Pferdeheilkunde – Equine Medicine 37 (2021) 3 (May/June) 204–214 DOI 10.21836/PEM20210301

Results of 654 trans-pars plana vitrectomies of equine eyes with recurrent uveitis – follow-up until 18 years after surgery

Bettina Wollanke, Hartmut Gerhards and Christine Schinagl

Equine Clinic, Ludwig-Maximilians-University, Munich, Germany

Summary: The aim of this study was to evaluate retrospectively the long-term success of trans-pars plana vitrectomy as a surgical treatment for equine recurrent uveitis (ERU). The focus was on postoperative recurrences of bouts of uveitis, unexpected development of cataracts or retinal detachments in eyes with early stages of ERU at the time of surgery, and the long-term preservation of the globe and vision. A total of 2158 vitrectomies were performed at the LMU Clinic for Horses from January 1997 to September 2015. Between April 2015 and August 2016, 654 of the vitrectomised eyes of 549 horses were followed up. The ophthalmological findings were evaluated either in a follow-up examination (105 eyes of 90 horses) or by telephone interviews with attending veterinarians and horse owners (549 eyes of 459 horses). The mean time of the follow-up examination was 7.7 years after vitrectomy (0.5 years up to 18 years). A recurrence of ERU was prevented in a total of 96.3% of the eyes that underwent vitrectomy. Recurrence of ERU was prevented in 97.1% of all eyes tested positive for an intraocular leptospiral infection at the time of surgery. The long-term preservation of vision succeeded in 413/549 eyes (75.2%, information given by attending veterinarians and horse owners) and 85/105 eyes (81%, follow-up examinations by one of the authors), respectively. The long-term preservation of the globe was successful in 617 of the 654 operated eyes (94.3%) regardless of the postoperative recurrence of uveitis and preservation of vision. Thus, the current study demonstrates that pars plana vitrectomy is an extremely successful surgical treatment of Leptospira-associated ERU that has long-term success in stopping the ERU-related progressing destruction of the eye, keeping the eye pain-free and, furthermore, in the case of early surgical intervention, preventing blindness. Cessation of uveitis and the prognosis for the long-term preservation of vision could best be achieved by surgical intervention at an early stage of the disease.

Keywords: equine recurrent uveitis, ERU, intraocular leptospiral infection, vitrectomy, long term results

Citation: Wollanke B., Gerhards H., Schinagl C. (2021) Results of 654 trans-pars plana vitrectomies of equine eyes with recurrent uveitis – follow-up until 18 years after surgery. Pferdeheilkunde 37, 204–214; DOI 10.21836/PEM20210301

Correspondence: PD Dr. Bettina Wollanke, Equine Clinic, Ludwig-Maximilians-University, Munich, Germany; b.wollanke@lmu.de

Submitted: March 22, 2021 | **Accepted:** April 13, 2021

Introduction

Equine recurrent uveitis (ERU) is considered the most common type of endogenous uveitis in horses and regarded as the most common equine eye disease (*Miller* and *Whitley* 1987, *Schwink* 1992, *Gerhards* and *Wollanke* 2001). Its prevalence varies widely depending on the geographic region. In Central Europe, it occurs in around 8–10% of the horse population (*Kómár* and *Szutter* 1968, *Szemes* and *Gerhards* 2000), whereas the ERU prevalence in the United States is reported to be between 1 and 25% (*Witmer* 1954, *McLaughlin* et al. 1992, *Schwink* 1992, *Dwyer* et al. 1995, *Gilger* and *Micheau* 2004, *Gilger* and *Deeg* 2011).

Equine recurrent uveitis is a sero-fibrinous inflammation of all parts of the uvea occurring in one or both eyes with the involvement of the adjacent eye structures. It is characterised by recurring episodes of intraocular inflammation, which lead to the progressive destruction of intraocular structures and, ultimately, to atrophy and blindness of the diseased eye (*Dwyer* et al. 1995, *Gerhards* and *Wollanke* 2001).

Until the late 20th century, signs of ERU could only be suppressed by means of conservative medical therapy or by enucleation. Despite vigorous topical and systemic treatment, the disease continued to progress ultimately resulting in globe destruction and blindness in most cases (*Werry* and *Gerhards* 1991, *Schwink* 1992, *Frühauf* et al. 1998, *Gilger* and *Michau* 2004, *Gerhards* and *Wollanke* 2006). Vitrectomy has been performed for a broad spectrum of diseases in human medicine for decades (*Diamond* and *Kaplan* 1978, 1979, *Klöti* 1981, *Werry* and *Honegger* 1987, *Verbraeken* 1996). After inserting a vitrectomy cutter into the vitreous chamber via the pars plana ciliaris, the vitreous body is cut into small pieces. This makes aspiration of the vitreous body, inflammatory products and cells through the lumen of the thin surgical instrument possible (*Klöti* 1981). Vitrectomy was later found to be a valuable method in both the diagnostic and therapeutic evaluation of chronic uveitis, and has been reported to reduce recurrences of chronic uveitis in humans (*Diamond* and *Kaplan* 1978, 1979, *Klöti* 1981, *Werry* and *Honegger* 1987, *Verbraeken* 1996). Inspired by vitreous surgeries in humans, *Werry* and *Gerhards* performed the first vitrectomies in

horses in 1989. During the early years, improved vision and a decrease of the uveitis episodes was observed (*Werry* and *Gerhards* 1991, 1992). As a result, the pars plana vitrectomy (PPV) was introduced as a surgical therapy for ERU in Germany (*Gerhards* et al. 1998, *Gerhards* et al. 1999).

A substantial amount of fresh intraocular material from eyes in florid uveitis-stages became available by routine vitrectomies after the establishment of this surgical technique. Intraocular leptospiral bacteria were routinely detected in the material analysed, which led to the identification of an intraocular leptospiral infection as the main cause of ERU in Central Europe (*Brem* et al. 1998, *Wollanke* et al. 1998a, *Wollanke* et al. 1998b, *Brem* et al. 1999, *Wollanke* et al. 2001, *Niedermaier* 2002, *Wollanke* 2002, *Hartskeerl* et al. 2004, *Wollanke* et al. 2004, *Niedermaier* et al. 2006, *Brandes* et al. 2007, *Baake* et al. 2016, *Voelter* et al. 2020). It has been determined that both aqueous and vitreous humours are suitable for testing for an intraocular leptospiral infection (*Babudieri* 1961, *Brem* et al. 1999, *Faber* et al. 2000, *Wollanke* 2002, *Gesell* 2004, *Hartskeerl* et al. 2004, *Niedermaier* et al. 2006, *Brandes* et al. 2007, *Roczek* 2008, *Loibl* 2009, *Baake* et al. 2016, *Dorrego-Keiter* et al. 2016, *OIE* 2018, *Voelter* et al. 2020). The microscopic agglutination test (MAT) is the method of choice among serological tests (*Bernard* 1993, *Farr* 1995, *OIE* 2018). The enzyme-linked immunosorbent assay (ELISA) is also available for serological testing as a highly sensitive and objective diagnostic method (*Loibl* 2009, *Loibl* et al. 2018, *Wollanke* et al. 2018). *Leptospira spp.* can also be cultivated from vitreous humour, but the polymerase chain reaction (PCR) is the method of choice for a reliable and fast direct pathogen detection (*Faber* et al. 2000).

The success of vitrectomy is due to the elimination of the intraocular leptospiral infection by removing the vitreous body which is considered the nidus for the persisting leptospiral infection (*Wollanke* et al. 2004, *Ackermann* 2021). Intraocular immunosuppressive mechanisms may prevent an effective elimination of intraocular pathogens by the immune system (*Wollanke* 2002, *Geißler* 2021). Therefore, leptospiral bacteria can persist for years in the vitreous body, which is regarded as an "immunological niche" (*Farr* 1995, *Wollanke* 2002, *Wollanke* et al. 2004). Furthermore, there is proof of intravitreal leptospiral biofilm formation in horses suffering from ERU (*Ackermann* 2021), which explains the clinical disease manifesting as a chronic intraocular infection leading to recurrent bouts of intraocular inflammation (*Geißler* 2021). It is plausible that both neutrophil extracellular traps (*Fingerhut* et al. 2019) and intraocular amyloid production associated with ERU may contribute to the intraocular biofilm (*Linke* et al. 2019).

