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Epidemiology of nosocomial bacteria resistant to antimicrobials

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SUMMARY

Nosocomial infections are a major challenge for public health because of the high rates of morbidity and mortality generated. It was considered that the excessive or inappropriate use of antibiotics triggers the emergence of resistant strains. Among the clinically important bacteria that most commonly cause nosocomial infections, Gram positive multiresistant pathogens stand out such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus spp* (VRE), and the Gram negative strains of *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas spp.* and *Acinetobacter baumannii* producing expanded spectrum β -lactamases (ES β L). This review describes the behavior of the main bacterial pathogens resistant to antibiotics that cause infections in Europe, United States, and Latin America, emphasizing studies of molecular epidemiology on a global scale, including the major epidemiological studies in Colombia. The genetic structure of *S. aureus* and *Enterococcus spp* strains shows a clonal characteristic favored by the predominance of a small number of clones with the capacity to spread globally, due probably to cross-infection. However, the introduction of MRSA strains from the community encourages genetic diversity, tending to establish a genetic polyclonal endemic structure in places like the United States. In Gram negative bacteria, the high genetic diversity among isolates, mainly in Latin American countries, indicates that the polyclonal spread is influenced by horizontal transfer of plasmids, by excessive exposure to antibiotics, and prolonged hospital stays. In Colombia, there is information on nosocomial resistant pathogens, but molecular epidemiological information is still scarce.

Keywords: Bacterial resistance; Antibiotics; Nosocomial infections; Epidemiology; Molecular epidemiology; Genetic diversity.

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Epidemiología de bacterias nosocomiales resistentes a los antimicrobianos

RESUMEN

Las infecciones nosocomiales constituyen un gran desafío para la salud pública por las altas tasas de morbilidad y mortalidad que generan. Se ha considerado que el uso inapropiado o excesivo de antibióticos desencadena la aparición de cepas resistentes. Entre las bacterias de importancia clínica que con mayor frecuencia causan infecciones nosocomiales, se destacan los patógenos Gram positivos multiresistentes como *Staphylococcus aureus* con resistencia a metilina (SARM) y *Enterococcus spp.* resistentes a vancomicina (ERV). En los Gram negativos, hay resistencia sobre todo con las cepas de *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas spp.* y *Acinetobacter baumannii* productoras de β -lactamasas de espectro extendido (BLEEs, en inglés: ES β L *expanded spectrum* β -lactamases). Esta revisión tiene como finalidad realizar una descripción del estado de la resistencia bacteriana a los antibióticos en los principales patógenos que causan infecciones nosocomiales en países de Europa, Estados Unidos y de Latinoamérica, destacando los estudios de epidemiología molecular

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a escala global e incluyendo los principales estudios epidemiológicos realizados en Colombia. La estructura genética de las cepas de *Staphylococcus aureus* y *Enterococcus* spp. evidencia una característica clonal favorecida por el predominio de un número pequeño de clones con capacidad de diseminarse en forma global, debida probablemente a infecciones cruzadas. Sin embargo, la introducción de cepas SARM desde la comunidad está favoreciendo la diversidad genética, tendiendo a establecerse una estructura genética policlonal en lugares endémicos como los Estados Unidos. En las bacterias Gram negativas, se destaca una alta diversidad genética entre los aislados, sobre todo en países de Latinoamérica, indicando que la diseminación sigue una estructura genética policlonal, influida por la transferencia horizontal de plásmidos, por la excesiva exposición a antibióticos y una estancia hospitalaria prolongada. En Colombia se dispone de información sobre los patógenos nosocomiales resistentes, pero la información epidemiológica molecular aún es escasa.

Palabras clave: Resistencia bacteriana a antibióticos; Antibióticos; Infecciones nosocomiales; Epidemiología; Epidemiología molecular; Diversidad genética.

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Currently, studies on epidemiology surveillance report increased bacterial resistance to antimicrobial agents and their association with nosocomial infection, contributing to greater morbidity and mortality rates¹. The nosocomial pathogens reported with the highest rates of resistance correspond to Gram-positive organisms like methicillin-resistant *Staphylococcus aureus* (MRSA). When vancomycin was introduced, the MRSA strains acquired resistance to this antibiotic, now denominated Vancomycin-Resistant *Staphylococcus aureus*² (VISA). Coinciding with this circumstance, the first strains of vancomycin-resistant *Enterococcus* spp. (VRE) appeared; now widely distributed worldwide³.

