

MRSA - free of side effects and successful treatment by phytotherapeutic varieties

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Summary

MRSA (methicillin-resistant *Staphylococcus aureus*) is a dreaded infection because antibiotic resistance mechanisms complicate its treatment. The prevalence is quite high and the incidence of costly partly with dramatic proportions. *Staphylococcus aureus* occurs ubiquitously and can only be influenced by appropriate hygienic prophylactic measures. Also problematic are antibiotic-treated animals, some of which have developed antibiotic resistance and are intended for the consumption by consumers. Hope for a successful and side effect free therapy for MRSA can be a combination of two phytotherapeutic varieties. Under the direction of Prof. Dr. Oliver Planz in the cell- biological Institute in Tübingen Haas Bach et al could show that the combination of special forms of wild oregano (*Origanum* sp.) and black currant (*Ribes nigrum* spec.) had antibacterial effects against MRSA. And at the Institute of General Medicine, University of Lübeck under the direction of Prof. Dr. Jens Martin Träder some infected patients could be successfully treated with the extracts in a first pilot study in vivo. No later than three weeks the successful treatment was confirmed by laboratory analyses.

Article

On July 12th in 2013 the „Ärzteblatt Online“ reported an investigation of the Veterinary Medicine University Hannover. The researchers found antibiotic-resistant germs in numerous healthy slaughtered chickens. From 120 samples resistant bacteria could be discovered in nearly 90 percent. The animals studied were from conventional farms and were considered healthy. A "permission for slaughtering without conditions" was given.

Other scientists from Hanover had recently found out that every broiler in Germany is treated an average of 10 of his 39 days of life with antibiotics [www.aerzteblatt-online.de, July 12th 2013]. In healthy people, antibiotic-resistant germs may be relatively harmless. The therapy is difficult, a disease is feared and what happens to sick people? There is a risk of a serious disease with a fatal outcome. This is an excerpt of the current situation.

Now in the phytotherapeutic sector apparently a new and successful therapy free from side effects for MRSA sufferers appeared: On the Phytotherapiekongress in March 2013 in Leipzig (Germany) the bacteriostatic effect of a new phytotherapeutic agent was first time reported. The effect of a combination of two plant extracts is particularly evident in MRSA bacteria (methicillin-resistant *Staphylococcus aureus*). These studies have now been confirmed clinically in some patients and nourish the hope of achieving a long lasting successful treatment of MRSA germs.

We start with a brief excursion into the relationships of resistance, prevalence and prevention of MRSA. MRSA is difficult to treat so far. MRSA is a dreaded germ from the *Staphylococcus* group. In the clinical language MRSA is often translated to “Multi Resistant *Staphylococcus Aureus*”.

This formulation is technically considered not precise; however, the term stands for the same resistance phenomenon. With increasing use of antibiotics since the 1960s these staphylococcal species increasingly occurs. In hospitals and care facilities, MRSA is considered to be a dreaded cause of hospital acquired infections.

Estimates suggest that approximately 170,000 MRSA infections are a burden for European health care systems with more than one million additional hospitalization days and additional costs of about 380 million EUR. An MRSA infection during a hospital stay in Germany increases the risk of dying, therefore, by a factor of 2.7. The German Society for Hospital Hygiene in 2009 estimated about 40,000 deaths annually by hospital infections [<http://www.dgkh.de/informationen>], and we have to keep in mind: MRSA is not recorded in Germany on the death certificate as a diagnosis.

In the UK, for example, an infection caused by MRSA is noted as the cause of death. Although there are not always visual symptoms, seen in a transmission, but the asymptomatic colonization of the carrier increases the risk of a potentially pathogenic bacterium for others.

This immunological disorder plays a role and the tendency to chronic inflammations. It may lead to the development of carbuncles, boils or pyomyositis. The resulting pneumonia, endocarditis, or toxic shock syndrome (TSS), including sepsis can end up lethal.

The mechanisms of resistance are promoted by nonspecific antibiotic therapies. Characteristic for MRSA is that they have acquired resistances against several classes of antibiotics, such as tetracyclines, or aminoglycosides and thus have a multi-drug resistance.

Above all, chronic recurrent infections with initially non-resistant *Staphylococcus* strains have to mentioned. These bacteria are apparently able to penetrate into the cells of the body.

