

ANALES MEDICOS

Volumen **48**
Volume

Número **1**
Number

Enero-Marzo **2003**
January-March

Artículo:

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Antibiotic resistance, public health problem

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ABSTRACT

Antibiotic resistance has become a major clinical and public health problem within the lifetime of most people living today. Confronted by increasing amounts of antibiotics over the past 50 years, bacteria have responded to the deluge with the propagation of progeny no longer susceptible to them. While it is clear that antibiotics are pivotal in the selection of bacterial resistance, the spread of resistance genes and of resistant bacteria also contributes to the problem. Selection of resistant forms can occur during or after antimicrobial treatment, antibiotic residues can be found in the environment for long periods of time after treatment. Beside antibiotics, there is the mounting use of other agents aimed at destroying bacteria, namely the surface antibacterials now available in many household products. These too enter the environment. The stage is thus set for an altered microbial ecology, not only in terms of resistant versus susceptible bacteria, but also in terms of the kinds of microorganisms surviving.

Key words: Antibiotics, public health problem, resistant bacteria, mutation rate.

RESUMEN

La resistencia a antibióticos representa uno de los principales problemas de la población en lo referente a salud pública y a la práctica clínica. Esto es debido al incesante incremento en el uso de antibióticos durante los últimos 50 años, además de que las bacterias resistentes a los antibióticos se han propagado de forma abrumadora. Es importante señalar que hace tiempo los antibióticos participan activamente en la selección de bacterias resistentes sin olvidar que la velocidad con la que aparecen genes de resistencia también contribuyen a dicho problema. La selección de microorganismos resistentes puede ocurrir durante o después de tratamientos con antimicrobianos, los residuos de antibióticos pueden establecerse en el ambiente durante periodos de tiempo considerables posterior al tratamiento. De forma paralela al uso de los antibióticos se presenta el empleo de otros agentes que se proponen para eliminar bacterias, como es el uso de bactericidas ahora disponibles en algunos productos domésticos. Estos últimos también tienen la capacidad de permanecer en el ambiente, participando en la dinámica de la ecología microbiana, en lo referente a resistencia contra la susceptibilidad bacteriana y en la supervivencia de diversos grupos de microorganismos.

Palabras clave: Antibióticos, problema de salud pública, resistencia bacteriana, proporción de mutación.

MECHANISMS OF ANTIBIOTIC RESISTANCE

The many mechanisms that bacteria exhibit to protect themselves from antibiotic can be classified into four basic types. Antibiotic modification is the best known: the resistant bacteria retain the same sensitive target as antibiotic sensitive strain, but the anti-

biotic is prevented from reaching it. This happens, for example, with β lactamases—the β lactamases enzymatically cleaves the four membered β lactam ring, rendering the antibiotic inactive. Most β lactamases act to some degree against both penicillins and cephalosporins, others are more specific—namely, cephalosporinases, for example AmpC enzyme found in *Enterobacter* spp, or penicillinases for example *Staphylococcus aureus* penicillinase. β lactamases are widespread among many bacterial species (both Gram positive and Gram negative) and exhibit varying degrees of inhibition by β lactamase inhibitors, such as clavulanic acid.¹

Some antibiotic resistant bacteria protect the target of antibiotic action by preventing the antibiotic from entering the cell or pumping it out faster than it

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Recibido para publicación: 04/09/02. Aceptado para publicación: 18/09/02.