Surgical removal of the vitreous humour and the associated leptospiral bacteria leads to the elimination of the "immunological memory" (inflammatory products and immunological factors) as well as the elimination of the intraocular infection and improves the circulation of liquid and clearance in the vitreous chamber after surgery (*Ulbig* and *Kampik* 1989). Removing as much of the vitreous humour and its fibrillary framework as possible also eliminates the "immunological niche" of the eye. As a result, a reinfection with *Leptospira spp.* seems to become impossible (*Klöti* 1981, *Werry* and *Honegger* 1987, *Verbraeken* 1996, *Wollanke* 2002, *Wollanke* et al. 2004).

The results of several studies on the outcome of the vitrectomy in eyes suffering from ERU indicate a significant advancement in its treatment (*Winterberg* and *Gerhards* 1997, *Frühauf* et al. 1998, *Gerhards* et al. 1998, *Gerhards* et al. 1999, *Wollanke* et al. 2004, *Von Borstel* et al. 2005, *Tömördy* et al. 2010, *Dorrego-Keiter* et al. 2017, *Schinagl* 2017, *Baake* et al. 2019, *Voelter* et al. 2020). The aim of this study was to analyse the success of the PPV as a surgical therapy of ERU based on a large number of patients and a long postoperative period. Regarding the postoperative recurrence of uveitis, the focus was on possible correlations between a postoperative relapse and pre-, intra- and postoperative factors, for example, anamnestic information, ocular findings or surgery-related complications. In addition, the long-term preservation of both vision and the globe, as well as the occurrence of secondary diseases were of interest.

Materials and Methods

From January 1997 to September 2015 a total of 2,158 vitrectomies have been performed by one surgeon (HG). This retrospective study was conducted from April 2015 to August 2016. At this time, some of the horses had been sold on, some horses had died in the meantime for various reasons and some owners could no longer be contacted. The outcome of 654 eyes of 549 horses with ERU that underwent PPV between January 1997 and September 2015 could be analysed retrospectively.

The selection of the patients for performing PPV had been based on typical anamnestic information or typical ocular findings in most cases (83.9%). Vitrectomy was conducted based on a preoperative paracentesis of the anterior chamber and determining an intraocular leptospiral infection using aqueous samples in 12.1%, because a preliminary report of recurrent inflammation was given for these eyes, but neither history nor ophthalmological findings were clearly giving an indication for surgery. In the other cases (4%), surgery was performed to improve the visual acuity (e.g. by removing vitreous humour opacities in some cases of glaucoma).

Diagnosis of ERU was based on anamnestic information (at least two episodes of uveitis) and/or typical signs of chronic uveitis, such as atrophy of the globe, posterior synechiae, inflammatory product deposits on the posterior lens capsule, cataract formation, inflammatory vitreal floaters, retinal folds or retinal detachment. A few horses were referred in the acute stage of uveitis. Typical findings were blepharospasm, epiphora, diffuse opacity of the cornea, aqueous flare, fibrin in the anterior chamber, miosis and diffuse vitreal cloudiness. A preoperative paracentesis of the anterior chamber was performed in cases of no clear ophthalmological findings in the sense of an ERU (in order to exclude phacogenic or traumatic uveitis). The aqueous samples were tested for antibodies directed against leptospires and used for culture and/or PCR.

At least some of the clinical findings in chronic ERU mentioned above had to be present, the eye must have suffered at least two episodes of uveitis or an intraocular leptospiral infection needed to be proven to justify the indication for vitrectomy. Blindness (by cataract or retinal detachment) was not consid-

ered a clear contraindication for surgery. Thus, at the request of some owners, vitrectomy was performed in these eyes in order to prevent further episodes of uveitis and to preserve the globe for cosmetic reasons. Surgical treatment was not recommended in cases of distinct atrophia bulbi or secondary glaucoma.

Medical records were examined to determine sex, age and breed of the horses as well as the history (duration of disease, number of preoperative uveitis episodes), pre- and postoperative ocular findings (vision, synechiae, findings on lens, vitreous humour and retina, globe size), results of laboratory testing for an intraocular leptospiral infection and intra- and postoperative complications. Sterile and undiluted vitreous humour samples were taken at the beginning of the vitrectomy in order to test them for a leptospiral infection. The laboratory tests applied included both serological methods (MAT and/or ELISA) and direct pathogen detection (culture and/or PCR). An intraocular leptospiral infection was regarded as proven if at least one of these tests was positive. The MAT was considered positive with titres of $\geq$ 1:100, because in ophthalmologically healthy eyes MAT-results are negative in 99,4 % (*Gesell* 2004).

The preoperative treatment of the patients started at least three days before surgery and included topical dexamethasone in combination with antibiotics two or three times daily, and eye drops or ointments containing atropine at least twice daily to induce a stable mydriasis, as well as systemic nonsteroidal anti-inflammatory drugs (NSAID). Surgery was performed exclusively in the quiescent intervals of the disease. The optical media should be as transparent as possible for transpupillary visualisation of the vitrectomy cutter during the surgery. Horses were sedated in the same way as for any other surgery with xylazine hydrochloride, levomethadone hydrochloride and fenpipramide hydrochloride. General anaesthesia was induced with ketamine and guaifenesin and maintained with isoflurane in all horses. Anaesthesia was considered deep enough when the palpebral reflex and a stronger nasal rotation of the globe were absent. No additional nerve blocks or topical anaesthetic eye drops were utilized.

The surgery was performed in lateral recumbency, with the affected eye uppermost. If posterior synechia and miosis prevented sufficient visualisation of the vitreous chamber, synechiolysis using hyaluronic acid or BSS solution was performed immediately prior to PPV. All cases of PPV were performed exactly as described previously (*Gerhards* and *Wollanke* 2005). Postoperative treatment consisted of topical dexamethasone ointment in combination with antibiotics for ten days after surgery, and topical atropine was administered once or twice daily for one to three days after surgery, depending on the size of the pupil. In cases with significant enough posterior synechia to warrant preoperative synechiolysis, atropine was applied twice daily for the same length of time that topical corticosteroid ointments were used. The horses were discharged from the clinic about five days after vitrectomy when the postoperative course was uneventful.

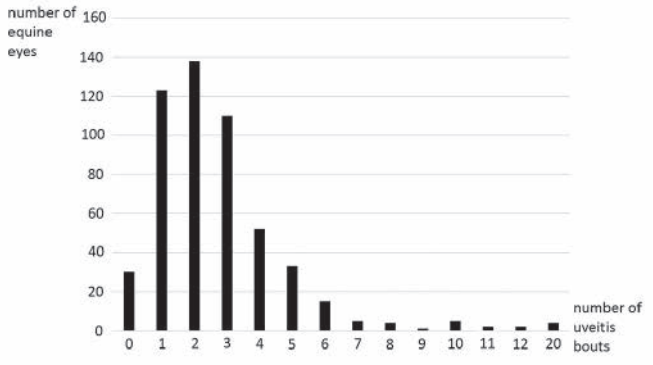

Fig. 1 Number of uveitis attacks prior to vitrectomy in 654 eyes suffering from ERU | *Anzahl der Uveitisschübe der 654 an ERU erkrankten Augen vor der Vitrektomie*

A total of 105 eyes of 90 horses were analysed in a follow-up examination by one of the authors (CS). In addition, horse owners and attending veterinarians were contacted by telephone to determine the long-term outcome of 549 eyes of 459 horses. The results of both follow-up exams and surveys were analysed separately by the same method.

For the ophthalmological follow-up examinations vision was assessed according to the horse's response to menace responses, dazzle and the direct and indirect pupillary reflexes. Additionally, the behaviour and the head and neck position of the horses were assessed. Following the inspection of the periocular and external ocular structures, including the eyelids, conjunctiva and sclera, a detailed ophthalmic examination was performed. Cornea, anterior chamber, iris and the anterior surface of the lens were examined using a focal light source. Following pharmacological mydriasis with tropicamide, a complete examination of the structures of the inner eye was performed using a direct ophthalmoscope. Subsequently, the intraocular pressure was measured by an applanation tonometer (Tono-Pen VETTM). A trans-palpebral ultrasound examination (7.5 MHz linear ultrasound probe) was performed to visualise the intraocular structures in cases where the posterior segment could not be completely examined due to substantial intraocular opacifications of the light refracting ocular media.

