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Antibiotic & Multi-Resistance

Do we need new antibiotics?

Many press articles in recent years have highlighted the enormous public health problem of multi-resistant bacteria [3,5,6]. Very generally, these articles or papers at conferences highlight the weak pace of new antibiotic discoveries, showing two curves juxtaposing the number of new antibiotics discovered with the appearance of cases of super-resistant bacteria. The crossing of these curves announces major public health problems, but this frightening situation must be placed in perspective because the old antibiotics still exist and there is no decrease in the number of antibiotics. A more accurate curve should count all the antibiotics available, and not only the new ones [1].

That being said, it is necessary to take stock of the subject to assess the impact of antibiotic resistance on public health and how to remedy it. And to do so, it is necessary to understand the mechanisms by which these multi-resistant pathogens appear.

A problem of availability

In practice, looking at the number of antibiotics available on pharmacy shelves, it must be acknowledged that the number of references is falling from year to year, despite the (all too rare) introductions of new active ingredients.

In fact, many antibiotics are stopped not for problems of toxicity or lack of efficacy, but for common problems of profitability.

With changes to standards and the very low prices and sales volumes of antibiotics compared to drugs for chronic conditions, it is not economically favorable to keep them on the market. For example, thioamphenicol is no longer available in France, even though it is still has a therapeutic interest.

Clofazimine is used for leprosy but is no longer marketed in France, even though it would be of very great interest in the treatment of tuberculosis, as the two pathogens have many similarities.

The origins of the development of multi-resistant bacteria

When multi-resistant bacteria appear, meticulous investigations are carried out to identify their origins and prevent their expansion [4].

Progress in methods for analyzing bacterial genomes, with the generalization of maldi-Tof, PCR and other high-throughput sequencing techniques, has made it possible to broaden the areas of exploration.

Paleo microbiology key to understanding antibiotic resistance

These techniques have even allowed the creation of new branches of microbiological research.

Paleo microbiology with the progress of bioinformatics has made it possible to study the genome of many bacteria found in ancient sediments or in fossils, for example.

The great surprise for paleo microbiologists was that they have found germs of resistance to modern antibiotics in fossil organisms that were several thousand years old.

1 Do we need new antibiotics. JM Rolain, C. Cabat,MT Jimeno, PE Fournier, D. Raoult. Clin microbiol Infect 2016;22:408-415
3 WHO updates list of drug-resistant bacteria most threatening to human health. WHO 17 May 2024
4 l'antibioresistance: qu'est-ce que c'est? Sante.gouv.fr
5 Quand le miracle antibiotique vire au cauchemar. Med sci 2010 26: 925-929. Medecinesciences.org
6 Résistance aux antibiotiques un phénomène massif et préoccupant. wwwinserm.fr/dossier/resistance-antibiotiques/

"Well before the use of antibiotics by man, resistance genes were already present".

Resistance existed before the medical use of antibiotics. In fact, most people have forgotten the true origin of antibiotics and their roles. Since the creation of life forms on earth, there has been a fight between organisms to develop.

A very large number of defense/attack mechanisms, particularly between fungi/yeasts and bacteria, have been established gradually over geological timescales. Many of our antibiotics have also been extracted from yeast or various penicilliums.

Very often, the organisms producing these toxic components must have their own defense system to avoid self-destruction. The best-known example is emipenem [2]. It is an antibiotic produced by bacteria and active against bacteria. It is a poison that can therefore kill its host, which led the bacteria synthesizing it to make a counterpoison to avoid dying. This type of toxin-antitoxin system is quite widespread.

Obviously, this type of discovery challenges some preconceived ideas. The main cause of the appearance of super-resistant bacteria is mainly medical use of antibiotics inducing the appearance of these resistant powers. Most antibiotic resistance genes are already present in nature before antibiotic substances are even isolated.

The application of selection pressure by antibiotics allows resistant strains to emerge by eliminating non-resistant bacteria. With gene transfer mechanisms, when a resistance gene is selected, it can spread in an uncontrolled manner.

EBOLA resurgences

This does not directly concern the subject of multi-resistant bacteria, but the periodic resurgence of the Ebola virus in Africa has raised many questions for epidemiologists [13]. Much work has been done to understand the resurgence of epidemics of this virus, and it is applicable to many cases of multi-resistant bacteria.

The reservoir of the virus has long been identified as being among tree bats, and researchers have noted that epidemic outbreaks systematically appear two years after deforestation operations.