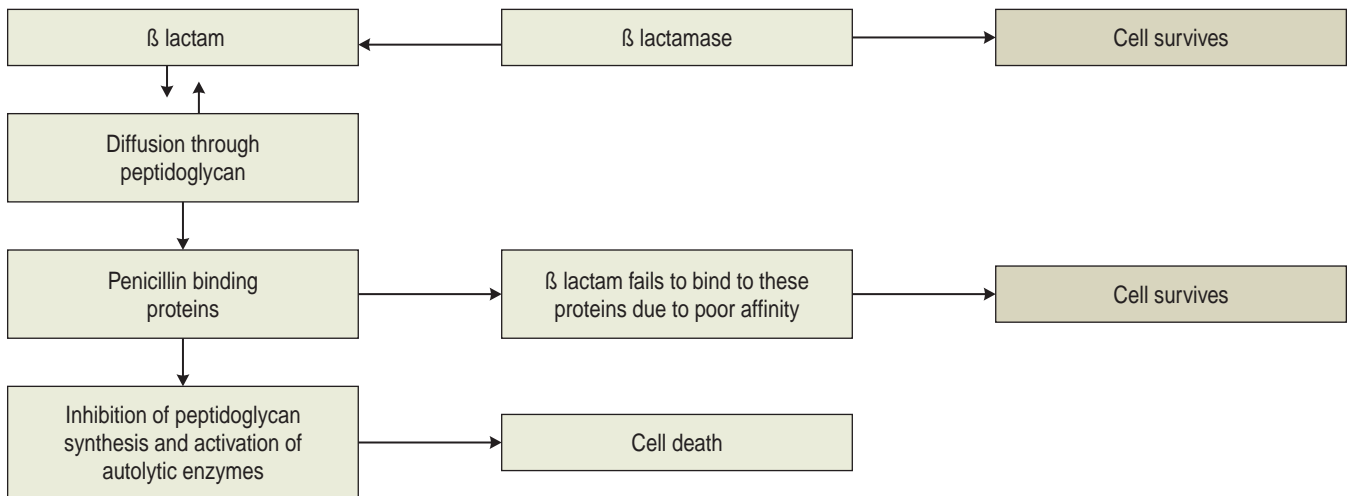
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can flow in (rather like a bilge pump in a boat). β lactam antibiotic in Gram negative bacteria gain access to the cell that depends on the antibiotic, through a water filled hollow membrane protein know as a porin (Figure 1). In the case of imipenem resistant *Pseudomonas aeruginosa*, lack of the specific D2 porin confers resistance, as imipenem cannot penetrate the cell. This mechanism is also seen with low level resistance to fluoroquinolones and aminoglycosides. Increased efflux via an energy-requiring transport pump is a well recognized mechanism for resistance to tetracyclines and is encoded

by a wide range of related genes, such as tet(A), that have become distributed in the enterobacteriaceae.^{2,3}

Alterations in the primary site of action may mean that the antibiotic penetrates the cell and reaches the target site but is unable to inhibit the activity of the target because of structural changes in the molecule. Enterococci are regarded as being inherently resistant to cephalosporins because the enzymes responsible for cell wall synthesis (production of the polymer peptidoglycan) know as penicillin binding proteins have a low affinity for them and therefore are not inhibited. Most strains of *Streptococcus pneumo-*

