The Evolution of the Resistance of *Staphylococcus aureus* Found on Healthcare Workers Correlated with Local Consumption of Antibiotics

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Objective. Correlate the evolution of the resistance of *Staphylococcus aureus* collected from healthcare workers with the local consumption of antibiotics. Materian and Methods. Open prospective research.Study Site. General Reference Hospital with 200 beds in a 700,000 inhabitant region, in Ponta Grossa, Paraná, Brazil. Results.Two collections (samples) of *Staphylococcus aureus* isolates were obtained from healthcare-workers during an approximate four-year interval. Samples 1 (n= 200) and 2 (n= 270) had this bacterium in 63 (32%) and 90 (33%) of the patients, respectively. At the same time, the annual consumption of antibiotics in DDD/1,000 patient-days was determined. The variation of resistance was significantly smaller (m.s.d.=12.11) for gentamycin ($p<0.01$) and (m.s.d.=9.22) for Tobramycin ($p<0.05$). The correlation between variation in resistance and antibiotic consumption was not significant. Workers studied in the two samples showed a significant ($p<0.01$) frequency ($\chi^2=10.44$) for persistent nasal carriage and for non carriage. Methicillin resistant *Staphylococcus aureus* was found in 12 (6%) patients of sample 1 and 11 patients (4%) of sample 2. Conclusions. Stability of resistance allows us to maintain therapeutic outlines. The variation in bacterial resistance in the twice-sampled population (n=105) indicated the selection pressure of the hospital environment. The resistance that was found is representative of the hospital microbiota; this relationship represents a biological model, based on the healthcare-workers' interaction with colonizing bacteria and nosocomial infections. New studies could improve this model for other bacteria, to determine the tendency for resistance and help guide the antibiotic use.

Key Words: *Staphylococcus aureus* nasal carriage, health-care workers, resistance and antibiotic consumption.

Staphylococcus aureus was the predominant microorganism in several reports of nosocomial infections [1,2], being mainly isolated from surgical sites. Approximately 20 to 30% of healthcare workers bear this bacteria and could transmit it [3,4]. Infection outbreaks have been reported from critical units, including burn wards, nurseries, intensive care units (ICU) and in clinical and surgical patients; they have been found to be related to inadequate use of antibiotics, lack of handwashing, insufficient nursing care, and presence carriers among the staff [5,6]. Controlling antibiotic use can reduce the appearance and spread of resistant bacteria [7,8]. From the 1970s to the 1990s an alarming tendency towards resistance to many antibiotics was found in *Staphylococcus aureus* isolates [9]. Studies made in several countries have demonstrated variation in resistance to antibiotics that is related to prescription practices [10-12]. Two types of *Staphylococcus aureus* have been found in nosocomial environments: permanent and transitory. The former can be found on healthcare-workers and in the hospital environment. The latter can be found in infected patients and in carriers, who are in transitory contact with the hospital. The everyday relationship between healthcare workers and patients could allow a renewal in the strains of both types of contaminants. Antibiotic use can provoke selection of resistant strains, causing more serious infections, longer institutionalization periods and higher costs for the Health Care System. The healthcare workers inserted in this epidemic chain have great importance in the increasing resistance of contaminants, serving as a source of information for empirical prescription of antibiotics.

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Material and Methods

Study population. From March 11 to April 29, 1996, and from December 1, 1999 to January 15, 2000, we analyzed 200 and 270 nasal *swab* cultures, respectively, of healthy healthcare workers of Santa Casa de Misericórdia de Ponta Grossa (SCMPG). They had not used nasal antiseptics or antibiotics for at least three weeks before the collection. The workers selected for this research were in direct contact with patients and with other staff.

Nasal culture. The samples were obtained by rubbing moist swabs imbibed in sterile physiological saline solution in both nasal cavities of each patient's nose. They were quickly inoculated into Baird-Parker Egg Volk-Tellurite medium and

Manitol Salt Agar, which are both selective (Oxoid), by the draining technique, and they were incubated aerobically at 37°C during 24 h.

