Chapter 3

Current Status of Colonization and Infection by Multiresistant Bacteria in the Spanish Intensive Care Unit: Resistance Zero Program

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Additional information is available at the end of the chapter

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Abstract

Current medicine, highly technified, and capable of amazing achievements, is not possible without the support of antibiotics. The problem of antibiotic resistance is almost as old as the antibiotics themselves. But at present, it is a serious threat to public health. We have to fight against antibiotic resistance in the hospital and in the out-of-hospital environment. The Resistance Zero program, promoted by the Spanish Society of Intensive Medicine, has achieved through a multidisciplinary approach with collaboration between doctors, nurses, cleaning staff and microbiologists, to control the colonization and infection by multiresistant germs in the environment of the Intensive Care Unit.

Keywords: antibiotic resistance, multiresistant bacteria, intensive care unit, colonization, infection

1. General concepts

1.1. Global data

The emergence of antibiotic and their use in clinical practice is one of the greatest achievements of Medicine. In the mid-twentieth century, its use became widespread, and it was thought that a rapid and definite eradication of infectious diseases was possible. However, the first resistant bacteria soon appeared, and antibiotic resistance has developed into a serious public health problem. It is estimated that up to 60% of nosocomial infections are caused by resistant germs both in Europe and in the United States. The Center for Disease Control and prevention (CDC)

in the United States has estimated that the problem of antibiotic resistance is responsible for 2 million infections and 23,000 deaths per year with a direct cost of 20 billion dollars, and losses of productivity equivalent to 33 billion dollars [1]; the European Center for Disease Control, ECDC, have estimated that accounts for 25,000 deaths and 1.5 billion € per year by infections by multiresistant bacteria (MRB) [2]. Some consequences of this problem are: increased cost of health care, increased rates of failure of antibiotic treatment and increased mortality. This is not a problem limited to certain regions or countries and resistance can spread quickly in our globalized world.

1.2. Intensive care unit generalities

Intensive care unit (ICU) accounts for less than 10% of total beds in most hospitals, but more than 20% of nosocomial infections are acquired in ICU [3]. Acquired in ICU infections pose significant morbidity, mortality and expense; they are the most frequent cause of death in non-cardiac ICUs and 40% of all ICU expenses [4]. In comparison with patients from other areas of the hospital, ICU patients have higher chronic comorbidity, more severe acute physiological deterioration and are relatively immunosuppressed [5]. Its management also implies a high degree of invasiveness, with use of intravascular catheter, contact with a large number of health personnel—predisposing to colonization and infection—and are subjected to an increased colonization pressure [5].

When a patient goes to the hospital today, he undergoes a more effective and complete care than in previous years. Advances in diagnostic and therapeutic methods mean improvements in care and may be accompanied by a greater number of associated complications. All these data are magnified in ICU; ICU patients are more vulnerable to develop infections during their stay and to become colonized/infected with MRB. Overcrowding in closed areas of these severely ill patients with multiple comorbidities and subjected to invasive devices are risk factors for the development of nosocomial infections.

There is a clear relationship between the appearance of resistance and the highest antibiotic consumption. Infections due to resistant germs/MRB have limited therapeutic options, so inadequate empirical treatments are prescribed, the start of the correct treatment is delayed and therapeutic failures increase. All this leads to longer ICU stay, costs and mortality, with worse prognosis of the patient.

The highest density of MRB is observed in ICU. The importance of adequate and early treatment is greater in critically ill patients; for all above, it is necessary to implement programs for the prevention and treatment of multiresistant bacteria MRB, both in the ICU and in the community—a great number of MRB can be related to inadequate or excessively prolonged treatments in the general ward or outside the hospital.

1.3. Antibiotic resistance mechanisms

The mechanisms related to the emergence of resistance are varied. Resistance can be intrinsic or acquired. the first occurs in certain germs that are not innately sensitive to certain antibiotics, by a special membrane structure or related to the mechanism of the antibiotic. There may be at the molecular level: modifications in the targets (nucleic acid, ribosomes, action points

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of certain antibiotics—such as penicillin-binding proteins, PBPs); alterations in the transmembrane passage (porins, mechanisms of uptake or active transport); enzyme production (beta-lactamases). The appearance of mutations in the genetic material of the bacteria or the transfer of resistance genes from other germs explains the transformation from sensible to resistant bacteria. The exposure to antibiotics induces the disappearance of a population sensitive, and the selection of resistant strains to the antibiotics that end up being predominant.

1.4. Definition of MRB

MRB are defined as those microorganisms resistant to three or more antibiotics, which must also have clinical relevance. The exception to this rule is methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE) cases, in which the resistance condition is given by only one antibiotic. The phenomenon of resistance constitutes a medical problem, since it becomes a difficulty for the treatment and also epidemiological relevance, given the possibility of transmission of the outbreak. The ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and Enterobacter especies) are a specific group of bacteria with clinical relevance, associated with health care, and with the capacity to develop antibiotic resistance [6].

1.5. Description of the MRB

P. aeruginosa (Pa) has a predilection for humid environments and usually contaminates aqueous solutions such as disinfectants or soaps, mechanical ventilation equipment, fiberoptic bronchoscopes, and so on. Resistance may appear in the course of an antibiotic treatment. Its main mechanism of resistance is the presence of extended-spectrum beta-lactamases (ESBL) and alterations in permeability (porin mutations and expulsion pumps).

Acinetobacter baumannii (Ab) contaminates and endemically colonizes the hospital environment. It is capable of surviving and rapidly developing resistance to the main classes of antibiotics, more frequently in summer [7]. Some strains can survive to environmental drying form months, which facilitates transmission via contamination of fómites in the hospital. The health personnel is usually carrier of Gram-negative bacilli (GNB) (30%). Outbreaks have been described in relation to contaminated mechanical ventilation equipment and manual transmission. Infections have also been described in war wounds and in situations of natural disasters. Sixty-three percent of bacterial isolation from war wounds in Iraq and Afghanistan corresponded to this germ [8]. Infections tend to appear in patients with long stay in the ICU and health centers, dependent on mechanical ventilation, central catheter carriers, and with prior treatment with third-generation cephalosporins, fluorquinolones or carbapenemes. Although patients with Ab infection have high mortality, it is not clear whether mortality can be attributed to infection or to life-threatening conditions [9]. Several factors are associated with mortality: isolation in blood cultures, presence of signs of sepsis/septic shock, resistance to imipenem, longer stay in ICU, pneumonia and diabetes mellitus [10]. Cases of community acquisition have been described in situations of chronic obstructive pulmonary disease (COPD), diabetes, alcoholism and cancer [11]. It has great capacity to acquire and accumulate

resistance genes from other GNB via plasmids/transposons, with low permeability for many antibiotics, constitutive ejection pumps, production of beta-lactamases and so on.

Klebsiella pneumoniae (Kp) contaminates the medical material although its main reservoir is the digestive tract and the hands of the health care personnel from where it can give rise to epidemic outbreaks. Its main mechanism of resistance is the production of beta-lactamases. The genes that encode them are transmitted by plasmids, which contribute to their rapid diffusion among other GNB.

MRSA shows resistance to methicillin by means of a protein encoded in the mecA gene and transported in the chromosomal cassette SCCmec. The frequent use of vancomycin has led to the emergence of strains with intermediate or complete resistance to vancomycin by acquisition of the gene through a plasmid. They currently constitute up to 50% of Staphylococcus infections.

1.6. Factors that predispose to infections by MRB

Certain elements as advanced age, functional dependence, cognitive deterioration and comorbidities, prolonged hospital stays, contact with personnel sanitary, intravascular catheters, bladder catheterization, previous antibiotic treatment, and so on, contribute to an increased selective pressure (leading to the emergence of MRB) and increased colonization pressure (through an ineffective environmental containment) [11].

1.7. Consequences of infection by MRB

The prognosis of MRB infections is not good, with an increase in hospital stay, mortality and economic costs [12]. These types of infections are usually resistant to empirical therapies, which implies a delay in starting the correct antibiotic treatment. Also derived from this, the use of second line treatment with lower bactericidal capacity and less favorable pharmodynamic/pharmacokinetic profile contributes to a higher incidence of adverse events. At times, a greater virulence of these germs has been described.

1.8. Colonization and infection

The difference between these two terms lies in the simple presence (colonization) or clinical involvement (infection). The oropharynx is colonized early by hospital flora, especially GNB, in critically ill patients. The risk of colonization increases with hospital stay and severity. In the same way, the administration of antibiotics systemically increases the risk of acquiring the carrier state. Patients with APACHE II greater than 20 are usually carriers of abnormal flora such as GNB and MRSA. The passage from colonization to infective germs is defined by the rupture of the natural defense mechanisms (neutropenia, immunosuppression), the pathogenicity of the germ itself, alteration of the intestinal flora by antibiotic therapy previously administered. Altered mechanisms of clearance of germs are suggested. A necessary factor for the development of the infection is the overgrowth; 20–40% of carrier patients develop an infection, so those carriers must be actively identified when we want to control an outbreak of infection by resistant flora.

