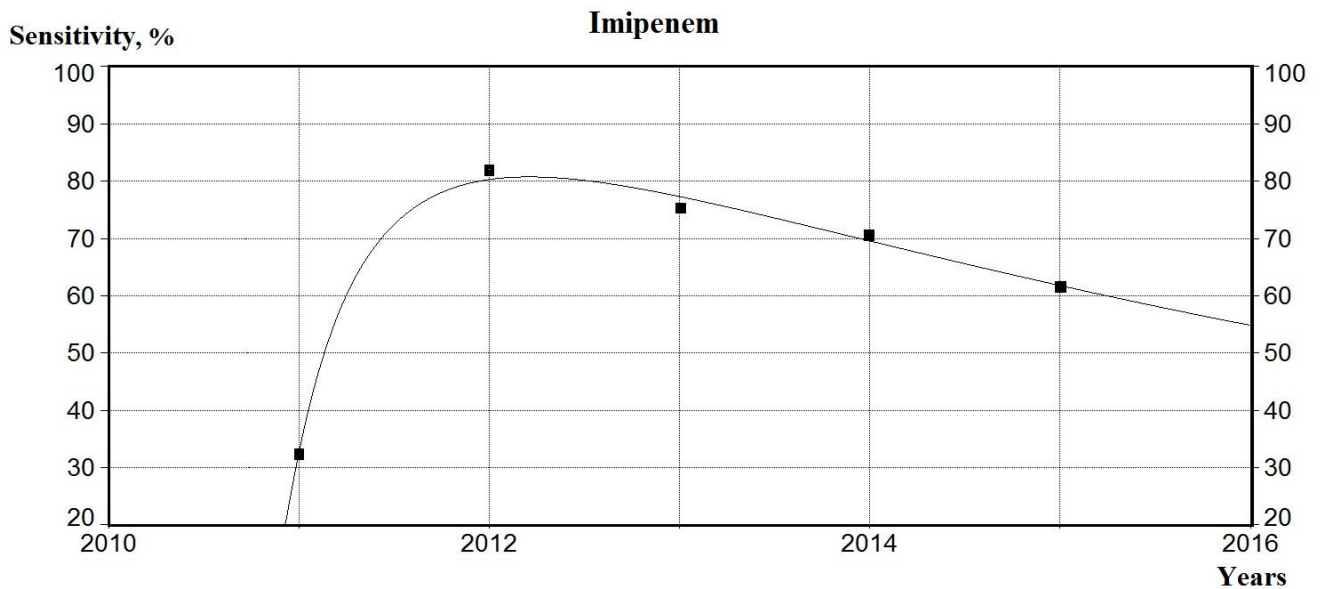
Fig. 3. Prognostic indexes of sensitivity of *S. aureus* to imipenem

In the case of meropenem we found some improvement of sensitivity in clinical strains of *S. aureus* for a little bit longer period of time (81,8 % - in 2012 year; 81,25 % - in 2013 year) with further decease to 58,82 % in 2014 year. (formula 4; fig. 4).