The *Staphylococcus aureus* strains were then tested for sensitivity to antibiotics, following the technique of Kirby and Bauer, recommended by NCCLS (National Committee for Clinical Laboratory Standards - USA) [13] using antibiogram disks.

Resistance level. The resistance level for each antibiotic was determined as the ratio between the number of resistant isolates and the total number of isolates, multiplied by 100.

Consuption of antibiotics and hospital occupation. The antibiotics consumed in the hospital between January 1996 and January 2000 were transformed into Defined Daily Dose (DDD), which corresponds to the quantity of antibiotics consumed by a patient in 24 h, as recommended by the Norwegian Medicinal Depots, modified according to World Health Organization (WHO) recommendations. After determining the hospitalar occupation in the same period, DDD was calculated for each 1,000 patient-days for each antimicrobial agent (Table 1).

Deocolonization. Healthcare-workers who were carriers of MRSA were decolonized with topical mupirocin, twice a day, for five days, with control cultures on the 7^{th} and 14^{th} days.

Statistical analysis . The percentages were transformed with the arc sine square root of "x" (x = percentage) and compared through the Tukey test. The χ^2 test was used to compare frequencies; and the exact Fisher test was used when the sample was very small [14].

Results

Among 200 workers of the first sample, 63 (31.5%) were positive for *Staphylococcus aureus*; while among 270 of the second sample, 90 (33.3%) were positive. There was no significant difference between these percentages. Based on the antibiogram, there was a variable degree of resistance (Table 2).

The relative resistance (in %) to the different antibiotics of the two samples was examined, and significant differences were found (minimal significant difference (m.s.d.) at $p = 0.05 = 9.22$ and m.s.d. at $p = 0.01 = 12.11$) between 1996 and 1999 for the antibiotic Gentamycins ($p < 0.01$) and for Tobramycin ($p < 0.05$).

The variation in the resistance of *Staphylococcus aureus* cultures from healthcare workers nasal swabs was compared to the variation of local consumption of antibiotics (Table 3); the correlation ($r = 0.089$) was not significant.

Among the 105 workers in the two samples, 54 were negative in samples 1 and 2, 17 were positive in sample 1 and negative in 2; 15 were negative in sample 1 and positive in 2; 19 were positive in both samples.

The independence between positivity/ negativity for *Staphylococcus aureus* in 1996 *versus* 1999 in the healthcare workers was significant at $p < 0.01$ ($\chi^2 = 10.44$), with a larger frequency than expected of double positives and double negatives.

Among the 105 healthcare workers researched in 1996 and 1999, 36 (34.2%) presented positive cultures for *Staphylococcus aureus* in 1996, and 34 (32.3%) in 1999. There was no significant difference between the two periods (m.s.d. at $p < 0.05 = 7.74$).

The antibiogram data indicated variations in resistance (Table 4), but this variation was not significant (m.s.d. = 13.42 at $p = 0.05$).

Also 12 cultures (6% of the total and 19% of the positive ones) of the first sample and 11 (4% of the total and 12.2% of the positive ones) of the second presented resistance to oxacillin. This makes them methicillin-resistant *Staphylococcus aureus* (MRSA). This difference was not significant (m.s.d. = 5.23 at $p = 0.05$).

Among the 105 workers, 19 gave positive cultures in both years; the antibiogram results are given in Table 5. There were significant differences in resistance only against Penicillin (m.s.d. at $p = 0.05 = 18.21$).

Discussion

The emergence of *Staphylococcus aureus* resistant to Vancomycin is the event with greatest impact on diseases caused by bacteria, since the development of antibiotics [15].

Resistance is associated with an increase in disease severity, along with increases in the period of institutionalization, long term sequels, high mortality and increasing treatment costs, including a need for alternative drugs [16].