They can protect themselves against antibiotics by using an intelligent escape procedure and this can prolong their survival from days to weeks so that they can multiply and spread all over the body. Currently also infections from animal reservoirs are discussed. The agricultural livestock represents a reservoir for MRSA, where also a zoonotic transmission to humans is common. Travelling to high-prevalence areas is another important risk factor.

The resistance mechanism of MRSA strains to antibiotics is due to the alteration of penicillin binding proteins (PBPs). Mostly also additional resistances against other groups of antibiotics exist. This bacterial transpeptidase is typically linking the components of the cell wall. Those building blocks are imitated by β -lactam antibiotics. However, they bind irreversibly to the transpeptidase, which is inactivated permanently by this mechanism. If enough transpeptidase is destroyed, new links cannot be formed, with the result that the cell wall synthesis ceases and the modified penicillin binding protein can no longer bind β -lactam antibiotics. So methicillin resistant "*staphylococcus aureus*" bacteria are resistant to all β -lactam antibiotics (penicillins, cephalosporins and carbapenems).

Resistances may be caused for example, by the use of disinfecting cleaning agents such as quaternary ammonium compounds (QAC). Also usual cationic surfactants play a role. In household cleaners, detergents, toothpastes, deodorants and soaps triclosan is used as a disinfectant and preservative. This substance is also associated with drug resistance.

Staphylococcus aureus is a spherical gram positive bacterium, which is usually arranged botryoidal. Staphylococci do not form spores, they are immobile and have a size between 0.8 and 1.2 microns. In the whole nature *Staphylococcus aureus* is found. In the upper respiratory tract and on the skin an infection is found in 25 to 30% of all people. Most strains of *Staphylococcus aureus* are colored orange to golden yellow, so it was thought for a long time to be the cause of yellowish pus. The shimmering gold dye on the surface of the bacteria comes from carotenoids. These pigments act as

an antioxidant and prevent chemical reactions with oxygen or other oxidizing substances. Thus, the bacterium protects itself against some substances that our immune system uses for defense.

The prevalence and the incidence of MRSA is expensive and increased dramatically. The prevalence is quite high. In Germany every year about 132,000 patients are diagnosed with MRSA in hospitals [Köck et al]. Some hospitals indicate clinically acquired infections with MRSA up to 30%. Still no entrance examination for MRSA is made at admission of patients. In Holland, for example, the entrance examination for MRSA has led to a significantly reduced incidence. Worldwide infections with MRSA germs are feared.

Especially in hospitals and clinics there is a high risk to get infected with such germs. Here the risk is especially high in the surgical intensive care units, the neonatal units and special treatment centers for burns.

The current data of the interactive antibiotic resistance surveillance database of the Robert Koch Institute (RKI) documented the incidence of the MRSA percentage at 21.9 % for 2009 (RKI: <https://ars.rki.de>, data as of 30.11.2010).

However, it is reported that in some areas of risk for MRSA are higher and the rates sometimes exceed 37%. By introducing a laboratory reporting requirement in 2009 (according to §7 of the Infection Protection Act) for the MRSA from blood cultures and liquors in Germany, an incidence of 1.94 / 100,000 population was determined (RKI/<http://www.nrz-hygiene.de>). The “technician health insurance” Schleswig-Holstein indicates a considerable increase in the incidence by +192%, from 2006 to 2009.

The risks for MRSA infections are known:

- Longer and repeatedly used antibiotic treatment
- Longer hospital stays
- Treatment in intensive care units
- Surgery
- Lack of hygiene, especially hand sanitizer

Adequate prophylaxis is useful. MRSA germs are mainly transmitted via the hands. Therefore, consistently organized and documented hygienic measures play an important role. A thorough “lege artis” performed hand disinfection should be obligatory. Disposable gloves, protective gowns and masks should be worn and should be regulated by the generated hygiene plans in hospitals, clinics and nursing homes.

A critical factor remains because among the nursing staff as also among physicians about 30% of them are carriers of these germs. Also the rescue service personnel, that is transporting patients into and out of the clinic may be a carrier of MRSA. The Robert Koch Institut (RKI) recommends screening examinations in hospitals only of the following groups:

1. Chronic long-term care patients with a catheterization or chronic wounds
2. Hospital staff as soon as a frequent detection of MRSA in more than two patients could be observed, which are in a spatial and temporal context, and if the germs were shown to be clonally identical

The RKI states that a general basic screening of all patients before admission to the clinic, and the screening of the entire nursing staff is too costly. Due to different state regulations in Germany, for example, the setting of a sanitary doctor in a clinic is not mandatory. Only five percent of the German clinics have hired a specialized doctor for hygiene.