In Gram-negative bacilli, resistance is given mainly by β -lactamase enzymes classified into two important groups: *expanded spectrum* β -lactamases (ESBL), codified in megaplasmids, and the inducible chromosomal β -lactamase⁴. The strains with ESBLs are reported mainly in *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus mirabilis*, and other species like *Enterobacter* sp. and *Citrobacter freundii*, becoming an important health problem, which has

rapidly increased and spread throughout the world⁵. Moreover, chromosomal β -lactamase is described in nonfermenting Gram-negative bacilli like *Citrobacter* spp., *Enterobacter* spp., *Serratia* spp., *Providencia* spp., *Pseudomonas* spp., and *Acinetobacter baumannii*. These bacteria are grouped under the acronym SPACE (S: *Serratia*; P: *Pseudomonas*; A: *Acinetobacter*; C: *Citrobacter*; E: *Enterobacter*). The greatest state of resistance in this group is principally reported in multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* spp. (MDRs)^{5,6}.

The state of world resistance of nosocomial pathogens, and of those appearing in community, is monitored by different surveillance programs, among which is the SENTRY program incorporating molecular typification of strains and the genotypification of the resistance as a mechanism of additional information, which permits following the world distribution of pathogenic microorganisms, within the denominated molecular epidemiology. Some of the molecular techniques used in this type of analysis include: ribotyping, genomic analysis of the amplified fragment length polymorphism (AFLP), pulsed field gel electrophoresis (PFGE), random amplification of polymorphic DNA (RAPD), arbitrary primed polymerase chain reaction (AP-PCR), amplification of repetitive element sequence-based PCR (rep-PCR), and multilocus sequence typification (MLST)⁷.

This review will address epidemiological studies reporting the state of antimicrobial resistance in nosocomial pathogens in developed nations like the United States and some European nations, in contrast with Latin American nations including Colombia.

State of antimicrobial resistance in the world. Worldwide, the state of resistance increased considerably in Gram-positive and Gram-negative pathogens. Reports indicate that among Gram-positive organisms *S. aureus* is one of the pathogens with the tendency to more quickly acquire resistance. This bacterium whose resistance has reached worldwide epidemic proportions, is naturally susceptible to most antibiotics developed. Resistance is often acquired by horizontal transfer of external origin genes, chromosomal mutation, and antibiotic selection. Most diseases produced by this bacterium are caused by MRSA strains, which have been on the rise in many countries both at the community level and hospitals².

In England, there are reports of increased proportion of MRSA isolates since 1990 at 2%, reaching its maximum peak at 43% in 2002⁸. In spite of the contention measures taken to diminish spread of the pathogen, by the end of 2010, MRSA epidemic outbreaks continue to be reported⁹. The epidemiological state of MRSA in other European nations registers similar behavior. In Spain, the MRSA strains have presented a notable increase in nosocomial infections in recent years¹⁰. However, in other countries the measures to control the spread of MRSA strains have had a positive effect; thus, for example, Denmark reports cases of MRSA infections since the 1970s, mortality in cases of bacteremia diminished notably until the year 2000¹¹.

In Asian nations like Japan, cases of patients developing infections through MRSA were 35.8% during the start of the decade of 2000¹². According to epidemiological studies, in the United States the MRSA strains presented a 32.4% rate of occurrence during 1997 and 2002¹³. For 2004 and 2005, the prevalence increased dramatically, favored by the spread of the strains in the community¹⁴.

For other Gram-positive bacteria, epidemiological surveillance systems indicate that the recurrence and spread of antibiotic resistant *Enterococcus* present differences between geographic areas³. According to the 2002 annual report by the European surveillance system (<http://www.earss.rivm.nl>), the prevalence of ampicillin-resistant *Enterococcus faecium* strains reached rates up to 10% in six European countries. This increase was even greater in some countries like Denmark¹⁵. Nevertheless, the epidemiological pattern changed during the last eight years, when resistance to vancomycin became evident in some ampicillin-resistant *Enterococcus* strains³. Resistance to vancomycin is mainly determined by the acquisition of transposons, with high power to spread among strains with different genetic determinants¹⁶. For the first decade of 2000, a high occurrence rate of VRE infections was registered in countries like Spain¹⁷.

