FAQ about the antibiotic Colistin and transferrable Colistin resistance in bacteria

Updated BfR FAQ, 18 January 2018

Colistin is an antimicrobial which is used predominantly in veterinary medicine to treat infections. In November 2015, resistance research led to the discovery of a new mechanism through which bacteria can pass on Colistin resistance properties to other bacteria. This scientific insight has led to a public discussion about the use of this antibiotic in animal production facilities and about the spread of resistance to Colistin. On this occasion, the BfR has summarised and answered FAQ on Colistin.

What is Colistin?

Colistin is a polypeptide antibiotic from the group of polymyxins. This antimicrobial is predominantly used in veterinary medicine in the treatment of intestinal diseases as well as other infections.

What does Colistin resistance mean?

If an antimicrobial no longer works against certain bacteria, these bacteria have developed resistance to the active ingredient. Colistin resistance exists if the minimum concentration of Colistin as the active ingredient for inhibiting the growth of a bacteria type is above the defined threshold value. According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), *Escherichia (E.) coli* and salmonella are considered resistant, if they still grow in the presence of over 2 mg Colistin/l of nutrient broth (epidemiological cut-off value).

The clinical breakpoint was defined as ≥8 mg/l by the “Clinical and Laboratory Standards Institute”. An infection with a pathogen which is resistant to this concentration cannot usually be treated effectively with Colistin.

What is the significance of Colistin in veterinary medicine?

Colistin is of considerable importance in veterinary medicine, especially in the treatment of infections of the gastrointestinal tract in production animals. In Germany, 107 tons of polypeptide antibiotics were dispensed to veterinarians and veterinary pharmacies in 2014 and 69 tons in 2016. Colistin accounted for most of that. Compared to 2011, the first year such data was recorded, this amounts to a decrease of 45.7 per cent (from 127 to 69 tons).

Is Colistin often used in human medicine?

Compared to other antibiotics, Colistin is rarely used in human medicine, because it is not well tolerated. Possible side effects include, for example, damage to the kidneys or the nervous system. Its significance for human medicine lies in the treatment of severe infections with gram-negative pathogens which are resistant to most of the commonly used antimicrobials including carbapenems. These treatments are only rarely necessary, since the number of infections with such pathogens is still low in Germany.

Is resistance to Colistin a new phenomenon?

No. Resistance to Colistin in isolates from animals has been reported for a number of years now. So far, scientists have acted on the assumption that they are dealing with a non-transferrable form of resistance which is firmly anchored in the chromosome of individual bacteria. The new aspect of the currently discussed Colistin resistance is that it is conferred by a gene which is transferred from one pathogen to another by means of a plasmid. A plasmid is a ring-shaped DNA molecule on which genes for different properties can be located and

which can be transferred relatively easily between pathogens. The gene discovered in 2015 is called *mcr-1* and was first described in China. More detailed studies have shown that this gene can also be integrated into the chromosome. This means that it can be passed on to all bacterial progeny.

Studies conducted in the aftermath of the detection of *mcr*-1 including work at the BfR have resulted in the description of additional transferrable genes, *mcr-2* to *mcr-5*, responsible for Colistin resistance in production animals.
Studies on the spread of these genes are currently being undertaken. The discovery of additional genes of this type is to be expected.

What specific measures do the new insights into Colistin resistance call for?
Studies conducted by the BfR showed that the gene *mcr-1* has been present in bacteria from production animals and foods in Germany since at least 2010 and that it can be located on different plasmids. It is now necessary to investigate by means of detailed additional studies how frequently this gene and similar ones is actually transferred, to which pathogens it is transmitted, and how resistance can spread. These are important insights which are indispensable in better assessing potential risks.

The detection of this Colistin resistance underscores the necessity of restricting the use of antimicrobials in production animals to an absolute minimum level required for therapy. This approach has been advocated by the BfR for years.

