FAQ about the antibiotic Colistin and transferable Colistin resistance in bacteria

Updated BfR FAQ, 3 August 2021

Colistin is an antimicrobial which is used predominantly in veterinary medicine to treat infections. In November 2015, a new mechanism was discovered which allows bacteria 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 husbandry and about the spread of resistance to colistin. This has prompted the BfR to put together a FAQ on colistin.

What is colistin?

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

What does colistin resistance mean?

If an antibiotic 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 is above the defined threshold value. According to the European Committee on Antibiotic Susceptibility Testing (EUCAST), *Escherichia* (*E.*) *coli* and *Salmonella* are considered resistant, if they still grow in a nutrient broth with a colistin concentration of over 2 mg/l.

How important is 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 66 tons in 2019. Colistin accounted for most of that. Compared to 2011, the first year such data were recorded, this amounts to a decrease of 48 percent (from 127 to 66 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 importance in human medicine lies in the treatment of severe infections with gram-negative pathogens which are resistant to most of the commonly used antibiotics including carbapenems, which are used to treat serious infections. 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?

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-transferable 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 bacterium to another by means of a mobile genetic element (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 bacteria. 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 transferable genes and their variants responsible for colistin resistance in production animals (*mcr-2* to *mcr-10*). Discovery of additional genes of this type should 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 2008. Therefore it is responsible for resistance among a portion of the resistant bacteria. The gene can be located on different plasmids. In addition, colistin resistance genes often appear in the presence of so-called jumping genes (transposons), which further transfer resistance within the bacterium, e.g. from plasmid to plasmid but also from chromosome to plasmid. It is now necessary to investigate by means of detailed additional studies how frequently this gene, and other similar ones, are actually transferred, to which pathogens they are transmitted, and how resistance may 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 antibiotics in production animals to an absolute minimum level required for therapy. This approach has been advocated by the BfR for some years now.

On the basis of the new findings, the European Medicines Agency (EMA) reviewed its assessment of colistin and published a report in July 2016. The EMA also recommends in its report that use of colistin be reduced to a minimum.

Is resistance to colistin often observed in bacteria that are transferred from animals to humans (zoonotic bacteria)?
Since 2010, colistin resistance among zoonotic pathogens and naturally occurring bacteria in the intestines of animals (commensal bacteria) has been systematically studied within the Federal-State zoonosis monitoring programme. From 2010 to 2015, the highest proportion of colistin-resistant pathogens was detected in *E. coli* from turkey (11.7 %) and chicken meat supply chains (6.0 %). In the same period, the proportion of resistant bacteria in the turkey meat supply chain has been marked by a slight decrease. In 2020, 7.5 % of isolates from the turkey meat supply chain and 6.9 % of isolates in the chicken meat supply chain exhibited colistin resistance. In isolates from the pork and veal supply chains, colistin resistance was observed less frequently. In 2019, no colistin resistance was detected in any of the randomly selected isolates in the pork supply chain, only sporadically in caecum samples from fattening calves (0.5%) and beef (1.4%). This resistance gene has not yet been detected in Germany among breeding poultry and in dairy products. A study of isolates tested by the BfR showed that of the *E. coli* isolates which had been shown to be colistin-resistant by resistance testing, the majority exhibited the transferable gene *mcr-1*.

Further information can be found in the scientific publication “Prevalence of *mcr*-1 in *E. coli* from Livestock and Food in Germany, 2010–2015”: https://www.bfr.bund.de/en/prevalence_of_mcr_1_in_e__coli_from_livestock_and_food_in_germany__2010_2015-198333.html

Colistin resistance is also observed in *Salmonella*. Here it is of direct relevance for consumer health protection due to the pathogenic properties of *Salmonella* for humans. Further information can be found in the scientific publication by Borowiak et al. (doi: 10.3389/fmicb.2020.00080).

Resistance genes of this type have now also been detected in other bacteria (e.g. *Citrobacter spp.*, *Klebsiella spp.*, *Acinetobacter spp.*), which underscores their transferability between bacteria of different genus.

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

The BfR has published the leaflet “Protection against foodborne infections in private households”, which summarises the most important hygiene rules for handling food. The hygiene tips contained in this leaflet apply equally to both resistant and susceptible bacteria: https://www.bfr.bund.de/cm/364/protection-against-foodborne-infections.pdf

Is the preventive use of colistin and other antibiotics permitted in production animals?
Antibiotics should only be used as prophylaxis in production animals in exceptional cases. In its guidelines on the prudent use of antibiotic substances in veterinary medicine, the Federal Veterinary Association recommends avoiding routine prophylaxis (https://www.bundestieraerztekammer.de/tieraerzte/leitlinien/downloads/Antibiotika-Leitlinien_01-2015.pdf). There are similar guidelines from the European Commission (https://ec.europa.eu/health/sites/default/files/antimicrobial_resistance/docs/2015_prudent_use_guidelines_en.pdf).

As part of group treatments, animals that are not yet sick are still frequently treated, 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 antibiotic use is to avoid the spread of the disease and the higher costs associated with treating animals once infected. 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 World Health Organisation (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 WHO bases this on the increasing frequency of the use of colistin to treat severe human infections with above all Enterobacterales and *Pseudomonas aeruginosa* in various parts of the world. The WHO also makes reference to the discovery of transferable colistin-resistance and the spread of this resistance via the food chain. The “Antimicrobial Advice ad hoc Expert Group” (AMEG), which is part of the European Medicines Agency (EMA), has classified the polymyxins, including colistin, in category B (“Restrict”). Accordingly, these antibiotics should only be used for the treatment of clinical diseases provided no other effective antibiotics from categories C (“Caution”) and D (“Prudence”) are available. Substances in these latter categories are of less importance for the treatment of humans, for example because there are still many alternatives to them for the treatment of certain infections. In addition and if possible, the use of category B substances should be based solely on a preceding resistance determination of the pathogen causing the infection.

Transferable colistin resistance in human bacteria is comparatively rare in Germany. As a result, the requirements for the use of colistin in human medicine have not yet changed.

Among production animals, the use of antibiotics has already declined sharply in recent years due to minimisation concepts, and individual action plans continue to be drawn up to reduce their use on farms with comparatively high levels of use. 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 antibiotic resistance.