Gram positive bacteria



Gram negative bacteria

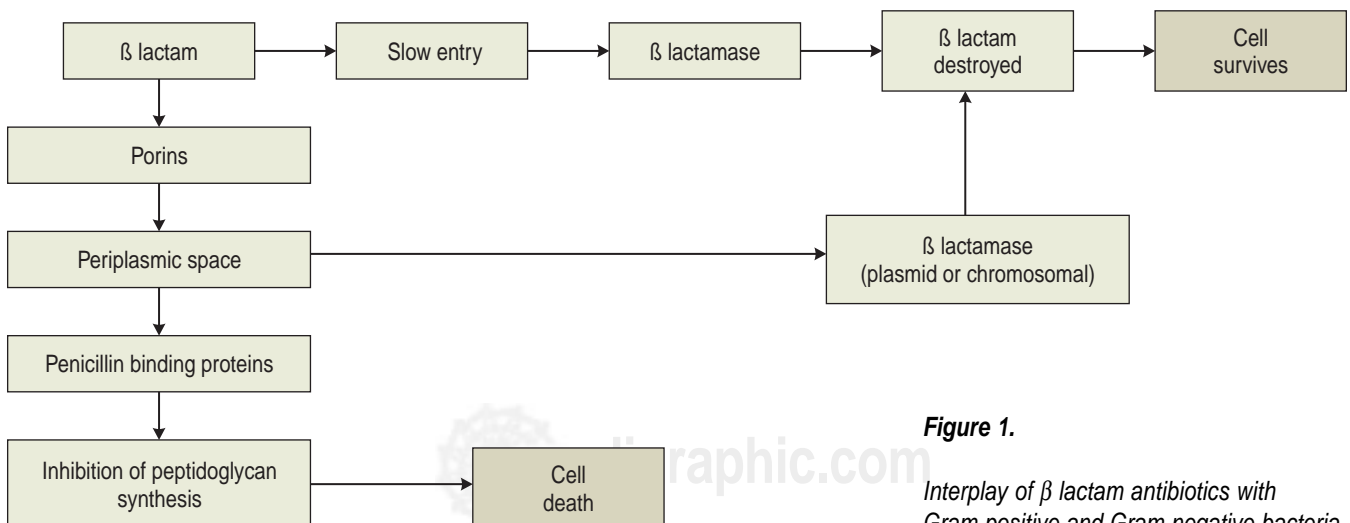


Figure 1.

Interplay of β lactam antibiotics with Gram positive and Gram negative bacteria.

niae are highly susceptible to both penicillins and cephalosporins but can acquire DNA from other bacteria, which changes the enzyme so that they develop a low affinity for penicillins.⁴ The altered enzyme still synthesises peptidoglycan but in now has a different structure. Mutants of *Streptococcus pyogenes* that are resistant to penicillin and express altered in the laboratory, but they have not been seen in patients, possibly because the cell wall can no longer bind the antiphagocytic M protein.⁵

The final mechanism by which bacteria may protect themselves from antibiotic is the production of an alternative target, usually an enzyme, that is resistant to inhibition by the antibiotic while continuing to produce the original sensitive target. This allows bacteria to survive in the face of selection: the alternative enzyme "bypasses" the effect of the antibiotic. The best known example of this mechanism is probably the alternative penicillin binding protein (PBP2a), which is produced in addition to the normal penicillin binding proteins by methicillin resistant *Staphylococcus aureus* (MRSA). The protein is encoded by the *mecA* gene, and because PBP2a is not inhibited by antibiotics such as flucloxacillin the cell continues to synthesise peptidoglycan and hence has a structurally sound cell wall.⁶ The appearance in 1987 of vancomycin resistant enterococci has aroused much interest because the genes involved can be transferred to *Staphylococcus aureus*, and this can thus theoretically result in a vancomycin resistant MRSA. The mechanism also represents a variant of the alternative target mechanism of resistance.⁷ In enterococci sensitive to vancomycin the normal target of vancomycin is a cell wall precursor that contains a pentapeptide that has a D-alanine-D-alanine terminus, to which the vancomycin binds, preventing further cell wall synthesis. If an enterococcus acquires the *vanA* gene cluster, however, it can now make an alternative cell wall precursor ending in D-alanine-D-lactose, to which vancomycin does not bind.

THE RISE IN ANTIMICROBIAL RESISTANCE

Antimicrobial resistance has also stimulates the search for new potent antimicrobials, altered but effective dosing regimens, and resistance control measures, such as the prudent use, optimal infection con-

trol practice, and vaccines to reduce colonization and subsequent infection.⁸ Among pathogens causing hospital infections, Gram positive cocci have become predominant over the past two decades. This trend is related to these pathogens capacity for accumulating antibiotic resistance determinants.⁹ A notable example is that of methicillin resistant strains of *Staphylococcus aureus* (MRSA), which emerged in the 1970's and increased in frequency as hospital pathogens during the 1980's in many countries with the notable exception of the Scandinavian countries and Netherlands.^{10,11} Countries with lower incidence of MRSA infections tend to be more restrictive in antibiotic use, to apply strict infection control measures, and to have better ratios of nurses to patients in their healthcare institutions. The rise in MRSA infections was initially associated with epidemics in large teaching hospitals, later spreading to the general hospital and nursing homes. Control strategies, such as contact isolation precaution and carrier decolonization with topical antimicrobials, met with varying degrees of success but seemed at least to slow down transmission.^{12,13}