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1.9. Exogenous-endogenous infections in the ICU

Infections can be classified according to origin and carrier status:

- Exogenous: nonpreceded by digestive colonization. The infective flora is endemic to the ICU. It constitutes 10–15% of the infections acquired in critical care.
- Endogenous: preceded by colonization of the digestive system by potentially pathogenic germs (PPG). It is endogenous primary if the patient already has them at the time of admission. It is usually precocious and represents 50% of registered infections. The endogenous secondary is caused by germs acquired in the ICU and colonizes the patient before causing the infection. They represent 35–40% of infections acquired in critical care.

The multimodal prevention of nosocomial pneumonia is based on these concepts. Primary endogenous pneumonias can be prevented with a short course of antibiotics such as cefotaxima that eliminates the colonizing germs of the oropharynx and upper respiratory tract of the carriers. Endogenous pneumonia is treated with the prevention of the carrier state with enteral antibiotics (PPG will not be able to adhere the coated mucosa of antibiotics). Exogenous pneumonia is prevented with hygienic measures.

1.10. Mechanisms of appearance and extension of resistance

The main responsible for the emergence and extension of resistance are the indiscriminate use of antibiotics and the transmission of resistant microorganism between humans (or between human and environment). The antibiotics exert a selective ecological pressure on the bacteria, thus promoting the appearance of resistance germs. Inadequate practices of prevention of the infection along with inadequate hygienic measures will favor the extension of the bacteria. The strategies to avoid these phenomena are aimed at a better use of antibiotics (reducing the selective pressure) and optimizing the infection control measures (reducing the colonization pressure) [13, 14].

Some measures aimed at a rational use of antibiotics are the following:

- Evaluation committees: formed by clinicians, pharmacists and microbiologists; pursue the effective and safe use of antimicrobials, evaluate and guide decision making; and implement educational programs to improve the use of antibiotics;
- implementation of clinical guidelines and protocols to promote the proper use of antibiotics;
- to use a form with pre-authorization for broad-spectrum antibiotics (non-specific restriction);
- preferred use of limited spectrum antibiotics (first-generation cephalosporin);
- personalized audit (mandatory consultation with infectious disease specialists to improve the appropriateness of antibiotic therapy and to reduce the use of broad spectrum antibiotics);
- to use predictive scores for MRB infections can be useful to minimize both the time to initiate appropriate antibiotic treatment and the unnecessary use of broad spectrum antibiotics.

While some measures of patient-patient transmission control are:

- hand washing;
- contact isolation measures (very important in case of MRSA, ERV and germs producers of ESBL), even grouping the colonized/infected patients (cohorting) and having staff exclusively dedicated to the care of these infectious patients;
- the use of universal contact precautions is not clear in all patients admitted to ICU;
- cutaneous decolonization/daily bath with chlorhexidine to colonized/infected patients (despite the limitations of the current studies) [15];
- decolonization of the upper respiratory tract and gastrointestinal tract. Several options: oropharyngeal decontamination with antiseptics (chlorhexidine); selective oropharyngeal decontamination (with nonabsorbable antibiotics applied to the oropharynx); and selective digestive decontamination (with nonabsorbable antibiotics applied to the oropharynx with intravenous antibiotics);
- surveillance of early infections by MRB (for early identification of these germs, control of outbreaks—imited in time—and situations of endemic increase of isolation);
- to implement strategies of infection prevention in relation to invasive devices (reduce the use of central venous catheters, bladder catheters, orotracheal tubes, etc);
- to regulate and monitor the process of cleaning, disinfection and environmental sterilization.

1.11. Proper antibiotic treatment

The evolution of an infectious process depends on the characteristics of the initial focus, the hemodynamic parameters, host factors, the responsible pathogen, in vitro antibiotic susceptibility tests and the precocity of the appropriate antibiotic treatment. The use of antibiotics is, at the same time, part of the problem and the solution when we talk about antibiotic resistance. Unfortunately, the emergence of resistance is faster than the creation of new antibiotics by the pharmaceutical industry. In general, the solution involves a global reduction in the consumption of antibiotics, although it is necessary to implement control programs aimed at rationalizing their use.

A frequently forgotten fact is that the majority of antibiotic consumption is done at the extrahospital level (Primary Care and food industry) [16]; it is necessary to regulate its use. Up to 50% of antibiotics prescribed at the hospital level are unnecessary, many of them are broad spectrum. The inadequate use of antibiotics increases the mortality of patients with severe sepsis, subjects them to unnecessary adverse effects and generates unjustified expenses. On the other hand, it is of vital importance to define the role of prophylactic antibiotic treatment and also differentiate the systemic inflammatory response syndrome of any cause from a real infectious process.

The loss of sensitivity to antibiotics is to be solved with several strategies: to speed up the development of new antimicrobials—the initiative "10 × 20" of the IDSA; 10 new antimicrobians available on 2020; to improve the mechanisms of infection control in health centers; and

to optimize the use of current antibiotics with the intention of extending their useful life. An adequate administration of antibiotics should be based on the following principles:

- early start (associated with microbiological cultures);
- proper choice of antibiotic: based on local ecology and habitual patterns of resistance;
- suitable doses, based on pharmacokinetic and pharmacodynamics data, taking into account that in critical patients the increase in volume of distribution, cardiac output and glomerular filtration requires the administration of doses that could be above the usual doses (currently available antibiotics rarely cause serious adverse effects);
- evaluate the need to maintain the started treatment: to remove unnecessary antibiotics by culture results, and if possible, to narrow the spectrum (de-escalation);
- adequate duration of antimicrobial treatment (usually too long due to the absence of evidence of optimal duration and for fear of suspending it if the evolution of the patient is good).

Different strategies have been described and tested to avoid resistance to antibiotic. Rotation consists of restricting in an established way an antibiotic or a class of antibiotics during a certain period of time, to reintroduce it later; the aim is to reduce the selective pressure exerted on the microbial flora and to minimize the appearance of resistance to rotated antibiotics. Cycling is to prescribe antibiotics according to a pre-established a priori sequence. In scheduling, an antibiotic or antibiotic class is replaced by another antibiotic or class with a comparable antimicrobial spectrum; there is change to another antimicrobial without returning to the initial agent. In rotation, there is a circular pattern. The usefulness of these strategies is theoretical. Periodic modifications would limit the generation of resistances by avoiding prolonged exposures to the same antimicrobial agent; the restriction of an antibiotic can result in the compensatory potentiation of the use of other unrestrained agents, with a later increase of resistance to these second agents. Also, the elimination for the selective pressure by an antibiotic when withdrawing its use does not imply the eradication of the genetic material responsible of the resistance. Despite the theoretical benefits of these strategies, their results are contradictory, and none of them have showed real benefit so far [17].

1.12. Epidemiological surveillance: multimodal prevention program

Epidemiological surveillance consists of the systematic collection, analysis and interpretation of data about a problem related to public health. The implementation of multimodal prevention programs must have the following elements: identification of problems, implementation plan, involvement of managers, record of compliance with objectives and, finally, the analysis of obstacles that may arise. An essential aspect of these programs is learning: the absence of adherence to the measures of the program due to lack of information or insufficient learning time should be avoided.

The antimicrobial stewardship programs bring together specialists in infectious diseases, clinical pharmacologists, clinical microbiologists, epidemiologists and other, sometimes also intensivists, all of them gathered for the purpose of an adequate prescription of antibiotics. But this is just one aspect of a complex problem like antibiotic resistance.

The 12 steps described by the CDC to prevent antibiotic resistance are the following:

- prevention of the infection:
- vaccine administration;
- removal the catheters (as soon as possible);
- effective diagnosis and treatment of the infection:
- analyze the sensitivity of the germ and to adapt the treatment to the pathogen;
- discuss with experts;
- appropriate use of antimicrobials:
- antibiotic control;
- knowledge of local microbiological data;
- treat the infection, not the colonization or the contamination;
- know how to refuse vancomycin;
- stop antibiotic treatment if patient has healed (propose the reduction of antibiotic treatment according to the clinical situation of the patient);
- prevention of the transmission:
- isolate the pathogen;
- break the chain of infection.

2. Resistance Zero (RZ) project

The Spanish Society of Intensive Care (SEMICYUC) has developed several projects with the aim of reducing infectious events (nosocomial infections): Bacteremia Zero (BZ) (catheter-related bacteremia) and Pneumonia Zero (NZ) (pneumonia associated with mechanical ventilation). After the implementation of these projects, a sustained decrease in the rate of such infections, and globally nosocomial infections has been achieved (**Figure 1**). It has been described that, surprisingly, the rate of pneumonia associated with mechanical ventilation began to decrease with the start of the BZ Project.

