Healthcare industry BW

Antibiotic resistance in hospitals

There is an alarming rise in infections caused by bacteria that are resistant to common antibiotics. A particular problem is nosocomial (hospital-acquired) infections of newborns, for which a Germany-wide surveillance system has been established. Novel natural substances with an antibiotic effect might be able to contain the danger.

Neonatal wards are faced with a high risk of infection

Hospitals are places of healing, or at least this is what they should be. However, approximately half a million people a year in Germany contract an infectious disease whilst they are in hospital, and between 10,000 and 15,000 die from the disease. The prevalence of infections is particularly high in intensive-care wards. Not only are patients in intensive-care wards particularly susceptible to infections, infectious pathogens can also easily enter the human body through medical equipment such as respiratory tubes and catheters, for example.

The increasing prevalence of bacterial strains that are resistant to antibiotics in clinical use is a matter of great concern, in particular the strains that are resistant to multiple antibiotics. The intensive use of antibiotics in hospitals and their generous prescription by doctors have led to the creation of an environment that promotes the selection of microbes with the relevant antibiotic resistance genes. Staphylococcus aureus (which can enter the bloodstream through open wounds and catheters and cause blood poisoning), Pseudomonas aeruginosa (P. aeruginosa infections are often associated with blue-green pus), Enterococcus faecium and Enterococcus faecalis (intestinal bacteria that occasionally lead to life-threatening sepsis in long-term hospitalized patients) and Klebsiella pneumoniae (a typical cause of pneumonia) are among the most dangerous nosocomial pathogens. They do not cause infections in healthy people with a functional immune system, but can become a serious problem in patients with weakened immune systems.

Fear of Klebsiella

Around one year ago, an alarming series of infections caused by bacteria of the genus Klebsiella occurred in the neonatal ward at the Bremen Central Hospital (Klinikum Mitte) and led to the death of three newborn babies. Particularly worrying was the fact that the bacteria were highly resistant to antibiotic treatment: they had a resistance gene that codes for the enzyme "extended spectrum β lactamase" (ESBL) that destroys almost all common antibiotics. Experts from the Robert Koch Institute in Berlin spent many months looking for the source of infection, with no success. The ward was closed for two months during which time it was restructured and thoroughly disinfected. It reopened in January 2012, but was closed again at the end of February after the recurrence of ESBL and the deaths of two more babies. The pathogens had the same genetic profile as those that caused the deaths of the three premature babies in 2011. Bremen's Health Senator then closed the ward completely and an investigation committee was set up to clarify the situation. The hospital was also searched by the police.

Paediatric centre at the Mannheim Medical School

The bacteria are so dangerous for preterm babies because the babies' immune system is not yet active and their skin cannot effectively protect them against environmental threats. In addition, they do not yet have their own intestinal bacterial flora that could ward off pathogenic competitors. However, the situation in Bremen was in some way different. In Bremen, the bacteria spread in the bloodstream and led to fatal blood poisoning (sepsis). It is known from other similar cases with a low detection rate that it is highly unlikely that it will be possible to detect the source of infection in this case. One possibility might be that a child was infected by its mother during birth – birth is far from being an aseptic process. Such infections are relatively frequent, but are restricted to individual cases. So there must be other reasons. Poor hospital hygiene is blamed for the series of infections

and deaths of the premature babies in the Bremen Central Hospital.

The national NEO-KISS surveillance system

Of all hospitalized children, premature babies with a birth weight of less than 1,500 g (3lb 5oz) are particularly prone to infections. Pneumonia and primary bloodstream infections (sepsis) are the most frequent and most serious infections. Although Klebsiella bacteria account for only around eight per cent of hospital-acquired infections, they nevertheless cause infections that are difficult to treat. Staphylococci and enterococci are far more frequent causes of nosocomial infections. It has been shown that the continuous recording of infections, the comparison of infection rates and the systematic analysis of data relevant to nosocomial infections can considerably reduce the frequency of these infections. This was why in 1996 a surveillance system called KISS ("Krankenhaus-Infektions-Surveillance-System"; Engl. Nosocomial Infection Surveillance System) was established on behalf of the German Ministry of Health.