In Asia, the VRE strains have been isolated from patients hospitalized and from the community, mainly in countries like Japan¹⁸ and South Korea¹⁹. The introduction of the pathogen into the community was primarily due to the consumption of contaminated meats^{18,19}. In the United States, as in Europe, public health problems generated by *Enterococcus* are

influenced by the recurrence of vancomycin-resistant nosocomial *Enterococcus faecium* outbreaks during the decade of 2000³. Epidemiological reports of Gram-negative bacteria point to bacteria from the family of ESBL-producing *Enterobacteriaceae*, as the main generators of nosocomial infections⁴.

An important presence of ESBL producing *K. pneumoniae* strains was reported in Southern and Western Europe during the late 1990's²⁰. The presence of these strains is still being reported during this decade in hospital wards in Italy²¹. In Spain, epidemiological records reveal that the participation of ESBL producing strains has been maintained in nosocomial infections; but with a preoccupying extension to the community²². The presence of these strains in the community is reported in other countries like Poland, France, and the United Kingdom, among others²³.

The epidemiological behavior of ESBL producing *K. pneumoniae* has generated serious public health problems in Asian nations like China²⁴, in African nations²⁵, and in the American continent, especially in the United States²⁶.

Ever since the determination of the presence of ESBLs for the first time in *E. coli* strains in Europe, the frequency of these strains transporting these resistance determinants has been kept high, as indicated by epidemiological reports in Spain²⁷ and France²⁸.

In the United States, during the last decade, the presence of ESBL producing *E. coli* strains in hospitals in different states²⁹, with a preoccupying increase in the community³⁰.

When studying the epidemiological behavior of nonfermenting enterobacteria, we found that the situation worsens and particularly with *A. baumannii* because this pathogen plays an important function in colonization and infection of patients, especially those Intensive Care Units (ICU) of hospitals worldwide^{31,32}.

Effective treatment against infections caused by *A. baumannii* was via carbapenem; however, resistance to this class of β -lactam antibiotic is now habitual³¹. Similar results were obtained with the use of other potentially effective antibiotics against *A. baumannii* like tetracyclines, last generation aminoglycosides, and sulbactam³².

The emergence of strains simultaneously resistant to three drugs, introduced the epidemiological term of multiresistance and resistance to all panresistance³¹⁻³³.

The presence of multiresistant strains in some European and Asian nations constitutes a serious public health problem³⁴; the situation turns more alarming with the emergence of multiresistant and panresistant *A. baumannii* strains^{31,33}.

Multiresistant strains often spread and cause epidemic outbreaks in entire cities, countries, and continents³⁴. The exchange of multiresistant strains between continents has been demonstrated, as evidenced by a study on molecular epidemiology, which determined the presence of multiresistant *A. baumannii* clones in hospitals in the United States and Europe, but with different genetic determinants³⁵. Nonetheless, the existence of identical clones has been identified in military and civilian personnel from the United States and the United Kingdom who had returned from operations in Afghanistan and Iraq^{36,37}.

Antimicrobial resistance in nosocomial pathogens in the world reveals greater prevalence of Gram-positive bacteria in Europe, especially MRSA strains. In contrast, the United States presents similarities in the presence of *Staphylococcus* spp., *Enterococcus* spp., and non-fermenting Gram-negative organisms. These results show the need for implementing government policies in integral health, which permit a better quality of life, involve nutritional conditions, adequate administration of wastes and of chemotherapeutics, as applied in several European countries in recent years.

State of resistance in Latin America. The first reports of resistance in nosocomial infections were made in Argentina and Brazil in the late 1990s³⁸. Reports in Latin America indicate that MRSA strains bear epidemiological importance in Mexican hospitals, as revealed by epidemiological studies conducted from 1997 to 2003³⁹ and in Venezuela in 2005, where the MRSA strains also signaled resistance to oxacilin, gentamicin, erythromycin, and tobramycin and in 93% of the cases it was due to the presence of the *mecA* gene⁴⁰. In Asunción, Paraguay, the prevalence of MRSA strains corresponded to 43.8%⁴¹ and in several cities in Argentina, especially in Córdoba with a 37% prevalence⁴².