In the Netherlands, however, the protective measures include the screening of all patients coming to the recording, the use of a hygiene specialist in each clinic and the cooperation of each antibiotic treatment with a microbiologist. Isolation may also prevent new cases.

The current therapeutic approaches for MRSA patients

MRSA is mostly treated with combinations of various antibiotic agents, such as glycopeptide antibiotics with rifampicin, clindamycin, gentamicin, depending on the results of susceptibility testing. Also combinations with fosfomycin and fusidic acid are possible. As a single agent linezolid can be used. Through resistances (penicillinases inactivate penicillin) penicillinase resistant isoxazolympenicillines (dicloxacillin, flucloxacillin, oxacillin) have been developed.

Through the additional development of resistances to other antibiotics substance classes (macrolides, lincosamides (clindamycin) quinolone antibiotics) is the therapy, despite antibiograms difficult, often unsuccessfully.

From the epidemiological, hygienic and clinical point of view it makes sense to remove the bacteria of contact persons with a proven colonization even when they are not themselves ill. Depending on the place of settlement, different measures are used.

In the nasal cavity mupirocin nasal ointment is used in the pharyngeal cavity disinfectant mouthwashes are used and on the skin of the entire body including the hair is washed with antiseptic soaps and solutions whose efficacy has been demonstrated against MRSA.

After three days swabs (from: the nose, throat, armpits, groin, may access from a wound or catheters) were taken and examined as proof of successful treatment.

Due to limited therapeutic options, a transmission of MRSA germs might lead to sepsis, and maybe come up with a fatal outcome. Therefore, there is a great need for effective antibacterial agents against MRSA infections.

Considering also, in addition to the sometimes unsuccessful action and side effects of antibiotic substances (gastrointestinal disorders with fungal colonization to mental health problems by loading the enteric system and altered neurotransmitter effect, nausea, diarrhea, skin rashes and lesions, headache, Vertigo, allergies, intolerance on the contained adjuvants to antibiotic resistance), it is logical to look out for effective substances without side effects and that are well-tolerated.

New phytotherapeutic successful approaches to MRSA

Under the direction of Prof. Dr. Oliver Planz Haas Bach et al in the cell biology institute in Tübingen it was shown that the combination of two plant extracts of special wild varieties of oregano (spec. *Origanum*) and black currant (spec. *Ribes nigrum*) had antibacterial effects against MRSA. The investigations were based on the agar diffusion test, growth inhibition, and the MIC50 test. All studies showed a strong inhibition of bacterial growth. Using washout experiments it could be shown that a good bacteriostatic effect was achieved. Furthermore, an efficacy of this combination was also found against other *Staphylococcus aureus* strains, as well as against *Pseudomonas*, *Salmonella* and *Yersinia*.

The tests were carried out generally in three independent experiments. Furthermore, three different types of experiments were carried out, which has helped to validate the results.

Meanwhile, at the Institute of General Medicine, University of Lübeck at Prof. Dr. Jens Martin Träder in a first pilot study, eight patients infected in the nasopharynx could be treated with the extract. A MRSA infection was confirmed by laboratory analysis prior to the treatment in seven subjects. The subjects used Kremo 058® dental cleaning pastilles (4x2 lozenges) for more than three weeks. Tolerability was rated as good. The taste was specified as "satisfactory to good". Already after about one week four patients studied and after two or three weeks at the latest six subjects had no longer a detectable MRSA infection.

These results demonstrate that the combination of the two phytotherapeutic agents has a very good antibacterial activity against the bacterial strains tested. The pilot study shows that the research results can be applied to clinical situations. Now in a Germany-wide, double-blind, randomized study, the results are reviewed.

Plant Portraits

Since the Roman era it is known that infectious diseases can be reduced through body and oral hygiene. Research from Dr. Pandalis using extracts from the herb a wild Variety of oregano (*Herba Origani vulgaris*) and from the leaves of a wild form of black currant (*Ribes nigri folium*) found that these extracts not only develop a strong cleansing power, but also provide new successful therapeutic approaches in MRSA and clearly show synergistic effects. In the following, the plant Oregano (*Herba Origani vulgaris*) and black currant leaves (*Ribes nigri folium*) are reviewed.

