

# TO REDUCE THE USE OF ANTIBIOTICS FOLLOW A SIMPLE RULE: USE THEM APPROPRIATELY

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Antibiotics are a unique category of therapeutic agents developed to treat bacterial infections. They inhibit and/or kill the bacterial pathogens. Almost 70 years of largely successful antibiotic usage all over the world have changed not only the face of infectious diseases, but also the bacterial world itself.

Sixty years ago a first warning from history came in the form of a spread of difficult to treat staphylococci - methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitals which was followed by alternating waves of emergence and the spread of new difficult to treat organisms and the development of new antibiotics designed to tackle emerging resistance. As the result of the initial treatment success, 35 years of slowdown regrettably happened in the research and launching of new antibiotics. Fortunately, serious warnings and even alarming messages have come from many authorities over the last two decades: a bleak picture of a possible post-antibiotic era was publicized and generated important political activity. Lord O'Neill's report released in July 2014 suggested ten key actions to address the potential global consequences of antimicrobial resistance (AMR). A United Nations high-level meeting on AMR was organized in September 2016 to discuss the coordinated global action in order to keep the benefits of antimicrobials in the near and distant future. The strategies to control AMR have been an important subject addressed by several countries following recommendations issued by the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE).

Although AMR is clearly related to the use and misuse of antibiotics in humans, animals and plants, we have to keep on using antibiotics, both old and new, but only when appropriate. There is no way to stop using antibiotics and there is no way to avoid either intrinsic or acquired resistance in bacteria. There are several approaches how to tackle AMR, the most frequent being systemic, routine surveillance of resistant bacteria and

antimicrobial consumption, the use of antibiotics only when needed and appropriate antibiotic prescribing (the antibiotic prescribed only against susceptible bacteria in an appropriate dose, by way of administration and duration). Unfortunately, since antibiotics have been historically used without strict rules in most countries, development of a strategy for appropriate and judicious use of antimicrobials to preserve their future effectiveness is the only ethically acceptable way being able to reduce the amount of total antibiotics used and to curb the expansion of AMR. As a prerequisite, all patients in need around the globe should have access to the high-quality antibiotics.

Numerous studies published over the past seven decades, frequently supported by the drug industry, generated sometimes useful, sometimes less useful, solutions on how to tackle the important questions concerning the appropriate use of antibiotics; however more studies are needed with designs adapted to respond to emerging questions. In addition, many guidelines and guidance documents have been produced and may need to be reviewed and updated to integrate new knowledge like age category of the patient, specific care required, infection type/site of infection, comorbidities, epidemiologic and geographic data, etc.

It is impossible to deny enormous efforts made during the last two decades to improve and broaden the view of the need for appropriate use of antibiotics in a wide variety of settings including communities, hospitals, long-term care facilities, day-care centres, food animals, companion animals, etc. Now a considerable challenge lies ahead of us and requires a high-level political involvement and support, specific approaches tailored to each and every group of stakeholders and substantial

financial support. Among the many approaches recommended to improve and reduce the antibiotic use, we have selected a few for a brief discussion.