The last project carried out is Resistance Zero (RZ). Its objectives are:

- Primary: reduce by 20% the appearance of one or more MRBs of Nosocomial origin that are identified during their admission in ICU;
- Secondary: describe the MRB map in spanish ICUs, differentiating those identified at the time of admission to the ICU and those that appear after 48 h of stay; promote and reinforce the safety culture in them; and create a network of UCIs, through the autonomous communities, that apply safe practices of demonstrated effectiveness.

The aim of the project is to minimize the three factors that influence the appearance of MRB in critical patients: the adequate prescription of antibiotics, the early detection of MRB and

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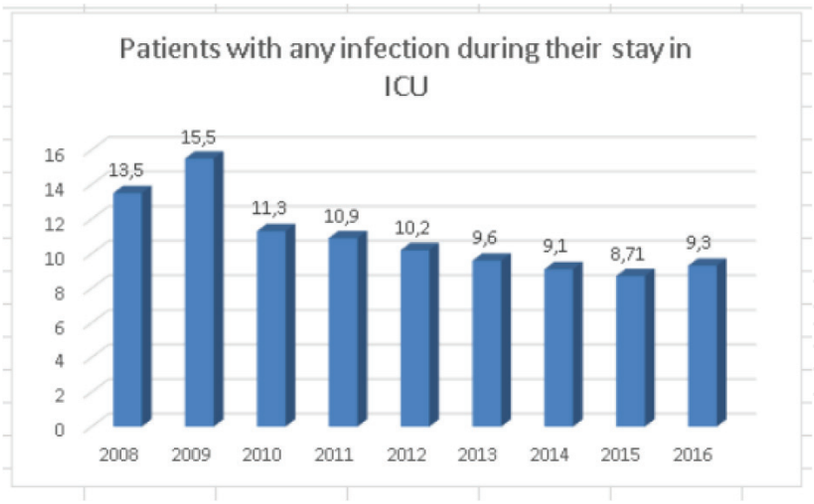

Figure 1. Decrease of acquired in ICU infection rate (patients with acquired in ICU infections for every 100 patients admitted to the ICU) during the different zero projects. Start of BZ 2009: Start of NZ 2011; start of Resistance Zero 2014.

the prevention of its spread/cross colonization, and the elimination of reservoirs. The MRBs in follow-up are: MRSA, VRE, Enterobacteria resistant to third generation cephalosporins, especially the ESBL producers, and those resistant to carbapenems, especially the carbapenemase producers; *P. aeruginosa* resistant to> = 3 families of antibiotics including: carbapenems, cephalosporins, piperaziline/tazobactam, fluoroquinolones, aminoglycosides, colistin; and *Acinetobacter baumannii* resistant to carbapenems.

The recommendations of the project are:

1. Identify in each ICU at least one intensivist physician responsible for the control of antibiotics, with experience in surveillance and infection control and in the management of antibiotics. Systematically evaluate the use of antibiotics in ICUs and advise physicians responsible for patients with the intention of assessing reasons for prescription (indication), assessing choice and correct administration (dose, interval, duration) and possibility of withdrawal or adjustment.
2. Administer antibiotics empirically active against MRB only in infections with systemic response (severe sepsis, septic shock (SS)), and high suspicion of being MRB based on present risk factors and local epidemiology. In other cases, it is recommended to use lower spectrum antibiotics and/or wait for microbiology results to start antibiotics directed to MRB (carbapenems, colistin, tigecycline, glycopeptides, daptomycin, linezolid). In critical surgical patients with infection data but without sepsis/SS, the start of antibiotic treatment can be delayed until microbiological confirmation, without this implying an increase in mortality or stay in the ICU.
3. Designate a nurse as a project reference and responsible for the control of precautions directed to preventing the transmission of MRB. Ensure the effective implementation of the handwashing strategy, and dispose of an alcohol-based preparation dispenser in each bed.
4. Perform an active search for the presence of MRB in all patients at the time of admission to the ICU, and at least once a week throughout their stay. The type and number of samples will be chosen according to the local epidemiology, and at a minimum, they will include

nasal, rectal and oropharyngeal swabs (tracheal aspirate in intubated patients); in addition, you can take other samples to control possible reservoirs (infections, skin ulcers, etc). The samples will be processed to identify the MRBs recommended by the local epidemiology, according to Microbiology and the infection control teams of each hospital.

5. At the time of admission of each patient in ICU, a checklist that includes several items (hospital admission>5 days in the previous 3 months, institutionalized-prison, social health centers, nursing homes-, colonized or infected by MRB) will be completed., antibiotics> = 7 days in the previous month -especially with third and fourth generation cephalosoporins, quinolones and carbapenemics-, chronic renal failure undergoing hemodialysis or chronic ambulatory peritoneal dialysis, and chronic pathology with a high incidence of MRB colonization/infection-cystic fibrosis, bronchiectasis, chronic ulcers-) with the objective of identifying those patients with high risk of being carriers of MRB. In patients with one or more risk factors, preventive contact precautions will be applied, and surveillance culture samples will be collected.

6. Control compliance with the different types of precautions that should be applied: standard, or based on transmission mechanisms (isolation). The precautions will vary according to the identified MRB and its transmission mechanism (drops, air, and contact). They are mandatory standards for all health personnel and for the families of the patient. Nursing empowerment must be recognized to control strict compliance. The presence of necessary material for its application must also be facilitated. Contact isolation should be practiced with the use of a coat and gloves before contacting the patient, and removing them before leaving the patient's environment (for a single use).

7. Have an updated protocol for daily and terminal cleaning of rooms occupied by patients with MRB. Several aspects must be agreed with the cleaning and Preventive Medicine teams of the hospital: the cleaning method (method, frequency, products, etc.) according to the type of surface and the fixed structures present, including the beds.

8. Elaborate a document for cleaning the clinical material and scanning devices in the ICU, commonly used in hospitalized patients, assessing whether cleaning, disinfection or sterilization is necessary. The importance of cleaning the sanitary material (fondendoscopes, fiberoptic bronchoscopes, etc.) and nonsanitary (computer keyboards, landline and mobile phones, keys, etc.) usually used in the ICU should be made aware. It is the responsibility of each worker to clean and disinfect appliances for personal use.

9. Include products containing chlorhexidine (4% soaps or other products impregnated with 2%) in the daily hygiene of patients colonized/infected with MRB, in addition to the obvious need for cleaning to eliminate organic waste.

10. Given the suspicion of an epidemic outbreak, it is recommended to typify at a molecular level the causative microorganism to know the clone responsible for the outbreak and its traceability. Studies of outbreaks based on phenotypic characteristics (antigenic, metabolic or antibiotic resistance properties) are insufficient to establish conclusive differences or similarities between microorganisms. The molecular typing allows us to know the transmission mechanisms of the pathogen to establish measures that prevent its dissemination. The centers that do not have means can submit the microbiological samples to the Resistance Vigilance Program of the National Microbiology Center of the Carlos III Health Institute (Madrid).

As additional recommendations, hand hygiene is very important, with the use of hydroalcoholic solution by health personnel before and after patient care. It is the most effective measure for the transmission of germs. Its purpose is to prevent the transmission of microorganisms in a bidirectional way between professionals and patients, besides protecting the care environment of pathogenic microorganisms. The priority method to perform hand hygiene in the absence of organic matter or visible dirt is the friction with alcohol-based products. They will not be used in case of contact with patients/surfaces contaminated with spores (C difficile). Gloves should be worn in several situations: when handling blood or body fluids, mucous membranes or non-intact skin, when transporting or touching surfaces stained with blood, liquids or body fluids, or performing any procedure of blood extraction or parenteral treatment. They must be changed if they are broken or contaminated, between one patient and another, and between procedures in the same patient. The misuse of gloves increases the risk of pathogen transmission, and its use never substitutes for hand hygiene.

The indicators used in the RZ project are:

- Rates of patients with one or more BMR acquired in ICU: number of patients admitted to the ICU with 1 or more MRBs identified after 48 h of admission (and up to 48 h after discharge from the ICU) for 1000 days of stay in ICU, or by 100 patients admitted. MRBs are evaluated in clinical samples (infections or colonizations) and in surveillance samples, but not in environmental samples.
- Rate of days free of antibiotics: number of days—patient who does not receive systemic antibiotics for 1000 days of ICU stay. All systemic antibiotics are included regardless of the reason for their use.
- Rate of antibiotic use in infections acquired in ICU: number of days - patient with systemic antibiotic treatment for infections acquired in ICU, for 1000 days of ICU stay.

The project is complex and flexible, and adapts to the reality of each hospital. It is also contemplated to apply an integral security plan that seeks to promote and strengthen the safety culture in the daily work in the ICUs. Health professionals who provide critical care to the critically ill patients must be aware of the security risks of our units. The culture in general safety of the unit must be evaluated. We must work proactively on the potential risks of critical patient care, and propose recommendations based on daily practice that tries to minimize them. The notification of errors should be encouraged, and a goal of improvement should be proposed over time, with follow-up of proposed measures to achieve it. We have developed daily checklist tools that assess the safety of the patient on a daily basis in the different spheres of their management, and even a list of daily objectives—need of tubes/catheters, assessing whether parenteral medication can be suspended or passed to oral route, possibility of discharge from the ICU, and so on.

