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Multiresistant pathogens – a self-inflicted threat?

Most bacterial infections have lost their capacity to cause terror thanks to antibiotics. However, the increase in antibiotic resistances is making the fight against bacterial pathogens rather difficult, and the widespread overuse and inappropriate use of antibiotics continues to fuel the increase in antibiotic-resistant bacteria. Strict surveillance strategies and hygiene rules have been in place for some years with the aim of ensuring the efficacy of new and existing antibiotics. However, bacteria are highly adaptable organisms and continue to remain a huge risk for human health.

Since 1928, when penicillin was the first natural antimicrobial to be discovered, antibiotics have been one of the most important tools in our fight against infectious diseases. Antibiotics act selectively on bacterial targets, thereby inhibiting the reproduction of bacteria or killing them. Despite the efficiency of antibiotics in fighting off bacterial infections, the application of antibiotics is associated with disadvantages that are increasingly coming to the fore. The application of antibiotics can cause a selective pressure in a population of bacteria where only the resistant bacteria are able to thrive. Those susceptible to antibiotics die off. Natural mutations in the bacteria's genetic material can lead to resistance to antibiotics in several ways, for example by modifying and hence eliminating the cell target that the antibiotic attacks or by closing the ports through which antibiotics enter the cell. Antibiotic resistance is no new phenomenon, but has also been found in ancient bacteria isolated from extreme natural habitats (1). Bacteria that have acquired resistance to antibiotics can replicate and spread their resistance traits to other bacteria by way of transformation, transduction and conjugation.

Electron microscope image of Staphylococcus aureus bacteria which have become resistant to many antibiotics.

The effects of microbial resistances on people's health are difficult to quantify because a nationwide register is still under development. The surveillance data currently available in Germany only refer to individual pathogen species, individual antibiotics and heterogeneous patient collectives. In 2012, staphylococci (25.6%) and E. coli (17.4%) were the most frequent of all pathogens identified in patient samples (2). These two pathogen species are also well known for their resistance to commonly used antibiotics. Methicillin-resistant Staphylococcus aureus (MRSA) strains, which accounted for the greatest proportion (15.4%) of all S. aureus strains analysed in 2012, are the most frequent and best-known pathogens that are resistant to multiple antibiotics (3). However, some other pathogens, including Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter species, Streptococcus pneumoniae and Enterococcus faecalis/faecium, are increasingly developing resistances to several antibiotics and are therefore posing an increasing risk for human health and health systems in general. For example, Pseudomonas aeruginosa isolates have been shown to be resistant to all antibiotics currently on the market.

Animal husbandry – fully dependent on antibiotics?

The generous use of antibiotics in the production of animals for food also favours the development of microbial resistance and the spread of bacteria that are resistant to antibiotics. Antibiotics that are used in food animals are usually used in sub-therapeutic doses for all animals rather than specifically for the treatment of sick animals. This leads to a high selective pressure. Inappropriate hygiene measures can then lead to the transfer of resistant pathogens to humans and to food. A new law (16th AMG – German Drug Act - amendment) will come into force in Germany on 1st April 2014 whose aim is to minimise the use of antibiotics in livestock farming. The frequency of antibiotics application on a farm will be used as an indicator for the need to minimise the use of antibiotics. The new law will give the veterinary drug monitoring bodies more control powers and require farmers to put in place measures for reducing the use of antibiotics to the therapeutic minimum required. However, livestock farming faces the problem that many animals do not survive long without high doses of antibiotics.

Danger of infection in hospitals

Bacteria that are resistant to several antibiotics are a huge problem, particularly in hospitals and nursing homes. While they

do not usually cause disease in healthy people, patients with weakened immune systems, i.e. elderly or sick people and newborn babies, are especially susceptible to bacterial infections. It is therefore crucial to put in place appropriate measures to avoid colonisation and infection of people with multiresistant bacteria.

These measures also include the examination of patients at risk before admission to hospital and the initiation of appropriate therapy if necessary in order to prevent pathogens from entering the hospital. The hospital infection surveillance system KISS was established in 1996 on behalf of the German Federal Health Ministry in order to record infections and analyse data relevant to nosocomial infections with the aim of reducing the frequency of these infections. It has a modular design and groups infections according to risk areas in the hospital, i.e. certain patient collectives such as neonates (NEO-KISS) and special wards such as intensive care wards (IST-KISS) where patients are particularly prone to infections (see article entitled "Antibiotic resistance in hospitals").

Hygiene, diagnosis, therapy – means and ways to control resistant pathogens

Specific measures need to be put in place in order to tackle the problem of multiresistant pathogens efficiently. The correct use of antibiotics and the enforcement of appropriate hygiene measures are instrumental in the prevention of infection in the field of human and veterinary medicine. The Baden-Württemberg MRE (multiresistant pathogen) networks play a crucial role in the development and enforcement of these measures.

Proportion of methicillin-resistant S. aureus isolates in European countries. © ECDC

The uniform surveillance of antibiotic consumption and resistance development is another mainstay of resistance management and is carried out by the European Antimicrobial Resistance Network (EARS-Net) (see article entitled "Call for responsible antibiotics prescription"). In everyday medical practice, it is then crucial to use state-of-the-art diagnostics and therapies for the effective identification of resistant bacteria and to put in place effective therapies. And last but not least, improving the education and training of health professionals with regard to effective hygiene measures and appropriate prescribing and use of antibiotics is crucial in the effort to reduce antibiotic resistance. In addition, researchers around the world are focused on the identification of new drugs against infections caused by bacteria that have become resistant to common antibiotics. Like penicillin in the early 20th century, new naturally occurring substances with novel mechanisms of action have become promising candidates for new antibiotics to treat bacterial infections. Only new substance classes that are able to damage bacteria in ways different from those of common antibiotics and against which the bacteria have not yet developed resistances have the potential to lead to long-term success. For example, the discovery of acyldepsipeptide antibiotics is another ray of hope in the fight against multiresistant bacteria. The binding of acyldepsipeptides to the bacterial Clp protease leads to a permanent increase in enzyme activity, which in turn leads to the uncontrolled degradation of vital proteins and hence death of the bacterial cells. Acyldepsipeptide antibiotics are therefore also effective against multiresistant MRSA bacteria (4). Whether and for how long they can be used for the elimination of resistant bacteria remains uncertain as bacteria have the capacity for rapid adaptation to changing environments, and hence new drugs.

Sources:

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3) European Antimicrobial Resistance Network

4) B. P. Conlon, E. S. Nakayasu, L. E. Fleck, M. D. LaFleur, V. M. Isabella, K. Coleman, S. N. Leonard, R. D. Smith, J. N. Adkins & K. Lewis: Activated ClpP kills persisters and eradicates a chronic biofilm infection; Nature 503, 365–370 (21th November 2013)

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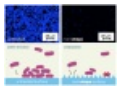

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