Before the interviews, a questionnaire was prepared, which allowed systematic questioning during each phone call. Key issues included questions about recurrence, assessment of vision and long-term complications (cataract, lens displacements, retinal detachment and glaucoma). Owners provided sufficient specific and credible information on 654 eyes of 549 horses. If the owner provided information about the condition of the lens or the retina, or about secondary diseases, such as glaucoma, this information originated from the attending veterinarians. Information determined from the medical records of the respective patients was compared with that obtained by interviews and follow-up examinations (recurrence of uveitis, vision, secondary diseases or enucleation).

Quantitative parameters were described using average and standard deviation. Data were checked for dependency in pairs using the chi square test, Fisher's exact test and Kruskal Wallis test. P values of $\leq$ 0.05 were considered to indicate statistical significance.

Results

Indication for performing PPV was based on typical anamnestic information and/or typical ocular findings in 83.9 % of the eyes. In 12.1 % of the eyes, in which neither history nor ophthalmological findings were clearly giving an indication

for surgery, vitrectomy was conducted based on preoperative paracentesis of the anterior chamber and determining an intraocular leptospiral infection using the aqueous humour sample. Surgery was performed in 4% either to improve the visual acuity (e.g. vitreous humour opacities in some cases of glaucoma or leopard-pattern associated uveitis) or at the owner's request, for example, to preserve an already blind eye.

Information about the duration of disease before vitrectomy was available in 480 out of 654 eyes. The average period between the first known episode of uveitis and surgery was about 11 months (from 6 days up to 13.7 years). Information about the number of preoperative uveitis attacks could be determined in 524 eyes, with the most frequent number being two episodes (Figure 1). A total of 521 out of 654 eyes (78.3%) were referred in the chronic stage of uveitis and showed more or less irreversible damage before vitrectomy (Table 1).

The mean age of the patients at the time of surgery was 7.7 years (range 1 to 25 years). Of the 549 horses analysed in the study, 275 were geldings, 231 were mares and 43 were stallions. Warmbloods constituted the most common breed with 317 horses (58%) followed by Icelandic horses (11%) which were the second most common breed with ERU presenting to the Equine Clinic of the University of Munich. A total of 81% of the horses in this study underwent vitrectomy in one eye and 19% in both eyes. There was an even distribution of globe laterality left (52%) and right (48%) eyes within the group of horses undergoing unilateral PPV.

Testing of intraocular fluid samples for leptospires was performed in 628 of the 654 operated eyes (96%). A total of 81.5% of the eyes examined tested positive for *Leptospira spp.* using MAT, ELISA, culture and PCR, but not every sample was examined with all test methods. Agglutinating antibodies directed against *L. grippotyphosa* was the most common finding. Not all methods of leptospiral diagnostic were initiated in every case due to their availability and costs.

Vitrectomy was performed without complications during surgery in 651 of 654 eyes (99.5%). One eye showed extended retinal folds preoperatively and suffered a retinal detachment during vitrectomy. Intraocular bleeding occurred in another eye. Haemostasis was achieved by increasing the hydrostatic pressure and intraocular blood could be removed during the course of the surgery by intensive lavage of the vitreous chamber. The vitreous chamber was clear at the time of discharge from the clinic. A temporarily loss of

Table 1 Ocular findings in 654 equine eyes prior to vitrectomy (Cataracta incipiens = insignificant cataract, less than 1/8 of the lens is affected; Cataracta immatura = incomplete cataract; Cataracta matura = complete cataract) | *Augenbefunde der 654 Pferdeaugen vor der Vitrektomie (Cataracta incipiens = unbedeutende Katarakt, weniger als 1/8 der Linse ist betroffen; Cataracta immatura = unvollständige Katarakt; Cataracta matura = vollständige milchige Katarakt*

Ocular findings		n	%
Vision (assessed by menace response and response to light)	positive	523	80
	delayed	52	8
	negative	79	12
Synechiae	none	464	70.9
	focal posterior synechiae	115	17.6
	extensive posterior synechiae	73	11.2
	anterior synechiae	2	0.3
Lens	transparent	241	36.8
	Cataracta incipiens, deposits on the post. lens capsule	355	54.3
	Cataracta immature	32	4.9
	Cataracta matura	17	2.6
	not available	9	1.4
Inflammatory debris within the vitreous	no inflammatory debris	168	25.7
	slight inflammatory debris	147	22.5
	moderate inflammatory debris	186	28.4
	high-grade inflammatory debris	125	19.1
	not available	28	4.3
Vitreal opacity	no vitreal opacity	303	46.3
	slight vitreal opacity	96	14.7
	moderate vitreal opacity	117	17.9
	high-grade vitreal opacity	94	14.4
	not available	44	6.7
Retina	no pathological findings	500	76.5
	retinal folds	59	9.0
	retinal detachment	14	2.1
	chorioretinal scarring	18	2.8
	not available	63	9.6

intraocular pressure occurred in one eye and increasing the hydrostatic pressure could not prevent a retinal detachment in this case.

Postoperative complications during the hospital stay were mostly only temporary and without further significance, however, vision was impaired in a few eyes or even lost (Table 2). Complications occurred in 16.2% of the eyes and consisted mostly of some fibrin in the anterior chamber, superficial corneal ulcers and hyphaema, all of which disappeared under conservative treatment. An impairment of vision or blindness occurred in nine eyes. Five of these eyes suffered from postoperative uveitis immediately after surgery, which could be treated conservatively in four eyes, whereas a second vitrectomy had to be performed ten days after the first surgery in one case and the eye finally developed a retinal detachment. Three eyes showed a high grade of vitreal opacity after surgery. In two of these eyes, vitrectomy had to be repeated to clear up the vitreous cavity. Three eyes went blind due to retinal detachment. One horse suffered a postoperative endophthalmitis caused by *Staphyloccoccus aureus* and while a second vitrectomy could preserve the globe of this horse, cataract formation and retinal detachment led to blindness. One patient showed severe vitreal haemorrhage after surgery, but a second vitrectomy successfully removed the intraocular blood. One horse went blind with a lens luxation followed by retinal detachment and one eye went blind without clinical evidence of the cause.

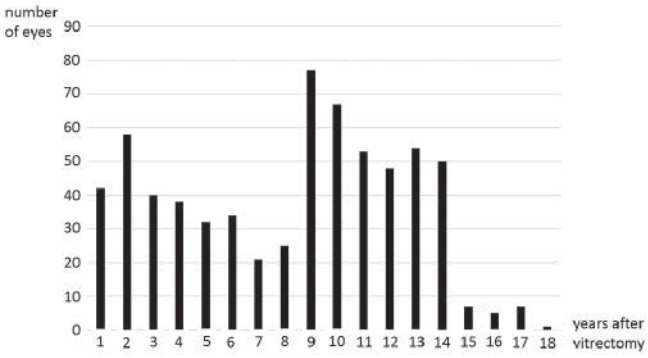

Fig. 2 Period of follow-up of 654 vitrectomized horse eyes (mean 7.7 years, standard deviation 4.4 years, median 8.4 years) | *Zeitraum der Nachverfolgung der 654 vitrektomierten Pferdeaugen (Mittelwert 7,7 Jahre, Standardabweichung 4,4 Jahre, Median 8,4 Jahre)*

Uveitis recurrences after vitrectomy

The mean time period between the surgery and the follow-up examination or survey was 7.7 years (range 6 months to 18 years) (Figure 2). None of the 105 eyes re-examined by CS showed signs of recurrence of uveitis. One or more postoperative relapses of uveitis in 24 of 654 eyes (3.7%) were reported by attending veterinarians and owners. However, some horses were referred after vitrectomies because of suspected recurrent uveitis, but the ophthalmological examination in the clinic revealed some chronic keratitis, corneal defects, lens luxations and/or glaucoma instead.

