WOUND HEALING DISORDER IN A HORSE, ASSOCIATED WITH ANTIMICROBIAL RESISTANT BACTERIA, RESOLVED WITH A HOMEOPATHIC REMEDY – A CASE REPORT

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- **Keywords: horse, homeopathy, antimicrobial resistant bacteria, antimicrobial resistance (AMR), wound healing disorder**

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Abstract

- A 4 year old trotter gelding was treated homeopathically for delayed wound healing associated with antimicrobial resistant bacteria. The horse failed to respond to antibiotic treatment with intravenous gentamicin and penicillin followed by oral sulfadiazin natrium and trimethoprim. Wound swab, bacterial examination, and microbial sensitivity test diagnosed ORS – Oxacillin Resistant Staphylococcus haemolyticus and Actinobacillus equuli.

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- At presentation for homeopathic treatment, the horse showed putrid inflammation, edema and seroma. Following treatment with a single dose of homeopathic silicea terra, resolution of clinical signs occurred. Homeopathic silicea terra is one of many homeopathic remedies that may be beneficial in treating cases of putrid wound healing disorders associated with antimicrobial resistant bacteria. Hence, considering the global threat of antimicrobial resistance (AMR), further studies should be conducted in cooperation with universities, animal clinics, and homeopathically trained veterinarians.

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Introduction

- Antimicrobials are essential medicines for the treatment of many microbial infections in humans and animals. Only a small number of antimicrobial agents with new mechanisms of action have been authorized in recent years for use in either humans or animals. Antimicrobial resistance (AMR) arising from the use of antimicrobial agents in veterinary medicine is a concern for public health due to the detection of increasing levels of resistance in foodborne zoonotic bacteria, particularly Gram-negative bacteria, and due to the detection of determinants of resistance such as Extended-spectrum beta-lactamases (ESBL) in bacteria from animals and in foodstuffs of animal origin (Törneke et al. 2015).

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- The “one-health approach” states that the impact on public health of the use of antimicrobials in animals should be minimized as far as possible. It is obvious that any non-essential usage of antimicrobials in animals should be curtailed: homeopathy may offer an appropriate alternative as homeopathy can be effective in bacterial infections.

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- For example, in a randomized, placebo controlled, double-blind study (Camerlink et al. 2010) homeopathic remedies were used as replacement to antibiotics to treat Escherichia coli (E. coli) diarrhoea in neonatal piglets. This study, published in 2010, showed that in the homeopathically treated group significantly fewer piglets were suffering from E. coli induced diarrhoea. In addition, the severity of the disease decreased and diarrhoea, if it occurred, was of shorter duration compared to the control group. The study was classified as high-quality by Mathie and Clausen (2014, 2015).

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- In another study, homeopathic treatment improved growth and survival against *V. alginolyticus* in juvenile *A. ventricosus*. This suggests that homeopathy is a viable treatment for this mollusk to reduce use of antibiotics in scallops and to combat the progressive increase in pathogen infections in mollusk hatcheries (Mazón-Suástegui et al. 2017).

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- In the recently published evaluation documents on the antimicrobial resistance (AMR) Action Plan of the EU Commission, CAM (complementary, alternative medicine), homeopathy included, is mentioned as a potential approach to the problem of AMR. The Evaluation of the Action Plan regarding the rising threats from AMR from the European Commission states in summary that 'the evaluation demonstrates the need for continuing coordination and collaboration on AMR research on developing new antimicrobials, rapid diagnostic tests, vaccines and alternative treatments' (European Commission 2016). Further research in CAM is particularly relevant in terms of the importance of the AMR problem in humans and animals.

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- Apart from clinical research, valuable preclinical results are already available. *In vitro* growth of methicillin-resistant Staphylococcus aureus (MRSA) was statistically significantly inhibited in the presence of atropa belladonna and MRSA nosode 6cH and 30cH compared to controls ($p < 0.0001;6$); and with combination of belladonna atropa or MRSA nosode 6cH and 30cH and oxacillin ($p < 0.001$). Belladonna atropa 30cH and MRSA nosode 6cH and 30cH significantly decreased bacterial DNAse production ($p < 0.001$) and reduced red blood cell lysis. Hence, cultures of MRSA treated with belladonna atropa or MRSA nosode became more vulnerable to the action of the antibiotic oxacillin (Passeti et al. 2017).

