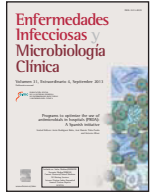




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Evaluation of new antimicrobials for the hospital formulary. Policies restricting antibiotic use in hospitals

Miquel Pujol^{a,*}, Olga Delgado^b, Francesc Puigventós^b, Juan E. Corzo^c, Emilia Cercenado^d and José Antonio Martínez^e

^aServicio de Enfermedades Infecciosas, Hospital Universitario de Bellvitge, IDIBELL, Universitat de Barcelona, Barcelona, Spain

^bServicio de Farmacia, Hospital Universitario Son Espases, Palma de Mallorca, Spain

^cUnidad de Enfermedades Infecciosas y Microbiología, Hospital Universitario de Valme, Sevilla, Spain

^dServicio de Enfermedades Infecciosas y Microbiología, Hospital General Universitario Gregorio Marañón, Madrid, Spain

^eServicio de Enfermedades Infecciosas, Hospital Clínic, IDIBAPS, Universitat de Barcelona, Barcelona, Spain

ABSTRACT

Keywords:

Antibiotic resistance

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Restrictive antimicrobial policies

In Spain, the inclusion of new antibiotics in hospital formularies is performed by the Infection Policy Committee or the Pharmacy and Therapeutic Committee, although now the decision is moving to a regional level. Criteria for the evaluation of new drugs include efficacy, safety and cost. For antimicrobial drugs evaluation it is necessary to consider local sensibility and impact in bacterial resistance to determinate the therapeutic positioning.

There is compelling evidence that the use of antibiotics is associated with increasing bacterial resistance, and a great number of antibiotics are used incorrectly. In order to decrease the inappropriate use of antibiotics, several approaches have been proposed. Limiting the use of antimicrobials through formulary restrictions, often aimed at drugs with a specific resistance profile, shows benefits in improving antimicrobial susceptibilities and decreasing colonization by drug-resistant organisms. However, the restriction of one agent may result in the increased utilization of other agents. By using antibiotic cycling, the amount of antibiotics is maintained below the threshold where bacterial resistance develops, thus preserving highly efficient antibiotics. Unfortunately, cumulative evidence to date suggests that antibiotic cycling has limited efficacy in preventing antibiotic resistance. Finally, although there is still little clinical evidence available on antibiotic heterogeneity, the use of most of the existing antimicrobial classes could limit the emergence of resistance.

This review summarizes information regarding antibiotic evaluation and available restrictive strategies to limit the use of antibiotics at hospitals with the aim of curtailing increasing antibiotic resistance.

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Evaluación de nuevos antibióticos para el formulario de hospital. Normas restrictivas del uso de antibióticos en los hospitales

RESUMEN

Palabras clave:

Resistencia antibiótica

Uso de antibióticos

Programas de optimización del uso de antibióticos

Políticas restrictivas de uso de antibióticos

En España, la evaluación de nuevos antibióticos para su inclusión en los formularios de los hospitales se realiza en la Comisión de Infecciones y la Comisión de Farmacia y Terapéutica, aunque hay una tendencia a que la decisión se traslade al ámbito de la comunidad autónoma. Los criterios de evaluación de nuevos medicamentos incluyen los datos de eficacia, seguridad y coste. En el caso de los antimicrobianos es necesario además valorar la sensibilidad local y el impacto en las resistencias bacterianas, para determinar su posicionamiento terapéutico.

Hay numerosas evidencias de que el consumo de antibióticos se asocia con un aumento de las resistencias bacterianas y, además, muchos antibióticos se utilizan de forma incorrecta. Para reducir el uso inadecuado de los antibióticos se han propuesto distintos abordajes. En primer lugar limitar el uso de antibióticos mediante formularios restrictivos, a menudo relacionados con antibióticos asociados a un perfil de resistencias determinado. Esta estrategia ha demostrado beneficios en sensibilidad y reducción de la colonización por microorganismos resistentes, aunque la restricción de un fármaco concreto pueda conllevar el aumento del consumo de otros. Mediante el uso cíclico de antibióticos se pretende que el consumo total de antibióticos

*Corresponding author.