Enterococci, commensal inhabitants of the intestinal and genital tracts, are rising in prominence as hospital pathogens.¹⁴ This rise is related to their natural resistance to most commonly used antibiotics and their capacity to acquire resistance to other antibiotics either by mutation (penicillin) or by transfer of resistance genes on plasmids and transposons (aminoglycosides and glycopeptides).^{10,14}

Multiple antibiotic resistance to useful classes of antibiotic, including the penicillins, cephalosporins, aminoglycosides and fluoroquinolones, has gradually increased among a number of Gram negative hospital pathogens, especially *Klebsiella pneumoniae*.^{14,15} *Enterobacter* spp,^{16,17} *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.^{18,19} Epidemic and endemic infections caused by these multiple resistant strain followed intense antibiotic use in many hospital, particularly in intensive care units.²⁰

RESISTANCE GENES AND MUTATION RATE

Antibiotic resistance can be achieved by horizontal acquisition of resistance genes, carried by transposons or plasmids), by recombination of foreign

DNA into the chromosome, or by mutation in different chromosomal loci. In studies of molecular evolutionary biology the term mutation rate is applied to estimations of the rate of mutation per nucleotide, per locus or eventually for the whole genome, and selective favorable, unfavorable, or neutral mutations are considered. Differing with this concept, the frequency of mutation measures all the mutants present in a given population, irrespective of whether the mutation events occurred early or late during the growth of the populations. In this respect, the frequency of mutants is a cross section of the bacterial population at a given time and reflects not only the mutation rate but also the history of the population before selection is applied.^{21,22}

In the case of antibiotic resistance, the mutation rate is frequently defined as the *in vitro* frequency at which detectable mutants arise in a bacterial population in the presence of a given antibiotic concentration.²¹

The methods for distinguishing the value of the observed frequency of mutants from the real mutation rate are not easy to apply and fluctuation test for analysis of the presence of jackpots of preexisting mutants in the tested populations have been developed.^{23,24} In the case of antibiotic resistance, the problem is complicated by the fact that the phenotype does not always reflect the same genotypes in all selected mutants, because mutations in different genes can produce similar antibiotic resistance phenotypes. As an example, when a quinolone resistance mutation rate is determined, this rate is actually the result of the combination of the mutation rate of the genes that encode the synthesis of GyrA, GyrB, ParA, ParC and several different multidrug resistance (MDR) systems.^{25,26} In this respect, the calculated "phenotypic" mutation rate is the result of several different "genotypic" mutation events. In fact, mutations in different loci produce different changes in MICs, and stable maintenance of heterogeneous antibiotic resistance expression classes in bacterial populations is a well know phenomenon.²⁷

Mutation rates can largely change for a given antibiotic depending on its concentration during selection.²⁸ Physiological conditions such as the availability of a given carbon source²⁹ or, in general, bacterial stress^{30,31} may regulate the mutation rate in bacteria. Furthermore, the existence of mutations that produce

mutator phenotypes in bacteria^{32,33} and the capability of some antibiotics to increase mutability greatly complicate studies of the effects of population dynamics on the emergence of antibiotic resistant mutants in bacteria. These element of variability severely challenge the possibility of predicting the real mutation rate just by simple experimental procedures like those frequently used in laboratory experiments.^{34,35}