Oregano (*Herba Origani vulgaris*)

The bacteriostatic effects of oregano have been demonstrated against various bacteria and fungi in numerous experiments and are summarized in the data collection HagerROM [Hager, 2011]. There it is also described that oregano may cause irritation to the skin in undiluted form.

The Commission E of the former Federal Health Office (BGA) stated in 1988 that the use of oregano bears no health risks. Oregano (*Origanum vulgare*) belongs to the genus of Doste in the mint family (Lamiaceae). It resembles the closely related marjoram (*Origanum majorana*), and is often referred to as Wild Marjoram, but it is slightly more hot [Franke, 1989] [Wyk, 2005].

The 60 centimeter-high perennials form square stems. Crimson flowers grow in “trugdoldigen” panicles. The crushed leaves have a characteristic smell. Oregano can be found growing wild throughout Europe to Central Asia. His preferred position is an alkaline soil.

In the kitchen he is used as a spice to tomato dishes, such as pizza, meat and potatoes. In folk medicine, oregano is used as a tea or powdered for respiratory, urinary tract and pelvic disorders, as well as in indigestion and rheumatism [Franke, 1989], [Wyk, 2005] [Blaschek & Ebel, 2011].

Oregano contains primarily essential oils (0.15-0.4%) and depending on the location, there are various chemotypes of oregano with varying contents and composition of essential oils.

It is rich in monoterpene hydrocarbons such as limonene, α - and β -pinene, ocimene and p -cymene, sesquiterpene hydrocarbons such as caryophyllene and β -bisabolene, the terpene phenol carvacrol, and linalool, α - and γ -terpinene, myrcene and thymol.

In addition, it contains flavones and flavone glycosides, phenolic acids, and other derivatives, such as rosmarinic acid and tannins are included with astringent effects. Due to its very high content of phenols it is bacteriostatic and should be used only orally because of skin irritant effects or it should be diluted with a carrier oil.

Description of Picture 1:

Studies on the toxicity of Kremo058®

The results of the studies show that Kremo058® compared to the control has no effect on cell growth even at a dilution of 1:8. It should be noted that in this experiment the cultured cells are conditioned used on the medium. No influence on cell growth (with 12.5% Kremo058® in the culture medium) can therefore be regarded as very remarkable safe.

Description of Picture 2:

Studies on the antibacterial action of Kremo058® against Methicillin-resistant *Staphylococcus aureus*.
Is Kremo058® acting bactericidal or bacteriostatic?

The studies clearly show the bacteriostatic effect of Kremo058®.

Study measuring the antibacterial activity of Kremo058® with the aid of the determination of growth curve

The results of these investigations show that up to a dilution of 1:5 for even 24 hours, no bacteria growth can be observed. At a dilution of 1:10, the bacterial growth is inhibited for at least seven hours.

Description of Picture 3:

Investigation of the antibacterial activity of Kremo058® with the determination of an MIC50 value

The MIC50 value is in these studies, as Kremo058® can be diluted so that 50% of bacterial growth is inhibited. The results of the investigations show that for type I to a dilution of 1:63 Kremo058® is able to inhibit 50% of bacterial growth. For Type II Kremo058®, this value is even higher (1:73). The tests were carried out three times.

Description of Picture 4:

Studies on the antibacterial action of Kremo058® against *Pseudomonas aeruginosa*, *Yersinia enterocolitica* and *Salmonella typhimurium*.

The studies show an additive effect against the bacterial strains listed here.

Black currant leaves (*Ribes nigri folium*)

The Black Currant (*Ribes nigrum*) belongs to the family of the gooseberry family (Grossulariaceae).

The German name currant based on the fact that the first berries mature around the Christian Midsummer (24 June) [Baeumler, 2007].

The stingless shrubbery are 1-2 m high and carry racemose inflorescences arranged with a yellowish-green color, which are reddish brown at the edges. From them the black berries develop after fertilization [Baeumler, 2007].