E-mail: mpujol@bellvitgehospital.cat (M. Pujol).

se mantenga por debajo de un determinado umbral a partir del cual se desarrollarían resistencias, lo que permitiría un uso ecológico de los antibióticos. Desafortunadamente, en la práctica la evidencia acumulada sugiere que el uso cíclico tiene una eficacia limitada para evitar las resistencias. Finalmente, la estrategia que en la actualidad se considera más prometedora está en relación con la diversificación o uso heterogéneo de antibióticos. El uso de diversas clases de antibióticos existentes, sin que se sobrecargue especialmente un grupo, podría limitar el desarrollo de resistencias de los diferentes antibióticos utilizados, aunque todavía hay poca evidencia en la eficacia de esta estrategia. Esta revisión resume la información disponible sobre la evaluación de antibióticos y las estrategias restrictivas existentes para limitar el uso de antibióticos en los hospitales, con el objetivo de reducir el aumento de las resistencias bacterianas.

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Evaluation of new antimicrobials for the hospital formulary

In Spain, the evaluation of new drugs for their inclusion in hospital formularies has traditionally been performed by the Pharmacy and Therapeutic Committee and for antimicrobials by the Infection and Antibiotic Policy Committee. These committees have been working together for decades on drug selection and positioning antibiotics within hospital protocols or treatment guidelines.¹ In recent years, with the emergence of structures for the evaluation of drugs in most of the autonomous regions, the evaluation of new drugs has changed from a hospital to a regional level. These changes have directly affected the use of antibiotics in the public health system in Spain in a more restrictive manner. For example, the last antimicrobial evaluated fidaxomicin, with the specified summary of product characteristics: "Treatment of *Clostridium difficile* infections in adults". The conditions for prescribing this new antibiotic in the public health system were restricted to "treatment for a second recurrence of *C. difficile* infection after the use of metronidazole and vancomycin, in third line treatment". At a national level, the "Coordination Group for Therapeutic Positioning" within the Permanent Commission of Pharmacy, invited members of all the Spanish Autonomous Communities to participate in the working group, and has published several reports in coordination with the Agencia Española de Medicamentos y Productos Sanitarios (The Spanish Agency for Medicines and Health Products, AEMPS), which defines guidelines for the use of the new drugs.²

Procedures and criteria for inclusion of new antimicrobials in hospital formularies

The evaluation of a new drug¹ is based on basic principles such as:

- Independence from a promotional environment and workload.
- Transparency in the assessment procedure and in the decision.
- Dissemination of the methodology and the information produced.
- Scientific rigor in evaluating the efficacy, safety, and cost.
- Determination of the risk-benefit and cost-effectiveness based on the methods and concepts of Evidence-Based Medicine (EBM) and economic studies.

Methodology for evaluation of new antimicrobials

The evaluation of a new drug is based on an analysis of the therapeutic value compared to those used as alternative therapy. Economic evaluation is performed using criteria of cost-effectiveness and budget impact. The position of the new drug in the hospital formulary is not limited to the inclusion but also defines its place in the guidelines.

The GENESIS Group from the Sociedad de Farmacia Hospitalaria (Society of Hospital Pharmacy, SEFH) has adopted several tools for drug evaluation such as the GINF guide,³ a standard format for drug evaluation, the MADRE program,⁴ and the GENESIS report,⁵ a model

of a report for the evaluation of new drugs. In Spain, the GENESIS report is currently the model of reference used for most hospitals and has been adopted by a majority of groups in charge of drug evaluation and health services.⁶

Specific criteria in the evaluation of antimicrobials

There are several aspects of antimicrobials that should be considered specifically in the evaluation and selection of new drugs:

Therapeutic use. The evaluation of a new drug for therapeutic use must take into account factors that depend on the specific disease, the patient and the drug. For antimicrobials it is necessary to consider two specific additional aspects: characteristics of the pathogen and the effects of the antimicrobial in the environment. Any administration of an antimicrobial, appropriate or not, determines the success of subsequent therapies, not only for the patient who has been treated, but also for patients who have never received these antimicrobials.