The abuse and generous use of antibiotics has been constantly referenced to be a main cause of AMR. Abuse of antibiotics in humans involves mainly the unnecessary prescriptions of antibiotics. When promoting concept of “the appropriate use” of antibiotics, the most difficult real life situation to face is to identify with high probability the cases where the prescription of antibiotics is absolutely useless. The general answer to this dilemma is relatively simple and straightforward: non-bacterial infections should not be treated with antibiotics. Patients with acute viral infections receiving antibiotics represent the major group of individuals where the unnecessary prescription of antibiotics should be avoided. An informed decision not to treat a patient (child or adult) with an upper respiratory tract infection with antibiotics in reality means that the physician should have 24/7 support of rapid diagnostic testing being able to reliably rule out bacterial infection, or to delay the treatment decision until receiving information generated by a more traditional (and slower) microbiological approach. At present, only limited number of point-of-care or near-the-bed tests with very narrow pathogen spectrum are available; however, more solutions (especially rapid point-of-care molecular tests) are entering the diagnostic market. For molecular point-of-care tests we wish to have self-contained, fully integrated sample-to-report devices that accept raw, untreated specimens, perform all of the molecular steps, and provide interpreted test results in less than an hour. The point-of-care test to diagnose group *A streptococcus* in a classical immunochromatographic or innovative molecular format is a good example of very useful point-of-care test, although other bacteria not targeted by the test may cause pharyngitis requiring antibiotic treatment. To overcome single test-single target concept, new molecular syndromic testing paradigm using highly multiplexed PCR platforms for analysing comprehensive panels of most probable pathogens, which can cause a particular clinical syndrome has been developed recently. This approach allows generation of multiple results from a single sample. At least some of the current platforms are designed to directly probe specimens (respiratory, stool, CSF, blood, urogenital) and positive blood culture bottles for an array of microorganisms and even provide some resistance/susceptibility information. Such an approach may have significant impact on patient care and management and redefine the diagnosis of infectious disease, but there are many obstacles to surmount and many challenges to tackle. Namely, although new diagnostic technologies enable expedited and more accurate microbiological diagnoses, diagnostic stewardship would be

necessary to ensure that these technologies conserve, rather than consume, additional healthcare resources and optimally affect patient care. In addition, antimicrobial stewardship is needed to ensure prompt appropriate clinical action to translate faster diagnostic test results in the laboratory into improved outcomes at the bedside.

The next intervention to reduce the use of antibiotics is to optimize the duration of antimicrobial treatment. Ideally, we should stop antibiotic treatment when the patient is objectively cured. The main problem lies in the fact that a substantial amount of evidence concerning optimal duration of treatment of many infectious diseases is relatively old and consequently founded on an old-fashioned approach that longer is better. We should design more clinical studies, which will challenge traditional treatment duration with shorter ones, although keeping in mind that the financial support from industry for such studies will be difficult to obtain. A potential innovative approach would be to identify reliable (host) markers to distinguish early responders from those requiring prolonged treatment. Useless prolonged antimicrobial treatment is also often reported in hospitalized patients. It is usually due to lack of oversight, thus strict compliance with recommendation to regularly review patient's antimicrobial therapy protocol is mandatory. Similar problem is noncompliance with existing guidelines and protocols concerning indications and duration of surgical and nonsurgical antimicrobial prophylaxis.

Another important and unresolved issue which needs to be addressed is excessive use of antibiotics in animals as growth-promoters. Antibiotics have been used as growth promoters in animal agriculture for more than 60 years. The ability of low doses antibiotics to promote growth of animals was discovered serendipitously in the 1940s and the addition of antibiotics to animal feed to stimulate growth has gradually turned into a global practice. The mechanisms of growth promotion are still not clearly understood, but the attributable risk for development and propagation of AMR in humans is apparent. In Europe concerns about AMR led to European Union-wide ban on the use of antibiotics as growth promoters in animal feed as of 1 January 2006. This ban is the final step in the phasing out of antibiotics used for non-medicinal purposes in European Union and is part of the European Commission overall strategy to tackle the AMR, due to antibiotic overexploitation or misuse. We hope that this action will be followed also in other countries.

In conclusion, we strongly believe that appropriate use of antibiotics is possible and the way forward to reduce the use of antibiotics. Due to its high complexity it requires a step by step approach involving large numbers of stakeholders. New studies with innovative and provocative designs are needed as well as continuous life-long education of all healthcare

professionals. All interventions aiming to promote appropriate use of antibiotics must be country-, region-, and hospital-tailored. The high-level political support, a generous budget, dedicated, enthusiastic and well-educated personnel are essential components of every programme aiming to control AMR by promotion of appropriate use of antibiotics. ■

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