Looking separately at samples from eyes with positive or negative laboratory results regarding a leptospiral involvement, recurrences in eyes with a positive laboratory result in at least one of the tests using intraocular samples (n = 512) occurred in 2.9% eyes, while in eyes from which fluid samples were tested negative regarding a leptospiral involvement (n = 116), recurrences were reported in 7.8%. The difference between those groups was significant (chi square test, $p = 0.027$).

No recurrences were detected in 96.3% of all eyes that underwent PPV and no recurrences of ERU were detected in 97.1% of all eyes from which intraocular samples were tested positive for a leptospiral infection at the time of surgery. Repeat laboratory testing was performed in four eyes from which fluid samples were tested positive for leptospires at the time of surgery and that experienced postoperative recurrences. Antibodies against *Leptospira spp.* were found in all of these eyes, while leptospiral DNA was detectable in one eye.

Long-term preservation of vision

Follow-up examinations by one author (CS) revealed that 81% of 105 eyes examined had normal vision up to 18 years after vitrectomy (Table 2). Significant cataract formation leading to blindness had developed in 12.4% of these eyes and retinal detachment was seen in 6.8%.

According to information from the attending veterinarians and owners, the long-term preservation of vision was successful in

Table 2 Postoperative findings of the 654 equine eyes during the hospital stay after vitrectomy | *Postoperative Befunde der 654 Pferdeaugen während des Klinikaufenthaltes nach Vitrektomie*

	n	[%]	Eyesight at time of discharge from the clinic
No complication	548	83.8	like before surgery or improvement
Fibrin in the anterior chamber	64	9.8	like before surgery
Corneal defect	20	3.1	like before surgery
Hyphaema	7	1.1	like before surgery
Uveitis	5	0.8	4 like before surgery, 1 blind
Retinal detachment	3	0.5	blind
Vitreal cloudiness	3	0.5	1 like before surgery, 1 impaired vision, 1 blind
Endophthalmitis	1	0.2	blind
Lens luxation	1	0.2	blind
Bleeding into the vitreous cavity	1	0.2	like before surgery
Blindness due to unknown cause	1	0.2	blind
Total	654	100	647 (99 %) like before surgery, 1 worse, 6 blind

75.2% of the operated eyes. In 64.2% of these eyes, vision was evaluated as unchanged since surgery, while reduced vision was assumed in 11% (Figure 3). Blindness due to cataract formation was reported in 15.6% and due to retinal detachment in 7.5% of the eyes, respectively. The information on these findings usually came from the attending veterinarian and were, therefore, considered to be reliable.

There was a significant correlation between the duration of the disease before vitrectomy and the long-term development of blindness: the earlier the vitrectomy was performed, the better the condition of the eyes at the time of surgery and the better the prognosis for long-term vision. The duration of disease before vitrectomy was significantly shorter (median 46 days) in eyes with long-term transparent lenses than in eyes with long-term development of mature cataracts (median 244 days) (Kruskal Wallis test, $p = 0.004$). This, in turn, had a significant influence on the long-term development of lens changes: in the follow-up examination, 94.7% (90% according to the reports from attending veterinarians and owners) of the preoperatively transparent lenses remained in this condition in the long term. Lenses with advanced damage at the time of surgery developed a mature cataract in 80% (results of follow-up examinations) and in 73.3% (according to the owner's reports), respectively. The correlation between advanced preoperative lens damage and development of mature cataract after surgery was significant (chi square test, $p < 0.001$). The development of a cataract was also associated with preoperative posterior synechiae (chi square test, $p < 0.001$) and moderate or high-grade inflammatory debris within the vitreous humour (chi square test, $p = 0.013$).

The condition of the retina at the time of surgery also was a decisive factor: If the retina was attached at the time of vitrectomy, in 90.9% (follow-up examination) and 94% (information from attending veterinarians) of cases, respectively, the retina was still attached after years. If there were retinal folds at the time of vitrectomy, retinal detachment was seen or reported postoperatively in 11.1% (follow-up examination) and in 22.7% (information from attending veterinarians) of the cases, respectively. Fisher's exact test revealed a significant correlation between preoperatively existing retinal folds and postoperative retinal detachment ($p < 0.001$). In addition, there was a significant correlation between retinal detachment and the preoperative occurrence of moderate to high-grade inflammatory debris within the vitreous humour (chi square test, $p = 0.001$).

Secondary glaucoma was diagnosed in 9.6% of the 654 operated eyes. In most cases, the increased intraocular pressure occurred many years after the vitrectomy and was significantly associated with the occurrence of blindness due to mature cataracts (chi square test, $p = 0.005$) and lens (sub-) luxation (chi square test, $p < 0.001$).

Regardless of the postoperative recurrence of uveitis and vision, the long-term preservation of the globe was successful in 617 of 654 eyes (94.3%), with 37 eyes requiring removal. The most common indication for enucleation was the development of secondary glaucoma (24/654, 3.7%). Other indications for enucleation were phthisis bulbi in four eyes, blindness and severe atrophy in two eyes, and a recurrence of bouts of uveitis in another two eyes.

Discussion

This study demonstrates the long-term success of the PPV in ERU. The frequent detection of leptospiral infections in intraocular samples from eyes suffering from ERU corresponds to the data of other European authors (*Brem* et al. 1998, *Wollanke* et al. 1998b, *Brem* et al. 1999, *Wollanke* et al. 2000, *Hartskeerl* et al. 2004, *Wollanke* et al. 2004, *Niedermaier* et al. 2006, *Brandes* et al. 2007, *Tömördy* et al. 2010, *Baake* et al. 2016, *Dorrego-Keiter* et al. 2017, *Sauvage* et al. 2018). As published in other studies (*Wollanke* 2002, *Tömördy* 2009, *Tömördy* et al. 2010, *Baake* et al. 2019, *Voelter* et al. 2020), the risk of the recurrence of uveitis after vitrectomy seems to be lowest if eyes are tested positive for an intraocular leptospiral infection at the time of surgery. Detection of an intraocular leptospiral infection in uveitic eyes in conjunction with the absence of uveitis after vitrectomy confirms the great importance of an intraocular leptospiral infection in the etiopathogenesis of ERU. All intraocular samples of this study were collected during the florid stage of infection and in the quiet intervals between uveitis recurrences. Eyes undergoing PPV are relatively well-preserved at the time of surgery and sampling of intraocular fluids. If samples are taken from eyes which are already blind and shrunken, the detection of a leptospiral infection might no longer be possible and this might explain the different results of some other studies (*Malalana* et al. 2017).

Some working groups throughout Europe regularly succeeded in detecting leptospiral antigens and antibodies from the vitreous humour of eyes affected with ERU (*Rossi* and *Kolochine-Erber* 1954, *Brem* et al. 1998, *Wollanke* et al. 1998b, *Brem* et al. 1999, *Wollanke* 2002, *Hartskeerl* et al. 2004, *Wollanke* et al. 2004, *Niedermaier* et al. 2006, *Brandes* et al. 2007, *Loibl* 2009, *Von Borstel* et al. 2010, *Baake* et al. 2016, *Loibl* et al. 2018, *Voelter* et al. 2020). *Gsell* et al. (1946) were the first to report high intraocular antibody titres in intraocular fluids from uveitic horses.