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- Homeopathy is a system of medicine developed by the German physician Samuel Hahnemann (1755–1843). It is based on the principle of "like cures like". Substances, that when tested, cause a set of signs in healthy individuals are used to cure those symptoms (signs in animals) shown by sick individuals. The tests are known as "provings" and are conducted using potentized, i.e. diluted and vigorously succussed dilutions of the original substance (Hahnemann 2003).

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- The purpose of this report is to describe a case of wound healing disorder in a horse, associated with antimicrobial resistant bacteria (Oxacillin Resistant Staphylococcus haemolyticus). In this patient, oral administration of homeopathic silicea terra resulted in resolution of signs and apparent disappearance of the bacterial organisms, though previous treatment with intravenous gentamicin and penicillin followed by oral sulfadiazin natrium and trimethoprim had been unsuccessful. This is the first reported case of clinical resolution of putrid inflammation, seroma, and edema as a wound healing disorder in a horse after treatment with silicea terra (acidum silicicum) C30.

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- **Case history, clinical findings, diagnosis, treatment, outcome**
- A 4 year old trotter gelding was presented at a clinic specialized on equine medicine in Austria on June 17, 2016, for treatment of acute injury of the right foreleg. The clinical examination revealed a deep lacerated wound (Fig. 1) at the radius reaching the anconeus (10 x 7cm) involving the cutaneous, subcutaneous, and muscular layer (M.ext.carpi rad. and M.ext.dig.comm.), several small cutaneous lacerations, as well as a mild lameness. Other exam findings were a slightly elevated pulse (44 beats/min), temperature of 38,0°C, a capillary refill time of 2 seconds, slight/moderate redness of the left and right conjunctiva, slightly enlarged mandibular lymph nodes but no further pathologic findings.

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- The digital X-rays showed no pathologic findings of the bones, however, air inclusions near the elbow joint. The cytologic examination of aspiration the joint fluid revealed no pathologic findings. Since involvement of the synovial structures of the anconeus could not be excluded, 500mg of Amikacin were instilled intraarticularly. The surgical treatment was performed under sedation and local anesthesia, primary wound closure was chosen as the preferred treatment option (vertical U sutures for the cutaneous layer, sutures saved by loop system, and sterile abdominal bandages) and a drain was placed due to loculation (Fig. 2). A wound dressing was applied for protection. Medical treatment included intravenous administration of Gentamicin, Penicillin, and Flunixin meglumine, furthermore oral administration of Omeprazole for 12 days.

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Figure 1: June 17, 2016 (after injury, before surgical treatment)	Figure 2: June 17, 2016 (after injury, after surgical treatment)
	

- During the next days, fever (38.4°C), lameness, seroma, and edema developed (Fig. 3), therefore a blood sample and wound swab were taken on June 27, 2016; bacterial culture and microbial sensitivity test were performed. Serum amyloid A concentration was moderately elevated (498 mg/l). On June 28, 2016, ultrasonographic examination revealed a fluid-filled cavity wound with floating echoic material, drainage revealed150ml of seroanguineous fluid. On June 29, 2016, necrotic tissue could be seen during endoscopic examination, and antibiotic treatment was changed to oral sulfadiazin natrium and trimethoprim.

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- On June 30, 2016, the results of the bacterial examination and sensitivity test revealed mecA positive, TSST negative, PVL negative ORS – Oxacillin Resistant Staphylococcus haemolyticus and Actinobacillus equuli (Table 1). The owner decided to take the horse home and off medication on June 29, 2016, after being informed about the risk of degenerative arthrosis of the anconeus due to septic joint inflammation potentially leading to lethal septicaemia.