DEVELOPMENT OF RESISTANCE BY INTERSPECIES RECOMBINATION

It is known from clinical trials that about 4% of infecting microorganisms (occurring in 5.6% of all infections treated) become resistant upon therapy.³⁶ There is also a correlation between the amount of antibiotics used and the level of resistance. Clones of such penicillin-resistant *Streptococcus pneumoniae* have spread locally and internationally under selective pressure.³⁷⁻³⁹

The rapid increase in resistant strains of bacterial species in the normal flora is not as commonly acknowledged, but there is increasing evidence that the normal flora represents a pool for selection of resistance genes, which may disseminate to other species and genera by horizontal transfer by conjugation, transduction or transformation.^{40,41}

The normal flora of mouth and pharynx is exposed to antibiotic when penicillins and other oral antibiotic are swallowed and, together with excretion of antibiotics by salivary glands, suppresses the viridans group of streptococci and other components of the normal flora.^{42,43} When bacteria are lysed by antibiotics such as penicillins, their DNA is released, which may promote horizontal gene transfer by transformation. Some pneumococci have become resistant to penicillin because of alterations in penicillin-binding protein 2 (PBP2), leading to decreased affinity for penicillins. There is now compelling evidence that these pneumococcal clones originated by importation of divergent regions in the PBP genes so called mosaic genes that originated from *Streptococcus mitis* and other oral streptococci. Similar mechanisms have been found in penicillin-resistant *Neisseria meningitidis* and *Neisseria gonorrhoeae* where the resistance genes have been derived from *Neisseria flavescens* and *Neisseria cinerea*.⁴⁴

The normal flora of the intestine is heavily exposed to incompletely absorbed oral antibiotics and to antibiotics excreted in the bile. These antibiotics suppress the normal flora and lead to development of resistance and superinfection.⁴⁵

S. epidermidis and other bacteria in the normal skin flora are exposed to antibiotics that are used for topical treatment. Also important is the impact on the normal skin flora of antibiotics excreted into the sweat. This has been shown to lead to rapid and prolonged colonization of the skin of volunteers with multiresistant *S. epidermidis*.^{46,47} This is likely to contribute to the widespread occurrence of multiresistant *S. epidermidis* in hospitals, which is associated with the amount of antibiotics used. Susceptibility testing is recommended to identify possible changes in antibiotic resistance to streptococci⁴⁸⁻⁵⁰

Application of antibiotics over the past 50 years has resulted in an unremitting increase in the numbers of commensal and pathogenic bacteria that are resistant to antimicrobial compounds. Although the increases in the background levels of resistance do not threaten control of these organisms, the result show that bacteria, even those not regularly or directly subjected to antibiotic challenge, have changed in response to increases in the application of antibiotics over the past several decades.