Studies in the United States showed markedly different results: some authors in North America found no evidence of a *Leptospira*-associated uveitis in their studies (Pearce et al. 2007, *Gilger* et al. 2008). Other US groups succeeded either in es-

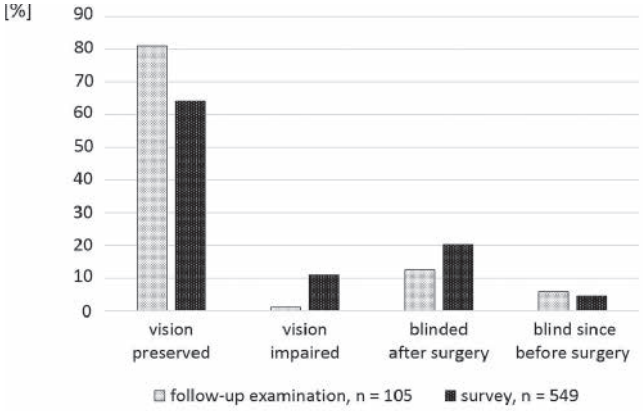

Fig. 3 Assessment of the vision of 654 equine eyes years after vitrectomy (see Fig. 2) and comparison of the follow-up examination and the survey of veterinarians and owners | *Beurteilung der Sehfähigkeit der 654 Pferdeaugen Jahre nach der Vitrektomie (s. Abb. 2) und Vergleich der Nachuntersuchung mit der Befragung von Tierärzten und Besitzern*

tablishing a link between intraocular leptospiral bacteria and recurrent uveitis or were even able to successfully detect leptospires in eyes affected with ERU (*Dwyer* et al. 1995, *Faber* et al. 2000, *Frellstedt* 2009, *Polle* et al. 2014). Furthermore, ERU could be induced in ponies by experimental intravenous injection of pathogenic leptospires. Uveitis was noticed after a time period of months and years after the bacteraemia (*Williams* 1968, 1971). It is possible that geographical and diagnostic laboratory variations play a major role in these different results. Regarding the results of *Polle* et al. (2014), an intraocular leptospiral infection should also be considered as a significant cause of ERU in some areas of the United States and vitrectomy should be contemplated.

Those eyes tested negative for leptospiral infection in the present study had a much higher risk of suffering from postoperative uveitis. However, a high percentage (92.2%) of all eyes with no evidence of intraocular leptospiral infection showed no recurrence of uveitis after vitrectomy.

These results might be due to inadequate laboratory diagnostics. False negative laboratory results may occur, especially if not all methods of Leptospira diagnostics (MAT, ELISA, culture and PCR) are used. Exclusively MAT was initiated in some cases in this study. MAT and ELISA are considered highly specific as antibodies can only be detected in the case of an intraocular leptospiral infection. Antibodies directed against leptospires cannot usually be detected in samples of ophthalmologically healthy eyes (*Wollanke* et al. 1998b, *Wollanke* et al. 2000, *Wollanke* et al. 2001, *Wollanke* 2002, *Wollanke* et al. 2004, *Gesell* 2004, *Loibl* 2009, *Loibl* et al. 2018, *Wollanke* et al. 2018). However, the MAT may lose sensitivity due to its dependence on living antigens and the subjective assessment (*Thiermann* 1984, *Levett* 2001). The ELISA appears to be more sensitive as it is often positive in the case of a negative MAT (*Loibl* 2009, *Loibl* et al. 2018, *Wollanke* et al. 2018, *Geiger* 2019). Therefore, if the MAT results with an intraocular sample are negative, it is recommended to proceed to an ELISA as a highly sensitive and objective diagnostic method (*Loibl* 2009). The PCR is the method of choice for direct pathogen detection (*Levett* 2001, *Faber* et al. 2000, *Roczek* 2008, *OIE* 2018). In most cases, antibodies directed against leptospires are the most sensitive laboratory test with intraocular samples for the diagnosis of a leptospiral-induced uveitis, however, solely culture or solely PCR were positive in a few cases.

It is recommended to perform all diagnostic tests available in order to minimise the risk of false negative results. Only the data available in the patient records could be used in this retrospective study. This is considered a weak point of retrospective studies, as missing information can distort the results. However, the large sample volume in this study ensures that the results of testing for correlation between an intraocular leptospiral infection and postoperative recurrence are meaningful.

False negative test results with samples from equine eyes suffering from ERU might occur and one explanation for these could be the biofilm formation of the leptospires inside the vitreous humour, which hides the bacteria from the immune system and, furthermore, can make the antigen-detection unreliable (*Ackermann* 2021, *Geißler* 2021).

Another reason for the rare appearance of postoperative uveitis in eyes tested negative for an intraocular leptospiral infection could be that the vitrectomy positively influences a uveitis caused by another agent. Histologically, an infiltration of the uvea by immunocompetent lymphocytes, considered to be "memory cells", can be found in eyes suffering from uveitis (*Chan* et al. 1987, *Werry* and *Gerhards* 1991, *Frühauf* et al. 1998, *Romeike* et al. 1998). Immunocompetent material, such as inflammatory cells, fibrin and inflammatory mediators (the "immunological memory") remains in the vitreous humour and can be reactivated for months after inflammation (*Werry* and *Gerhards* 1991, *Winterberg* and *Gerhards* 1997, *Frühauf* et al. 1998). This would mean that, regardless of the primary cause of inflammation, vitrectomy is able to stop or at least to delay further episodes of ERU by removing the vitreous humour and, thus, deleting the "immunological memory". According to the literature, leptospires are the only infectious cause of ERU which is regularly detected in affected eyes (*Wollanke* et al. 1998a). Nevertheless, it is conceivable that other antigens, which have not yet been identified, can also cause a recurrent uveitis.

In addition to focusing on infectious causes, current ophthalmological research is also studying the genetic predisposition for ERU. This includes, among other things, breed predisposition in horses with leopard-coat colour (*Angelos* et al. 1988, *Dwyer* et al. 1995, *Kulbrock* et al. 2013, *Baumgart* 2014, *Baumgart* and *Gerhards* 2014) and an increased risk for Warmbloods with the specific MHC class I haplotype ELA-A9 (*Deeg* et al. 2004). Other authors consider ERU as an autoimmune-mediated disease caused by any agent (*Gilger* et al. 1999, *Deeg* et al. 2001, *Deeg* et al. 2002, *Deeg* et al. 2004, *Deeg* et al. 2006, *Deeg* 2008, *Gilger* et al. 2008, *Gilger* 2010, 2015). Therefore, uveitis in horses belongs to a disease complex and can show variable symptoms and courses. Different clinical appearances of uveitis may have various causes, depending on genetic predisposition, breed predisposition and the respective regional epidemiological situation regarding leptospiral infections. Furthermore, the nomenclature, definition of "ERU" and interpretation of some ocular findings causes misunderstandings and disagreements regarding the aetiology and the best treatment option of eyes suffering from uveitis. Alternative treatment options are described but have shorter follow-up times, only a few patients and less success in preventing further bouts of uveitis (*Divers* et al. 2008, *Gilger* et al. 2010, *Popp* et al. 2013, *Waid* et al. 2018, *Fischer* et al. 2019, *Voelter* et al. 2020).

The present study demonstrates the great success of vitrectomy as a surgical therapy for ERU caused by an intraocular leptospiral infection. In the course of the operation, the surgeon removes not only the intraocular infection, but also the immunocompetent cells, inflammatory mediators and inflammatory products, as well as the pathologically changed vitreous humour with its fibres and, thus, the "immunological niche" (*Klöti* 1981, *Werry* and *Honegger* 1987, *Verbraeken* 1996, *Wollanke* 2002, *Wollanke* et al. 2004, *Geißler* 2021). In addition, the vitrectomy leads to an improvement of fluid circulation and, thus, clearance in the vitreous cavity, which prevents a reinfection by *Leptospira spp.* (*Wollanke* et al. 2004). However, ocular antigenic proteins in structures of the inner eye (lens, retina) are not removed. If uveitis is caused

by an autoimmune reaction to ocular antigens or if it is a breed-related uveitis, vitrectomy cannot influence the course of the disease as effectively as is possible in ERU-eyes with leptospiral involvement. Therefore, thorough patient selection is of great importance to ensure the success of PPV.

Regarding the four eyes from which intraocular samples were retested for an intraocular leptospiral infection because of the recurrences of uveitis and which again showed positive results, insufficient removal of the vitreous humour during the first surgery because of impaired intraocular surgical vision due to the beginning of cataracts or synechiae could be one explanation. It is possible that the remaining vitreous humour still maintained the "immunological niche" and, thus, the intraocular leptospiral persistence, possibly in the form of biofilm formation. This could have caused ERU postoperatively. In conclusion, vitrectomy must attempt to remove the vitreous humour as completely as possible to prevent postoperative recurrences. One study showed that antibody titres in the eye decrease steadily after a successful vitrectomy (*Wollanke* et al. 2004). The longer the time span after surgery, the more marked the decrease of antibody titres becomes. One year after vitrectomy, no leptospiral antibodies were detectable in aqueous fluid samples using MAT (*Wollanke* et al. 2004). In order to ensure the removal of as much vitreous humour as possible, some factors are decisive: the right surgical technique (double-port PPV), appropriate instruments adapted to the size of the equine eye and surgical experience in the field of vitreous surgery (*Winterberg* and *Gerhards* 1997, *Gerhards* and *Wollanke* 2005, *Von Borstel* et al. 2005).

