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Clinical signs, therapy, and outcome of infective endocarditis in horses – two cases

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Summary: Objective of the study was to describe two different cases of equine infective endocarditis and to emphasis the challenges which occur in diagnostic work-up, therapeutic options and outcome of this rare and often fatal disease. Both cases had a history of recurrent fever, apathy, and a recently developed heart murmur. Both horses were unresponsive to pre-treatment with antibiotics and antiphlogistics. At admission, the horse with infective aortic endocarditis presented various unspecific clinical signs and was subjected to several complementary examinations that were required for definite diagnosis. Despite antibiotic and anti-inflammatory treatment, the horse developed ataxia and obtundation. Change of the antibiotic treatment regimen did not stop the horse's condition worsening, resulting in euthanasia 11 days after admission to the hospital. Post-mortem examination confirmed diagnosis of infective endocarditis and inflammation of several extracardiac organs likely due to embolism. Actinobacillus equuli monoculture was identified from aortic valve tissue which was sensitive to all applied antibiotics. The second horse was diagnosed with infective tricuspid valve endocarditis at an early disease stage during a routine vaccination vet check. It responded well to antibiotic and anti-inflammatory treatment during hospitalization. Serial follow-up examinations including exercise tests and echocardiography were performed up to 18 months after discharge from the clinic and confirmed cure of infection with persistence of tricuspid valve regurgitation allowing the horse to gradually return to training. The two cases emphasise the difficulties in diagnosis and treatment of infective endocarditis which are often time consuming and expensive in line with a poor prognosis. However, cure of infection and resolving of clinical symptoms are possible, although rare. The key factor for successful management is an early definite diagnosis which requires the equine practitioners' awareness for this disease. Outcome and prognosis are also highly dependent on anatomical structures affected.

Keywords: endocarditis, aortic valve, tricuspid valve, bacteraemia, valvulitis, Actinobacillus equuli, echocardiography, cardiovascular system, horse

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Introduction

Infective endocarditis is a rare cardiac disease in horses.[1–4] It has a worldwide distribution, and it is observed in a wide range of breeds.[5–8] All age groups can be affected; however, younger equids are at higher risk of developing infective endocarditis.[9] It has been hypothesised that geldings and stallions are more often affected than mares.[5,10–12] Equine endocarditis is mostly presented as valvulitis. The mural endocardium and the chordae tendineae are only occasionally involved.[13,14] The mitral valve is most frequently affected, followed by the aortic valve, presumably as a consequence of the high-pressure load in the left heart and subsequent high mechanical strain of the aortic and mitral valves.[5,8,12,15–17]

Two different forms of infective endocarditis are described: An acute and a subacute or chronic form with most cases of endocarditis in horses being subacute or chronic.[9,10] Clinical signs differ remarkably between the two forms: signs of acute endocarditis include pyrexia, depression, reluctance to move, and rapid development of clinical signs of cardiac insufficiency such as oedema and increased jugular filling. The subacute or chronic form is characterised by weight loss, shifting lameness, poor performance, intermittent pyrexia, depression, and a heart murmur with signs generally lasting for weeks to months.[9] Although a heart murmur is often present in horses affected by endocarditis, it is not found in all cases.[3,4,6,16,18] Seventy-four percent of horses that were diagnosed with endocarditis post-mortem, showed unspecific signs.[16] The prognosis of infective endocarditis is poor and early diagnosis is a major factor for the success of medical treatment emphasising the importance of the equine practitioners' awareness to this disease.[9]

The following two cases demonstrate diagnostic work-up, therapy and different outcome of infective endocarditis.

Case 1

Case 1, a 565 kg, 14-year-old Oldenburg warmblood gelding was referred to the equine teaching hospital of the University of Veterinary Medicine Vienna, Austria because of a nine day-long history of recurrent fever of up to 40.2 °C, tachycardia, petechiae of the mucosal membranes of the head, apathy and a heart murmur. Within the nine days prior to admission the horse was treated with various medications such as flunixin meglumine, penicillin G, gentamicin, oxytetracycline, vitamin C, metamizole and dexamethasone by the referring veterinarian. PCR analysis from a nasal swab for Equine Virus Arteritis, Equine Herpes Virus 1 and 4 (EHV1/4), Equine Influenza Virus and Streptococcus equi equi as well as PCR analysis from whole blood for Anaplasma phagocytophilum and an antibody assay for Equine Infectious Anaemia (Coggins test) were negative.

At admission, the horse presented with a temperature of 40.6 °C, a heartrate of 60 bpm, a respiratory rate of 16 breaths/min and petechiation of the mucous membranes. On the left side of the thorax a holosystolic heart murmur grade 2/6 (crescendo) with the point of maximal intensity in the fourth intercostal space (ICS) was present. In addition, a band-shaped holodiastolic murmur grade 2/6 was present at the left side with the point of maximal intensity also at the fourth ICS.