This project has preceded and promoted the creation of a new National System for the Surveillance of Infection Related to Health Care in Spain, in agreement with the Ministry of Health.

3. European data. ECDC

Data on infections associated with healthcare acquired in ICU are assessed by the ECDC. Recent data (2015) [1, 2] show that 8.3% of patients who remain in the ICU for more than

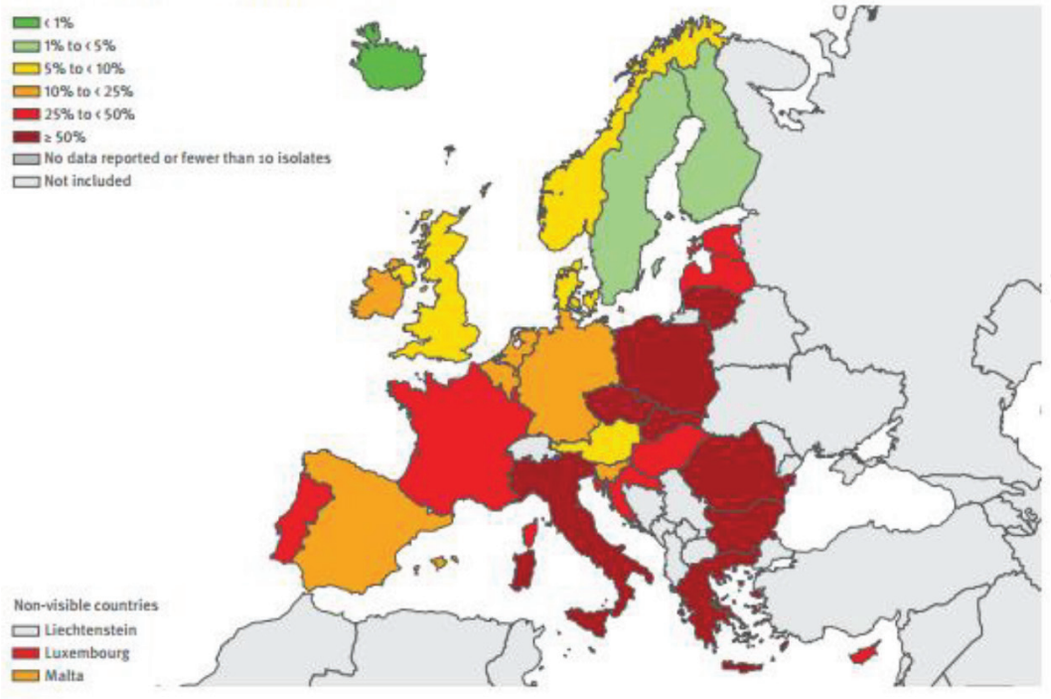

Figure 2. North-south and west-east gradient of % resistance of *K. pneumoniae* to third generation cephalosporins.

48 h develop at least one infection (pneumonia, bacteremia or urinary tract infection). The most frequent causal germs are *P. aeruginosa* (pneumonia), *Staphylococcus* spp. coagulase-negative (bacteremia) and *Escherichia coli* (urinary tract infections). On average, 23.1% of *S. aureus* are MRSA; 3.4% of Enterococci are VRE. Resistance to third generation penicillin is described in variable percentages in E coli (20%), Klebsiella (43%) and Enterobacter (42%); resistance to carbapenems is also noticeable in Klebsiella (11%), *Pseudomonas aeruginosa* (24%) and *Acinetobacter baumannii* (69% of averages). In a report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) of 2016 [2], the main surveillance system in the European Union on bacteria that can cause serious infections, broad variations are described in relation to bacterial species, antimicrobial group and geographical region. For many combinations of bacterial species (*E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Acinetobacter*, *S. aureus*, *Enterococcus*)—resistance to antimicrobial groups, there is a growing gradient from north to south, and from west to east, perhaps in relation to variations in the use of antimicrobials, infection prevention and control practices, and differences in diagnosis and healthcare utilization patterns between countries [18]. Overall, there seems to be a slowly increasing resistance over time (in the 2013–2016 interval) of E coli resistant to one of the three key antimicrobial groups (fluoroquinolones, third generation cephalosporins and aminoglycosides), with a tendency to stabilize the percentage of *K. pneumoniae* resistances (**Figure 2**).

4. Global data in Spain: ENVIN study: RZ project

The national study of nosocomial infection surveillance (ENVIN) represents the effort maintained over time (since 1994) to know and reduce the prevalence of nosocomial infection

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in ICUs. It describes nosocomial infections (NI) acquired in ICUs associated with invasive instrumentation. The data are collected mainly during the second quarter of the year (few units carry out the project throughout the year). The more frequent NI in the ICU are urinary infections associated with urinary catheter (31.87%), followed by ventilation-associated pneumonia (29.97%) and bacteremia (catheter-associated bacteriemia in 11.31%). In recent years, there has been a relative increase in the former ones and a decrease in the latter. The most frequently isolated germs in ICU infections (excluding bacteremia from other foci) are: *E. coli* (14.1%), *P. aeruginosa* (12.9%), *K. pneumoniae* (9.8%), *S. epidermidis* (8.2%), *S. aureus* (4.9%), *C. albicans* (4.8%), *E. cloacae* (3.5%), *S. marcescens* (2.7%), and so on. The type of reported patients is variable: medical (44%), 19.5% of surgeries scheduled, 10.3% of urgent surgeries and 19.8% of coronary patients. The extrinsic risk factors for nosocomial infections are: antibiotics before admission (21.1%), antibiotic treatment in ICU (64%), surgery in 30 days before (32.8%), urgent surgery during their stay in ICU (10.2%), central venous catheter (63.9%), mechanical ventilation (42.4%), bladder catheter (76.4%), parenteral nutrition (8.3%), and so on.

The implementation of the RZ project is more complex than the previous programs. It involves the collaboration of more staff and services, so the number of participating ICUs has been lower (of>190 in the first two projects, compared to 103 in RZ). In the following graphs, the evolution of the different indicators collected in the project is reviewed.

The evolution by quarters of the frequency of colonization/infection of patients with MRB, per 100 patients admitted, throughout the development of the RZ project is observed in **Figure 3**, with an ascending tendency with peaks coinciding with the collection periods of data from the ENVIN project (second quarter of each year). The average value throughout the project is 6.23 patients per 100 admissions. The colonization/infection plot for 1000 stays is similar.

Throughout the RZ project, there is an increase in the isolation of germs at the admission (acquisition prior to admission to the ICU) versus isolation during their stay (discrete decrease),

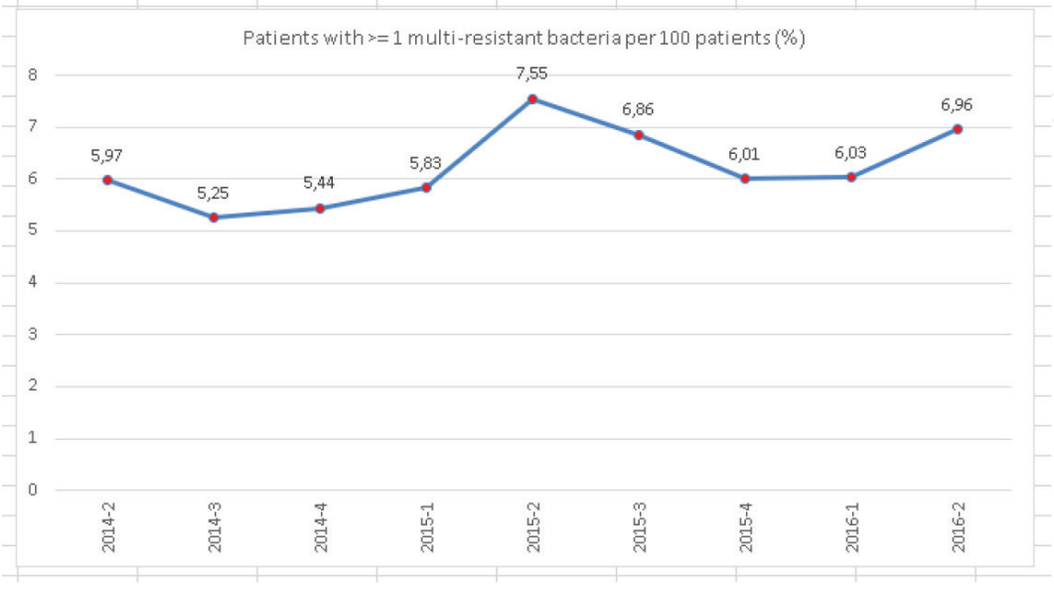

Figure 3. Temporal variation of the rate of MRB colonization/infection in ICU.

taking into account colonizations and infections (**Figure 4**). The average value during the project is 3.84 patients% (previous) and 2.60% (during), with an increase of the previous ones of 26% and a decrease of those acquired during the ICU admission of 16.7%.