In spite of the great epidemiological relevance of *S. aureus* in Latin American nations, cases of infection due to VRE are reported in hospitals in Argentina⁴³, Chile⁴⁴, and Perú⁴⁵. Among Gram-positive bacteria, those most frequently reported causing nosocomial

infections correspond to ESBL producing *E. coli* in Chile, Argentina, Brazil⁴⁶, Perú, and Bolivia⁴⁷. The *K. pneumoniae* strains turned out to be ESBL producing by 27.6% in Mexico and by 47.5% in Brazil⁴⁶. In Chile, it is reported that poor use of antibiotics like ceftriaxone was important in promoting the spread of ESBL producing *K. pneumoniae* strains⁴⁸.

The presence of multiresistant *A. baumannii* has generated serious public health problems with reports of epidemic outbreaks in hospitals in Argentina⁴⁹ and, according to SENTRY, in hospitals of Brazil, Chile, and Uruguay⁵⁰, among other countries.

The principal studies on resistance of nosocomial bacteria have been conducted in Argentina, Brazil, and Chile. According to reports, it was observed that the highest resistance rates among MRSA strains exist in Venezuela, while for Argentina, Brazil, México, Perú, and Bolivia resistance is most alarmingly registered in the *Enterobacteriaceae* family, with a special tendency in the propagation of *A. baumannii*. However, there is a lower distribution in resistance measured for ESBLs in southern cone Latin American nations, especially enteropathogens like *E. coli* and *K. pneumoniae*. In contrast, we observed greater resistance tendency in countries like México and Brazil for these same pathogens. For *Enterobacter* spp. a tendency to diminished resistance was observed in recent years, primarily in Southern hemisphere nations.

State of resistance in Colombia. Epidemiological studies conducted in Bogotá by Álvarez *et al.*⁵¹, in early 2000 reveal predominance of bacteria from the *Enterobacteriaceae* family, with a 34% prevalence for *K. pneumoniae*, 37% for *P. aeruginosa*, and 38% for *A. baumannii*, these last are imipenem resistant. In another study conducted in 2002 and 2003, the most frequent nosocomial microorganisms corresponded to *S. aureus* at 24%, *E. coli* at 18%, *P. aeruginosa* at 9%, *A. baumannii* at 6%⁵². A molecular epidemiology study of ESBL producing strains determined the significant presence of *K. pneumoniae*⁵³, with the prevalence of a unique clone in hospitals in different cities⁵⁴.

In 2006, a molecular study was conducted on metallo- β -lactamase (M β L) producing *A. baumannii* strains in clinical isolates in Intensive Care Units at hospitals in Bogotá⁵⁵. The data obtained by the CIDEIM group in 2004, including several hospitals in Colombia, report the presence of imipenem-resistant *A. baumannii* and

*P. aeruginosa*⁵⁶.

Among the resistance observed in the Gram-positive cocci, the MRSA strains showed resistance rates between 24% and 48% in studies carried out in hospitals of Bogotá⁵⁷; these data are similar to those recorded in Paraguay with a predominant clone. Data reported for VRE revealed low prevalence. Toward more populated zones in our country, we observed a high percentage of resistance in ESBL producing Gram-negative bacteria. For *Enterobacter* spp. strains, we observed a greater rate of resistance in cities in the Atlantic Coast. In the Andean region and in the Atlantic Coast, we noted a high percentage of resistance in bacteria like *P. aeruginosa* and *A. baumannii*.

Molecular epidemiology of nosocomial bacteria.

Global epidemiology of the state of resistance in nosocomial bacteria is variable and it is very much related to policies in each nation. Thus, for example, when analyzing the genetic structure of the *Enterococcus* spp. resistant population the greatest prevalence is registered in the United States, reaching endemic situations with clonal dispersion³. However, this characteristic has changed in recent years, favored by the introduction of endemic strains from the community onto the hospital environment with new resistance determinants, generating a polyclonal dispersion tendency as observed in Europa¹⁷. Although the incidence rate of VRE infection at the intrahospital level is low, the high frequency of colonization at the community level is perhaps favored by the introduction of resistant strains through the consumption of farm animals as evidenced by some reports^{18,19}.

