Commentary
A mathematical model using stress-induced genetic variation mechanisms to prevent emergence of resistant bacteria

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Abstract:
Over the past few decades, the emergence of multidrug resistance (MDR) to antibiotics in bacteria has led to major difficulties in the management of infected patients. At present, there is a serious lack of development of new antibacterial agents. Mathematical models are one approach to understand how antibiotic usage patterns may be optimized. However, the classical approach to modeling the emergence of MDR relies on the simplifying assumption that resistance is acquired at a constant rate. In their model, Obolski and Hadany introduced the notion of horizontal gene transfer and stress-induced mutation, antibiotics constituting an environmental stressor of particular relevance. Finally, from this complex mathematical model, authors proposed prediction for minimizing MDR in bacteria depending on strategies of antibiotic treatment.

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Keywords: Antibiotic resistance, Mathematical models, Multidrug resistance
Background
Over the past few decades, the emergence of bacteria resistant to multiple antimicrobial agents has led to major difficulties in the management of infected patients. This has required significant changes to our approaches to the use of antibiotics and should lead to new ways of thinking about the production of effective antibacterial drugs. Unfortunately, at present, there is a serious lack of development of new antibacterial agents notably concerning Gram-negative bacilli. Programs, supported by the medical community and government organizations, were implemented to limit the emergence of multidrug resistance (MDR) to antibiotics: reducing the inappropriate use of antibiotics (not treating colonization, antibiotic use is best suited to the clinical situation) and improving standards of hygiene to prevent cross-transmission. It is clear that these measures were not sufficient to stop the process [1]. Other approaches are possible such as modeling the emergence of MDR. The authors' objective of this study was to explore the impact of genetic variation induced by antibiotic stress on the spread of MDR in a hospital unit [2]. The purpose of such models is to understand how antibiotic usage patterns may be optimized.

Clinical importance of the mathematical model
In their rational Obolski and Hadany highlighted the importance of three different strategies of antibiotic prescribing to minimize the emergence of MDR. The authors noted the interest of each strategy against the risk of emergence of this MDR, indicating that more antibiotics were used in combining than in mixing or cycling. They emphasize that the classical approach to modeling the emergence of MDR relies on the simplifying assumption that resistance is acquired at a constant rate, ignoring recent data on the effect of environmental stress on mechanisms of acquired resistance. This erroneous assumption could be the cause of frequent reserves in the conclusions of these models. Moreover, the actual effect of a single intervention in a complex situation is often difficult to grasp [3-8]. The originality of the model used by Obolski and Hadany is to introduce the notion of horizontal gene transfer (HGT) and stress-induced mutation (SIM), antibiotics constituting an environmental stressor of particular relevance. The authors justify this hypothesis by showing examples of stress-induced HGT and SIM for various microorganisms that may be encountered in community-acquired infections (Streptococcus pneumoniae, Escherichia coli), nosocomial (Pseudomonas aeruginosa, E. coli) or epidemic infections (Vibrio cholerae). The model is used, but adapted
to integrate the concepts of stress-induced HGT and SIM [9]. The authors also introduce some constraints in the model: (i) the bacterial pathogens are assumed to accompany other ailments and not be the main reason for hospitalization, (ii) since the bacterial infection is not the main reason of hospitalization, patients leave the hospital or die at a rate proportional to their frequency, (iii) hospital occupancy is kept constant, (iv) there are no double-resistant bacteria in the hospital initially, and that their frequency in the general population is negligible. Concerning the SIM, they also considered for modeling the relative persistence of antibiotic resistance when there is no direct antibiotic use. The introduction of change of levels of antibiotic resistance persistence and stress-induced mutation has had different consequences in terms of proportion of infected patients and emergence of resistance. The introduction of different level assumptions (antibiotic resistance persistence and stress-induced mutation) has had different consequences in terms of proportion of infected patients and emergence of resistance. Indeed, the latter two parameters may vary either in the same direction or in the opposite direction in functions of the hypotheses. Another mechanism of acquisition of antibiotic resistance studied in this model was the HGT. The latter was studied in defining an encounter rate between bacteria. The authors also considered situations in which the bacteria were or were not under antibiotic stress. They developed the notion of time required for the cellular mechanisms to induce or repress HGT. They defined the extreme situation where the HGT rates of bacteria transmitted from patient A to patient B depend only on the stress of the bacteria experienced while residing in patient A. Thus, assessing the effects of different antibiotic regimens with respect to the encounter rates between bacteria is complex.

Finally, from this complex mathematical model, based on the important concepts of SIM and HGT, several conclusions can be proposed. The authors have shown relation between stress-induced genetic variation and emergence of double resistance. Combining performs very poorly in inhibiting double resistance emergence when genetic variation is stress-induced. Cycling is the preferred strategy with respect to the acquisition of resistance through SIM. When there is stress-induced HGT, cycling and mixing are the favored strategies. The speed of change in HGT frequencies in response to antibiotic stress determines the choice of strategy, between mixing and cycling. The authors noted that their prediction hold even for very mild increase of HGT and mutation rates under antibiotic stress in comparison with those described in the literature. However, the cited publications were referring to in vitro studies [10-13]
**Future directions and conclusions**

The present model showed that combining was more efficient than mixing and cycling by a small amount, when it comes to minimizing infection. Regarding double resistance emergence, both mixing and cycling were more efficient than combining when variation is stress-induced.

The authors have described the limits of their work: they did not consider the possible fitness cost of antibiotic resistance neither the influence of stochastic events (epidemic outbursts of bacteria and extinction of rare bacterial strains for long periods of time, human errors in the form of dosage errors, lack of compliance to hospital guidelines) on the dynamics. Other limiting factors were mentioned: patient age, relative efficiency of the different antibiotics and drug interactions. In our opinion, other limits may have been mentioned: the problems of nonadherence, self-medication, outpatient antibiotic use, and the state of immunosuppression of the patient treated.

Mathematical model such as that built by Obolski and Hadany is an important step to regulate the consumption of antibiotics. The originality of this model is the study of stress-induced genetic variation mechanisms on resistance emergence and minimization of infection. However, in the literature, it is usual that models consider only a single pathogen or a single mechanism of resistance acquisition and it is not sure they can be applied to other clinical situations. At the same time, in the aim to try to stop the continuing spiral of resistance, it is necessary to develop other research programs: campaigns to educate the public and healthcare workers [14], novel avenues for drugs targeting against infectious agents [15-16], the development of phage strategies [17,18] and new conjugate vaccines [19], the use of new agents such as probiotics or antivirulence drugs [20,21], the use of new diagnostic tools to differentiate colonization from infection [22]. Only a multidisciplinary approach will make winning the fight against MDR bacteria.
**Competing interests**
The authors declare that they have no competing interests.

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References


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