In relation to the germs acquired in the ICU, there was a slight increase in colonization (5%) and a significant decrease in MRB infections (45%) (**Figure 5**), with average values of 1.75% patients colonized and 1.09% of infected.

Figure 1 (see above) and the following ones (**Figures 6–8**) show the tendencies initiated with the BZ and NZ projects of descent of patients admitted to the ICU with an infection (up to 8.7%, **Figure 1**), of reducing the use of antibiotics (up to 19.5% of patients, **Figure 6**), of reducing the days of antibiotic treatment (DOT, up to 109.7 per 1000 stays, **Figure 7**) and increasing days without antibiotic treatment (up to 40%, **Figure 8**). A rate of 2.15 antibiotics per patient with antibiotic treatment is described in 2016.

MRB colonization-infection rates change in successive years (**Figure 9**), with significant increases in enterobacteria carrying ESBL and carbapenemases and decrease in *A. baumannii*, *P. aeruginosa* and MRSA.

We can distinguish between the isolation of germs upon admission and during their stay, which can allow us to distinguish the predominant MRB germs that the patient "brings" to the ICU with those that he/she "acquires" during his stay. **Figure 10** shows that Acinetobacter infections appear mostly during their stay, against infections by ESBL-producing germs that are mostly present at admission.

Figures 11 and **12** show an important variability in the different autonomous communities, both in the MRB isolation rate (global of 6.23 per 100 patients) and in the isolated MRB types, for a total of 3195 isolated MRBs.

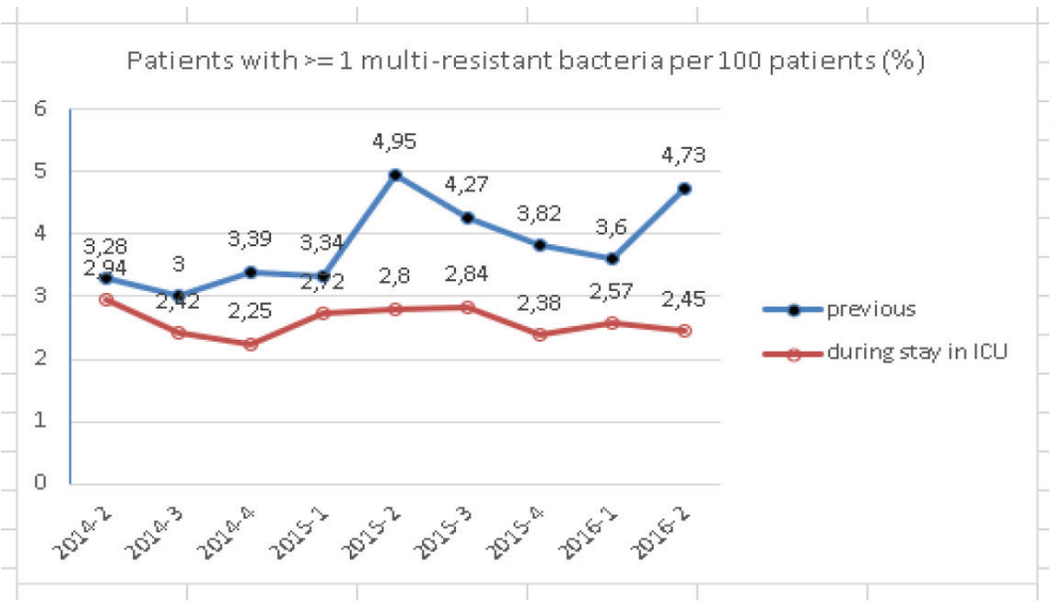

Figure 4. Evolution of BMR isolates prior to admission to the ICU and during admission.

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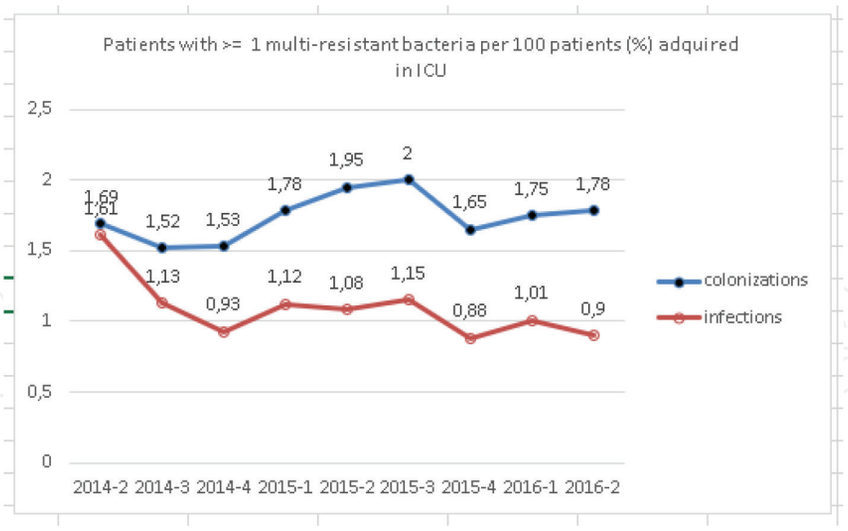

Figure 5. Evolution of colonized and infected patients during their stay in the ICU.

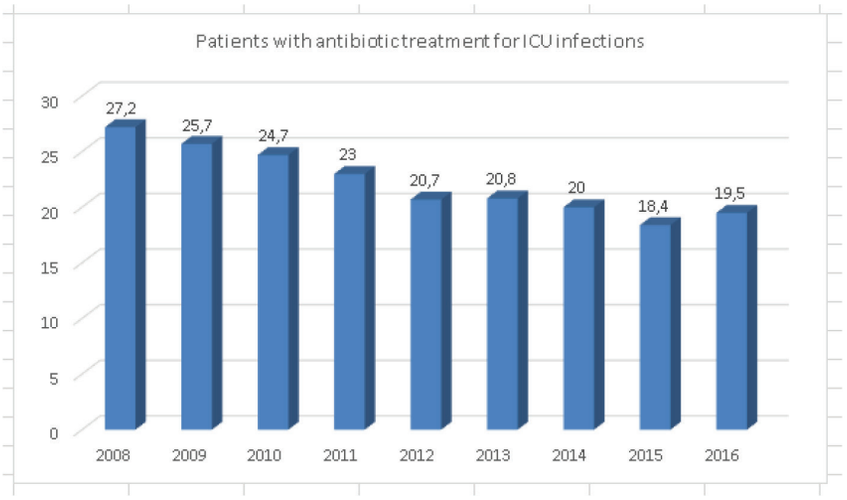

Figure 6. Reduction in the use of antibiotics over time.

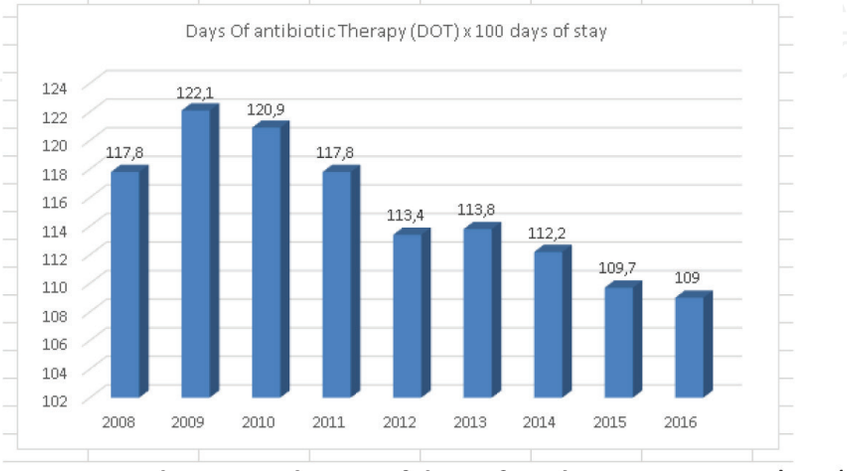

Figure 7. Reduction in the use of days of antibiotic treatment (DOT) for 100 stays in the recent years.