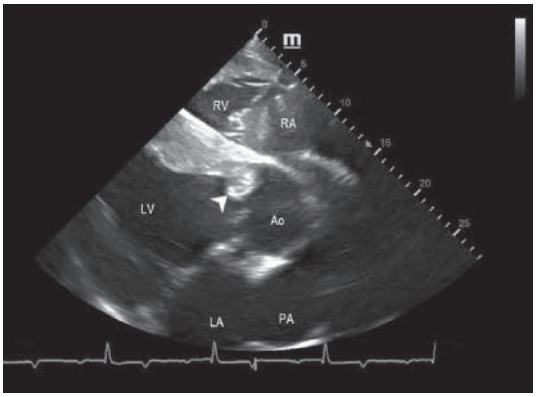

Fig. 1a Case 1. Right parasternal long axis view of the left ventricular outflow tract in diastole. Note the vegetation of the aortic valve (arrowhead). Right ventricle (RV), right atrium (RA), left ventricle (LV), aorta (Ao), left atrium (LA), pulmonary artery (PA). | *Fall 1. Rechtsparasternale Langachsenansicht des linksventrikulären Ausflusstrakts in der Diastole. Man beachte die Vegetation der Aortenklappe (Pfeilspitze). Rechter Ventrikel (RV), rechter Vorhof (RA), linker Ventrikel (LV), Aorta (Ao), linker Vorhof (LA), Pulmonalarterie (PA).*

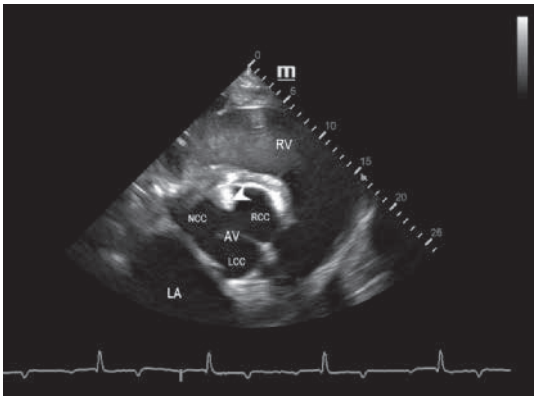

Fig. 1b Case 1. Right parasternal short axis view of the aortic valve (AV). Note the vegetation of the non-coronary cusp (NCC) and right coronary cusp (RCC) (arrowhead). Left coronary cusp (LCC), right ventricle (RV), left atrium (LA). | *Fall 1. Rechts parasternale Kurzachsenansicht der Aortenklappe (AV). Man beachte die Vegetation des nichtkoronaren Höckers (NCC) und des rechten koronaren Höckers (RCC) (Pfeilspitze). Linker Koronarhöcker (LCC), rechter Ventrikel (RV), linker Vorhof (LA).*

Transcutaneous ultrasonographic examination of the abdomen and the lungs (Mindray Z50 Vet, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., PRC, 2–5 MHz convex array transducer) were found to be unremarkable. Echocardiography (Mindray DC-70, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., PRC, 3.8 MHz P4–2E phased array transducer) revealed a thickening (vegetation) of the base of the right and noncoronary aortic valve cusps in the right parasternal long axis and short axis views of the left ventricular outflow tract (Figure 1a and b). Colour flow Doppler showed a holodiastolic turbulent regurgitation signal from the aortic valve, filling 2/3 of the left ventricle length. The systolic heart murmur could be due to turbulent blood flow at the thickened aortic valve or represent a functional murmur. The mitral valve showed no abnormalities. The left ventricle diastolic diameter measured 13.79 cm, in M-mode short axis view at the chordal level (Allometric scaling of this measurement to 500 kg it was calculated to be 13.2 cm) (Table 1). At a heartrate of 60 bpm, the ventricles appeared hypokinetic with a fractional shortening of 19 % (Table 1). Left ventricle size, shape and regurgitant jet size are the classical semi-quantitative measurements to assess aortic regurgitation (AR) severity concluding to a moderate categorization in this case.[19] The ECG (Televet 100, Engel Engineering Services, Heusenstamm, Germany) showed an average heartrate of 60 bpm with sinus tachycardia up to 90 bpm as well as 12 premature atrial complexes in one hour. Complete blood count (Table 2) revealed thrombocytopenia, leucocytosis, and neutrophilia. Considering the patient´s history, these findings lead to the suspected diagnosis of an infective endocarditis at the aortic valve. Therefore, treatment with flunixin meglumine (1.1 mg/kg IV bid), cefquinome (1 mg/kg IM bid) and omeprazole (1 mg/kg PO sid) was initiated with the addition of pentoxifylline (10 mg/kg PO tid) from day four onward.

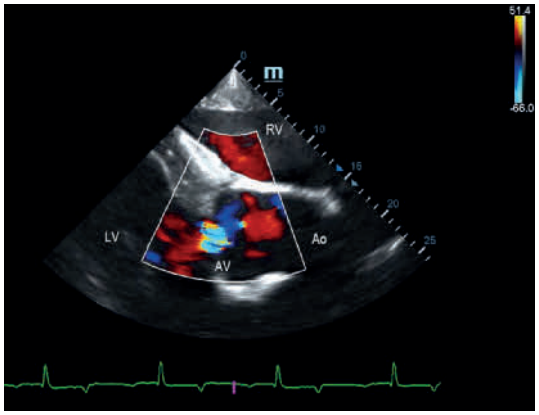

Fig. 1c Case 1. Right parasternal long axis view with colour flow Doppler of the left ventricular outflow tract. Note the turbulent flow through the aortic valve (AV) in diastole. Right ventricle (RV), left ventricle (LV), aorta (Ao), aortic valve (AV). | *Fall 1. Rechtsparasternale Langachsenansicht mit Farbflussdoppler des linksventrikulären Ausflusstrakts. Beachten Sie die turbulente Strömung durch die Aortenklappe (AV) in der Diastole. Rechter Ventrikel (RV), linker Ventrikel (LV), Aorta (Ao), Aortenklappe (AV).*