Efficacy. Antimicrobials are highly effective treatments. They are virtually the only drugs with curative purposes in which the efficacy is evaluated by clinical or microbiological cure rates. However, clinical trials performed for the registration of new antimicrobials are usually designed as "non-inferiority" with a delta value ranging from 10%-20%. This designation has occurred with the recent introduction of ceftaroline,⁷ and fidaxomicin.⁸ All of these antibiotics have been evaluated regarding their efficacy as therapeutic equivalents to comparator antimicrobials. Even if a greater efficacy has not been demonstrated, the role of new antibiotics could be significant in patients without clinical responses to infection or regarding local sensitivity patterns as well as antibiotic selection pressure.

Safety assessment. Because the planned duration of an antimicrobial in terms of days of therapy is usually short, the assessment of safety for antimicrobials has the advantage of short-term results. However, it is important to note that antibiotics are the second most involved in drug toxicity problems⁹ and some antimicrobials, such as temafloxacin and grepafloxacin, have been withdrawn from the market for safety issues.¹⁰

Price. Antimicrobials cost has been decreased due to the loss of patents and generic brand introduction. However, for the purpose of economic evaluation, availability of oral treatment must be considered.

Therapeutic positioning. To define the drug positioning at the hospital formulary, it is necessary to assess all aspects related to its antimicrobial action, spectrum of activity, pharmacokinetics/pharmacodynamics (PK/PD) profile, low tissue penetration, such as bone or the central nervous system, and to assess local microbiological

patterns according to the source of infection and its susceptibility to antibiotics. Although all antibiotics are potentially capable of inducing collateral damage,¹¹ penicillin and their combinations are less frequently related to superinfections and *C. difficile* associated diarrhea than cephalosporins or quinolones. Finally, diversification on the use of antibiotics to reduce the selective utilization of an antimicrobial can justify the availability of new antimicrobial.¹²

Restrictive policies in antibiotic use at the hospital

Antimicrobial restriction policies can be implemented by antimicrobial stewardship programs (ASP) in various ways: through the availability of local therapeutic guides, specific requests for the use of certain drugs, formulary restrictions with prior- or after-dispensing individual approval, implementation of an automatic suspension order, and periodic rotation and diversification of antimicrobial drugs.^{13,14}

Formulary restriction or exclusion

The exclusion of certain drugs from the local therapeutic guide is a primary restrictive action.¹³ Antimicrobial drugs unable to provide additional benefits over existing drugs should not be approved in the hospital. As noted in the previous section, the approval of a new antimicrobial drug in a hospital is a complex process that may become controversial. The new drug profile (available clinical trials, observational studies, safety data, in vitro and experimental models, cost-effectiveness analysis) and the local epidemiological environment have an important impact on drug approval decisions. The hospital antibiotic team, as an important part of the ASP, plays a critical role in contributing to a correct assessment of new antimicrobial drugs through a suitable and homogeneous methodology.^{13,14} Antimicrobial restrictions related to the existence of a hospital therapeutic guide have an immediate effect, reducing antibiotic consumption and related costs. However, there is no evidence that this reduction correlates with a parallel decline in antibiotic resistance.

Formulary restriction strategies

Prescription approval or formulary restriction strategies, should be a responsibility of the hospital antibiotic team, which is in charge of reviewing antibiotic order forms (either paper or electronic format) to trigger an initial evaluation prior to dispensing or after dispensing (the next morning or within "1-3 calendar days").¹⁵ Selected agents may be entirely unavailable (formulary-based restriction), available for only certain indications (criteria-based restriction), or available only after approval by some authority (preauthorization-based restriction).¹⁶ These actions are often aimed at drugs with specific resistance profiles or epidemiological characteristics such as carbapenems, linezolid, daptomycin, colistin or tigecycline.¹⁷ From an economic perspective, restriction policies can reduce drug use and drug costs without adversely affecting patient outcomes.¹⁸

Limiting inappropriate use of antimicrobial drugs also shows benefits in terms of improving antimicrobial susceptibilities and decreasing colonization by drug-resistant organisms (e.g., cephalosporins and *Klebsiella* spp.).¹⁹ A potential drawback to this process is that the restriction of one agent may result in the increased utilization of another agent. This phenomenon has been described figuratively as "squeezing the balloon".²⁰ However, some programs have shown a lack of association between antimicrobial restriction and improvements in organism susceptibilities or patient outcomes.²¹ Studies with formulary restrictions alone may not yield the desired results and should be combined with other strategies aimed at reducing inappropriate antimicrobial use.