Antibiotics should be preserved for the future. Their appropriate use could retard or prevent the emergence and spread of resistant bacteria [17].

Healthcare workers, who are nasal carriers, are an important source of *Staphylococcus aureus*. Almost 25% of these workers are stable nasal carriers, and 30% to 50% of them also possess the bacteria on their hands [18,19].

We observed stability in the evolution of resistance to the more frequently prescribed antibiotics for *Staphylococcus aureus* control, such as oxacillin, cefalotin, clindamycin, cotrimoxazol, and vancomycin, as well as chloramphenicol and amicacyn; while there was a decrease in the resistance to gentamycin and tobramycin. There was an increased tendency for resistance to ciprofloxacin and rifampicin. The resistance levels to ampicillin, erythromycin, penicillin and tetracycline have led to the abandonment of these drugs in therapeutics. It is well known that the abusive use of antibiotics promotes the emergence of bacterial resistance [20]. It is still being discussed, however, if decreases in the use of a determined

Table 1. Antibiotic consumption, measured as defined daily dose per 1000 patient days in Santa Casa de Misericórdia de Ponta Grossa hospital from 1996-1999

Antibiotic	1996	1997	1998	1999	Total
Amikacin	1,097.50	672.00	874.50	827.00	3,471.00
Ampicillin	769.67	468.00	328.33	332.25	1,898.25
Cefalotin	5,639.25	8,233.25	6,195.25	4,253.00	24,320.75
Cefatoxim	214.00	151.67	153.67	113.00	632.34
Ciprofloxacin	563.50	357.50	696.00	567.00	2,184.00
Clindamycin	14.00	0.00	53.75	308.25	376.00
Chloramphenicol	358.50	264.75	285.25	122.50	1,031.00
Cotrimoxazol	1,141.50	1,568.00	1,165.50	944.50	4,819.50
Erythromycin	9.75	24.50	42.75	30.50	107.50
Gentamycin	2,797.00	3,109.33	2,785.67	1,917.67	10,609.67
Oxacillin	74.25	246.75	109.25	1,050.00	1,480.25
Penicillin	2,703.75	1,786.50	1,168.25	1,305.75	6,964.25
Rifampicin	0.00	0.00	8,00	46.00	54.00
Tetracycline	0.00	0.00	0.00	0.00	0.00
Tobramycin	97.00	8.33	35.67	29.33	170.33
Vancomycin	61.00	239.75	576.25	394.00	1,271.00
Total	15,540.67	17,130.33	14,478.09	12,240.75	59,389.84

Table 2. Frequency of resistance to antibiotics in the two samples of *Staphylococcus aureus* isolated from healthcare workers in 1996 (sample 1) and 1999 (sample 2)

Antibiotic	Sample 1		Sample 2	
	N=63	%	N=90	%
Amikacin	8	12.7	8	8.8
Ampicillin	57	90.4	83	92.2
Cefalotin	12	19.0	11	12.2
Cefotaxim	13	20.6	11	12.2
Ciprofloxacin	8	12.7	16	17.7
Clindamycin	14	22.2	14	15.5
Chloramphenicol	18	28.5	16	17.7
Cotrimazin	15	23.8	13	14.4
Erythromycin	28	44.8	47	52.2
Gentamycin	19	30.1	11	12.2
Oxacillin	12	19.0	11	12.2
Penicillin	60	95.2	88	97.7
Rifampicin	4	6.3	6	6.6
Tetracycline	20	31.7	30	33.3
Tobramycin	24	38.0	18	20.0
Vancomycin	0	0	0	0

antibiotic are accompanied by reduction in resistance [21]. Studies show that bacterial resistance parallels the use of antimicrobials. The increase in the fluoroquinolone and cephalosporin use leads to higher resistance to such drugs [22-26], while the increase in the susceptibility of important nosocomial pathogens to the aminoglicosydes, in response to a decrease in their use in the last years, has been making it possible to return to the old antibiotics, which are less toxic and wide spectrum [21,22].