In fact, African epidemiologists have understood that after deforestation, the ecosystem is so disrupted that bats can no longer find food locally. Deforestation induces dissemination of colonies and consequently an increase in contacts with humans, creating new sources of contamination.

Gorillas and termites

Without any contact with pharmaceutical treatments, gorillas are often carriers of multi-resistant Klebsilla pneumonia bacteria, despite never having received antibiotic treatment [11].

After investigation, it was found that the resistance comes from the termites they eat. The termites have been cultivating fungi that eat cellulose in their termite mounds for millions of years. In termite mounds, millions of springtails naturally secrete antibiotics, including penicillin and cephalosporins. The termite mounds thus place selection pressure on the klebsiella, selecting multi-resistant bacteria that are then eaten by the termites and gorillas, but also sometimes by humans. In some African villages, 'termite mound soup' is a traditional remedy for angina. The termite mound extract has antibiotic properties.

These examples show that disruptions [10] to ecosystems are a key factor in the dissemination of new strains that can pose health problems directly or through the emergence of pre-existing antibiotic resistance genes.[12]

Intensive farming - the key to the problem

Intensive farming also drives selection of multi-resistant bacteria, as it uses huge quantities of antibiotics to avoid infections.

In many countries, antibiotics are also used as growth promoters.

Vancomycin is one of the antibiotics of choice to treat resistant infections, but widespread resistance was soon observed in humans. In fact, the resistant strains had been selected in turkey farms treated with avoporcin in order to make them gain 30% weight. These treatments led to the selection of enterococcus strains that lead to many urinary tract infections in humans and are resistant to vancomycin.

2 Emergence of resistance to carbapenems in Acinetobacter baumannii in Europe: clinical impact and therapeutic options. Inter. Journal of antimicrobial agents. Marie Kempf, JM. Rolain. Vol 39, issue 2 feb2012

10 Why do arthropods secrete β-lactams? https://www.elsevier.com/open-access. 2018 published by Elsevier. Pierre Pontarotti1-2, Didier Raoult

11 Gorilla gorilla gorilla gut: a potential reservoir of pathogenic bacteria as revealed using culturomics and molecular tools. Fadi Bittar1, Mamadou B. Keita1, Jean-Christophe Lagier1, Martine Peeters2, Eric Delaporte2 & Didier Raoult1. SCIENTIFIC REPORTS 11/2014 | 4 : 7174

12 Antimicrobial resistant enteric bacteria are widely distributed amongst people, animals and the environment in Tanzania. Murugan Subbiah1,7, Mark A. Caudell1,2,7*, Colette Mair3,7, Margaret A. Davis1, Louise Matthews, Robert J. Quinla, Marsha B. Quinlan , Beatus Lyimo , Joram Buz, Julius Keyyu & Douglas R. Call. Nature communication (2020)11:228

13 The nexus between forest fragmentation in Africa and Ebola virus disease outbreaks. Maria Cristina Rulli, Monia Santini, David T S Hayman & Paolo D'Odorico. Scientific Reports 2017 | 7:41613

Multi-resistant bacteria develop when they encounter a terrain to conquer

Stopping the use of avoporcin has helped to reduce resistance to vancomycin. [9]

In both cases, the quantities of antibiotics used by these practices are several orders of magnitude greater than the uses of antibiotics for human use.

The problem of pesticides

A great many pesticides and herbicides have antibiotic properties. The much-debated glyphosate is a perfect example. During its development, Monsanto filed patents for its use as an antibiotic. The use of thousands of tons of these components on a global scale destroys the microfauna of agricultural land and exerts huge selection pressure in the soils, which also induces the appearance of resistant strains.

How to deal with it

By a better understanding of the origin and dynamics of multi-resistant bacteria, it is possible to define ways to reduce their risks of emergence.

Resistance genes are not due to antibiotics, but are selected by them.

Alleviate selection pressure

To avoid the appearance of multi-resistant bacteria, it is essential to act on the most important origins. Agriculture must clearly rethink its practices to make massive reductions to the use of antibiotic products and herbicides/pesticides with antibiotic properties.

Understand the dynamics of resistance genes

Multi-resistant bacteria develop when they encounter a terrain to conquer. When a patient is treated with an unsuitable antibiotic, it destroys a large part of the patient's microbiota, which leaves the field open to the resistant bacteria that can increase their growth and pathogenic power.

It is not uncommon for the dreaded Clostridium difficile to be found in the stools of patients living in low-income countries without any symptoms, while the same strain causes considerable mortality in infected patients in Western countries.