A correlation between the preoperative course of the disease and the outcome regarding postoperative recurrence and findings on lens and retina, respectively, could be observed consistently in the present study. Eyes with postoperative recurrence have suffered more preoperative episodes of uveitis than eyes without further inflammation. If an increased number of uveitis attacks leads to the increased damage of the eye affected, this correlation may be due to more preoperative lesions. *Alexander* and *Keller* (1990) also observed that with each uveitis episode, permanent damage in the eye increases. *Frühauf* et al. (1998) noticed a higher recurrence rate in those eyes which already had severe intraocular damage preoperatively. This can be due to the fact that intraocular damage leads to an accumulation of immunologically active substances, which, in turn, can favour a recurrence of uveitis. In addition, advanced eye damage, such as a narrow pupil and lens opacities, can limit the transpupillary visual field and, thus, make surgery more difficult. This can lead to an insufficient removal of vitreous humour and, thus, to the persistence of the leptospiral infection. Regarding both lens and retinal findings, it was found that eyes which were in a better condition at the time of surgery, had a correspondingly shorter preoperative disease duration. This, in turn, also had a positive effect on the long-term preservation of vision. The more advanced the intraocular damage before surgery, the worse the prognosis for vision. Numerous other authors also share this conclusion (*Werry* and *Gerhards* 1991, *Winterberg* and *Gerhards* 1997, *Frühauf* et al. 1998, *Gerhards* and *Wollanke* 2001, 2005, *Von Borstel* et al. 2005, *Tömördy* 2009, *Schinagl* 2017, *Baake* et al. 2019). In summary, an early surgical intervention in the course of the disease can improve the prognosis regarding the postoperative recurrence of leptospiral uveitis as well as the prognosis for preserving vision.

Conclusions

Results of the present study clearly demonstrate, that recurrent attacks of uveitis in equine eyes caused by intraocular leptospiral infection could be prevented by PPV in 97.1 % of cases. Thus, PPV has proved to be a highly successful surgical therapy of leptospiral ERU. However, proper patient selection is essential in order to ensure success. In order to keep false negative results regarding an intraocular leptospiral infection as low as possible, preoperative testing of aqueous humour for a leptospiral infection is recommended by means of MAT, ELISA and PCR in cases in which no typical findings during ophthalmologic examination are detectable. The latter might be the case if only few or mild or very consequently treated uveitis bouts had occurred. Vitrectomy must remove as much vitreous humour as possible, thereby eliminating the "immunological niche" of the vitreous to prevent postoperative recurrences of uveitis. To achieve this, ophthalmo-surgical experience with equine eyes, optimal surgical technique and equipment adapted to the equine eye is crucial. Early surgical intervention in the course of the disease can prevent postoperative recurrence and improves the long-term preservation of vision.

Disclosure Statement

The authors declare no conflict of interest related to this report.

References

Ackermann K. (forthcoming 2021) Darstellung von Leptospiren und deren Biofilmbildung in Glaskörperproben aus an equiner rezidivierender Uveitis erkrankten Augen. Diss. Med. Vet. Munich

Alexander C. S., Keller H. (1990) Ätiologie und Vorkommen der periodischen Augenentzündung des Pferdes im Raum Berlin. Tierarztl. Prax. 18, 623–627

Angelos J., Oppenheim Y., Rebhun W., Mohammed H., Antczak D. F. (1988) Evaluation of breed as a risk factor for sarcoid and uveitis in horses. Anim. Genet. 19, 417–425

Baake E. I. A., Von Borstel M., Rohn K., Ohnesorge B. (2016) Intraokularer Leptospirennachweis mittels PCR, MAT, ELISA und Kultur von Pferden mit equiner rezidivierender Uveitis (ERU) in verschiedenen Laboren. Pferdeheilkunde 32, 346–356; DOI 10.21836/PEM20160407

Baake E. I. A., Von Borstel M., Rohn K., Boevé M. H., Ohnesorge B. (2019) Long-term ophthalmologic examinations of eyes with equine recurrent uveitis after pars plana vitrectomy. Pferdeheilkunde 35, 220–233; DOI 10.21836/PEM20190303

Babudieri B. (1961) Laboratory diagnosis of leptospirosis. Bull. World Health Organ. 24, 45–58

Baumgart A. (2014) Cyclosporin A und dessen möglicher Einsatz bei der Tigerschecken-Uveitis. Diss. Med. Vet. Munich; DOI 10.5282/edoc.16899

Baumgart A., Gerhards H. (2014) Characteristics of uveitis in horses with leopard coat color and potential use of cyclosporine A in its therapy in Germany. Pferdeheilkunde 30, 626–632; DOI 10.21836/PEM20140601

Bernard W. V. (1993) Leptospirosis. Vet. Clin. North Am. Equine Pract. 9, 435–444

Brandes K., Wollanke B., Niedermaier G., Brem S., Gerhards H. (2007) Recurrent uveitis in horses: vitreal examinations with ultrastructural detection of leptospires. J. Vet. Med. A Physiol. Pathol. Clin. Med. 54, 270–275; DOI 10.1111/j.1439-0442.2007.00921.x

Brem S., Gerhards H., Wollanke B., Meyer P., Kopp H. (1998) Intraokularer Leptospirennachweis bei 4 Pferden mit rezidivierender Uveitis (ERU). Berl. Münch. Tierärztl. Wschr. 111, 415–417

Brem S., Gerhards H., Wollanke B., Meyer P., Kopp H. (1999) 35 leptospira isolated from the vitreous body of 32 horses with recurrent uveitis (ERU). Berl. Münch. Tierärztl. Wschr. 112, 390–393

Chan C.-C., Wetzig R. P., Nussenblatt R. B., Palestine A. G., Stevens G. (1987) Iris lymphocytic infiltration in patients with clinically quiescent uveitis. Am. J. Ophthalmol. 104, 508–515

Deeg C. A. (2008) Ocular immunology in equine recurrent uveitis. Vet. Ophthalmol. 11 (Suppl 1), 61–65; DOI 10.1111/j.1463-5224.2008.00625.x.

Deeg C. A., Kaspers B., Gerhards H., Thurau S. R., Wollanke B., Wildner G. (2001) Immune responses to retinal autoantigens and peptides in equine recurrent uveitis. Invest. Ophthalmol. Vis. Sci. 42, 393–398

Deeg C. A., Marti E., Gaillard C., Kaspers B. (2004) Equine recurrent Uveitis is strongly associated with the MHC class I haplotype ELA-A9. Equine Vet. J. 36, 73–75; DOI 10.2746/0425164044864651

Deeg C. A., Pompetzki D., Raith A. J., Hauck S. M., Amann B., Suppmann S., Goebel T. W., Olazabal U., Gerhards H., Reese S., Stangassinger M., Kaspers B., Ueffing M. (2006) Identification and functional validation of novel autoantigens in equine uveitis. Mol. Cell. Proteomics 5, 1462–1470; DOI 10.1074/mcp.M500352-MCP200

Deeg C. A., Thurau S. R., Gerhards H., Ehrenhofer M., Wildner G., Kaspers B. (2002) Uveitis in horses induced by interphotoreceptor retinoid-binding protein is similar to the spontaneous disease. Eur. J. Immunol. 32), 2598–2606; https://onlinelibrary.wiley.com/doi/pdf/10.1002/1521-4141%28200209%2932%3A9%3C2598%3A%3AAID-IMMU2598%3E3.0.CO%3B2-%23

Diamond J. G., Kaplan H. J. (1978) Lensectomy and vitrectomy for complicated cataract secondary to uveitis. Arch. Ophthalmol. 96, 1798–1804