The leaves of the black currant are named as *Ribes nigri folium* (folium = Latin "leave"). The blackcurrant is growing wild in front of the North European alder swamps and its growing in cultivated forms. The harvest of the leaves takes place in June and the fruits ripe in June/July [Baeumler, 2007] [Wyk, 2005]. In central and northern Europe, the bush is known only since the 16th century as a medicinal plant. In folk medicine the leaves are used as a remedy for whooping cough and spasmodic cough and are used for irrigation therapy of the urinary tract, taken preventively in kidney semolina, as well as diarrhea treatment in the form of teas. An external application is described for insect bites and wounds. The leaves of the black currant are recognized by the European Scientific Cooperative on Phytotherapy (ES COP) as drug for rheumatic diseases [Baeumler, 2007]. Their effect is described in animal experiments as diuretic (aquaretic), weak saluretic and hypotensive [Schilcher, 2010].

The leaves of the black currant contain a wide range of ethereal oils from the group of mono-, di- and sesquiterpenes. In addition, the ingredients consist of 0.5% of flavonoids, including the fungicidal Sakuranetin. The string and effective antioxidant effect of the plant is mainly coming from the group of polyphenols flavonoids, vitamin C and tocopherols.

The richly represented proanthocyanidins [Baeumler, 2007] are as proanthocyanidins part of the oligomeric compounds and bound with catechins as basic building blocks [Hänsel & Sticher, 2010].

By reacting as antioxidants with oxygen-rich compounds and free radicals, they can prevent the formation of lipid peroxides in the human body.

If, for example, the polyunsaturated fatty acids in the low-density lipoprotein (LDL) particles are oxidized to peroxides, this promotes indirectly the formation of the so-called foam cells, which are deposited as plaques on the inner walls of arteries and thus cause atherosclerosis [Watz & Leitzman, 1999].

Oligomeric proanthocyanidins are also selectively inhibiting cyclooxygenase COX-2 which is responsible for the formation of prostaglandins as mediators of pain [Meyer, 2004].

Another antioxidant active ingredient in *Ribes nigri folium* is caffeic acid which is belonging to the group of phenolic acids. It is generally believed that phenolic acids act synergistically with each other and also with other biologically active plant substances, so their anti-oxidative effects are more pronounced by this interaction than of the individual components alone [Watz & Leitzman, 1999].

From a nutritional and medical point of view, this is again an argument why plant extracts with their overall complex composition are preferred to act against pathogens than (mostly synthetic) single agents.

Two therapeutic recommendations of the author

In the naturopathic treatment it is possible to treat MRSA by the basic regulation of the immune system.

1. For example Isotherapy Notakehl D5 tablets can be used (put at night into a mouth bag) and Sanukehl Staph D6. However, when administered no suppressive therapy should be done at the same time, but could be started after a two-week wash out phase.
2. Quite good experiences I could do with the “Rechtsregulate”-principle from Dr. Niedermeier Pharma in inflammatory processes. The anti-inflammatory, antimicrobial, immunomodulatory, and antioxidant substances and acid removing cascade-fermented “Regulates” contain highly active phytonutrients, amino acids, flavonoids, ellagic acid, phenolic acids, flavanols, flavones and can be both internally and externally applied.

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Leitlinien und weiterführende Links im Internet

- www.rki.de > Infektionskrankheiten > Staphylokokken/
Hinweise zu Infektionskrankheiten – Merkblätter für Ärzte, Prävention und Bekämpfungsmaßnahmen MRSA und Krankenhaushygiene
- www.rki.de > Infektionsschutz > Krankenhaushygiene >
Empfehlungen der Kommission für Krankenhaushygiene/
Hinweise MRSA-spezifische Leitlinien des RKI, Desinfektionsmittel, Entsorgung gebrauchter
Artikel, Wiederaufbereitung von Medizinprodukten
- www.rki.de > Infektionsschutz > Krankenhaushygiene/
Empfehlungen der Kommission für Krankenhaushygiene > Infektionsprävention in Heimen
- www.lqi.bayern.de > Gesundheit > Hygiene > cMRSA - community acquired Methicillinresistente *Staphylococcus aureus*
- www.lqi.bayern.de > Gesundheit > Hygiene > cMRSA bei Bewohnern und Personal in Altenpflegeheimen
- www.medizin.uni-tuebingen.de/mikrobiologie/mrsa.html/Hinweise zum Umgang mit aus dem Krankenhaus entlassenen, MRSAkolonisierten Personen.

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