The resistance found in our samples, when compared to the resistance of *Staphylococcus aureus* in other hospitals, shows a shared trend of increase against ciprofloxacin and stabilization and decrease of resistance against the aminoglicosydes, especially gentamycin.

A fundamental condition for the emergence of resistance is exposure to the antimicrobial agent to which the resistance is addressed [20]. When comparing the variation of resistance with antibiotic consumption in the period, it was not

Table 3. Comparison between variations in antibiotic consumption and resistance of *Staphylococcus aureus*

Antibiotic	Consumption			Resistance		
	1996	1999	Variation	1996	1999	Variation
Amikacin	1,097.50	827.00	-270.50	12.7%	8.8%	-3.9
Ampicillin	769.67	332.25	-437.42	90.4%	92.2%	1.8
Cefalotin	5,639.25	4,253.00	-1,386.25	19.0%	14.2%	-4.8
Cefotaxim	214.00	113.00	-101.00	20.6%	12.2%	-8.4
Ciprofloxacin	563.50	567.00	3.50	12.7%	17.7%	5.0
Clindamicin	14.00	308.25	294.25	22.2%	15.5%	-6.7
Chloramphenicol	358.50	122.50	-236.00	28.5%	17.7%	-10.8
Cotrimoxazol	1,141.50	944.50	-197.00	23.8%	14.4%	-9.4
Erythromycin	9.75	30.50	20.75	44.8%	52.2%	7.4
Gentamycin	2,797.00	1,917.67	-879.33	30.1%	12.2%	-17.9
Oxacillin	74.25	1,050.00	975.75	19.0%	12.2%	-6.8
Penicillin	2,703.75	1,305.75	-1,398.00	95.2%	97.7%	2.5
Rifampicin	0	46.00	46.00	6.3%	6.6%	0.3
Tetracicline	0	0	0	31.7%	33.3%	1.6
Tobramycin	97.00	29.33	-67.67	38.0%	20.0%	-18.0
Vancomycin	61.00	394.00	333.00	0%	0%	0

Table 4. Frequency of resistance to antibiotics of *Staphylococcus aureus* isolates taken from healthcare workers in 1996 (sample 1) and 1999 (sample 2)

Antibiotic	Sample 1		Sample 2	
	N=36	%	N=34	%
Amikacin	5	13.8	4	11.7
Ampicillin	32	88.8	33	97.0
Cefalotin	5	13.8	6	17.6
Cefotaxim	6	16.6	6	17.6
Ciprofloxacin	4	11.1	10	29.4
Clindamicin	6	16.6	7	20.5
Chloramphenicol	09	25.0	8	23.5
Cotrimoxazol	6	16.6	7	20.5
Erythromycin	14	38.8	21	61.7
Gentamycin	11	30.5	5	14.7
Oxacillin	05	13.8	6	17.6
Penicillin	33	91.6	34	100.0
Rifampicin	2	5.5	3	8.8
Tetracycline	13	36.1	14	41.1
Tobramycin	13	36.1	7	20.5
Vancomycin	0	0	0	0

significant, though there was a certain tendency in some drugs.

In our study, the decrease in consumption of amikacin, cefalotin, cefotaxim, chloramphenicol, cotrimoxazol, gentamycin and tobramycin was accompanied by a decrease in the resistance to these antibiotics. The increased consumption of ciprofloxacin, erythromycin and rifampicin was accompanied by increased resistance to these drugs.

Although a decrease in the consumption of ampicillin, penicillin and tetracycline was observed, there was an increase in resistance to these drugs. The presence of residues of antibiotics used in agriculture and in livestock, as well as the bacterial selection due to such use could be responsible for the presence of resistant microorganisms in environments where those drugs are not used for human therapeutics [27,28].

There was increase in the clindamycin and oxacillin consumption, along with a decrease in resistance to these drugs. All the strains were sensitive to vancomycin, in spite of increased consumption of this antibiotic.