Diamond J. G., Kaplan H. J. (1979) Uveitis: effect of vitrectomy combined with lensectomy. Ophthalmol. 86, 1320–1327

Divers T. J., Irby N. L., Mohammed H. O., Schwark W. S. (2008) Ocular penetration of intravenously administered enrofloxacin in the horse. Equine Vet. J. 40, 167–170; DOI 10.2746/042516408X255972

Dorrego-Keiter E., Tóth J., Dikker L., Sielhorst J., Schusser G. F. (2016) Detection of leptospira by culture of vitreous humor and detection of antibodies against leptospira in vitreous humor and serum of 225 horses with equine recurrent uveitis. Berl. Münch. Tierärztl. Wschr. 129, 209–215; DOI 10.2376/0005-9366-129-15085

Dorrego-Keiter E., Tóth J., Dikker L., Sielhorst J., Schusser G. F. (2017) Langzeitergebnisse der Pars-Plana-Vitrektomie in Abhängigkeit vom Leptospiren-Antikörper-Nachweis im Glaskörper bei 118 Pferden mit Equiner Rezidivierender Uveitis (ERU). Pferdeheilkunde 33, 112–118; DOI 10.21836/PEM20170201

Dwyer A. E., Crockett R. S., Kalsow C. M. (1995) Association of leptospiral seroreactivity and breed with uveitis and blindness in horses: 372 cases (1986–1993). J. Am. Vet. Med. Assoc. 207, 1327–1331

Faber N. A., Crawford M., LeFebvre R. B., Buyukmihci N. C., Madigan J. E., Willits N. H. (2000) Detection of Leptospira spp. in the aqueous humor of horses with naturally acquired recurrent uveitis. J. Clin. Microbiol. 38, 2731–2733; DOI 10.1128/JCM.38.7.2731-2733.2000

Farr R. W. (1995) Leptospirosis. Clin. Infect. Dis. 21, 1–6; DOI 10.1093/clinids/21.1.1

Fingerhut L., Ohnesorge B., Von Borstel M., Schumski A., Strutzberg-Minder K., Mörgelin M., Deeg C. A., Haagsman H. P., Beineke A., Von Köckritz-Blickwede M., De Buhr N. (2019) Neutrophil extracellular traps in the pathogenesis of equine recurrent uveitis (ERU). Cells 8, 1528; DOI 10.3390/cells8121528

Fischer B. M., McMullen Jr R. M., Reese S., Brehm W. (2019) Intravitreal injection of low-dose gentamicin for the treatment of recurrent or persistent uveitis in horses: Preliminary results. BMC Vet. Res. 15, 29; DOI 10.1186/s12917-018-1722-7

Frellstedt L. (2009) Equine recurrent uveitis: a clinical manifestation of leptospirosis. Equine Vet. Educ. 21, 546–553; DOI 10.2746/095777309X467853

Frühauf B., Ohnesorge B., Deegen E., Boeve M. (1998) Surgical management of equine recurrent uveitis with single port pars plana vitrectomy. Vet. Ophthalmol. 1, 137–151; DOI 10.1046/j.1463-5224.1998.00030.x

Geiger T. (2019) Evaluierung des SNAP-Lepto® (ELISA-Schnelltest) für den Nachweis von Antikörpern gegen LipL32 inSerum und intraokularem Probenmaterial von Pferden als Diagnostikum der Leptospiren-induzierten equinen rezidivierenden Uveitis (ERU). Diss. Med. Vet. Munich; DOI 10.5282/edoc.24938

Geißler P. K. (2021). Biofilm-Bildung als Pathogenitätsmechanismus bei persistierenden Infektionen und ihre mögliche Rolle bei der Equinen Rezidivierenden Uveitis. Diss. Med. Vet. Munich

Gerhards H., Wollanke B. (2001) Uveitis bei Pferden – Diagnose und Therapie. Pferdeheilkunde 17, 319–329; DOI 10.21836/PEM20010402

Gerhards H., Wollanke B. (2005) Surgical treatment of equine recurrent uveitis: trans-pars-plana vitrectomy in horses. In: *Gilger B. C.* (ed.). Equine Ophthalmology, 1st edition, Elsevier Saunders, 314–319

Gerhards H., Wollanke B. (2006) Equine Rezidivierende Uveitis. In: *Dietz O., Huskamp B.* (eds.). Handbuch Pferdepraxis. Stuttgart, Enke Verlag, 775–786

Gerhards H., Wollanke B., Brem S. (1999) Vitrectomy as a diagnostic and therapeutic approach for equine recurrent uveitis (ERU). Proc. 45th Ann. Conv. AAEP, Albuquerque, 89–93

Gerhards H., Wollanke B., Winterberg A., Werry H. (1998) Technique for and results with surgical treatment of equine recurrent uveitis (ERU). Proc. 29th Ann. Meeting Am. College Vet. Ophthalmologists, Seattle, 30

Gesell S. (2004) Gibt es eine asymptomatische intraokulare Leptospireninfektion beim Pferd? Dissertation, Diss. Med. Vet. Munich; DOI 10.5282/edoc.2527

Gilger B. C. (2010) Equine recurrent uveitis: the viewpoint from the USA. Equine Vet. J. Supplement 2010, 57–61; DOI 10.1111/j.2042-3306.2010.tb05636.x

Gilger B. C. (2015) Recurrent Uveitis. In: *Felippe M. J.* (ed.): Equine Clinical Immunology, Wiley Blackwell, 121–126; DOI 10.1002/9781119086512

Gilger B. C., Deeg C. A. (2011) Equine Recurrent Uveitis. In: *Gilger B. C.* (editor). Equine Ophthalmology, 2nd edition, Elsevier Saunders, 317–349

Gilger B. C., Malok E., Cutter K. V. (1999) Characterization of T-lymphocytes in the anterior uvea of eyes with chronic equine recurrent uveitis. Vet. Immunol. Immunopathol. 71, 17–28; DOI 10.1016/s0165-2427 (99)00082-3

Gilger B. C., Michau T. M. (2004) Equine recurrent uveitis: new methods of management. Vet. Clin. North Am. Equine Pract. 20, 417–427; DOI 10.1016/j.cveq.2004.04.010.

Gilger B. C., Salmon J. H., Yi N. Y. (2008) Role of bacteria in the pathogenesis of recurrent uveitis in horses from the southeastern United States. Am. J. Vet. Res. 69, 1329–1335; DOI 10.2460/ajvr.69.10.1329

Gilger B. C., Wilkie D. A., Clode A. B., McMullen Jr R. J., Utter M. E., Komaromy A. M., Brooks D. E., Salmon J. H. (2010) Long-term outcome after implantation of a suprachoroidal cyclosporine drug delivery device in horses with recurrent uveitis. Vet. Ophthalmol. 13, 294–300; DOI 10.1111/j.1463-5224.2010.00807.x

Gsell O., Rehsteiner K., Verrey F. (1946) Iridocyclitis als Spätfolge von Leptospirosis Pomona (Schweinehüterkrankheit). Ophthalmologica 112, 320–334.