In the analysis of the VRE world population structure were identified 55 sequence types (ST) with 4 clonal complexes (CC2, CC9, CC10, CC21); complexes denominated CC2 and CC9 are the most frequent and circulate primarily in Central Europe and America^{3,17}.

For MRSA strains, large-scale population genetics studies published in 1999 and 2000, identified five clonal complexes or pandemics: Iberian Clone, Brazilian Clone, Hungarian Clone, New York/Japan Clone, and Pediatric Clone⁵⁸.

Current epidemiological studies have demonstrated that the pediatric clone is the most frequent with resistance to β -lactam antibiotics; this clone has been identified in isolates from Poland, the United States, Argentina, and Colombia. Some researchers suggest

that because of their stability over time and their great power to spread throughout the continents it may be the oldest MRSA clone⁵⁹. The second clone with great power to spread is the Iberian clone found in isolates from several European countries, mainly Portugal, Spain, as well as the United States, where it has been identified in New York city hospitals¹⁴. The New York/Japan clone is highly predominant in Asian nations¹².

The first molecular work to determine MRSA clones in Latin America was done in 2001, finding that the Brazilian clone was present in 79% of the strains in Argentina, Chile, and Uruguay³⁸. In Brazil, intrahospital infections caused by *Staphylococcus* spp corresponded to 80% to 90% through MRSA and all the strains with the Brazilian clone profile. The pediatric clone was detected in Paraguay⁴¹, Argentina⁴², Chile⁴⁶, and Colombia⁵⁷. México registered strains sharing the New York clone profile and a group of strains with a unique diversity classified as M clone³⁹.

Dissemination of an MRSA resistant clone among Latin America countries including Chile, Paraguay, Argentina, and Brazil was detected in the late 1990s³⁸. It was, thereafter, confirmed by studies conducted by Sader *et al.*⁴⁶, in 2000.

The population genetics study of Gram-negative bacteria with ESBLs shows a high diversity, as with *K. pneumoniae* and *E. coli* strains^{21,22,26-28}. Some studies reveal clonal dispersion for the population of *K. pneumoniae* and *E. coli*^{26,27}. The study conducted by Deshpande *et al.*⁶⁰ in 2004 determined that the ribotypes identified in the ESBL producing strains from Europe, the United States, and Latin America were restricted to one continent or to one country in particular, except for a clone from the United States and Europe with a shared pattern. Pattern similar results were obtained from analysis done on MDR *K. pneumoniae* strains isolated from epidemic outbreaks in different hospitals in European countries, the data reveal great variability in the resistance patterns, but they all belonged to the same clone²¹. The variation was because the resistance measured via diverse mechanisms like: integrons transporting the *aadB* gene (which confers resistance to gentamicin); in other strains because of the presence of the *aadA* gene (which confers resistance to streptomycin), or to the presence of both genes in a transposon^{5,24,25}. In all the strains analyzed, a mutation was determined in the *gyrA* gene, which confers resistance

to ciprofloxacin and the presence of the SHV-5 gene in the resistance mediated by ESβLs⁶¹.

In the population structure of the *E. coli* strains, we noted similar behavior to *K. pneumoniae*. We found that the β-lactamase producing *E. coli* strains in hospitals in Paris was a clone that was primarily spread, according to findings in a hospital in Tunisia and in the Central African Republic²⁸. Researchers suggest that the spread was probably due to characteristic of the clone, with an extraordinary tendency to colonizing or via horizontal transfer of plasmids on mosaics transporting the resistance gene²⁸.

In Latin America, there are studies of *E. coli* population genetics in Brazil conducted by Martins-Loureiro *et al.*⁶², in 2001, who found 6 clones in a group of 42 epidemiologically related strains, with 9 PFGE profiles of resistance to the antimicrobial (A-I). The most frequent clones were: A with 5 profiles, B with 3 profiles and D with 5 profiles. According to the profiles and to the isolation periods, clones A, A1, B, and D caused three outbreaks during the study period.