The audit of the use of antibiotics in SCMPG has been guiding the clinical staff in the use of the most appropriate therapeutics.

Table 5. Frequency of resistance to antibiotics of *Staphylococcus aureus* isolates collected from healthcare workers in 1996 (sample 1) and 1999 (sample 2)

Antibiotic	Sample 1		Sample 2	
	N=19	%	N=19	%
Amikacin	2	10.5	3	15.7
Ampicillin	18	94.7	19	100.0
Cefalotin	3	15.7	3	15.7
Cefotaxim	3	15.7	3	15.7
Ciprofloxacin	2	10.5	5	26.3
Clindamycin	2	10.5	4	21.0
Chloramphenicol	6	31.5	4	21.0
Cotrimoxazol	3	15.7	3	15.7
Erythromycin	7	36.8	10	52.6
Gentamycin	5	26.3	3	15.7
Oxacillin	3	15.7	3	15.7
Penicillin	17	89.4	19	100.0
Rifampicin	01	5.2	01	5.2
Tetracycline	8	42.1	8	42.1
Tobramycin	7	36.8	3	15.7
Vancomycin	0	0	0	0

The lowered aminoglicosyde consumption in the last years was due to the emergence of the 3rd generation cephalosporins of and of the quinolones, less toxic and of wider spectrum; though we expect that they should induce increased resistance.

The increase in the consumption of oxacillin with consequent decrease in the use of cephalotin was due to the orientation of the Hospital Infection Control Commission (CCIH) for treatment of infections due to MSSA.

Although we cannot quantify the threshold of resistance of *Staphylococcus aureus* to the antibiotics tested in the SCMPG, we could consider that the variation of the resistance of this population (n=105) is due solely to the selection pressure in the hospital environment on the bacteria.

Our efforts to revert resistance requires new knowledge regarding the consequences of the use of antibiotics; we cannot concern ourselves exclusively with curing the bacterial disease, without regard to how we favor resistant strains [28]. Besides selection pressure, new strains can be introduced into a nosocomial area through patients [29,30] or by healthcare-workers [5,31-33].

The extensive use of antibiotics in the hospital also results in their presence in the environment. Patients and healthcare workers are indirectly exposed to the action of the antimicrobials that act on endogenous microbiota, selecting resistant bacteria that are dispersed through individual contact [34].

The presence of methicillin-resistant *Staphylococcus aureus* (MRSA) in both samples, 6% in 1996 and 4% in 1999, did not vary significantly; different from what has been reported by most published studies [24,35]. It is clear that these bacteria are endemic.

Decolonization of MRSA carriers in institutions is a strategy to reduce human bacterial storage in patients and healthcare workers [36].

When determining the resistance of bacteria that colonize healthcare –workers, we also sample a larger reservoir of bacteria with potential to cause infection. They are representative of the endemic microbiota, which can be renovated in daily nosocomial activities [18]. Although at the moment they are not causing infection, they have potential for hospital resistance. It is necessary to prevent and prepare for the emergence and evolution of resistant populations of bacteria [37,38].

While orientation concerning the use of prophylactic antibiotics or of empirical therapeutics based on the resistance of the nosocomial infections (transitory bacteria) could vary month to month, the data obtained from healthcare workers are more stable. They allow us to develop a more durable policy of orientation for the consumption of antibiotics.

The study of such relationships is a biological model based on the interaction of healthcare workers with colonizing bacteria and with hospital infections. The carrier workers act not only as a source of possible infection, but also of information about treatment.

Additional studies using this model should be involve periodic sampling, and they should include other bacteria and allow analyses of tendencies, to guide the consumption of antibiotics in order to improve their usefulness.

References

1. Panlilio A., Culver D.H., Gaynes R.P., et al. Methicillin-resistant *Staphylococcus aureus* in U.S. hospitals,1975-1991. Infect Control Hosp Epidemiol **1992**;13:582-6.