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Table 1: 30 June 2016 – Institute for Microbiology, Department for Pathology, University of Veterinary Medicine, Vienna

Bei der bakteriologischen/mykologischen Untersuchung wurde(n) nachgewiesen:

Material	Grad	Keim	Bemerkungen
	mgr.	häm. koagulaseneg. *Staphylococcus* sp. - **CAVE ORS!**	
	mgr.	*Actinobacillus equuli*	

Resistenztest: S = sensibel R = resistent I = intermediär

häm. koagulaseneg. *Staphylococcus* sp. - **CAVE ORS!**	PEN	AMP	AMX	AMC	PIP	TZP	FOX	OXA	CEF	CFZ	CPD	CAZ	CTX	XLN	VEC	CEQ	FEP	IPM	MEM	ETP	ATM	ENO	MAR	PRA	CIP	AMK	GEN	TOB
	R			R			R							R	R	R						R	R		R	R	R	
	DOX	TET	TGC	AZM	ERY	CHL	TUL	TYL	CLI	FAC	VAN	TEC	LZD	STX	PMB	CST	FOF	RIF	MUP	NIT								
	R	R	S	R	R	S			R			S	S	R				S		S								
Actinobacillus equuli	PEN	AMP	AMX	AMC	PIP	TZP	FOX	OXA	CEF	CFZ	CPD	CAZ	CTX	XLN	VEC	CEQ	FEP	IPM	MEM	ETP	ATM	ENO	MAR	PRA	CIP	AMK	GEN	TOB
	S	S	S	S										S	S	S						S	S					
	DOX	TET	TGC	AZM	ERY	CHL	TUL	TYL	CLI	FAC	VAN	TEC	LZD	STX	PMB	CST	FOF	RIF	MUP	NIT								
	S	S		S		S								S														

Figure 3: 29 June 2016 (2 weeks after surgical treatment - seroma, edema, necrosis)

- Veterinary Treatment and Diagnostics from June 17 to 30, 2016
- Date(s) Procedures, Medications, Diagnostics
- 17 June 2016 Surgical repair and drainage, Amikacin (Biklin) 2, 500 mg IA once
- 17 to 28 June 2016 Gentamicin (Gentavan) 3, 6.6 mg/kg bwt SID, Penicillin (Penicillin G-Natrium) 4, 30,000 IU/kg bwt QID, Flunixin meglumine (Finadyne) 5, 1.1 mg/kg bwt BID IV, Omeprazole (Gastrogard) 6, 1 mg/kg bwt SID PO
- 29 June 2016 Sulfadiazin natrium and Trimthoprim (5:1 mixed) (Equibactin) 7, 15 mg/kg bwt SID PO

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- The first homeopathic consultation with the author took place on July 5, 2016. The horse was presented with putrid inflammation, edema, seroma – a well known post surgery wound healing disorder – associated with antimicrobial resistant bacteria. Physical examination showed a mild depression mood (eyes were half closed), a weak pulse, and a moderately elevated respiraty rate (22 breaths/min). Both submandibular lymph nodes were slightly enlarged. The body condition was poor, moderate atrophy of the long back muscle was observed. Both hind legs showed mild edema at the cannon bone.

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- Wound edges were moderately hardened; there was no pain on palpation in the wound surroundings. Distal from the wound, moderate edema reached the fetlock. The wound secretion was bland, thick, yellow purulent and included serosanguinous material. Wound cleaning was not tolerated without sedation and/or local anesthesia. When the horse was awake it showed a sensible, very gentle, nice character. There was mild lameness observed while walking. Temperature, heart rate, heart / lung / gut auscultation were within normal limits (37.4°C). The horse had been used for trotting races in the past but was considered to be too slow. Dandruff on the whole body and especially on the head was observed. The owner stated that the body condition was worse when she bought the horse.

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- Constitutional homeopathic therapy was started on July 5, 2016, by giving the homeopathic remedy silicea terra CH30, three globules once a day for three days. In addition to the homeopathic treatment, hyaluronic acid sodium salt spray was locally applied by the owner from July 1 until July 15, 2016, hence this local therapy was started four days before the homeopathic treatment.