The heartrate dropped within normal limits (40 bpm), but the horse was lethargic and inappetent for the next two days. On day three of hospitalization, a sudden onset of ataxia grade 3/5 in the hind limbs and grade 1/5 in the front limbs was observed. Oedema on the right hind limb developed. However, WBC slightly improved (Table 2). On day four, the ataxia progressed, and a cerebrospinal fluid (CSF) sample was taken at the lumbosacral site. Macroscopically, CSF was clear and colourless, and cytology did not reveal any pathology. PCR tests for EHV1/4, pestiviruses, flaviviruses and a bacterial culture of the CSF were negative. Fever dropped to normal temperature on day two but increased up to 39.8 °C from day six onward. On day six, WBC increased again, whilst SAA decreased (Table 2). In the following days, the clinical signs remained unchanged. A total of three sterile blood samples were taken during fever peaks on day 3, 9 and 10, but all blood cultures were negative. On day ten additional medication with doxycycline (10 mg/kg PO bid) was started.

There was no improvement of the clinical signs within 24 hours after change of the antibiotic regime. Echocardiographic evaluation on day 11 showed no changes compared to day 1. Due to the guarded prognosis and the lacking response to the treatment, the owners decided on euthanasia of the horse.

Post-mortem examination revealed a thickening of the right coronary cusp and noncoronary cusp of the aortic valve with a fibrinous-purulent covering (Figure 2). The left ventricle showed moderate eccentric hypertrophy and a purulent myocarditis with formation of fibrotic scar tissue. A bacteriological examination of the aortic valve revealed a monoculture of Actinobacillus equuli. The antibiogram showed high sensitivity to all applied antibiotics. Further, an acute purulent disseminated inflammation of the cerebrum, cerebellum and cervical spinal cord with associated haemorrhage was noticed explaining the observed neurologic signs. Purulent disseminated inflammatory foci were also seen in the liver and the kidneys. Alveolar and interstitial oedema was found in the lungs with round cell and granulocytic infiltrates, but no abscessation. Spreading to other organs was likely due to thromboembolism.

Case 2

Case 2, a 560 kg, 9-year-old Hanoverian warmblood gelding was referred to the Equine Clinic Bargteheide, Germany because of a 1-month history of recurrent pyrexia of up to 39 °C, apathy, increased leucocytosis up to 20×10^9/L, recurrent peripheral oedema and a recently developed holosystolic heart murmur grade 2/6 on the right side of the thorax. The gelding had a history of a failed routine vet check for vaccination due to an acute mild respiratory infection and increased temperature (38.3 °C). At this time, the horse was alert and did not show any signs of performance insufficiency. Clinical examination of both jugular veins was unremarkable. The horse was treated with secretolytics (dembrexine, 0.33 mg/kg PO bid for 10 days) and unspecific immunostimulant (inactivated Parapox ovis virus, 230 IFN units, two IM injections at a 48-hours interval). Clinical signs resolved and temperature returned to normal. The follow-up examination performed by the referring vet revealed recurrent pyrexia. Despite treatment with procaine penicillin (15.000 IE/kg IM sid for nine days) and phenylbutazone (single initial dose 4.5 mg/kg IV and maintenance dose 2.5 mg/kg PO bid for five days) the horse developed peripheral oedema, apathy, and a leuco-

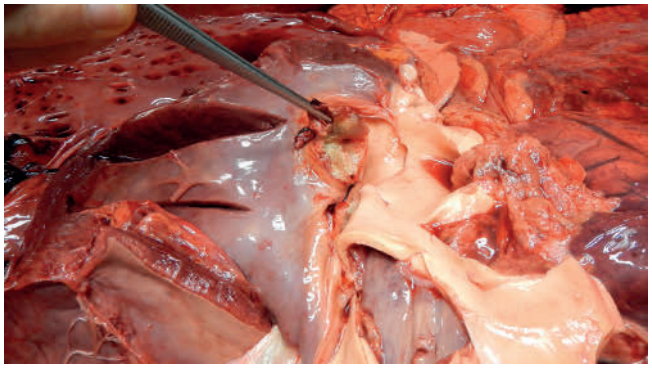

Fig. 2 Case 1. Left ventricle with aortic valve endocarditis. | *Fall 1. Linker Ventrikel mit Aortenklappen-Endokarditis.*