$$Meropenem = \sqrt{(a + cx) / (1 + bx + dx^2)}, \tag{4}$$

Where $a = -3.2257222$; $b = -0.00099410164$; $c = 0.0016043868$; $d = 2.470596 \cdot 10^{-7}$ $r^2 = 0.9840$; error 1,6 %.
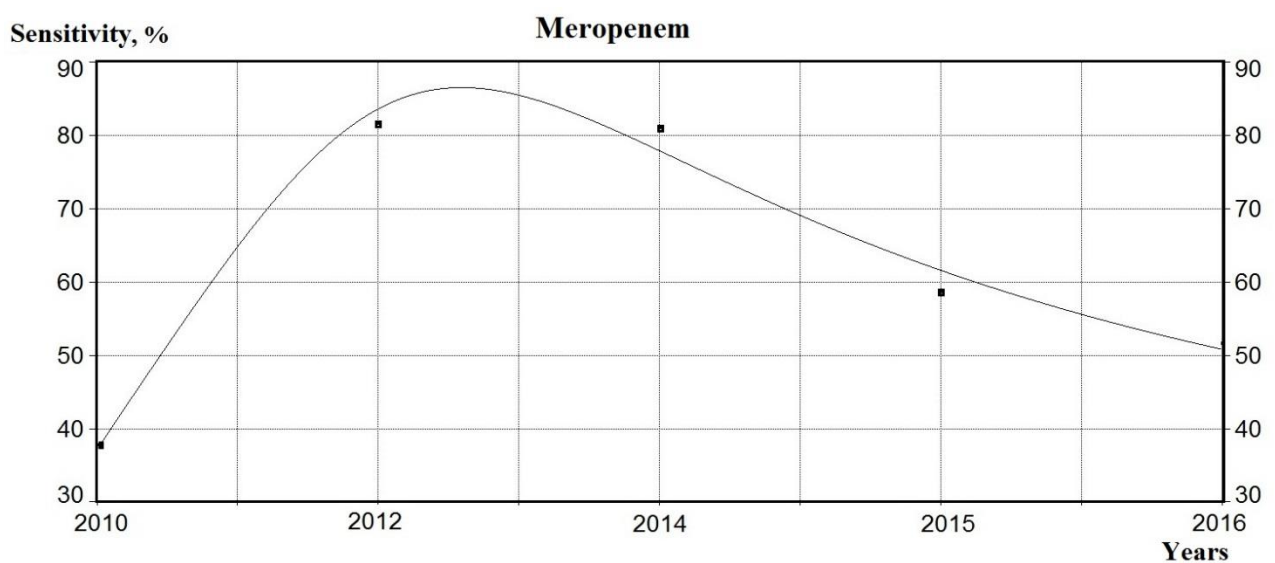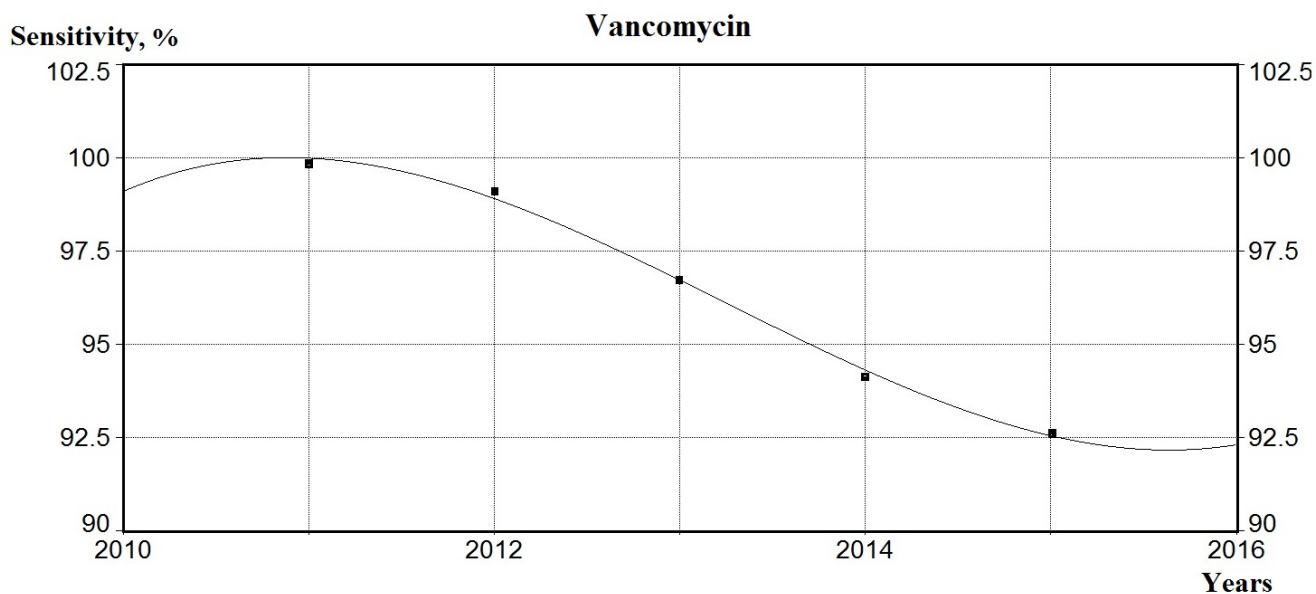

Fig. 4. Prognostic indexes of sensitivity of *S. aureus* to meropenem

Due to the mathematical analysis of perennial research of sensitivity to carbapenems in *S. aureus* clinical strains, it was possible to build the graph of prognostic criteria of sensitivity, which reflected the tendency of decreasing of general sensitivity level in *Staphylococcus* to imipenem and meropenem. When *S. aureus* were isolated from such patients, empiric administration of imipenem or meropenem may be considered inappropriate without previous microbiological confirmation of their antimicrobial activity.

The problem of determining of sensitivity in *Staphylococci* to glycopeptides is essentially actual in conditions of increasing resistance in clinical strains of *Staphylococcus* to such antibiotics as penicillin and cephalosporin has; increased incidence of purulent-inflammatory complications in burn patients, caused by methicillin-resistant strains of *S. aureus*. Antistaphylococcus activity of vancomycin, as the drug of choice when nosocomial infections, caused by methicillin-resistant strains of *Staphylococcus*, take place, has shown some hesitation of its effectiveness during five years.

$$Vancomycin = a + b \cdot x^2 + c \cdot x^3 + \frac{d}{x^2}, \qquad (5)$$

Where $a = 5,9512836 \cdot 10^8$; $b = -220,24286$; $c = 0,058344464$;

$d = -7,236514 \cdot 10^{14}$; $r^2 = 0.9923$; error 0,77 %.