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Date Start / end	Remedy, potency, remedy form (globules, dilution, pills, injection)	Repetition, dosage, route
July 5-7 2016	Silicea terra C30, globules, 1	Once a day, three globules, oral

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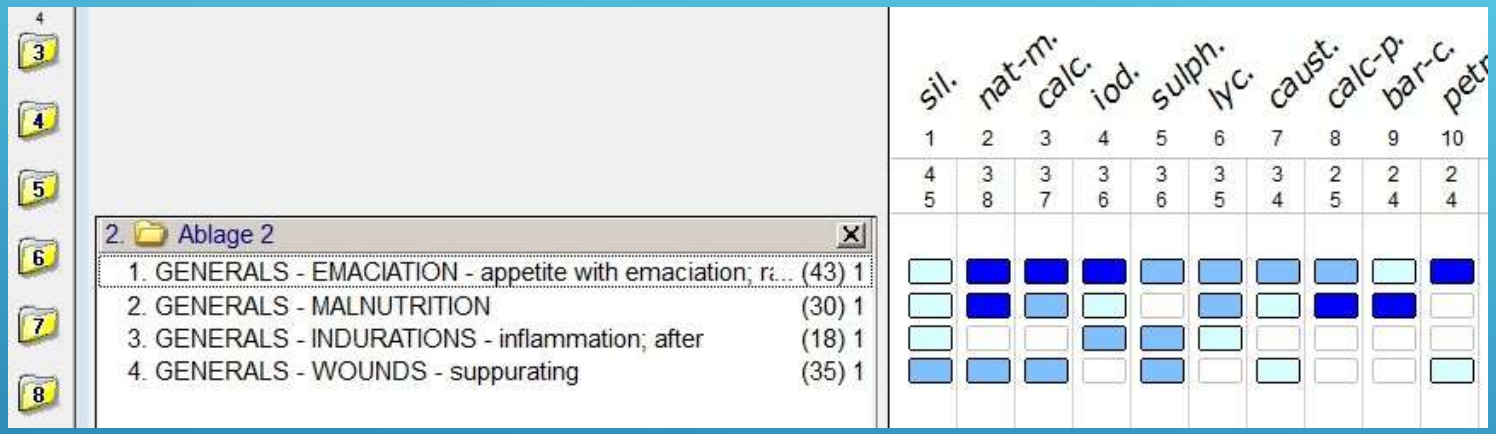

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- The remedy was chosen due to emaciation with appetite, malnutrition in the past, hardened wound edges post inflammation, and putrid inflammation of the wound. The repertorisation programme used was Radar 10 (Fig.6). Apart from the chosen signs, the horses' gentle, sensible, and careful behavior guided the choice to the simile, silicea terra.

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- Improvement was noted by the owner during the first week day by day. Ten days after administration of the homeopathic remedy, the horse presented with soft wound edges, there was no pus, no swelling, no pain on palpation, so the wound showed a normal healing process (Fig. 4). There was no lameness observed during walking. Clinical examination findings were now within normal limits, bacteria were not examined any more but the clinical picture showed no more signs of bacterial infection.

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Figure 4: 15 July 2016 (Ten days after constitutional homeopathic treatment) - Five weeks later the horse presented with the wound closed (Fig. 5).

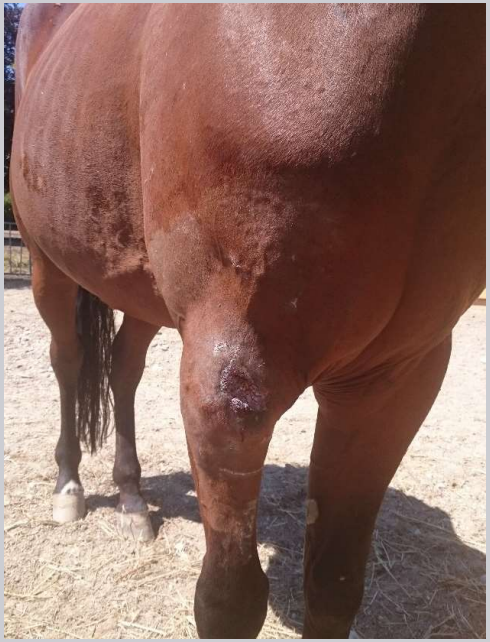

Figure 5: 9 August 2016 (Five weeks after constitutional homeopathic treatment) - The horse's wound has remained cured with no recidivism as of August 2017.