Tab. 1 Echocardiographic measurements of case 1 (aortic valve endocarditis). Pathologic changes are highlighted in red. LV - left ventricle, IVS - interventricular septum thickness, LVID - left ventricle internal diameter, LVFW - left ventricle free wall, FS - fractional shortening, LA - left atrium, Ao – aorta, sx – short axis, PA – pulmonary artery, D – diameter, d - diastole, s - systole. | *Echokardiographische Messungen von Fall 1 (Aortenklappenendokarditis). Pathologische Veränderungen sind in rot hervorgehoben. LV - linker Ventrikel, IVS - interventrikuläre Septumdicke, LVID - Innendurchmesser des linken Ventrikels, LVFW - freie Wand des linken Ventrikels, FS - fraktionierte Verkürzung, LA - linker Vorhof, Ao - Aorta, sx - kurze Achse, PA - Pulmonalarterie, D - Durchmesser, d - Diastole, s - Systole.*

Variable	Unit	Case 1 (aortic valve endocarditis)	Reference range*
Linear measurements of LV size and function (anatomic M-mode, right-parasternal short-axis view at the chordal level)			
IVSd	cm	4.32	3, 2 ± 0,4
IVSs	cm	4.28	4, 4 ± 0,4
LVIDd	cm	13.79 (13.2°)	11, 2 ± 0,9
LVIDs	cm	11.15	6, 8 ± 0,9
LVFWd	cm	2.16	2, 5 ± 0,4
LVFWs	cm	3.29	4, 5 ± 0,6
LV FS	%	19.12	40 ± 5
LV mass	g	5926	3575 ± 677
Measurements of LA size (left parasternal long axis view, left atrium diameter at end-systole)			
LA_{max} diameter	cm	13.73	13.6 ± 1.1
Aortic and PA dimensions, ratio of LAsx to Ao			
Ao sinus diameter	cm	8.9	8.0 ± 0.7
PA diameter	cm	9.74	
LAsx/AoD	-	0.99	< 1.2 [6,67]

*Reference ranges for warmblood horses.[65] unless stated otherwise. °Allometric scaling of measured diameters to 500 kg. | **Referenzbereiche für Warmblutpferde.[65], sofern nicht anders angegeben. °Allometrische Skalierung des gemessenen Durchmessers auf 500 kg.*

cytosis. Respiratory tract endoscopy was unremarkable, and PCR analysis for Streptococcus equi equi and Streptococcus zooepidemicus from a guttural pouch wash was negative. The horse was referred to the clinic for further diagnostic work-up.

At admission, the horse was presented with a heartrate of 60 bpm and a respiratory rate of 16 breaths/min. On the right side of the thorax a holosystolic heart murmur grade 2/6 with the point of maximal intensity in the fourth ICS was present.

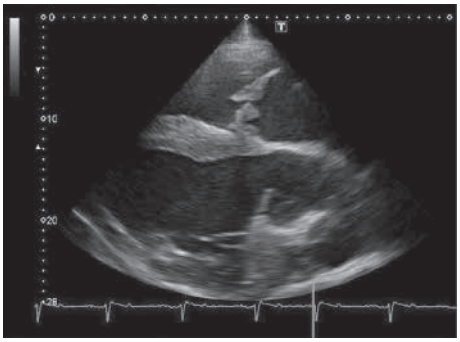

Fig. 3a Case 2. Right parasternal long axis view revealed a homogeneous thickening of the tricuspid valve cusps (arrow). Right ventricle (RV), right atrium (RA). 3.5MHz Phased-Array transducer at a depth of 28 cm. | *Fall 2. In der parasternalen Ansicht der langen Achse rechts zeigte sich eine homogene Verdickung der Trikuspidalklappenhöcker (Pfeil). Rechter Ventrikel (RV), rechter Vorhof (RA). 3,5-MHz-Phased-Array-Schallkopf in einer Tiefe von 28 cm.*

Ultrasonography was performed using the ultrasound machine Toshiba Aplio 400 (Toshiba Medical Systems, Neuss, Germany) with a 3.5 MHz phased array transducer (echocardiography) and a curvilinear transducer operating at 4MHz (lung sonography). Transcutaneous ultrasonographic examination

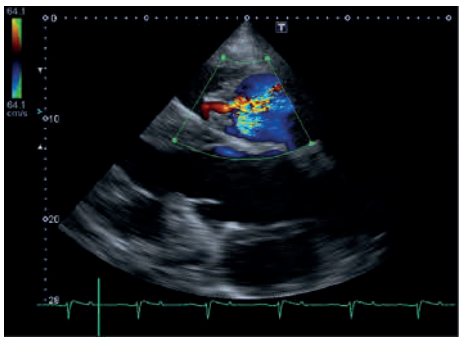

Fig. 3b Case 2. Right parasternal long axis view with colour flow Doppler focussed on the tricuspid valve. Note the area of turbulent blood flow in the right atrium (RA) during systole, consistent with tricuspid regurgitation. Right ventricle (RV), 3.5MHz Phased-Array transducer at a depth of 28 cm. | *Fall 2. In der parasternalen Ansicht der langen Achse rechts zeigte sich eine homogene Verdickung der Trikuspidalklappenhöcker (Pfeil). Rechter Ventrikel (RV), rechter Vorhof (RA). Rechtsparasternale Langachsenansicht mit Farbflussdoppler, fokussiert auf die Trikuspidalklappe.Man beachte den Bereich mit turbulentem Blutfluss im rechten Vorhof (RA) während der Systole, der auf eine Trikuspidalregurgitation hinweist.Rechter Ventrikel (RV), 3,5-MHz-Phased-Array-Schallkopf in einer Tiefe von 28 cm.*