2. PROAHSA. Boletim de indicadores. Programa de Estudos Avançados em Administração Hospitalar e de Sistemas de Saúde do HC da FMUSP e da EAESP da Fundação Getúlio Vargas, v.8, p.1-4, **2000**.
3. Geubbels E.L.P.E., Groota J.M., Berg J.M.J.V.D., Boer A.S. An operating surveillance system of surgical-site infections in the Netherlands: results of the PREZIES national surveillance network. Infect Control Hosp Epidemiol **2000**;21:311-8.
4. Boyce J.M. Preventing Staphylococcal infections by eradicating nasal carriage of *Staphylococcus aureus*: Proceeding with caution. Infect Control Hosp Epidemiol **1996**;17:775-9.
5. Fascia P., Martin I., Mallaval F.O., et al. Implication potentielle d'etudiants infirmiers dans la transmission de *Staphylococcus aureus* resistant 'a la méthicillin e lors d'une épidémie nosocomiale. Pathol Biol (Paris) **2003**;51(8-9):479-82.
6. Sheretz R.J., Reagan D.R., Hampton K.D., et al. A cloud adult: The *Staphylococcus aureus*-virus interaction revisited. Ann Intern Med **1996**;(124):539-47.
7. Goldeman D.A., Weinstein R.A., Wenzel R.P, et al. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. JAMA **1996**;275:234-40.
8. Kampf G., Adena S., Ruden H., Weist K. Inducibility and potential role of Mec A-gene-positive oxacillin-susceptible *Staphylococcus aureus* from colonized healthcare workers as a source for nosocomial infections. J Hosp Infect **2003**;54(2):124-9.
9. Nichols R.L. Postoperative Infections in the age of drug-resistant Gram-positive bacteria. Am J Med **1998**;104(5 A):11s-16s.
10. Fridkin S.K., Steward C.D., Edwards J.R., et al. Surveillance of antimicrobial use and antimicrobial resistance in United States hospitals: Project ICARE Phase 2. Clin Infect Dis **1999**;29:245-52.
11. Monnet D.L., Archibald L.K., Phillips L. et al. Antimicrobial use and resistance in eight US hospitals: Complexities of Analysis and modeling. Infect Control Hosp Epidemiol **1998**;19:388-94.
12. Norazah A., Lim V.K., Munirah S.N., Kamel A.G. *Staphylococcus aureus* carriagein selected communities and their antibiotic susceptibility patterns Med J Malaysia **2003**;58(2):255-61.
13. NNIS - National Nosocomial Infection Surveillance Report. Data Summary from October 1986- April 1997. Atlanta GA: Hospital Infections Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Public Health Service, U.S. Department of Health and Human Services, **1997**:1-24.
14. Gomes S.P. Curso de estatística experimental. 13ª ed. São Paulo: Nobel, **1990**, 468p.
15. Edmond M.B., Wenzel R.P., Pasculle A.W. Vancomycin-resistant *Staphylococcus aureus*: perspectives on measures needed for control. Ann Intern Med **1996**;124:329-34.
16. Cohen F.L., Tartasky D. State of the Science – microbial resistance to drug therapy: a review. Am J Infect Control **1997**;25:51-64.
17. Isturiz R.E., Carbon C. Antibiotic use in developing countries. Infect Control Hosp Epidemiol **2000**;21:394-7.
18. Cespedes C., Miller M., Quagliarello B., Vavagiakis P. et al. Differences between *Staphilococcus aureus* isolates from medical and non medical hospital personnel. J Clin Microbiol **2002**;40(7):2594-7.
19. Wenzel R.P. Healthcare workers and the incidence of nosocomial infection: can treatment of one influence the other?- A brief review. J Chemother **1994**;(6)suppl:s33-s40.
20. McGowan Jr. J.E. Strategies for study of the role of cycling on antimicrobial use and resistance. Infect Control Hosp Epidemiol **2000**;21(suppl.):s36-s43.