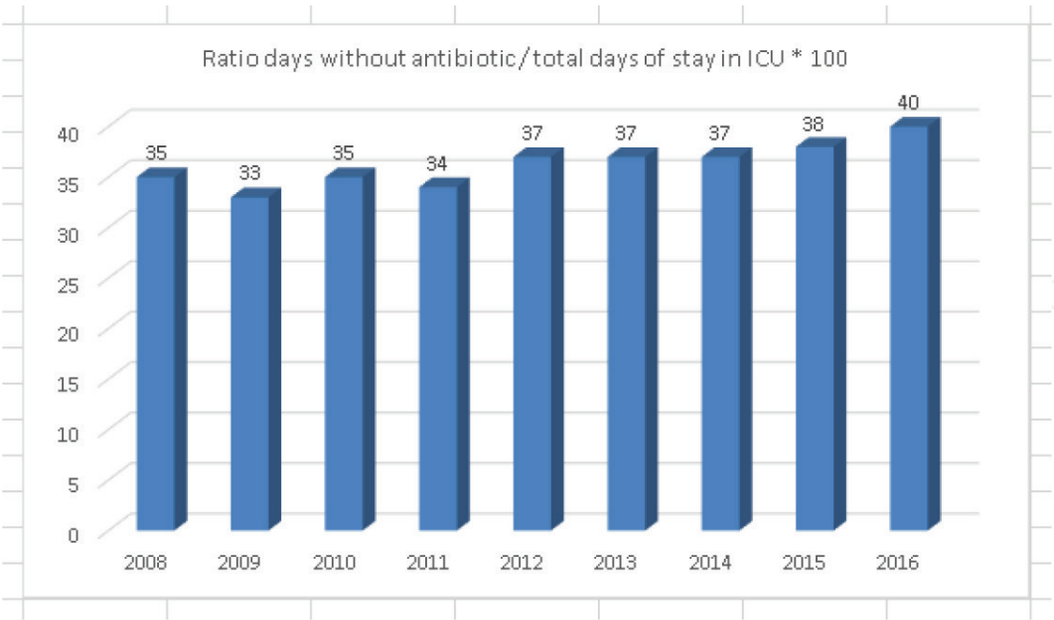

Figure 8. Increase in the number of days in the ICU without antibiotic treatment over the years.

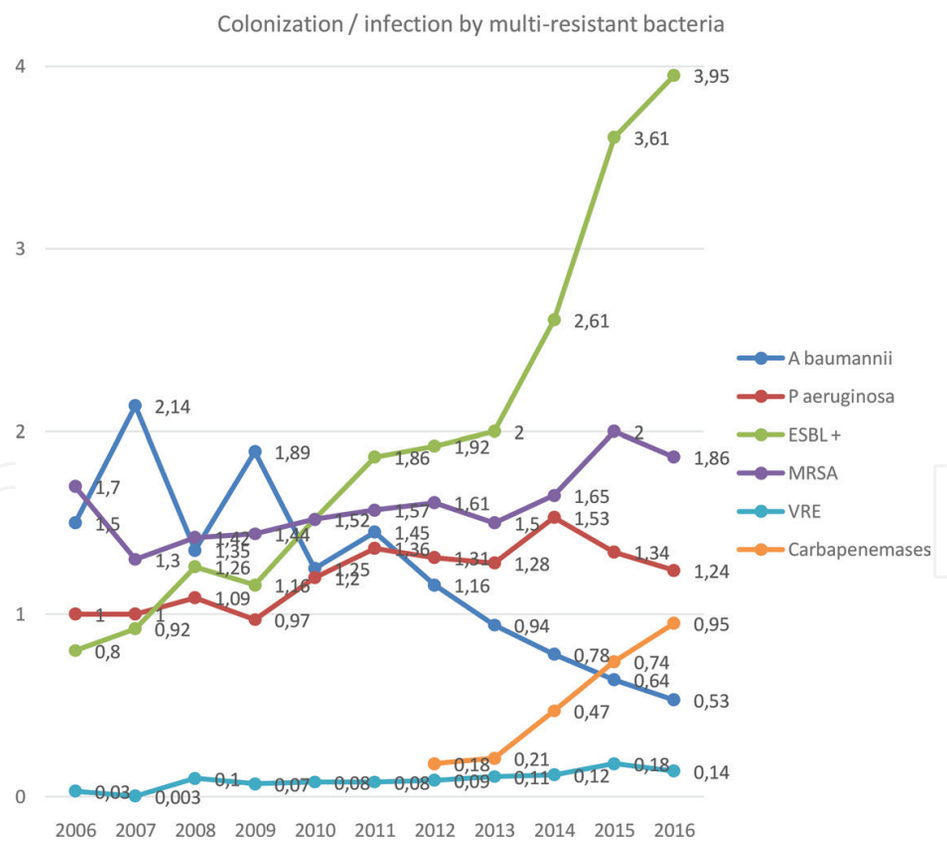

Figure 9. Infection/colonization by MRB. ENVIN study in the interval 2006–2016.

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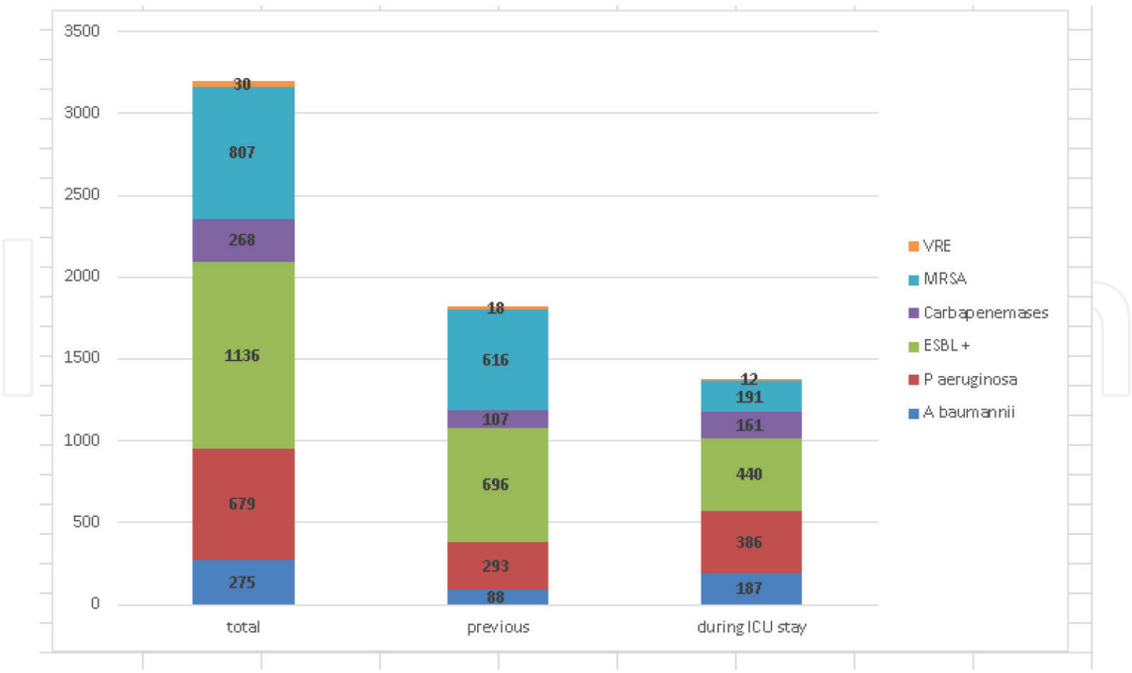

Figure 10. Isolation of MR germs in the RZ period globally, upon admission and during their stay in the ICU.

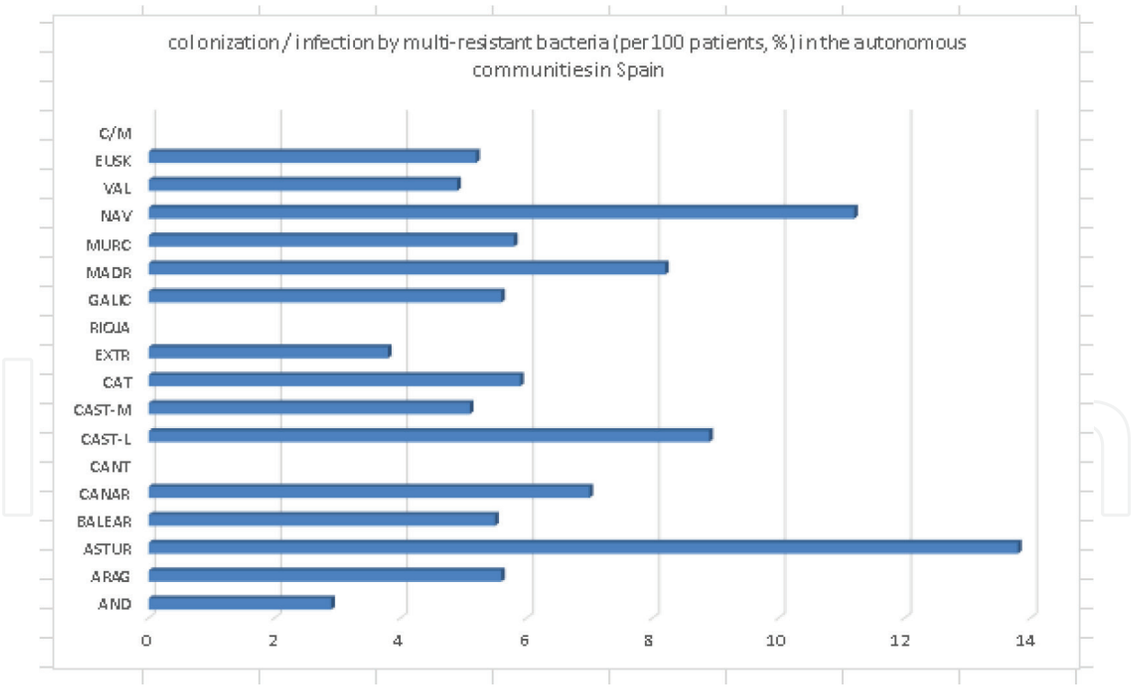

Figure 11. Isolation rate in the different autonomous communities. AND Andalucia, ARAG Aragón, ASTUR Asturias, BALEAR Balearic Islands, CANAR Canary Islands, CAST-L Castilla-León, CAST-M Castilla-La Mancha, CAT Catalonia, EXTR Extremadura, RIOJA La RIOJA, GALIC Galicia, MADR Madrid, MURC Murcia,NAV Navarra, VAL Valencian community, EUSK Euskadi, C/M Ceuta/Melilla.

