What is Antibiotic Resistance?

G. Kahlmeter

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The World Health Organization states that we are in “a race against time to develop new antibiotics” (1). There are few antibiotics in drug development, which sparks the question: is this situation because the pharmaceutical industry has run out of ideas or because return on investment is considered poor? The lack of antibiotics, coupled with the global spread of resistant bacteria between countries, requires immediate and decisive actions from governments worldwide. Despite the enormous strides made with antiretrovirals and vaccines, such as in the Ebola case, a new class of antibiotics has still not been discovered for more than three decades. New members in already known groups of antimicrobials may have been developed, and some of these compounds have been combined with beta-lactamase inhibitors. But a truly new class has not been found, nor is it likely to appear in the near future. It is, therefore, important to conserve the antibiotics that we have. Central to ongoing global efforts to beat and prevent antimicrobial resistance is finding and using a common standard definition of what it is, as this approach will help ensure we are fighting resistance on a like-for-like basis.

Defining antimicrobial resistance

Resistance is “the likelihood of failure of therapy with a specific agent for a specific organism at one or several alternative dosages” (2). Resistance is related to a trait inherent in the microorganism and may be intrinsic (i.e., expected because something is present or lacking, which makes sufficient activity of the agent highly unlikely) or acquired (i.e., unexpected in that the microorganism has acquired a new trait, which obviates the success of therapy).

In some cases, clinical resistance can be predicted from the presence or absence of a specific resistance gene or mechanism. In most cases, however, resistance needs to be defined in relation to a concentration of the antimicrobial agent that will fail to inhibit the growth of the microorganism. The lowest concentration needed to inhibit the growth of the organism is called the minimum inhibitory concentration (MIC). The concentration that can distinguish between therapeutic success and failure is called a clinical breakpoint. Therapeutic success is considered to be likely “if the MIC of the organism is less than or equal to the breakpoint” and not likely “if the MIC of the organism is higher than the breakpoint concentration.” A typical breakpoint is susceptible, S≤1, and resistant, R>4mg/L (3). The interpretation is that “an organism of a defined species with an MIC less than or equal to 1” is to be categorized as ‘susceptible’ (i.e., possible to treat with the agreed standard dosing of the agent in question), whereas an “organism with an MIC above 4” is to be categorized as ‘resistant’ (i.e., not possible to treat even with the highest possible dose) (3). Everything in between is categorized as ‘intermediate’ (i.e., treatable given an increase in dosage) (3). As new resistance mechanisms develop, dosing schemes need to be revised to include other infections or bacteria in addition to those originally evaluated. It is also important to review and sometimes revise the definitions of breakpoints.

Over the past 15 years, common breakpoints for Europe have been established by the European community of microbiologists through the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Before then, there was no international consensus on these breakpoints. Although an increasing number of countries are now adopting the EUCAST

recommendations, there are still many laboratories that use other systems; for instance, the United States uses standards recommended by the Clinical Laboratory Standards Institute (CLSI). On a practical level, the lack of an international consensus means antimicrobial agents may have different breakpoints in different countries, and thus, the same microorganism may be susceptible in one country and resistant in another. To be able to tackle the problem of antibiotic resistance, a like-for-like comparison on a global scale is needed.

Since the 1970s, breakpoint committees such as EUCAST have determined the breakpoints for phenotypic antimicrobial susceptibility testing as part of the regulatory processes for the approval of new drugs. EUCAST deals with breakpoints and technical aspects of phenotypic *in-vitro* antimicrobial susceptibility testing and functions as the breakpoint committee of EMA. EUCAST consists of a dedicated group of scientists, mostly from the field of clinical microbiology with long traditions of developing methods and breakpoints within the field of susceptibility testing of bacteria and fungi. Funding is from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and contracts for services are with the European Centre for Disease prevention and Control (ECDC).

In 2008, only 20-30% of European nations adopted the EUCAST guidelines. Since then, this figure has increased to 90% in 2015, with several non-European countries following suit, including nations such as Australia, New Zealand, South Africa, and Morocco. However, despite the recent success of EUCAST, there are still undecided countries. In many countries, laboratories make individual decisions and, where this is the case, it is not unusual for countries to end up with the unfortunate situation of having more than one susceptibility system. The absence of a harmonized global standard is detrimental to both patient care and ongoing programmes of resistance surveillance. In the United Kingdom, the British Society for Antimicrobial Chemotherapy (BSAC) recently recommended that UK laboratories adopt the EUCAST guidelines. Laboratories were informed that the BSAC recommended method will not be updated until after the end of 2015. In the United States, there are two sets of breakpoints, those decided by the US Food and Drug Administration as part of the registration process and those recommended by CLSI for which there are also disk diffusion guidelines and zone diameter breakpoints. To complicate matters further, a group of US scientists now work as an integral part of EUCAST.

Everyone agrees that international unity on a single definition of breakpoints for use in phenotypic susceptibility testing would be beneficial, not only in efforts to conduct everyday susceptibility testing, but also in combatting antimicrobial resistance and the dissemination of resistant organisms and in the development of new agents and diagnostics.

EUCAST has now developed breakpoints in existing agents and shown that for almost 10 years, the process for addressing new agents works. Together with EMA, EUCAST has determined breakpoints for approximately 10 new agents and is currently occupied with several compounds that are still being processed. It is essential that companies in the process of developing new agents seek contact with EUCAST early in the development cycle to obtain advice on the procedure. EUCAST can also help pave the way for the development of antimicrobial susceptibility testing (AST) material needed for susceptibility testing of the new agent.

To ESCMID, antimicrobial resistance in all its forms and implications is of prime concern and importance. Cooperation over borders is, therefore, crucial, from national borders and borders between the profession and governmental organizations, to those between the

profession and industry and between clinical microbiologists and infectious disease specialists. EUCAST is a good example of successful international cooperation.

To help keep the community informed, EUCAST will stage the annual EUCAST four-hour workshop at the European Congress of Clinical Microbiology and Infectious Diseases, as well as a number of sessions on antimicrobial resistance, antimicrobial stewardship, antimicrobial susceptibility testing, and new methods to support the rapid choice of a relevant antimicrobial for therapy.

References

1. WHO, Bulletin, Race to develop new antibiotics, accessed 29 Feb. 2016.
2. EUCAST, Expert rules in antimicrobial susceptibility testing, version 1, April 2008, accessed 29 Feb. 2016.
3. EUCAST, About Clinical Breakpoint Tables, accessed 29 Feb. 2016.

Article Details

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