Conclusion:

- With regard to horses, only little research has been performed so far to examine either the prevalence or mechanisms of resistance of several significant bacterial species. Therefore, the need for increased surveillance exists. There has been limited evaluation of risk factors associated with either carriage or infection with antimicrobial-resistant bacteria, with some consistent effects of antimicrobial treatment noted. However, antimicrobial exposure has not been the sole reason identified for resistance and many risk factors are currently undetermined (Maddox et al. 2015).

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- To date, most epidemiological studies of antimicrobial resistant (AMR) bacteria from horses have focused on resistance in Staphylococci and Escherichia coli. In particular, organisms such as MRSA and extended spectrum b-lactamase (ESBL)-producing E. coli have attracted much attention due to significant multidrug resistance often observed. Methicillin-resistant Staphylococcus aureus has been identified as a cause of infection, with a low prevalence of nasal carriage by horses in the community, but higher for hospitalized horses. Resistance to a variety of antimicrobial agents is common within the genus.

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- Antimicrobial resistant Escherichia coli (including multidrug-resistant and extended spectrum b-lactamase-producing isolates) have caused infections and been documented in faecal carriage by horses, with many significant resistance mechanisms identified. More sporadic reports and molecular characterization exist for resistance in other bacteria such as Enterococci, Salmonella, Acinetobacter, and Pseudomonas species (Maddox et al. 2015).

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- In 2013, Kern and Perreten concluded that Methicillin-resistant coagulase-negative Staphylococci (MRCoNS) from animal infection sites are genetically heterogeneous multidrug-resistant strains that represent a new challenge in the prevention and therapy of infections in veterinary clinics (Kern and Perreten 2013). In this study, many animals were given more than one antibiotic course, with some animals receiving 5 to 14 courses of an antibiotic before the MRCoNS infection was diagnosed. MRCoNS are associated with serious infections in animals and have become a challenge for therapy.

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- Similar to Methicillin-resistant Staphylococcus pseudointermedius (MRSP), more than two-thirds of the MRCoNS exhibit resistance to fluoroquinolones, macrolides, lincosamides, and aminoglycosides, in addition to resistance to b-lactams, suggesting that they have been selected through the frequent use of antibiotics (Kern and Perreten 2013).

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- In recent studies, the prevalence of clinical S. epidermidis and, in particular, S. haemolyticus isolates resistant to oxacillin has now reached about 80% or more. As occurs with MRSA, oxacillin-resistant CoNS isolates are, in general, more often multiresistant than oxacillin susceptible isolates (Becker et al. 2014).

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- The CoNS species identified in this study were the same as the ones causing nosocomial infections in humans, with S. epidermidis and S. haemolyticus being the most prevalent in animals and humans (Santos Sanches et al. 2000). The presence of clones similar to those causing infections in humans highlights the importance of careful surveillance of infectious bacterial diseases, the need to implement infection control programmes, and the prudent use of antibiotics in veterinary settings (Kern and Perreten 2013).

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- The study by Skärlina and colleagues (2015) provides evidence that reduction of bacterial numbers can be achieved without antimicrobials. Wound lavage and debridement is widely used for the management of equine wounds; however, the use of hydrosurgical debridement reduced bacterial numbers in an open wound model by 99.7% more than sharp debridement and saline irrigation. These findings and observations suggest that there are opportunities for more targeted, 'smart' use of antimicrobials in the perioperative period, rather than simply more antimicrobials.