Numerous German hospitals have joined KISS. The data are collected at the National Reference Centre for the Surveillance of Nosocomial Infections at the Charité in Berlin. As premature babies run a particularly high risk of contracting nosocomial infections, the NEO-KISS (Nosocomial Infection Surveillance System for Preterm Infants in Neonatology Departments and ICUs) focuses in particular on this patient group. More than 200 neonatal wards report their infections to NEO-KISS. In addition to the Robert Koch Institute, another important cooperation partner of the NEO-KISS Reference Centre is Professor Dr. Markus Dettenkofer from the Institute of Environmental Medicine and Hospital Hygiene at Freiburg University. At present, around 33 per cent of all "at risk neonates" in intensive care wards contract at least one nosocomial infection. The objective of NEO-KISS is to make nationwide reference data about the frequency of nosocomial infections about preterm infants more widely available and drastically reduce the high number of infections.

Spread of resistant pathogens

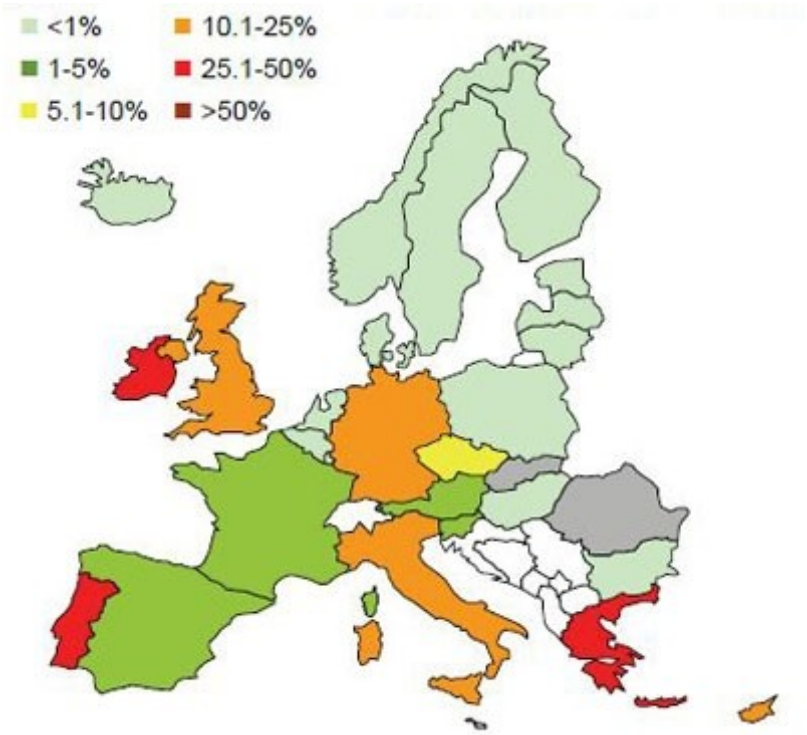
Prof. Dr. Horst Schroten, Director of the Department of Paediatric and Adolescent Medicine at Mannheim Medical Faculty

The prevention of infectious diseases in children, in particular diseases caused by antibiotic resistant bacteria, was also a major topic at the 20th Annual Meeting of the German Society of Paediatric Infectiology which was held in the Rosengarten Congress Centre in Mannheim from 19th to 21st April 2012. The panel discussion focused on "Outbreaks of multiresistant infectious agents – how can we prevent this, what can we do?", which is a particular topic of current interest. "Two factors seem to play a major role in the prevention of infections. The first is vaccination. Diseases such as measles, mumps and whooping cough have only become less frightening thanks to effective vaccination programmes," noted Professor Dr. Horst Schroten, Director of the Department of Paediatric and

Adolescent Medicine at the Mannheim Medical Faculty. He also pointed out that all parents who are reluctant to have their children vaccinated because they are worried about the harm this could cause should consider the fact that the benefit of immunization is far higher than the risk of a severe complication arising from the vaccine.

In areas where immunizations are not (yet) possible, greater focus must be put on hygiene in order to prevent multiple infections from occurring. Hygienic conditions are necessary for babies, but even more so for the doctors and care personnel in hospitals. It is not for nothing that "wash your hands – wash your hands – wash your hands" is the most important element in the code of hygiene.

Multiresistant Staphylococcus aureus strains are particularly dangerous as they are responsible for many difficult-to-treat infections in humans, in particular in hospitalized patients. Penicillin was widely used in the 1940s and it would not take long before staphylococci with an enzyme that could degrade penicillin were discovered. Another antibiotic, i.e. the penicillin derivative methicillin, was specifically developed to counteract this situation. However, as little as two years after methicillin was placed on the market, new bacterial strains appeared that had mechanisms that could metabolize methicillin. In the meantime, methicillin-resistant Staphylococcus aureus (MRSA) strains have become a worldwide threat to human health.