Tab. 2 Laboratory abnormalities of two horses with infective endocarditis during hospitalization: Case 1 (aortic valve endocarditis) was euthanized on day 11 due to poor prognosis. Case 2 (tricuspid valve endocarditis) was discharged from the clinic on day 25. Pathologic changes are highlighted in red. d - day of hospitalisation. | *Laboratory abnormalities of two horses with infective endocarditis during hospitalization: Case 1 (aortic valve endocarditis) was euthanized on day 11 due to poor prognosis. Case 2 (tricuspid valve endocarditis) was discharged from the clinic on day 25. Pathologic changes are highlighted in red. d - day of hospitalisation.*

Parameter	Case 1					Case 2				
	d1	d3	d6	d8	Reference range*	d1	d9	d15	d25	Reference range*
RBC (×10¹²/L)	8.0	7.0	7.0	8.0	6.5–11.0	6.88	6.46	-	7.07	6.00–12.00
Haemoglobin (mmol/L)	7.45	6.83	6.83	7.45	6.21–11.17	6.76	6.27	-	6.89	6.83–10.55
Haematocrit (%)	30	33	32	31	32–55	31	29	-	33	37–55
Platelets (×10⁹/L)	49	65	111	80	90–300	154	174	-	154	100–300
WBC (×10⁹/L)	19.95	11.77	17.33	18.99	5.00–10.00	8.9	10.4	-	10.5	5.0–10.0
Lymphocytes (×10⁹/L)	2.91	0.74	0.71	1.35	1.00–4.50	-	-	-	1.95	1.50–4.00
Neutrophils (×10⁹/L)	16.49	10.23	16.16	17.00	3.00–7.00	-	-	-	7.88	3.00–7.00
Basophils (×10⁹/L)	0.50	0.07	0.12	0.04	< 0.20	-	-	-	0.21	< 0.15
Eosinophils (×10⁹/L)	0.01	0.08	0.08	0.05	< 0.50	-	-	-	0.11	< 0.35
SAA (mg/L)	-	3531	2709	-	< 10	476	319	< 5.0	< 5.0	< 5.0
Fibrinogen (mg/dl)	-	-	-	-	-	-	-	-	452	132–452
Albumin (g/L)	-	20	-	-	20.0–40.0	-	-	-	24.8	29.0–44.0
Total protein (g/L)	-	70	-	-	55–75	-	-	-	71	56–73
Cardiac Troponin I (µg/L)	-	< 0.1	-	< 0.1	Δ	-	-	-	-	-

* Reference values were used as validated by the central laboratory of Vetmeduni Vienna unless stated elsewhere (case 1) and by Synlab Augsburg (case 2). Δ Measured on Immulite 2000Xpi (Siemens) with ELISA solid-phase, competitive chemiluminescent enzyme immunoassay, detection limits 0.2–180 ng/ml, not validated for horses. | ** Die Referenzwerte wurden, soweit nicht anders angegeben, vom Zentrallabor der Vetmeduni Vienna (Fall 1) und von Synlab Augsburg (Fall 2) validiert. Δ Gemessen am Immulite 2000Xpi (Siemens) mit ELISA-Festphasen-, kompetitivem Chemilumineszenz-Enzym-Immunoassay, Nachweisgrenzen 0,2–180 ng/ml, nicht für Pferde validiert.*

of the lungs revealed a few comet tail echoes in the left ventral lung field. Echocardiographic right parasternal long axis and short axis views revealed homogeneous thickening of the tricuspid valve cusps (Figure 3a). Colour flow Doppler showed a holosystolic turbulent regurgitation signal from the tricuspid valve, filling 2/3 of the right ventricle length (Figure 3b). There were no other abnormalities during echocardiography. The ECG (Televet 100, Engel Engineering Services, Heusenstamm, Germany) showed an average heartrate of 60 bpm with sinus tachycardia. Laboratory analyses revealed an increase in SAA (476 mg/L, reference range < 5 mg/L) and a slight decrease in haemoglobin (6.67 mmol/L, reference range 6.83–10.55 mmol/L), other parameters were within normal limits. Since the horse had been treated with antibiotics before, blood culture was negative as expected. The horse was diagnosed with an infective endocarditis at the tricuspid valve.

Antibiotic treatment was changed to intravenous application of penicillin G (22.000 IE/kg IV qid). Flunixin meglumine (1.1 mg/kg PO bid) was additionally given for 10 ten days. The heartrate dropped within normal limits (40 bpm) within a few days. After 26 days, the antibiotic treatment was changed to oral trimpethoprim sulfadiazine (20 mg/kg PO bid). Additional treatment with quinapril (0.2 mg/kg PO sid) and acetylsalicylic acid (10 mg/kg PO) was initiated and the horse was discharged from the clinic. Oral trimethoprim-sulfadiazine administration was continued for 25 days, acetylsalicylic acid was given for eight weeks, followed by a reduced dose (5 mg/kg PO sid) for 18 months. Quinapril was also administered for 18 months. Daily control of body temperature was performed for three months with no abnormalities being detected. A field exercise test two months after discharge from the clinic revealed no abnormalities despite the persistence of a holosystolic heart murmur grade 2/6 at rest with the point of maximal intensity in the fourth ICS on the right side of the thorax which changed to grade 3/6 after exercise. The horse went back to daily routine work and exercise intensity was gradually increased. Follow-up examinations including clinical examination, exercise test and echocardiography were performed after 3, 6 and 18 months. Echocardiography revealed a gradually decrease in tricuspid valve thickening with simultaneous increase in tricuspid valve regurgitation within 6 months (Figure 4). Heart dimensions remained unchanged. After 18 months the horse performed well reaching its primordial level. Clinical and echocardiographic examination documented unchanged findings in respect to heart murmur, heart dimensions and tricuspid valve regurgitation.