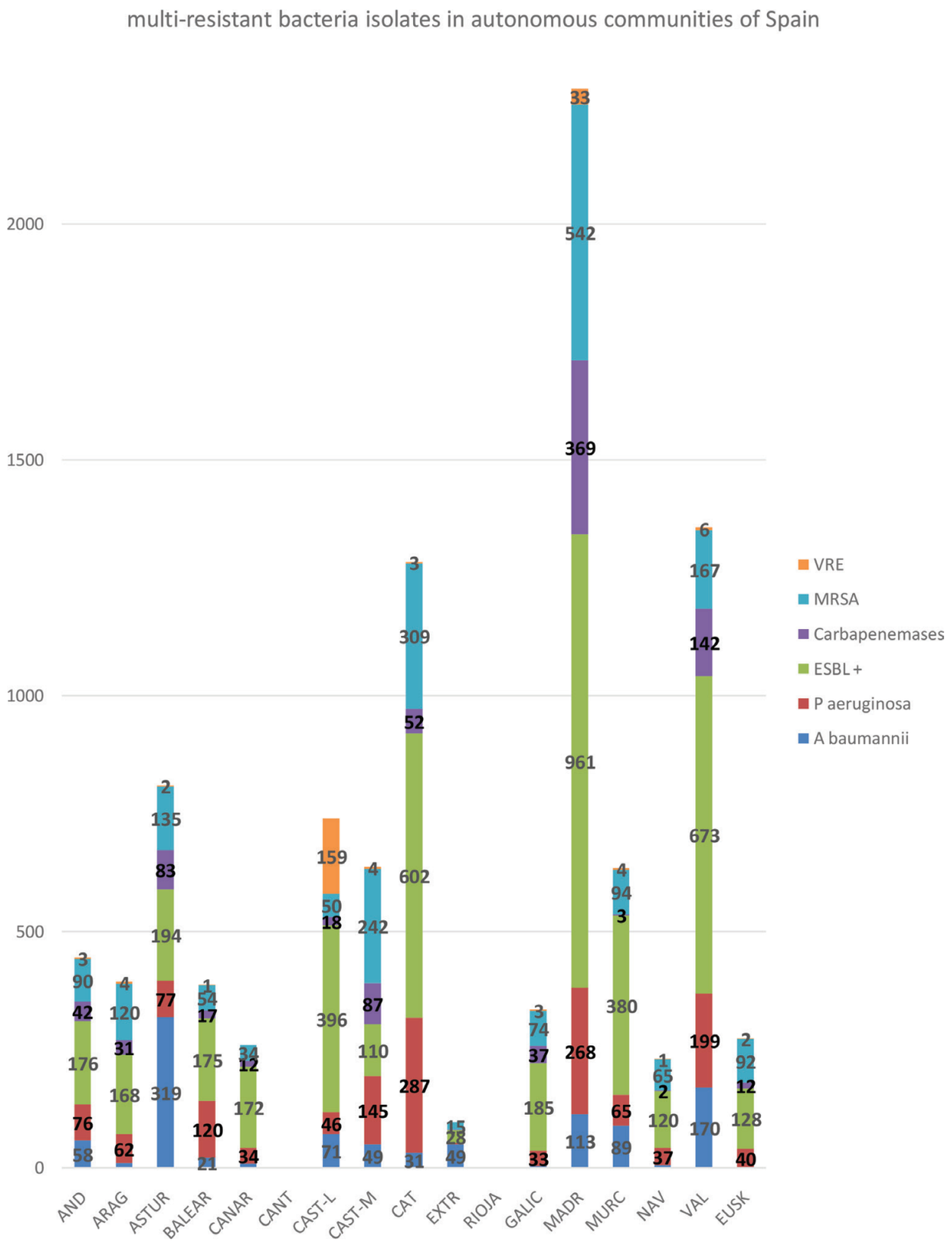

Figure 12. Heterogeneity of MRB isolates, counting colonizations and infections, during the period of RZ study. In most autonomous communities, the most frequent type of MRB is ESBL producing GNB. The presence of *A. baumannii* has become much less frequent, except in Extremadura and Asturias. In the Canary Islands, there are 0 VRE isolates; in Extremadura, there are zero isolates of VRE, one isolation of carbapenemase producing germ and three isolates of *P. aeruginosa*; there are few isolates of *A. baumannii* in Aragón [9], Canary Islands [8], Galicia [3] and Navarra [5]; and finally there is no isolation (0) of *A. baumannii* in Euskadi.

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5. Data of the ICU of the hospital of Sagunto

Our unit starts the data collection in the ENVIN project the same year of its beginning (1994). We started the RZ project in April 2014, and until now (January 2018) have followed the guidelines of the RZ project in the prevention and management of patients with MRB. We reported 195 isolates in 179 patients for 46 months, with 1966 admissions and a rate of 9.1 patients with MRB/100 admissions (**Figure 13**).

In our unit, a high prevalence of *A. baumannii* was initially observed, without a clear seasonal profile. Over time, there is a decrease in *A. baumannii* and an increase in the ESBL carrier

Figure 13. Occurrence of MRB in our ICU Fromm the beginning of RZ project until February 2018. Acinetobacter supposes globally a 25% of isolates, with a rate of 50% of ESBL producer germs.

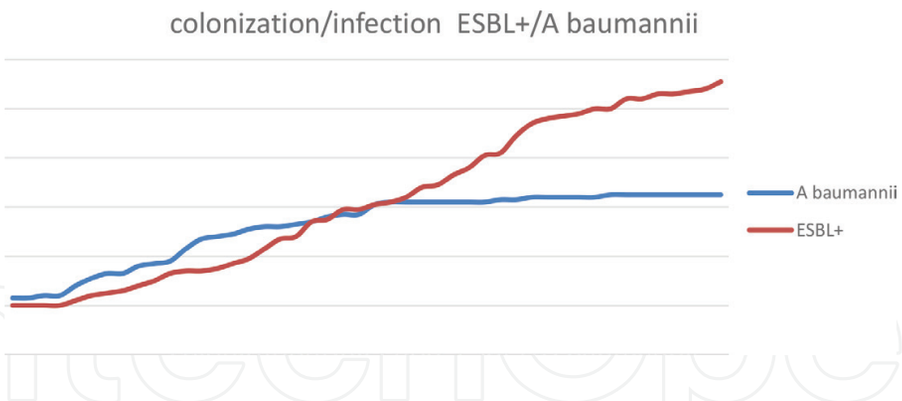

Figure 14. Accumulated frequency of colonized and infected patients by *A. baumannii* and ESBL producer germs.

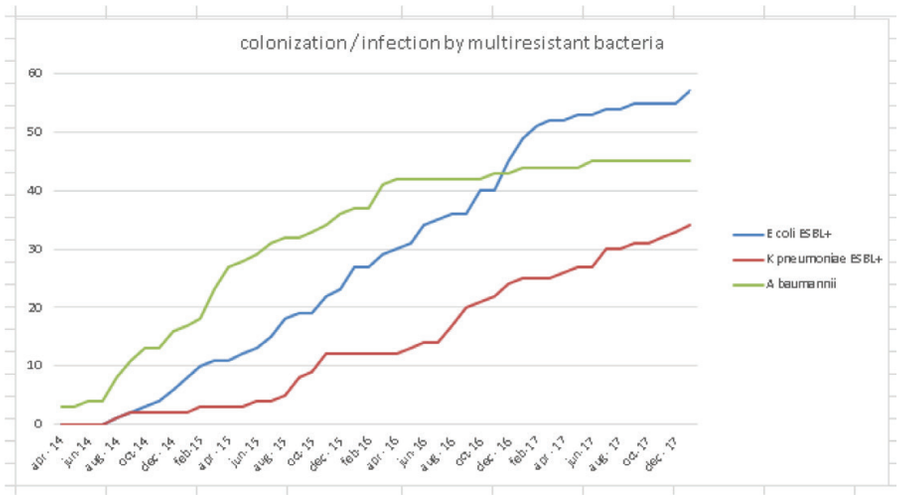

Figure 15. Accumulated frequency of colonized and infected patients by the most frequently isolated germs in the ICU of the hospital of Sagunto.