On the basis of the new findings, the European Medicines Agency (EMA) reviewed its assessment of Colistin and published a report in July 2016 in which the EMA recommends that use of Colistin be reduced to a minimum. At the same time, the use of active ingredients with special significance for humans (“critically important” according to the WHO list) as well as overall antimicrobial use should not be increased. It is also recommended that Colistin be assigned to a higher risk category (Category 2 of the AMEG classification: antimicrobials used in veterinary medicine where the risk for public health is currently estimated as higher).

Is resistance to Colistin often observed in pathogens that are transferred from animals to humans?
As part of resistance monitoring of zoonotic pathogens and naturally occurring bacteria in the intestine of animals (commensal bacteria), Colistin resistance has been systematically studied since 2010. In the time period from 2010 to 2015, the highest proportion of Colistin-resistant pathogens was detected in *E. coli* from the turkey (11.7 %) and chicken meat chains (6.0 %). The proportion of resistant bacteria in this area has been marked by a slight decrease between 2010/2011 and 2015. In 2016 Colistin resistance in the turkey meat chain was at 8.7 %, in the chicken meat chain at 6.1 %. In isolates from the foodchains of pigs (1.4 %) and veal (1.8 %), Colistin resistance was observed less frequently. For breeding poultry, in the beef cattle chain and for dairy products, this resistance gene has not been detected in Germany yet. A study of isolates tested by the BfR showed that of the *E. coli* isolates which resistance testing had shown to be Colistin-resistant, the majority was carrying the transferrable gene *mcr-1*.

More details information can be found in the publication “Prevalence of *mcr-1* in *E. coli* from Livestock and Food in Germany, 2010–2015”:
http://dx.doi.org/10.1371/journal.pone.0159863

How can consumers protect themselves against resistant pathogens in food?
Hygienic measures during transport, storage and preparation of food offer protection against pathogens that are resistant to antimicrobials. For example, raw meat should be heated to 70 degrees Celsius at the core for at least two minutes before it is consumed. When handling raw meat, great care must be taken to ensure that the germs are not transferred to other foods via the hands or utensils (e.g. knives, chopping boards).

The BfR has published the leaflet “Consumer tips: protection against food poisoning in private households”. It summarises the most important rules of hygiene for handling food. The hygiene tips contained in this leaflet equally apply to resistant and susceptible pathogens:
http://www.bfr.bund.de/cm/350/verbrauchertipps_schutz_vor_lebensmittelinfektionen_im_privathaushalt.pdf

Is the preventive use of Colistin and other antibiotics permitted in production animals?
Antibiotics should not be used as prophylaxis in production animals. In its guidelines on the prudent use of antimicrobial substances in veterinary medicine, the European Commission recommends avoidance of routine prophylaxis.

As part of population treatments, animals that are not sick yet are frequently treated as well in order to prevent the spread of the disease within the animal population. In such cases, the veterinarians in charge act on the assumption that these animals have already been in contact with the pathogens. The aim of this use of antimicrobials is to avoid the spread of the disease and the more costly treatment of already affected animals. In these circumstances, Colistin is used like all other substances.

Do special rules apply to the use of Colistin in human and veterinary medicine?
Colistin has been regarded by the WHO as one of the “highest priority critically important antimicrobials” since 2017. These are active substances with the highest priority in the group of critically important antibiotics. The upgrading of the importance of Colistin is justified by the increasing frequency of the use of Colistin to treat severe human infections with above all *Enterobacteriaceae* and *Pseudomonas aeruginosa* in various parts of the world according WHO. The WHO also makes reference to the discovery of transferrable resistance to Colistin and the spread of this resistance via the food chain.

The requirements for the use of Colistin in human medicine have not changed for the time being as a result of the detection of the transferrable resistance gene. However, Colistin should, like all other antimicrobials, be used sparingly in animals. The targeted use of antibiotics complies with the “one health approach” according to which human and veterinary medicine should cooperate closely in order to prevent the spread of antimicrobial resistance.

More information on the topic of transferrable Colistin at the BfR website

Press release: Transferrable colistin resistance found in bacteria from German farm animals.
http://www.bfr.bund.de/en/press_information/2016/01/transferrable_colistin_resistance_found_in_bacteria_from_german_farm_animals-196150.html

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