Preauthorization formulary restriction

The preauthorization formulary restriction may result in immediate improved outcomes for hospitals. Benefits are usually related to antimicrobial consumption with financial savings and can be also accompanied by a decrease in antibiotic resistance.²² Nevertheless, there are several pitfalls to the preauthorization approach. Each restricted antibiotic order is time consuming and antibiotic therapy may be delayed with this extra step, potentially endangering septic patients for whom delays of every hour are associated with decreases in survival. These concerns can be minimized by allowing the first dose of an antibiotic without question and instead focusing efforts on longer-term treatment decisions. Also, preauthorization formulary restrictions bring a sense of loss of autonomy for the prescriber and may be accompanied by mechanisms to override the restriction,¹³ such as incorrect application approval or prescription after hours, preventing proper assessment by the antibiotic team.

Proper implementation of this strategy requires sufficient resources with continuous availability of the antibiotic team 24 hours a day every day, or at least periods of 12 hours a day.¹⁷ The availability of computer applications integrating clinical and microbiological information in real time ("expert programs") can facilitate the implementation of these measures, although there is little experience to date.²³ Pre-authorization must be supported by medical leadership in order to foster good relationships between practitioners and antibiotic team members.¹⁵ An open feedback loop that allows real-time communication between the ordering provider and antibiotic team members is necessary for proper facilitation of patient-specific concerns and antimicrobial expertise. When agreement is not possible, an appeal process must exist to help reach an agreement and to avoid potential injury to the patient.

Scheduled suspension orders

The application of automatic or scheduled suspension orders of an antibiotic also requires a suitable computer support. This measure aims to reduce antibiotic consumption by limiting the duration of treatment with the objective of reducing selection pressure and resistance. It provides the secondary benefit of reducing hospital costs associated with lower antibiotic consumption. The simplest application and best-documented example of this measure is to suspend scheduled surgical prophylaxis to prevent prolonged and inappropriate use of antibiotics.¹⁴ There is less experience in other settings, although some studies have found that its implementation is not an added risk to patients.²⁴ A proper clinical assessment is essential to implementing this strategy. Procalcitonin levels or some specific scores such as clinical pulmonary infection scores may be helpful to achieve this goal, particularly in Intensive Care Units.^{25,26}

Antibiotic cycling

In an attempt to control antibiotic use and the development of bacterial resistance, several strategies to modulate and optimize the pattern of use of antibiotics have been proposed.²⁷ Antibiotic cycling refers to the rotation of antimicrobial agents: one specific agent or class of agents is withdrawn from use during a predefined time period, switched to another, and reintroduced at a later time.²⁸ True antimicrobial cycling requires a return to the antimicrobial or antimicrobials that were first used. This systematic rotation must be used in empirical and directed therapy and can be applied within an institution, either hospital-wide or confined to specific units, more frequently in intensive care units. The objective of antibiotic cycling is to avoid or reverse the development of antimicrobial resistance and to slow the evolution and spread of antibiotic resistance in hospitals. By using antibiotic cycling, the amount of utilized

antibiotics is maintained below the threshold at which bacterial resistance develops, thus preserving highly efficient antibiotics.²⁹ From a theoretical point of view, antibiotic cycling could be useful in epidemics due to bacteria that are resistant to narrow-spectrum antibiotics. Cycling should enhance the bacterial susceptibility to these agents, and it also could be useful to prevent or control high resistance rates when two antibiotics with similar efficacy are used in surgical prophylaxis. The introduction of a new antibiotic may offer an opportunity to slow the emergence of resistance to this antibiotic and to enhance the susceptibility of the pathogens to the alternative antimicrobial used in rotation. Finally, antibiotic cycling may be useful to optimize the efficacy of two antimicrobials when they are used in combination therapy.^{28,29}

The basic rationale for cycling is that fluctuating selection pressures will reduce the rate of adaptation or the ability of an evolving population to track its environment. By reducing the rate of resistant pathogens, the rates of mutation and genetic transference will also be reduced, as will the risk of selection of resistant strains. Rotation will also diminish the expression of a mechanism of resistance by minimizing the exposure of the antibiotic to the pathogen. Under a cycling program, the clonal population experiences consistent selective conditions until the next cycle, usually a period of months.