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- To date, many studies identify methods for enhancing antimicrobial stewardship, through selection, dosing and timing of antimicrobials in equine practice. They form the basis by which clinicians might change their clinical practice in order to use fewer antimicrobials or a more targeted therapy. It still remains to be determined how big a problem AMR will be for the equine veterinary profession, either through greater difficulties in effectively treating horses with bacterial infections, or through external political pressure to restrict veterinary access to antimicrobials. It is open to conjecture whether freedom to prescribe for the benefit of patients will be a freedom which will be allowed by society in the future (Bowen and Clegg 2015).

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- Considering the global threat of anti-microbial resistance, such promising areas as homeopathy deserve investment in further research, in particular high-quality randomized clinical trials. Case reports and case series are of high value when it comes to everyday clinical practice.

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- In June 2017, the EU Commission adopted the new "European One Health Action Plan" against Antimicrobial Resistance (AMR) which contains even more references to the need of alternatives to antibiotics than its predecessor (European Commission 2017). Some quotes to be mentioned:

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- - More research is needed to develop new medicinal products, therapeutics, and alternative treatments.
- - The Commission will support research into the development of new antimicrobials and alternative products for humans and animals.
- - The Commission will support SMEs in their R&D efforts towards innovative and/or alternative therapeutic approaches for the treatment or prevention of bacterial infections.

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- - Developing new antimicrobials or alternative therapies require significant and long-term investments.
- - The involvement of HTA bodies in AMR-related discussions could raise their awareness on AMR when assessing the added value of new antimicrobials and alternatives, diagnostics or a combination thereof.
- - The Commission will support research into the development of new economic models, exploring and analyzing incentives to boost the development of new therapeutics, alternatives, vaccines, and diagnostics.

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- Homeopathic remedies are prescribed based on the concept of "like cures like". A substance is given to healthy human provers, who then record their mental, emotional, and physical symptoms that arise as a result of the remedy's effects. The symptoms are collated and recorded in so-called materiae medicae and repertories.

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- In selecting the appropriate remedy, emphasis is given to signs that are strong in the case (emaciation with appetite, putrid inflammation of the wound, gentle, sensible, careful character) as well as signs that differentiate one patient from another (hardened wound edges post inflammation). The horses´ signs of emaciation with appetite, hardened wound edges post inflammation, putrid inflammation of the wound as well as the gentle, careful, sensible character and the history of malnutrition, corresponded with what is documented for silicea terra in the homeopathic provings and materia medica (Boger 2008; Vermeulen 2000).

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- In this case report, the horse was given a preparation diluted 1:100 and vigorously succussed, 30 times. The homeopathic remedy was prepared according to the European Pharmacopoeia.

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- After oral administration of the homeopathic remedy silicea terra, the horse in this case report experienced a dramatic clinical improvement and apparent disappearance of the multiresistant bacteria (mecA positive, TSST negative, PVL negative ORS – Oxacillin Resistant Staphylococcus haemolyticus) and Actinobacillus equuli including a follow-up time of more than one year. The selection of a homeopathic medicine for a specific patient is based on the patient's unique characteristic manifestation of the illness versus the etiological agent.

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- In light of the global threat of AMR, the “one health approach”, and the request by European Commission for further research in such promising areas as CAM, homeopathy included, this case report indicates that further study of the use of silicea terra and other homeopathic remedies in cases of infections with multiresistant bacteria in horses, or even animals in general should be conducted.

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- Cooperation between equine clinics or general practice animal clinics with homeopathic veterinarians would be of high value for patients suffering from infections with multiresistant bacteria. Further studies, preferable pragmatic randomized controlled trials, could then be conducted by cooperating teams.

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- Authors' declaration of interests: I declare that there is no conflict of interests.
- 1 Homeocur, Retz, Lower Austria, Austria
- 2 Bristol-Myers Squibb SRL, Anagni, Italy
- 3 Vana GmbH, Wien, Wien, Austria
- 4 Sandoz GmbH, Kundl, Tyrol, Austria
- 5 Schering Plough Sante Animale, Segre, France
- 6 Merial S.A.S., Toulouse, France
- 7 Produlab Pharma B.V., SJ Raamsdonksveer, The Netherlands

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