Fig. 5. Prognostic indexes of sensitivity of *S. aureus* to vancomycin

The study of antimicrobial activity of vancomycin has shown its high effectiveness against *S. aureus* as pathogens of purulent-inflammatory complications. Antibiotic sensitivity of *S. aureus* to vancomycin was the highest in 2011 − 2012 years (fig. 5). Further research gave the possibility to find out the appearance of increased quantity of vancomycin-resistant strains of *S. aureus*. However, the

percent of sensitive *Staphylococcus* isolates decreased on 7,5 % and was 92,5 % (2015 year). Conducted mathematical analysis has showed the decreasing sensitivity to vancomycin in clinical strains of *S. aureus*. Such decreasing tendency of antibiotic sensitivity was linear. Nevertheless, according to the formula (5) of prognostic model, for soon there was determined high effectiveness of vancomycin against *S. aureus*.

In modern medicine, antibiotic drug linezolid, belonging to oxazolidinones is widely used for the treatment of purulent-inflammatory complications, caused multiantibioticoresistant strains of *S. aureus*. Mechanism of its action realises by the way of inhibition of protein synthesis in bacterial ribosomes.

$$Linezolidum = a + bx^2 \cdot \ln(x) + cx^3, \qquad (6)$$

where $a = -322918,46$; $b = 0,036074835$; $c = -9,6732098 \cdot 10^{-5}$; $r^2 = 0.9975$; error 0,25 %.
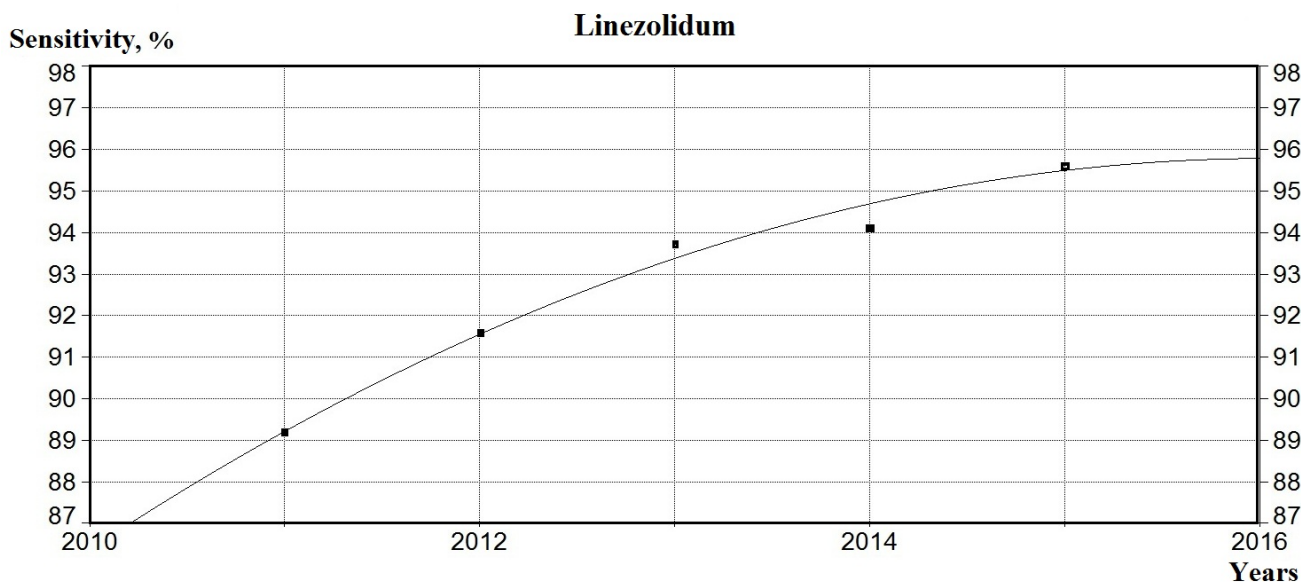
Fig. 6. Prognostic indexes of sensitivity of *S. aureus* to linezolid

The effectiveness of linezolid obviously is conditioned with the absence of decussate resistance with other antibiotic, whereas this antibiotic influence on the early stages of translation process in bacteria. In our research of sensitivity of *S. aureus* strains to linezolid, its effectiveness was found in 89 – 96 % of cases. Gradual increasing of quantity of sensitive *S. aureus* clinical strains with lineal tendency has been found for 2011 – 2015 years. It has proven the recovery of sensitivity of this pathogen to linezolid (formula 6; fig. 6).

Conclusions

1. The data of five years monitoring give the possibility to conduct analytical expression for prognostication of sensitivity to beta-lactam antibiotics, glycopeptides, and oxazolidinones in clinical strains of *S. aureus*.

2. Prognostic mathematical indexes demonstrate unfavorable dynamics of decreasing sensitivity to oxacillin, ceftriaxone, carbapenems (imipenem, meropenem) in clinical strains of *S. aureus*. The sensitivity of *Staphylococcus* to vancomycin decreases (92,5 %) and continues to be high to linezolid (96 %).

3. Prognostic criteria of *S. aureus* sensitivity to antibiotics point out at the difficulties of administration of effective antibiotic for prophylaxis and treatment of patients. Such situation postulates the necessity of use new methods and modern antimicrobial drugs for the prophylaxis and treatment of *Staphylococcus* infection in patients.

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