Clinical studies

Most studies that have analyzed the impact of cycling have been performed within intensive care units, involving cycling regimens targeted for treatment of suspected gram-negative bacterial infections. Initial studies suggested that this strategy had at least short-term success in reducing the rates of bacterial resistance as well as the incidence of nosocomial infections caused by gram-negative bacilli. In one study performed over a period of one year, a switch from cephalosporins to carbapenems reduced the incidence of cephalosporin-resistant gram-negative infections in a hospital. However, this decline in the frequency of cephalosporin resistance was countered by an increase of carbapenem resistance.^{19,20} Gerding et al.³⁰ reported parallel increases in the rate of gentamicin use and the prevalence of gentamicin-resistant, gram-negative organisms when gentamicin replaced amikacin as the agent available. During the next 10 years, amikacin alternated with gentamicin in a cycling fashion, and the prevalence of gentamicin resistance dipped and peaked in alternation with amikacin resistance. After several cycles, the resistance problem stabilized at a low level. Gruson et al.³¹ demonstrated that antimicrobial cycling in medical ICUs by restriction of both ciprofloxacin and ceftazidime and a rotation policy using cefepime and piperacillin/tazobactam, significantly reduced specific antimicrobial resistance during the overall cycling period. Raymond et al.³² studied the impact of rotating empirical antimicrobial regimens among patients in three ICUs during a 2-year period. In this study, two regimens were cycled: carbapenems (for peritonitis), and ciprofloxacin + clindamycin (for pneumonia), were alternated with cefepime + metronidazole (for peritonitis), and piperacillin/tazobactam (for pneumonia). The incidence of nosocomial infection due to resistant gram-positive and gram-negative pathogens significantly decreased from 14.6 and 7.7/100 admissions, respectively in the baseline period, to 7.8 and 2.5/100 admissions over the intervention period. However, the population of patients who had these infections during the intervention period differed from that of the baseline period and a waterless hand hygiene agent was introduced during the cycling period, which may have significantly reduced cross-transmission of resistant organisms. Martínez et al.³³ compared a mixing versus a cycling strategy of use of anti-Pseudomonas antibiotics on the acquisition of resistant gram-negative bacilli in the critical care setting. They concluded that a strategy of monthly rotation of anti-Pseudomonas β -lactams and ciprofloxacin performed better than a strategy of mixing in the

acquisition of *P. aeruginosa* resistant to selected β -lactams. In a recent study, Ginn et al.³⁴ evaluated the clinical and microbiological outcomes in two ICUs, which both alternated cefepime with piperacillin/tazobactam in four-month cycles. They observed increased colonization and infection by antibiotic-resistant bacteria in cefepime cycles, returning to baseline in piperacillin/tazobactam cycles.

The efficacy of antibiotic cycling has also been evaluated outside ICUs. Domínguez et al.³⁵ analyzed the impact of cycling four antimicrobial regimens (ceftazidime+vancomycin, imipenem, aztreonam + cephazolin, and ciprofloxacin+clindamycin) as the empirical treatment of hematologic patients. Over the study period, both the number of isolates and the rate of enterococcal infections significantly increased at the end of the study but they also observed a significant decrease in the incidence of infections due to *Enterobacter cloacae*. Cumpston et al.³⁶ evaluated the role of empiric antibiotic cycling over a long-term follow-up period in preventing antibiotic resistance in a prospective cohort of hematological malignancy patients with neutropenic fever. Over a period of 3 years, antibiotics were cycled every 8 months (period A), and over a period of 4 additional years, antibiotics were cycled every 3 months (period B). The rates of bacteremia and resistance were compared to a retrospective cohort (pre-cycling period). The rate of gram-negative bacteremia decreased when compared to periods A and B, most likely due to implementation of quinolone prophylaxis. Gram-negative resistance remained stable, with the exception of an increase in quinolone resistance during the cycling periods. Gram-positive bacteremia rates remained stable, but vancomycin-resistant *Enterococcus* increased significantly during cycling periods.