REFERENCES

- Livermore DM. β -lactamases in laboratory and clinical resistance. *Clin Microbiol Rev* 1995; 8: 557-584.
- Barriga AG, Rojas ML, Peredo LVM. Actualidades en los patrones de resistencia a los antimicrobianos. *Rev Mex Patol Clin* 2001; 48: 65-69.
- Chopra J, Hawkey PM, Hinton M. Tetracyclines, molecular and clinical aspects. *J Antimicrob Chemother* 1992; 29: 247-277.
- Tomasz A, Munoz R. β -lactam antibiotic resistance in Gram positive bacteria pathogens of the upper respiratory tract: a brief overview of mechanisms. *Microbiol Drug Resistance* 1995; 1: 103-109.
- Garcia-Bustos J, Tomasz A. A biological price of antibiotic resistance: major changes in the peptidoglycan structure of penicillin-resistant pneumococci. *Proc Natl Acad Sci USA* 1990; 87: 5415-5419.
- Michel M, Gutmann L. Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: therapeutic realities and possibilities. *Lancet* 1997; 349: 1901-1906.
- Leclercq R, Courvalin P. Resistance to glycopeptides in enterococci. *Clin Infect Dis* 1997; 24: 545-556.
- Craig WA. Temas del futuro de la resistencia antimicrobiana. *Enf Infecc Micro* 2000; 20: 172-177.
- Levy SB. Factors impacting on the problem of antibiotic resistance. *J Antimicrob Chemother* 2002; 49: 25-30.
- Cohen ML. Epidemiology of drug resistance: implications for a post-antimicrobial era. *Science* 1992; 257: 1050-1055.
- Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoine MH et al. The prevalence of nosocomial infection in intensive care units in Europe. *JAMA* 1995; 274: 639-644.
- Vandenbroucke-Grauls C. Management of methicillin-resistant *Staphylococcus aureus* in the Netherlands. *Rev Med Microbiol* 1998; 9: 109-116.
- Mulligan ME, Murray-Leisure KA, Ribner BS, Standiford HC, John JF, Korvick JA 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: 313-328.
- Gold HS, Moellering RC. Antimicrobial-drug resistance. *N Engl J Med* 1996; 335: 1445-1453.
- Livermore DM, Yuan M. Antibiotic resistance and production of extended-spectrum β -lactamases amongst *Klebsiella spp* from intensive care units in Europe. *J Antimicrob Chemother* 1996; 38: 409-424.
- Chow JW, Fine MJ, Shlaes DM, Quinn JP, Hooper DC, Johnson MP et al. Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med* 1991; 115: 585-590.
- De Cheldre Y, Maes N, Rost F, De Ryck R, Clevenbergh P, Vincent JL et al. Molecular epidemiology of an outbreak of multidrug-resistant *Enterobacter aerogenes* infections and *in vivo* emergence of imipenem resistance. *J Clin Microbiol* 1997; 35: 152-160.
- Towner KJ. Clinical importance and antibiotic resistance of *Acinetobacter spp*. *J Med Microbiol* 1997; 46: 721-746.
- Struelens MJ, Carlier E, Maes N, Serruys E, Quint WGV, van Belkum A. Nosocomial colonization and infection with multiresistant *Acinetobacter baumannii*: Outbreak delineation using DNA macrorestriction analysis and PCR-fingerprinting. *J Hosp Infect* 1993; 25: 15-32.
- McGowan JE. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. *J Infect Dis* 1983; 5: 1033-1048.
- Davies JE. Origins, acquisition and dissemination of antibiotic resistance determinants. *Ciba Found Symp* 1997; 207: 15-27.
- Fluit AdC, Visser MR, Schmitz FJ. Molecular detection of antimicrobial resistance. *Clin Microbiol Rev* 2001; 14: 836-871.
- Lederberg J, Lederberg EM. Replica plating and indirect selection of bacterial mutants. *J Bacteriol* 1952; 63: 399-406.
- Luria SE, Delbruck M. Mutations of bacteria from virus sensitivity to virus resistance. *Genetics* 1943; 28: 491-511
- Hopper DC. Mechanisms of fluoroquinolone resistance. *Drug Resis Updates* 1999; 2: 38-55.
- Martinez JL, Alonso A, Gomez-Gomez JM, Baquero F. Quinolone resistance by mutations in chromosomal gyrase genes. Just the tip of the iceberg? *J Antimicrob Chemother* 1998; 42: 683-688.
- Figueiredo AM, Ha E, Kreiswirth BN, Lencastre de H, Noel GJ, Senterfit L, Tomasz A. *In vitro* stability of heterogeneous expression classes in clinical isolates of methicillin-resistant staphylococci. *J Infect Dis* 1991; 164: 883-887.
- Kohler T, Michea-Hamzehpour M, Plesiat P, Kahr AL, Pechere JC. Differential selection of multidrug efflux systems by quinolones in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 1997; 41: 2540-2543.
- Hughes D, Andersson DI. Carbon starvation of *Salmonella typhimurium* does not cause a general increase of mutation rates. *J Bacteriol* 1997; 179: 6688-6691.

