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Editorial

# Prudent use of antimicrobial agents: Revisiting concepts and estimating perspectives in a global world

## Uso prudente de los antibióticos: revisión de los conceptos y análisis de las perspectivas en un mundo globalizado

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The concept "prudent use of antibiotics" was coined in opposition to a widely extended belief during the 1960s to the1980s on the prescription of antimicrobial agents. Accordingly with this view, medical and veterinary practitioners were frequently acting in a non-prudent or irresponsible way when prescribing antimicrobials.[1] The term "prudent use" acquired international relevance as an educational slogan aiming at contributing to the reduction of resistance rates in pathogenic microorganisms, as there was growing evidence of a correlation between levels of antibiotic consumption and levels of antibiotic resistance. In this context, the "imprudent use" meant the use of antibiotics considering *only* the real or potential benefits of prescription on the presumed infected patient, disregarding its potential negative effects on the society (including economic costs) or the environment. In contrast, the "prudent use" meant educated appropriate prescription, using antimicrobials only in cases in which their administration was fully justified on objective grounds.

The time has arrived to refine those notions. First, imprudent use should not be considered as equivalent to "minimal use". Because of the simplicity of the concept and its favourable economical consequences, conventional health managers are prone to consider,for instance, that countries or regions with a low antibiotic consumption *per capita* have a better policy of antibiotic use. However, in the absence of reliable statistics on the local prevalence of infections requiring antibiotic therapy, it is simply impossible to know if the consumption is appropriate or not.[2] Second, we should accept that we are very far from knowing with certainty the circumstances in which antibiotic therapy should be considered as inappropriate. The NNTB index (number of individuals needed to treat for a benefit in one of them) does not cast any more light on the topic.[3] Note, that in the case of a total absence of risk of antibiotic over-usage, a policy of extended use could be beneficial, particularly if the targeted infection is an important one. How many cases of bacteremic pneumonia in the elderly, or acute bacterial meningitis in children, are indeed prevented (treated before clinical symptoms) by "unjustified" use of antibiotics? What are the deleterious consequences of an excess of restriction in use? We are only now beginning to understand the downstream consequences of restricting antibiotics on outcomes and costs. We are hampered by the lack of a universal ethical framework and information on outcomes.[4] Only in recent years we have started to extend databases and the required bioinformatic analytic tools able to address these questions. In reality, we are still awaiting rigorous scientific study about the risks and benefits of antibiotic use.[5]

The main ecological effect of antibiotics is promoting the emergence, spread, and diversification of antibiotic resistance genetic determinants, and consequently of the bacterial organisms carrying them, and is widely considered as the greatest risk associated to the imprudent extended use of these drugs. Although we do not have any major objection to adhere to this statement, we should also refine some common beliefs on this matter. First, the expected (stoichiometric) proportionality between the levels of antibiotic use and antibiotic resistance does not always occur. For instance, epidemics of fully-susceptible bacteria might reduce resistance in a region with high use; conversely, epidemics of resistant bacteria or resistance plasmids might occur in regions with appropriate levels of usage, unexpectedly increasing resistance.[6,7]

The decrease in antibiotic usage might not have consequences on antibiotic resistance rates, frequently because the resistance determinants are harboured by bacteria at very low biological cost.[8,9] Second, and more importantly, we should be ashamed of confessing that, after three-quarters of a century from the discovery of antibiotic resistance, we still lack solid data about the true impact of antibiotic resistance in the morbidity and

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mortality of most bacterial infections. Not every infection produced by bacteria carrying antibiotic resistance determinants is refractory to therapy, nor are all infections caused by antibiotic susceptible organisms responsive to antibiotics. Finally, resistance might help to keep the synergistic interactions with our intestinal microbiota.[10] But, in general, what we want to stress here is that the prudent use of antibiotics should be placed in a global ecological dimension.

The yearly total production of antibiotics can be estimated between 100,000–200,000 tons annually, and about one-half of it is used in outside humans.[11] Considering that most antibiotics exert their action at concentrations close to 1 ug/ml, that amount of antimicrobials is enough to cover the entire surface of the Earth with inhibitory concentrations, in other words, able to alter the populational genetic structure of microbes. Indeed the environment near to antibiotic producing factories might be heavily polluted: more than 20 ug/ml of oxytetracycline was detected in the treated effluent from a drug producing industry in China.[12] Moreover, antibiotics are not easily removed from the environment, and some families of them might remain active for extended periods of time. Resistance is present in environmental locations without a history of antibiotic pollution.[13] Nevertheless, the study of historical soils has demonstrated that the introduction of antibiotics has produced the increase in the prevalence of specific resistance determinants in environmental, non-clinical ecosystems.[14]

Antibiotic release is probably one of the major anthropogenic effects on the Microbiosphere, altering the microbial systems. Of course part of this alteration is predictable as antibiotic resistance, but unpredictable effects are most likely to occur, such as changes in the interactions between microbes or with animals, plants, or influencing basic cycles of life in the common Earth environment.[15–17] Therefore, the use of industrial antibiotics in agriculture, farming, and human or veterinary medicine converges to a single, cooperative effect, changing bacterial ecology, not only in different environments, but in the common environment. The main problem is the existing connectivity between all environments, human, farming, and agricultural, so that the antibiotic-imposed effect in one of them has consequences in all the others. As regards the undesirable consequences of antibiotic resistance, connection between the different environments occurs essentially in two ways, and will be considered in the following paragraphs. First, dispersal and migration of biological units involved in antibiotic resistance, as bacterial communities (metacommunities), bacterial clones, mobile genetic elements, and, in general, gene dispersal.[18] Second, there is dispersal of antimicrobial eco-toxic agents, which results in the production of selective gradients and stressor effects, and in the increase of microbial evolutionary rates. Combined migration of antibiotics and antibiotic-resistance biological units results in evolutionary-active interactions that occur in four main eco-genetic reactors: i) the intestinal microbiota of humans and animals; ii) the highly antibiotic-exposed areas with high rates of bacterial transmission, like hospitals (particularly newborn wards and intensive care units), iii) waste water, effluents, and sewage treatment plants, and iv) soil, sediments, surface and ground water,[19] which contribute to the escalation of the emergence and spread of antimicrobial resistance.

In the short term, the prudent use of antibiotics has a major beneficiary effect that justifies all measures: the severely ill patient whose health depends on the maintenance of antibiotic control of infections. If antibiotic-resistance were surpassing a threshold-limit, the consequences on the current standards of hospital-based medicine (including long-term-care facilities for elderly people) could be severely compromised. Albeit rare, there are already examples of resistant organisms to all available antimicrobials causing disease and death in the intense care setting. In the long term, the effect that the anthropogenic release of antibiotics has already caused in the genetic structure of bacterial populations is probably irreversible, and will influence the evolutionary future of microbes on the Earth.[16] Social norms should be established in a context of Conservation Medicine,[20] widening the limited scope of ''prudent use'' to be able to provide new equilibriums between humans and the Microbiosphere.

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