21. Tambyah P.A., Kumarasinghe G., Chow C.et al. Antibiotic use and antimicrobial resistance in nosocomial pathogens: longitudinal surveillance data suggests that we can go back to previously popular but currently under-used regimes. Infect Control Hosp Epidemiol **2000**;21:92.
22. Cercenado E., Sanchez-Carrillo C., Alcala L., Bouza E. Grupo de trabajo para el estudio de Estafilococos. Rev Clin Esp **1997**;197:(Suppl)s212-s8.
23. Chambers H.F. Treatment of infection and colonization caused by methicillin-resistant *Staphilococcus aureus*. Infect Control Hosp Epidemiol **1991**;12:29-35.
24. Mulligan M.E., Murray-Leisure K.A., Ribner B.S., et al. Methicillin-resistant *Staphylococcus aureus*: a consensus review of the microbiology, pathogenesis, and epidemiology with implications for prevention and management. Am J Med **1993**;94:313-28.
25. Rodrigues J.N., Amaral J.L.G., Lene I.L., et al. Molecular epidemiology and antimicrobial susceptibility testing – testing of quinolone-resistant *Staphylococcus aureus* strains isolated in Brazil. Diagn Microbiol Infect Dis **1993**;16:9-16.
26. Venezia R.A., Damaracki B.E., Evans A.M., et al. Fluoroquinolones enhance the expression of high level Oxacillin resistant *Staphylococcus aureus*. Infect Control Hosp Epidemiol **2000**;21:124.
27. Hawkey P.M. The origins and molecular basis of antibiotic resistance. BMJ **1998**;317:657-60.
28. Levy S.B. The Challenge of antibiotics resistance. Available in: <http://www.sciam.com/1998/0398issue/0398levy.htmL>. Acessed on: 14 Aug. **2000**.
29. Goosens H., Sprenger M.J.W. Community acquired infections and bacterial resistance. BMJ **1998**;317:654-7.
30. Lucet J.C., Chevret S., Durand-Zaleski I.,et al. Prevalence and risk factors for carriage of methicillin-resistant *Staphylococcus aureus* at admission to the intensive care unit: results of a multicenter study. Arch Intern Med **2003**;163(2):181-8.
31. Cookson B., Peters B., Webster M., et al. Staff carriage of epidemic Methicillin-resistant *Staphylococcus aureus*. J Clin Microbiol **1989**;27:1471-76.
32. McGowan Jr. J.E. Drug resistance and nosocomial infections: epidemiology and prevention strategies. In: Finch R.G., Williams R.J. (eds.) Balliere's Clinical Infectious Diseases. London: Balliere Tindall, **1999**;5:177-92.
33. Sader H.S., Pignatari A.C., Hollis R.J., et al. Oxacillin and quinolone-resistant *Staphylococcus aureus* in São Paulo, Brazil: a multicenter molecular epidemiology study. Infect Control Hosp Epidemiol **1993**;14:260-4.
34. McGowan Jr. J.E. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. Rev Infect Dis **1983**;5:1033-48.
35. Goetz A., Poseyk, Fleming J., et al. Methicillin-resistant *Staphylococcus aureus* in the community: a hospital based study. Infect. Control Hosp. Epidemiol. **1999**;20:689-91.
36. Strausbaugh L.J., Jacobson C., Sewell, D.L., et al. Antimicrobial therapy for methicillin-resistant *Staphylococcus aureus* colonization in residents and staff of a veterans affairs nursing home care unit. Infect Control Hosp Epidemiol **1992**;13:151-9.
37. Armostrong G.L., Conn L.A., Pinner R.W. Trends in infectious disease mortality in the United States during the 20th century. JAMA **1999**;281:61-6.
38. Baquero F., Negri M.C., Morosini M.I., Blazquez J. Antibiotic-selective environments. Clin Infect Dis **1998**; 27:(suppl) s5-s11.