In general, cycling studies performed to date have many limitations on the ability to interpret and generalize their findings, and it is difficult to determine whether any meaningful impact on resistance has occurred as a result of a cycling program.³⁷ The influence of several factors on the mechanisms of emergence and spread of resistance in microorganisms makes it difficult to establish a cause-effect relationship and in addition, in most studies compliance with the cycling programs varied. Although antimicrobial cycling is attractive in theory for its relative feasibility and ease of implementation, several publications indicate that as many as 10%-50% of patients are exposed to antimicrobials that are "off-cycle" due to the clinician's concerns about allergies, side effects, or consistency with guidelines.^{31,32} Moreover, the efficacy and harmful effects associated with cycling programs are unknown and further clinical studies are necessary to clarify the effect of cycling on antibiotic resistance.

Because ideal studies may not be possible, several authors have developed theoretical models to predict the impact of cycling.^{38,39} Bergstrom et al.³⁹ developed a mathematical model of antimicrobial cycling in a hospital setting and used this model to explore the efficacy of cycling programs. They found that cycling was unlikely to reduce either the evolution or the spread of antibiotic resistance. Moreover, with this model, they predicted that alternative drug-use strategies such as mixing, in which each treated patient receives one of several drug classes used simultaneously in the hospital, would be more effective: the more antibiotics used, the better. The explanation for this event is that heterogeneous antibiotic use slows the spread of resistance and mixing imposes greater heterogeneity than does cycling; as a consequence, cycling is unlikely to be effective. These results may explain the limited success reported thus far from clinical trials of antimicrobial cycling. However, the results of this study also suggested that cycling may not always be a poorer alternative to mixing. If resistance is acquired by horizontal transfer of genes, the likelihood of acquiring resistance to both antibiotics can be less with cycling than with mixing. However, because of the higher overall frequencies of resistance to single antibiotics, if acquired resistance to both antibiotics is through mutation, cycling is a poorer alternative to mixing. Another mathematical model showed

that when more than one antibiotic was employed, sequential use of different antibiotics in the population (cycling) was always inferior to treatment strategies where, at any given time, equal fractions of the population received different antibiotics.⁴⁰

In summary, although changing the availability of classes of agents appears to reduce the prevalence of resistance, new resistance mechanisms may rapidly emerge. Antibiotic cycling may be one way to change prescribing practices by clinicians; however this strategy does not prevent antibiotic misuse and needs to be applied in a complete antibiotic optimization program.

Antibiotic diversification

Treatment strategies in which, at any given time, equal fractions of the population receive different antibiotics, is a modality of antibiotic use called mixing.⁴⁰ Mixing acts like a cycling strategy with zero duration of cycles. Mixing can be accomplished according to a schedule, such as promoting the use of a different class of antibiotic in each consecutive patient with a suspected or proven infection, or in an unplanned manner by just offering several antibiotic choices for a given condition to the attending clinician.

Promoting diversification is the strategy called "periodic antibiotic monitoring and supervision (PAMS)".⁴¹ During PAMS, a set of several antibiotics is selected for intervention and each component is either promoted, restricted or left off-supervision during a scheduled period of time (usually three months) according to their frequency of use and/or the prevalence of resistance of an indicating microorganism (e.g., *P. aeruginosa*) observed during the preceding term.

Antibiotic diversification in clinical practice

Several studies, all performed in the intensive care setting, have shown that priority given to a single antibiotic class during periods ≥ 3 months may not only promote resistance in gram-negative bacilli to the drug in question (whether this is a fluoroquinolone or a β -lactam) but may also have prolonged effects and foster multiple-drug resistance.^{42,43} In an investigation⁴³ carried out in a surgical ICU, the prevalence of resistance was assessed along four successive 4-month rotation schemes of levofloxacin, then ceftiofime, then again levofloxacin and then piperacillin-tazobactam, with 96% adherence to the program. The prevalence of resistance in gram-negatives to both ceftiofime and piperacillin-tazobactam peaked during the periods of preferential use of one or the other β -lactam (as if they were the same antibiotic), and the prevalence of levofloxacin resistance did not decrease during the last period of piperacillin-tazobactam predominant use. In another study,⁴⁴ a scheduled change of carbapenems, cefepime, ciprofloxacin and piperacillin/tazobactam at 3-month intervals during one year led to a significant increase in the rates of resistance to cefepime and piperacillin-tazobactam among gram-negative bacilli. The resistance occurred mainly during the periods of preferential use of these antibiotics (18%-22% in comparison to 1%-4% in the before-period). In addition, a 21% rate of organisms resistant to more than one drug (compared with 5% in the before-period) was observed. However, the increase in resistance to ciprofloxacin and carbapenems was not as substantial and did not reach statistical significance. Similar findings for gram-negative bacilli were obtained in another study in which cephalosporins, β -lactamase-inhibitor combinations and fluoroquinolones were rotated at 8 month intervals.⁴⁵ In this study, there was a marked drop in the susceptibility of *P. aeruginosa* to ciprofloxacin during prioritization of both quinolones and β -lactamase-inhibitor combinations. In addition, quinolone periods were associated with an increase in resistance to imipenem. However, no significant changes in the prevalence of resistance to β -lactamase-inhibitor combinations or cephalosporins were noted during their respective periods of predominant use. These studies showed that