In a competitive environment with a multitude of bacteria, multi-resistant pathogens cannot develop freely and remain in low numbers.

The life cycle of multi-resistant genes

When bacteria no longer have a competitive advantage via a gene, they can lose it over successive generations and mutations and a multi-resistant bacterium can therefore become sensitive to certain antibiotics again. This parameter is most likely one of the mechanisms that regulates the periodic nature of epidemics.

Optimizing doses

Better use of existing antibiotics is also an important area to explore.

The tests carried out to adapt the best antibiotics to a patient are standardized with standardized antibiograms. We are a long way from personalized medicine.

Most antibiotics are defined by minimum effective doses, but for a given antibiotic it is rare to have data for a specific strain infecting a particular patient. Sometimes a change in dosage or treatment regimen would allow resistance to be lifted. Rapid microbiology techniques would allow personalized treatment to be implemented.

To summarize

Super-resistant bacteria represent a real risk to global public health, and basing a strategy solely on the discovery of new antibiotics is an unacceptable risk.

We should try to be smart and act first on the root causes that are allowing these super-resistant bacteria to emerge.

All the examples cited in this article show that the discovery of new antibiotics is not the only solution to avoid an epidemic catastrophe caused by the emergence of certain multi-resistant bacteria.

Firstly, it is therefore urgent to act rationally and drastically reduce the use of antibiotics in livestock farming as a growth factor or to prevent infection. The immense quantities used for these uses inevitably lead to the creation of new multi-resistant strains.

It is also necessary to massively reduce the phytosanitary products that have antibiotic activities. In practice, a large portion of these products do have antibiotic activity.

This would have 2 major direct benefits:

- It would limit the risk of the emergence of super-resistant bacteria in livestock farms

7 Enquête sur les usines d'antibiotiques indiennes, fabriques d'antibiorésistance. Le monde 11 décembre 2018

8 En Inde, la recette parfaite pour faire émerger des superbactéries. Le monde 10 décembre 2018

9 L'utilisation au Canada d'antimicrobiens chez les animaux destinés à l'alimentation : les conséquences pour la résistance et la santé humaine. Direction des médicaments vétérinaire du canada juin 2002. https://www.canada.ca/fr/sante-canada/services/medicaments-produits-sante/rapports-publications/medicaments-veterinaires/utilisation-canada-antimicrobiens-chez-animaux-destines-alimentation-consequences-resistance-sante-humaine-sante-canada-2002.html

- It would directly reduce manufacturing and therefore the pollution of these components from old antibiotic production plants. Since the anti-pollution standards in these plants are at best random, these plants can induce the emergence of super-resistant bacteria following massive discharges [7,8].

Obviously, these first two measures make it necessary to thoroughly review agricultural models in many countries. Those that do not make these changes will most likely be faced sooner or later with epidemic outbreaks that will not always be easy to control.

The emergence of these bacteria must then be controlled to avoid any epidemics or pandemics. Most health systems around the world have already adopted good practices that absolutely must be preserved and optimized.

Relearning how to use existing antibiotics properly by optimizing dosages and treatment regimens is another obvious step. We must be able to make the most of the pharmacodynamic and pharmacokinetic characteristics of these old molecules that have provided great services in the past.

It is essential to rework old antibiotics and substances previously used (colored derivatives) to optimize their use by working on dosages, pharmacokinetic optimizations, and combinations of antibiotics with each other or with inhibitors of the enzymes produced by these super bacteria. Advances in biology should open up vast fields of research.

All the studies conducted on the interest of microbial biodiversity for humans are now clear. It is imperative to take a serious look at the possibility of getting help from 'good bacteria'. This may seem counterintuitive, but in the event of infection, we could very well consider combating the resistant bacteria with cocktails of living bacteria in symbiosis in our microbiota, so as not to leave the field open to problematic bacteria. In the same vein, it would also be relevant to rediscover the use of phages, which are exceptionally effective against certain germs in some cases. Progress in genome analysis makes it possible to define phage cocktails that allow us to consider the development of personalized medicine.

Finally, of course, we must obviously continue our efforts to find new antibiotics.

The struggle between organisms is such an integral part of the living world that it has generated an incalculable number of swords to defend us and shields of resistance. By searching, we will inevitably find new substances to add to our range of therapeutic swords. We just have to find the right one before the generalization of those shields causes epidemics... A great challenge for years to come. ■