30. Foster PL. Adaptive mutation: the uses of adversity. *Annu Rev Microbiol* 1993; 47: 467-504.
31. Shapiro JA. Genome organization, natural genetic engineering and adaptive mutation. *Trends Genet* 1997; 13: 98-104.
32. LeClerc JE, Li B, Payne WL, Cebula TA. High mutation frequencies among *Escherichia coli* and *Salmonella* pathogens. *Science* 1996; 274: 1208-1211.
33. Taddei F, Radman M, Maynard-Smith J, Toupance B, Gouyon PH, Godelle B. Role of mutator alleles in adaptative evolution. *Nature* 1997; 387: 700-702.
34. Mamber SW, Kolek B, Brookshire KW, Bonner DP, Fung-Tomc J. Activity of quinolones in the Ames *Salmonella* TA102 mutagenicity test and other bacterial genotoxicity assays. *Antimicrob Agents Chemother* 1993; 37: 213-217.
35. Ren L, Rahman MS, Humayun MZ. *Escherichia coli* cells exposed to streptomycin display a mutator phenotype. *J Bacteriol* 1999; 181: 1043-1044.
36. Fish DN, Piscitelli SC, Danzinger LH. Development of resistance during antimicrobial therapy: A review of antibiotic classes and patient characteristics in 173 studies. *Pharmacotherapy* 1995; 15: 279-291.
37. Kristinsson KG, Hjalmsdottir M, Steingrimsdottir O. Increasing penicillin resistance in pneumococci in Iceland. *Lancet* 1992; 339: 1606-1607.
38. Ekdahl K, Cars O. Role of communicable disease control measures in affecting the spread of resistant pneumococci the Swedish model. *Clin Microbiol Infect* 1998; 5 (suppl 4): S48-54.
39. Tomasz A. The challenge of multiresistant *Streptococcus pneumoniae*: international initiatives in day-care centers and the use of molecular epidemiologic techniques. *Clin Microbiol Infect* 1998; 5, (suppl 4): S64-68.
40. Davies J. Inactivation of antibiotics and the dissemination of resistance genes. *Science* 1994; 264: 375-382.
41. Houndt T, Ochman H. Long-term shifts in patterns of antibiotic resistance in enteric bacteria. *Appl Environ Microbiol* 2000; 66: 5406-5409.
42. Grahn E, Holm SE. Penicillin concentration in saliva and its influence on bacterial interference. *Scand J Infect Dis* 1987; 19: 235-241.
43. Nord CE, Heimdahl A, Kager L. Antimicrobial induced alterations of the human oropharyngeal and intestinal microflora. *Scand J Infect Dis* 1986; 49: 64-72.
44. Spratt BG. Resistance to antibiotic mediated by target alterations. *Science* 1994; 264: 388-393.
45. Edlund C, Nord CE. Ecological impact of antimicrobial agents on human intestinal microflora. *Alpe Adria Microbiol J* 1993; 3: 137-164.
46. Hoiby N, Johansen HK. Ciprofloxacin in sweat and antibiotic resistance. The Copenhagen Study Group on Antibiotics in Sweat. *Lancet* 1995; 346: 1235.
47. Hoiby N, Jarlov JO, Kemp M, Tvede M, Bangsbo JM, Kjerulf A et al. Excretion of ciprofloxacin in sweat and multiresistant *Staphylococcus epidermidis*. *Lancet* 1997; 349: 167-169.
48. Gahm-Hansen B. Coagulase-negative staphylococci and micrococci in clinical microbiology. *Danish Med Bulletin* 1987; 34: 96-114.
49. Jarlov JO, Hoiby N. Coagulase-negative staphylococci in a major Danish university hospital: diversity in antibiotic susceptibility between wards. *Acta Path Microbiol Immunol Scand* 1998; 106: 411-416.
50. Rodríguez RS, Calderón JE, Gómez BD, Espinosa ML. Características de la resistencia antimicrobiana de una colección clínica de *Streptococcus pyogenes*. *Sal Pub Mex* 2000; 42: 226-229.