homogeneous exposure to a given antibiotic class may not prevent the development of resistance to other classes and that withdrawal of exposure may not necessarily be followed by a decrease in resistance as quickly as predicted by mathematical models. Obviously, the presumption of independence between different classes of antibiotics on the selection of resistance is too simplistic. Piperacillin-tazobactam and anti-pseudomonal cephalosporins can both exert similar pressure for the selection of de-repressed inducible chromosomal β -lactamase producers among non-fermentative and enteric gram-negative bacilli. In the same manner, quinolones and several β -lactams can favor the emergence of multi-drug resistance in *P. aeruginosa* strains through the selection of mutants over-expressing efflux pumps.⁴⁶ However, it is difficult to ascertain why a given antibiotic or class does not produce the same resistance outcome in all studies. The discrepancy in these results may be due to differences in the actual prevalence of use of the involved antibiotics, the predominantly administered agent within a class (levofloxacin vs. ciprofloxacin, for instance) or the particular pair of antibiotic class-microorganism considered.

In view of the rapid ascent of resistance associated with the predominant use of a single antibiotic, a more reasonable approach would be to promote continuous heterogeneity. There are several clinical studies that support this approach. Two studies have specifically addressed the issue of comparing cycling with mixing^{33,42} in the ICU setting. In one of them,³³ a 4-month period of monthly rotation of antipseudomonal β -lactams and ciprofloxacin was associated with a lower acquisition rate of *P. aeruginosa* resistant to cefepime when compared with a 4-month mixing period. However, adherence to cycling was relatively poor, with no more than 45% of patients receiving the scheduled antibiotic within a given cycle. This means that there was, in fact, a good deal of mixing during the intended cycling. In the second study,⁴² several strategies producing different "rates" of mixing and cycling (of 4 months' duration) were compared. It was observed that during the rotation period there was a lower Peterson index, meaning less heterogeneity than in the mixing periods, and this lower index was associated with an outbreak of a carbapenem-resistant *A. baumannii*, an increase in ESBL-producing Enterobacteriaceae and a higher incidence of *E. faecalis* infections. PAMS, when used as a hospital-wide policy, has also been associated with an increase in the heterogeneity of antibiotic use and with a corresponding decrease in the incidence of patients with resistant and multidrug-resistant gram-negative bacilli.⁴¹ However, it must be acknowledged that not all hospital-based studies have found an independent association between indexes of antibiotic diversity and prevalence of resistance.⁴⁷

Although there is sufficient evidence that homogeneous use of a single antibiotic class will lead to a rapid increase of resistance in hospitals, there is no definitive answer to the question of which strategy of diversification would be best. There is also no evidence that heterogeneous use of antibiotics can stop the progression of multiple-drug resistance or improve patient's outcomes.⁴⁸ Currently, in many hospitals and some communities there is a significant prevalence of patients already carrying multiple-drug resistant microorganisms against which many available antibiotics represent a single class in terms of selective pressure. Incorporating antibiotics with activity against these pathogens into the strategies of heterogeneity is problematic, since at least for some potential candidates there may be a risk of toxicity or lower efficacy. In any case, it must be taken into account that no policy of heterogeneous antibiotic use is a safeguard that allows the relaxation of current good practices of antibiotic prescription and management of sepsis, infection control, and common sense.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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