Discussion

The two cases of infective endocarditis presented with very different clinical courses. Despite their dissimilarities, both are representatives for typical equine endocarditis cases emphasising the heterogeneity in clinical course and outcome of this rare disease.

The exact pathogenesis of subacute infective endocarditis in horses is unknown. It is hypothesized that the pathomechanism in horses is similar to the one described in human patients[14]: Initial damage of the endothelium through local blood flow turbulences sets the stage for inflammation, pro-

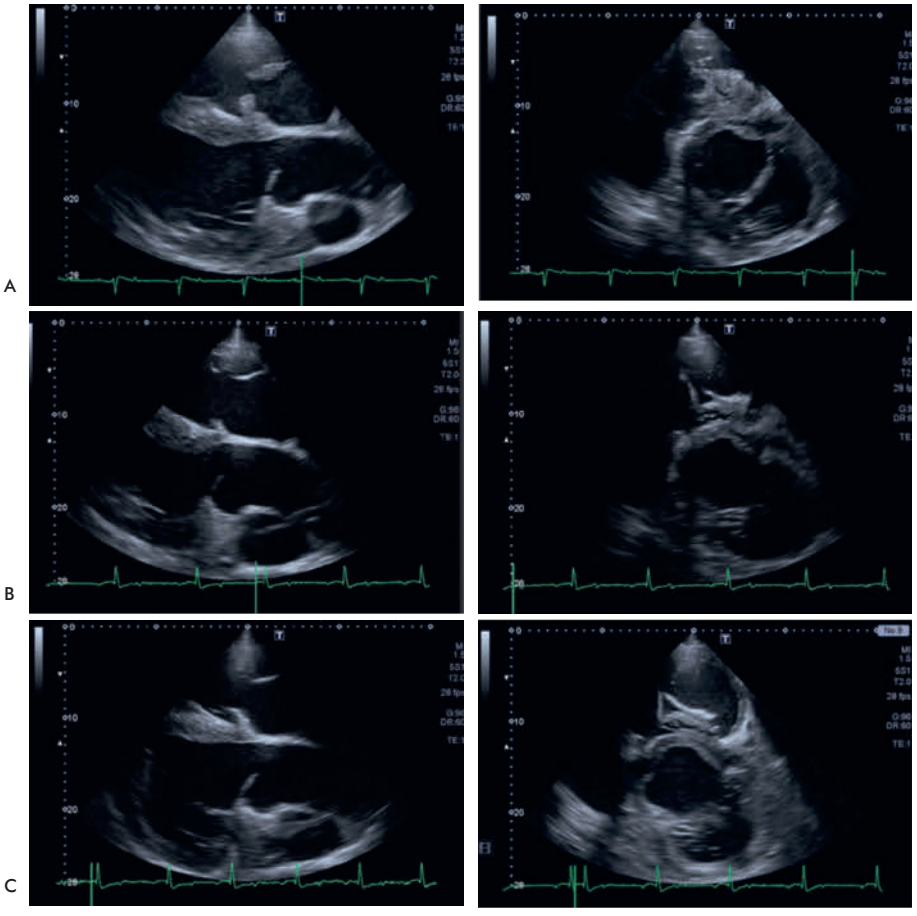

Fig. 2 Case 2. Right parasternal long axis and short axis view of the tricuspid valve at time of admission (A) and during follow-up examinations after 6 months (B) and 18 months (C). | *Case 2. Right parasternal long axis and short axis view of the tricuspid valve at time of admission (A) and during follow-up examinations after 6 months (B) and 18 months (C).*

coagulant stimulation and easy bacterial attachment.[16,19] Thrombocytes and fibrin attach to the collagen fibres of the damaged endothelial tissue resulting in a subsequent formation of a thrombus.[16] Bacterial colonisation of the thrombus occurs during bacteraemia which is asymptomatic in most cases.[20,21] Bacteraemia may be the consequence of any tissue trauma accompanied by introduction of microorganisms into the blood, for examples during dental treatments, urinary catheterisation and surgery.[14] Thrombophlebitis is a reported cause of bacteraemia resulting in tricuspid valve endocarditis in horses.[12,22] However, in many cases including the two cases described here it is not possible to identify the cause of the bacteraemia.[5,10,23]

The microbial agents find the intracardiac thrombus a favourable site for nesting. They interact mainly with the platelets forming a vegetation complex in which bacteria are well protected from the immune system and antimicrobials.[24,25]