Spread of the vancomycin resistance of Enterococcus strains in Europe
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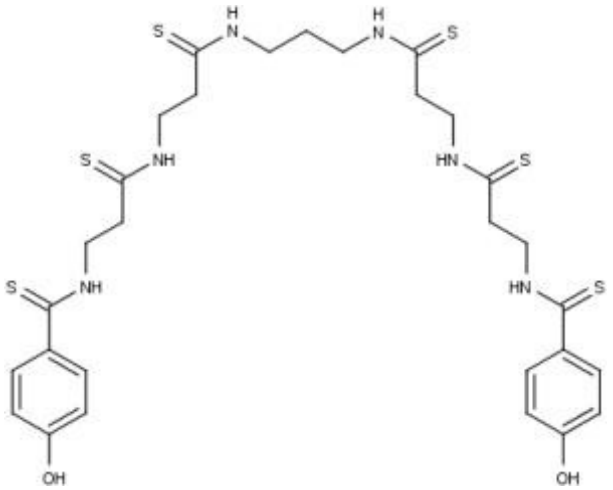
The Robert Koch Institute's updated list on the "Prioritization of transmissible infectious agents under the aspect of surveillance and epidemiological research" (Epidemiological Bulletin of 7th November 2011) gives MRSA the highest priority level (ed. note: MRSA should actually be replaced by the term ORSA as methicillin has been replaced by oxacillin, which is very similar to methicillin; however, the abbreviation MRSA is still frequently used). Vancomycin-resistant enterococci (VRE) pose similar problems. Vancomycin, which has a different mechanism of action from penicillins and cephalosporins (ed. note: they inhibit the formation of peptidoglycan cross-links in the bacterial cell wall) seemed to be an effective weapon against all bacteria that appeared to be resistant to all common antibiotics. A large number of enterococcal infections in countries such as Portugal, Greece and Ireland are caused by VRE, and the prevalence of VRE infections is also increasing in Germany.

A completely new class of antibiotics



Closthioamide, representative of a completely new type of antibiotics

Given the circumstances, the development of a completely new type of antibiotic, closthioamide, by researchers from the Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute is of particular significance. Dr. Thorger Lincke, who was instrumental in the development of closthioamide, was invited by the Heidelberg Technology Park to give a talk in Heidelberg on 24th April 2012 on the discovery of this drug, which has been shown to have an excellent effect against MRSA and VRE.

Researchers from Jena led by Professor Dr. Christian Hertweck succeeded in stimulating the soil bacterium Clostridium cellulolyticum to produce the antibiotic closthioamide upon the addition of an aqueous soil extract to the growth medium. Clostridia are strictly anaerobic bacteria that only grow in the absence of oxygen. Closthioamide is the first secondary metabolite isolated from strictly anaerobic bacteriia. This example thus shows that anaerobic bacteria provide a hitherto unharvested field of antibiotics that are different from the ones in clinical use. The genome of C. cellulolyticum, a bacterium that grows in plant compost where it degrades the cellulose of dead plants, has recently been sequenced. The researchers found that the bacterium possessed genes for the synthesis of previously unknown natural compounds and which are inactive under normal laboratory conditions. All attempts to change the culture conditions and stimulate the synthesis of the compounds failed. Only when the researchers added an aqueous extract of the soil from which the bacteria were isolated did this stimulate the synthesis of closthioamide.

This new polythioamide antibiotic is a rather unusual, sulphur-rich molecule whose effect against pathogens such as MRSA and VRE is now being investigated in detail. Closthioamide might be used as the basis for developing a new generation of antibiotics which would give the researchers a slight lead over – at least temporarily - the infective pathogens that are continuously accumulating mutations and hence producing new types of resistance.

Publication:

Lincke T, Behnken S, Ishida K, Roth M, Hertweck C: Closthioamide: An unprecedented polythioamide antibiotic from the strictly anaerobic bacterium Clostridium cellulolyticum. Angewandte Chemie, Vol. 122, pp. 2055-2057 (2010).

Article

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The article is part of the following dossiers

Human infectious diseases: new threats

Multiresistant pathogens – a self-inflicted threat?

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