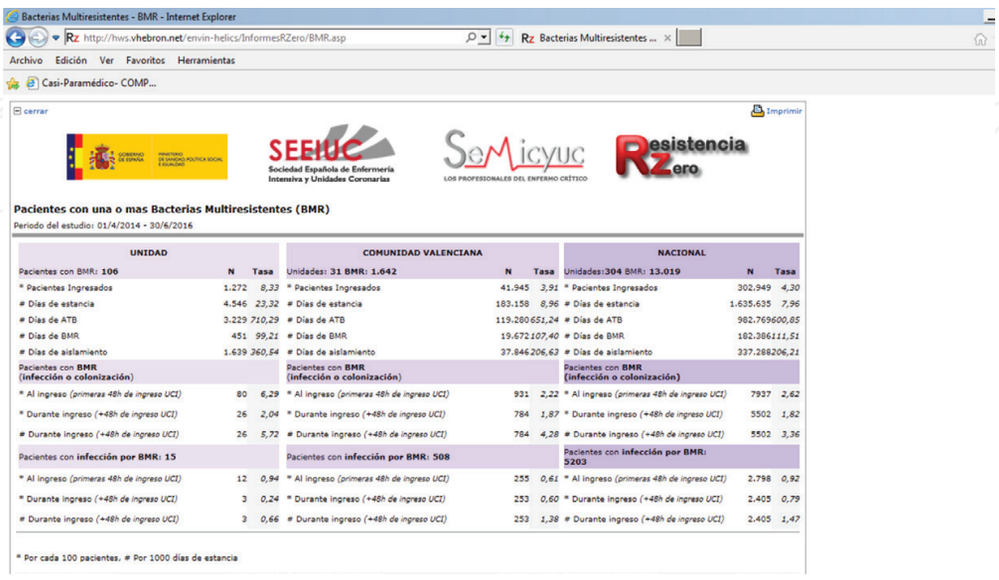

Figure 16. Indicators of the RZ project at the local (hospital of Sagunto), regional (Valencian community) and national (Spain) levels.

Relación de Bacterias Multirresistentes al ingreso y durante el ingreso

UNIDAD	N	%	COMUNIDAD VALENCIANA	N	%	NACIONAL	N	%
SARM (MRSA)	12	10,08	SARM (MRSA)	433	21,46	SARM (MRSA)	3230	21,20
Enterococo resistente Vancomicina	1	0,84	Enterococo resistente Vancomicina	9	0,45	Enterococo resistente Vancomicina	273	1,79
Pseudomonas multirresistente	13	10,92	Pseudomonas multirresistente	337	16,70	Pseudomonas multirresistente	2560	16,80
Acinetobacter R-Imipenem	42	35,29	Acinetobacter R-Imipenem	212	10,51	Acinetobacter R-Imipenem	1397	9,17
Enterobacteria - BLEE	51	42,86	Enterobacteria - BLEE	859	42,57	Enterobacteria - BLEE	6396	41,98
BGN - Carbapenemasa	0	0,00	BGN - Carbapenemasa	168	8,33	BGN - Carbapenemasa	1380	9,06
TOTAL	119		TOTAL	2018		TOTAL	15236	

Relación de Bacterias Multirresistentes durante el ingreso incluyendo colonización e infección

UNIDAD	N	%	COMUNIDAD VALENCIANA	N	%	NACIONAL	N	%
SARM (MRSA)	0	0,00	SARM (MRSA)	113	11,36	SARM (MRSA)	731	11,46
Enterococo resistente Vancomicina	0	0,00	Enterococo resistente Vancomicina	3	0,30	Enterococo resistente Vancomicina	114	1,79
Pseudomonas multirresistente	3	10,00	Pseudomonas multirresistente	217	21,81	Pseudomonas multirresistente	1472	23,08
Acinetobacter R-Imipenem	19	63,33	Acinetobacter R-Imipenem	139	13,97	Acinetobacter R-Imipenem	948	14,86
Enterobacteria - BLEE	8	26,67	Enterobacteria - BLEE	403	40,50	Enterobacteria - BLEE	2365	37,08
BGN - Carbapenemasa	0	0,00	BGN - Carbapenemasa	120	12,06	BGN - Carbapenemasa	748	11,73
TOTAL	30		TOTAL	995		TOTAL	6378	

Relación de Bacterias Multirresistentes durante el ingreso solo infección

UNIDAD	N	%	COMUNIDAD VALENCIANA	N	%	NACIONAL	N	%
SARM (MRSA)	0	0,00	SARM (MRSA)	18	6,19	SARM (MRSA)	316	11,72
Enterococo resistente Vancomicina	0	0,00	Enterococo resistente Vancomicina	2	0,69	Enterococo resistente Vancomicina	23	0,85
Pseudomonas multirresistente	1	33,33	Pseudomonas multirresistente	102	35,05	Pseudomonas multirresistente	830	30,79
Acinetobacter R-Imipenem	2	66,67	Acinetobacter R-Imipenem	46	15,81	Acinetobacter R-Imipenem	403	14,95
Enterobacteria - BLEE	0	0,00	Enterobacteria - BLEE	99	34,02	Enterobacteria - BLEE	881	32,68
BGN - Carbapenemasa	0	0,00	BGN - Carbapenemasa	24	8,25	BGN - Carbapenemasa	243	9,01
TOTAL	3		TOTAL	291		TOTAL	2696	

Figure 17. MRB isolated at admission and during their stay, such as colonization or infection, at the local, regional and national levels.

bacteria, and a slowly increasing incidence of MRSA and *P. aeruginosa* (**Figure 13**). Assessing the cumulative incidence, there is a catch-up of the ESBL + germs to the initially predominant Acinetobacter at the end of 2015–beginning of 2016 (**Figure 14**); if we separate the ESBL + germs, the highest cumulative frequency of E coli than of *A. baumannii* is observed at the end of 2016. In the last months also, the frequency of occurrence of *K. pneumoniae* is higher than that of *A. baumannii* (**Figure 15**).

During the RZ project, in our unit, 80 MRB were detected on admission and 26 during stay; this implies a global estimate, during the entire project period, of 6.29 patients with BMR at admission for every 100 admitted patients, and 2.04 patients with BMR during their stay in ICU per 100 patients admitted and 5.72 patients for 1000 stays. The income indicator is significantly higher than that of the Valencian Community (2.22%) and the national one (2.62%); and the indicators during their income are only slightly larger than the regional (1.87 and 4.28‰) and national (1.82 and 3.36‰) estimates (**Figure 16**). There have only been three nosocomial infections for BMR acquired in ICU during this RZ period, 1 for Pa and 2 for Ab, with a BMR infection rate acquired in ICU lower (0.24 per 100 patients admitted to ICU) than the regional (0.60%) and the national rates (0.79%).

The profile of germs is different: predominance in our unit of germs producing ESBL + (42.8%) and *A. baumannii* (35.3%), with a lower presence of *P. aeruginosa* (10.9%) and MRSA (10.1%). %); while at the regional and national level, the most common germs in decreasing order are Enterobacteria ESBL + (42.6% regional and 42% national), MRSA (21.5 and 21.2%), *P. aeruginosa* (16.7 and 16.8%), *A. baumannii* (10.5 and 9.2%) and GNB producers of carbapenemases (8.3 and 9.1%) (**Figure 17**).

6. Conclusions

The problem of multidrug resistance is serious. The loss of efficacy of antibiotics, within our current technified medicine, would limit procedures such as transplants, complex surgeries, the management of cancer patients, and so on. It is the responsibility of EVERYBODY to make an efficient use of antibiotics. We must remember that a large part of the use of these molecules is done at the industrial level, out of sanitary management.

The striking finding of the NORTH-SOUTH and WEST-EAST gradient of MRB isolates frequency can have several explanations: different policies of antibiotic use, environmental conditions (heat) that favors the persistence of certain germs in the hospital environment, variable culture of security within the hospital centers, and so on.

The RZ project, despite the difficulties in its development, shows efficacy in reducing MRB infections acquired in the ICU. It has been achieved up to 40% of the days in ICU without the use of antibiotics. The number of germs discovered at the time of admission is greater than during the stay in ICU. The MRBs that caused colonization acquired in ICU increased, while the infections acquired by BMR decreased. A great proportion of MRSA and ESBL among isolated microorganisms has been documented on admission, and germs producers of carbapenemases, *P. aeruginosa* and *A. baumannii* are more frequent during their stay in the ICU. There are important differences between autonomous communities; there may even be differences between different units of critics of the same hospital. The active search for MRB in patients at the time of admission has doubled its detection. The application of the recommended measures in RZ has achieved to reduce acquired MRB infections acquired up to 45%.

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