In contrast to human infective endocarditis in which Staphylococcus aureus has become the main incriminating species[25], different pathogens are commonly found in equine infective endocarditis such as Streptococcus sp, Actinobacillus sp., Rhodococcus equi, Candida parapsilosis, Erysipelothrix rusiopathiae, Meningocoocus sp, Staphylococcus aureus, Pseudomonas aeruginosa, E. coli, Serratia marcescens, Stenotrophomonas maltophilia and Bacillus sp..[5,6,12,14,23,26,27–32] In 2007 a case of a mare suffering from endocarditis linked to Actinobacillus equuli subsp. equuli, like the first case described in the current study was published.[33] Actinobacillus equuli is known to be a commensal on equine mucous membranes, which can be isolated from healthy horses.[34,35] Actinobacillus equuli subs. equuli is associated with bacterial pneumonia, peritonitis, nephritis, cystitis, orchitis and the sleepy foal syndrome, but data is limited on its pathogenicity and its virulence factors.[33,36] Further research is therefore needed to elucidate its potential role in the pathogenesis of infective endocarditis.

The interaction between bacteria and platelets results into a vegetation growth that can lead to perforation of valves, rupture of chordae tendineae or papillary muscles, insufficiency or stenosis of valves and disturbance of electric stimuli. Consequently, congestive heart failure can develop, which is the most frequent cause of death in horses with infective endocarditis.[10,12,23]

In addition to the localised cardiac pathology, infective endocarditis can have systemic effects and may result into extracardiac organ failure. Thromboembolism originating from the left heart valves can distribute the infection to the kidneys, joints, meninges and the spleen. In case 1 (aortic endocarditis) the deterioration of clinical signs, the development of neurological symptoms and the findings of gross pathology during necropsy strongly indicate such distribution of infective thrombotic material into several extracardiac organs in this horse, although no evidentiary bacteriological examination was performed on samples from these sites. Hyperglobulinaemia and circulation of antibody-antigen complexes as a consequence of persisting infection, are other common findings leading to immunologic inflammation in joints, blood vessels and the kidneys, and thus may result in deterioration of clinical signs.[7,24,37]

Aseptic degenerative valvulitis, which is quite common on the aortic valve of middle aged and older horses.[38,39] was initially considered as differential diagnosis for case 1. In degenerative cases, the left coronary cusp shows nodular or less commonly homogenous general thickening, but all cusps can be affected.[38,39,40,41]

In case 2 the tricuspid valve was affected. In contrast to the left heart, the right ventricle is a high-volume low-pressure pump. Consequently, metastatic thrombi are less likely to be released from the cardiac site. However, emboli of the lungs, pneumonia and pulmonary abscesses as a consequence of tricuspic valve endocarditis are described.[5,8,12]

In conformity with published data, the horse presented with right heart endocarditis had a better outcome than the horse with aortic valve endocarditis. It is hypothesised that the low pressure within the right chambers is the reason that infective endocarditis of the right heart is better tolerated and less likely to lead to a heart failure than left sided endocarditis. Due to this, a better prognosis can be given.[12,42] On the other hand, the lower pressure can lead to formation of much larger colonies, which can result in stenosis of the valve and the development of a cor pulmonale emphasising the need for long term follow-up examinations.[8,42]

Therefore, early definite diagnosis and initiation of early aggressive antibiotic therapy is crucial to prevent the release of bacteria and emboli and thus manifestation of metastatic disease. Thorough clinical examinations of horses presented for routine health checks and vaccinations may identify suspected cases of infective endocarditis at an early stage of disease as demonstrated in case 2. The common lack of specific signs requires a combination of clinical, haematology, biochemistry, bacterial blood culture, ultrasound examination and an ECG.[6,12,16] As shown in the presented cases mild anaemia and a leucocytosis with neutrophilia are common hematologic findings. In case hypergammaglobulinaemia is present, changes in biochemistry profile such as hyperfibrinogenaemia, hypalbuminaemia and hyperproteinaemia are often reported, but could not be found in both cases described here. Depending on which organs are affected, several other parameters can be changed as well.[10,21] Elevation of cardiac troponin I in horses has been quoted from 0,03 ng/ml.[43]

ECG can remain unchanged in cases of endocarditis. In mild cases it might only show sinus tachycardia, whereas in more severe cases arrhythmias due to myocarditis can appear.[14]

Case 1 showed a holodiastolic murmur 2/6 with its PM in the fourth ICS on the left side, which fits the regurgitation signal at the aortic valve, even though band-shaped form diastolic murmurs are seldom heard.

Echocardiography is essential for confirmation of diagnosis and for assessment of therapeutic response and prognosis.[12,44] In 2007 in a study on measurements on left atrium size an in between days intraobserver variability between 2.9 and 9.6 % was evaluated.[45] This variability explains some of the variation in follow-up echocardiographic examinations. Small endocardium lesions can be missed because objects smaller than 2–4 mm are not detectable in transcutaneous

heart ultrasound.[11,16] Although the increased quality of ultrasound equipment could likely improve this detection limit.