In Colombia, molecular epidemiology studies have evidenced similar behavior to that registered in the rest of the Latin American nations; thus, for example, the molecular characterization of *K. pneumoniae* with ESβLs obtained from patients in a third-level hospital in Bogotá revealed that the genetic variability was related to nosocomial infections of endogenous origin rather than cross infections^{53,54}. In this analysis, the isolates were grouped by PFGE and REP-PCR into 11 and 12 electrophoretic patterns, respectively⁵⁴. In studies published by Espinal *et al.*⁵³, in 2004, it was shown that all *K. pneumoniae* isolates were ESβL producers and the genotyping by PFGE and BOX-PCR grouped two isolates from hospital environments, as well as eight isolates that caused infection in an epidemic clonal group. The isolate from a thermometer was not associated to the epidemic clonal group and revealed a different resistance pattern.

The estate of molecular epidemiology of non-fermenting pathogens shows increased prevalence of infections due to resistant strains. In the United States, the most frequent *P. aeruginosa* and *A. baumannii* clonal outbreaks have been detected in cities like New York with a ribotype identical to one reported in Spain, but with a different PFGE pattern³⁵. Likewise, common clones have been identified in isolates from the United States and the United Kingdom^{36,37}. These studies

demonstrate that in Latin American nations, the resistance pattern is more widespread, with MDR strains predominating as principal etiological agents for nosocomial infection that are gaining importance in community-type infections^{49,50,55}.

Regarding the population structure of *A. baumannii*, there are important studies like those conducted in European hospitals during the early part of the 2000 decade, which identified a great diversity of clones specifically resistant to polymyxin β, aminocycline, imipenem, rifampin, sulbactam, meropenem, amikacin, and doxycycline³⁴. In Latin American countries, the most important studies on this pathogen are reported in Argentina where it has been determined that *A. baumannii* strains resistant to carbapenems with shared profile with a clone isolated in Israel⁴⁹.

In studies carried out in Colombia, much work was done on molecular characterization during 2003 and 2004 in nosocomial isolates among which there is *A. baumannii*, which caused an epidemic outbreak in a hospital in Bogotá and the determination of associated factors. In this study, it was determined that the isolates were resistant to multiple antibiotics and were genetically related with a similarity percentage greater than 97%⁵². In studies done by Pinzón *et al.*⁵⁵, in 2006, 9 (A-1) groups were identified; the E group was made up of 39.2% of the isolates and a clone comprising three environmental isolates and two recovered from patients.

Molecular epidemiology studies on Gram-positive pathogens evidence the predominance of a small number of clones responsible for Staphylococcal infection throughout the world, *i.e.*, they are able to disseminate globally (pandemic MRSA clones), probably favored by cross infections with strains closely related among hospitals and distant locations.

In Gram-negative bacteria, the high genetic diversity among the isolates of the enterobacteria, primarily in Latin American countries, indicates that dissemination is polyclonal in the hospital environment, influenced by the horizontal transference of plasmids among different strains, which are under high selective pressure by broad-spectrum antibiotics. For fermenting enterobacteria with resistance mediated by ESβLs, polyclonal-type dispersion is established characterized by high genetic diversity, perhaps associated to the selection of resistant organisms caused by excessive exposure to antibiotics and prolonged hospital stays.

PERSPECTIVES

In Latin America, bacterial resistance in hospitals presents a high variety with small differences among countries, including Colombia. Nevertheless, molecular epidemiology studies conducted until now in the country have been limited to some regions; it is necessary to carry out a nationwide population genetics study integrating nosocomial pathogens from different places, including greater impact Gram-positive organisms like MRSA strains, and among the Gram-negative organisms, fermenting enteric bacteria like *K. pneumoniae* and *E. coli*, and non-fermenting bacteria, especially *A. baumannii*, which has currently become a serious morbidity and mortality problem in the country. It is necessary to determine if the microorganism follows a behavior similar to that observed in other Latin American nations and its genetic relationship with strains circulating in other regions of the world.

The use of molecular epidemiology in the study of nosocomial infections has been fundamental for the formulation and evaluation of control measures, for the purpose of diminishing the propagation of resistant clones. With this strategy, we are able to determine the factors contributing to the epidemic superiority of the clones, the surprisingly high level of expression of certain virulence genes, and their survival ability in the environment. These factors are important in adopting measures to control the dispersion of resistant pathogens and avoid the emergence of strains with greater degrees of resistance and pathogenicity.

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