Blood culture is an important key to the choice of antibiotic for causative treatment of infective endocarditis. The number of bacteria in the blood may fluctuate and lead to negative blood culture results.[46] Ideally culture should be taken prior to the application of antibiotics.[20] It has been shown that antibiotics slow down the growth of bacteria in blood culture medium and that the samples should be incubated 10–14 days if the patient was already treated with antibiotics.[21] *Karchmer* suggested that taking the samples during peak temperature may have no effect on the presence of bacteria in blood.[20] In human medicine, the use of antimicrobial removal devices increases the likelihood of a positive blood culture in patients receiving antimicrobial treatment.[47] Unfortunately, we could not get a positive bacterial blood culture in either of the two cases. Antibiotics in case 1 were chosen because of the good penetrating properties of doxycycline in most organs and tissues which makes it very likely to penetrate the myocardium as well.[48] Therapy with a fourth-generation cephalosporin in case 1 was initiated without a culture because of worsening clinical signs despite antibiotic therapy with penicillin and gentamycin for 9 days. Further, penicillin has a much higher binding to plasma proteins.[48] Penicillin is nearly exclusively reversible bound to albumin.[50] and has no activity against bacteria when bound to albumin.[49,50] Protein binding is one of the main factors to interfere penetration of antibiotics into the tissue.[51,52] In contrast, cefquinome has a plasma protein binding of only 20–30%.[53] A good penetration to synovial fluid of horses.[52] and extravascular fluids of pigs.[54,55] have been demonstrated recently; therefore, good penetration of fibrin matrix as seen in endocarditis seems likely. If therapy is attempted, owners and veterinarians should be aware of the long duration of therapy, as well as high costs in line with guarded to poor prognosis. If the valvular infection and inflammation are successfully treated, a low-grade valve regurgitation often persists which requires long-term echocardiographic monitoring in order to assess risks associated with riding.[14]

For treatment, high doses of bactericide antibiotics over a long period are required, preferably chosen based on an antibiogram received from a blood culture. If no antibiogram is available, broad-spectrum antibiotics are advised.[21] Bacteria in the fibrin matrix are hard to reach and devitalise.[56,57] Therefore, the administration of antibiotics over four to six weeks is recommended.[6,23,57] Despite the antibiogram showing that the infective agent was sensitive to all antibiotics used in case 1, it could not prevent the spreading of the infection to other body systems, leading to treatment failure.

For the treatment of inflammation and secondary signs NSAIDs should be administered.[57,58]

Additionally, treatment with pentoxifylline in case 1 was started, for its immune-modulating and anti-inflammatory properties to reduce fibrosis formation in the endocardium.[59,60]

In human infective endocarditis the use of anticoagulant therapy has been used for decades, however it remains a controversial issue.[61,62] Particularly the increased risk of intracranial haemorrhage is reason not to administer anticoagulant drugs, particularly in infective endocarditis affecting the mitral or aortic valve.[63] Despite this hypothesis there are several studies demonstrating that antiplatelet drugs such as acetyl-salicylic acid significantly reduce the risk of embolic thrombi and prevent growth of increased intracardiac infective thrombus formation, irrespective of the cardiac region affected by endocarditis.[25,64] In horses, acetyl-salicylic acid is used for treating diseases with increased platelet activation such as endotoxemia or laminitis, but data on therapeutic effects on infective endocarditis are lacking. In case 2 in which only the tricuspid valve was affected, there was a risk of intracardiac thrombic growth which may eventually lead to a cor pulmonale as well as a risk of metastatic pulmonary embolic thrombi resulting in pulmonary infection or even abscesses. Therefore, we decided to administer acetyl-salicylic acid with a positive outcome. However further research is necessary to investigate the potential of acetyl-salicylic acid as a therapeutic drug for treatment of infective endocarditis in horses.

During evaluation of the first case presented, a retrospective data analysis of the hospital records of the Vetmeduni Vienna Equine hospital was performed.

Between January 2014 and December 2017, 126 cases receiving a cardiologic examination were identified using the hospital management software Tierspitalinformationssystem (TIS) (Vetware). After exclusion of incomplete records only the presented case remained as a diagnosed endocarditis. This results in a prevalence of endocarditis in horses presented with signs attributable to the cardiovascular system or heart as primary affected organ of 0,79%.

Porter reported a much higher prevalence of 5,9% of endocarditis cases in a retrospective case series.[9] The percentage might be higher in the study published by *Porter*, because only horses with an initial differential diagnosis of endocarditis were included.

Conclusion

The awareness for the existence of infective endocarditis and its variable clinical expressions is crucial for the equine practitioner since early diagnosis and long-term therapy are key factors for a successful outcome. The two presented cases show, how different endocarditis cases can develop, and that diagnosis often is not easy. Despite the correct diagnosis, intensive treatment, and correctly chosen antibiotics in case 1, the infection could not be prevented from spreading to other organs and led thereby to the horse's euthanasia. However, successful treatment and return to athletic level can be achieved in some cases, as illustrated by case 2.

Conflict of interest statement

The authors declare no conflict of interest.

Statement of informed consent

The animal owner's consent was obtained according to the policies and procedures of the Vetmeduni Vienna, Austria

(case 1) and of the Equine Clinic Bargteheide, Gerrmany (case 2).

Authors contributions

Anja Cehak and Matthias C. Jehle contributed to the work in equal proportion both as first authors.

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