Hartskeerl R. A., Goris M. G., Brem S., Meyer P., Kopp H., Gerhards H., Wollanke B. (2004) Classification of leptospira from the eyes of horses suffering from recurrent uveitis. J. Vet. Med. B, Infect. Dis. Vet. Public Health 51, 110–115; DOI 10.1111/j.1439-0450.2004.00740.x

Klöti R. (1981) Vitrektomie bei chronischer Uveitis und anderen entzündlichen Eintrübungen des Glaskörpers. In: *Jaeger W.* (ed.). Uveitis, J. F. Bergmann Verlag, 233–241

Kómár G., Szutter L. (1968) Die innere periodische Augenentzündung ("Mondblindheit") der Pferde (Iridocyclochorioiditis recidiva equorum). Tierärztliche Augenheilkunde, Berlin, Parey Verlag

Kulbrock M., Von Borstel M., Rohn K., Distl O., Ohnesorge B. (2013) Studie zu Häufigkeit und Schweregrad der Equinen Rezidivierenden Uveitis bei Warmblütern. Pferdeheilkunde 29, 27–36; DOI 10.21836/PEM20130105

Levett P. N. (2001) Leptospirosis. Microbiol. Rev. 14, 296–326; DOI 10.1128/CMR.14.2.296-326.2001

Linke R. P., Brandes K., Cielewiczc M. B., Gerhards H., Wollanke B. (2019) Ocular leptospiral infection leads to ciliary induction and local AA-amyloidosis in horses. Amyloid 26, 127–128; DOI 10.1080/13506129.2019.1584100

Loibl J. K. (2009) Immunologische und mikrobiologische Untersuchungen zur intraokular persistierenden Leptospireninfektion bei Pferden mit rezidivierender Uveitis. Diss. Med. Vet. Munich; DOI 10.5282/edoc.10508

Loibl J., Gerhards H., Brem S., Wollanke B. (2018) Improving the laboratory diagnosis of leptospiral uveitis in horses by using an indirect ELISA for the detection of antibodies against Leptospira spp. in intraocular samples. Pferdeheilkunde 34, 267–277; DOI 10.21836/PEM20180308

Malalana F., Blundell R. J., Pinchbeck G. L., McGowan C. M. (2017) The role of Leptospira spp. in horses affected with recurrent uveitis in the UK. Equine Vet. J. 49, 706–709; DOI 10.1111/evj.12683

McLaughlin S. A., Whitley R. D., Gilger B. C. (1992) Diagnosis and treatment of lens diseases. Vet. Clin. North Am. Equine Pract. 8, 575–585

Miller T. R., Whitley R. D. (1987) Uveitis in horses. Mod. Vet. Pract. 14, 351–357

Niedermaier G. (2002) Elektronenmikroskopische Untersuchung des Glaskörpers des Pferdes mit equiner rezidivierender Uveitis. Diss. Med. Vet. Munich

Niedermaier G., Wollanke B., Hoffmann R., Brem S., Gerhards H. (2006) Darstellung von Leptospiren im Glaskörper augengesunder und an ERU erkrankter Pferde mittels Transmissions-Elektronenmikroskopie. Dtsch. Tierärztl. Wschr. 113), 401–432

OIE. 3.1.12. Leptospirosis. OIE Terrestrial Manual 2018. World Organisation for Animal Health, 503–516; www.oie.int; www.oie.int/fileadmin/Home/eng/Health_standards/tahm/3.01.12_LEPTO.pdf

Pearce J. W., Galle L. E., Kleiboeker S. B., Turk J. R., Schommer S. K., Dubielizig R. R., Mitchell W. J., Moore C. P., Giuliano E. A. (2007) Detection of Leptospira interrogans DNA and antigen in fixed equine eyes affected with end-stage equine recurrent uveitis. Official publication of the Am. Assoc. Vet. Lab. Diagnosticians, J. Vet. Diagn. Invest. 19, 686–690; DOI 10.1177/104063870701900611

Polle F., Storey E., Eades S., Alt D., Hornsby R., Zuerner R., Carter R. (2014) Role of intraocular Leptospira infections in the pathogenesis of equine recurrent uveitis in the Southern United States. J. Equine Vet. Sci. 34, 1300–1306; DOI 10.1016/j.jevs.2014.09.010

Popp M., Gerhards H., Wollanke B. (2013) Enrofloxacin concentrations in the vitreous of horses with equine recurrent uveitis (ERU) after repeated intravenous administration. Pferdeheilkunde 29, 574–580; DOI 10.21836/PEM20130501

Roczek A. H. (2008) Entwicklung einer quantitativen PCR zum Nachweis von DNA pathogener Leptospiren in Glaskörper- und Kammerwasserproben von Pferden. Dissertation, Diss. Med. Vet. Munich; DOI 10.5282/edoc.8333

Romeike A., Brügmann M., Drommer W. (1998) Immunohistochemical studies in equine recurrent uveitis (ERU). Vet. Pathol. 35, 515–526; DOI 10.1177/030098589803500606

Rossi P., Kolochine-Erber B. (1954): Iridocyclites des équidés et leptospiroses. Revue Pathol. Générale Comparée 54, 432–477

Sauvage A. C., Monclin S. J., Elansary M., Hansen P., Grauwels M. F. (2018) Detection of intraocular Leptospira spp. by real-time polymerase chain reaction in horses with recurrent uveitis in Belgium. Equine Vet. J. 51, 299–303; DOI 10.1111/evj.13012

Schinagl C. (2017) Pars-Plana-Vitrektomie bei Equiner Rezidivierender Uveitis – Langzeitergebnisse zu Rezidivfreiheit, Sehfähigkeit und Bulbuserhalt bei 654 Augen von 549 Pferden. Diss. Med. Vet. Munich; DOI 10.5282/edoc.22115

Schwink K. L. (1992) Equine uveitis. Vet. Clin. North Am. Equine Pract. 8, 557–574

Szemes P. A., Gerhards H. (2000) Untersuchungen zur Prävalenz der equinen rezidivierenden Uveitis im Großraum Köln-Bonn. Prakt. Tierarzt 8, 408–420

Thiermann A. B. (1984) Leptospirosis: current developments and trends. J. Am. Vet. Med. Assoc. 184, 722–725

Tömördy E. (2009) Verlaufsstudie nach Vitrektomie bei equiner rezidivierender Uveitis. Dr. med. vet., Zürich, Vetsuisse Faculty, Section of Ophthalmology, 98

Tömördy E., Hässig M., Spiess B. M. (2010) The outcome of pars plana vitrectomy in horses with equine recurrent uveitis with regard to the presence or absence of intravitreal antibodies against various serovars of Leptospira interrogans. Pferdeheilkunde 26, 251–254; DOI 10.21836/PEM20100222

Ulbig M., Kampik A. (1989) Pars plana-Vitrektomie bei chronischer Uveitis des Kindes. Klin. Mbl. Augenheilk. 194, 10-12

Voelter K., Vial Z., Pot S. A., Spiess B. M. (2020) Leptospiral antibody prevalence and surgical treatment outcome in horses with Equine Recurrent Uveitis (ERU) in Switzerland. Vet. Ophthalmol. 23, 648–658; DOI 10.1111/vop.12767

Von Borstel M., Oey L., Strutzberg-Minder K., Boevé M. H., Ohnesorge B. (2010) Direkter und indirekter Nachweis von Leptospiren aus Glaskörperproben von Pferden mit ERU. Pferdeheilkunde 26, 219–225; DOI 10.21836/PEM20100217

Von Borstel M., von Oppen T., Glitz F., Frühauf B., Deegen E., Boevé M. H., Ohnesorge B. (2005) Langzeitergebnisse der Pars plana Vitrektomie (double port) bei Equiner Rezidivierender Uveitis. Pferdeheilkunde 21, 13–18; DOI 10.21836/PEM20050102

Verbraeken H. (1996) Therapeutic pars plana vitrectomy for chronic uveitis: a retrospective study of the long-term results. Graefes Arch. Clin. Exp. Ophthalmol. 234, 288–293

Waid H., Tóth J., Buijs L., Schusser G. F. (2018) Clinical experiences after the insertion of a Cyclosporine-A drug delivery device in horses with Equine Recurrent Uveitis. Pferdeheilkunde 34, 113–120; DOI 10.21836/PEM20180202

Werry H., Gerhards H. (1991) Möglichkeiten der und Indikationen zur chirurgischen Behandlung der equinen rezidivierenden Uveitis (ERU). Pferdeheilkunde 7, 321–331; DOI 10.21836/PEM19910602

Werry H., Gerhards H. (1992) The surgical therapy of equine recurrent uveitis. Tierärztl. Prax. 20, 178–186

Werry H., Honegger H. (1987) Pars-plana Vitrektomie bei chronischer Uveitis. Klin. Monatsbl. Augenheilkunde 191, 9–12

Williams R. D. (1968) The presence and duration of persistence of Leptospira pomona in equine intraocular tissues following experimentally induced systemic infection. M.S. Thesis, Purdue University, Lafayette, Ind.

Williams R. D. (1971) Equine uveitis: A model system for the study of immunologically mediated tissue injury. PhD Thesis, Purdue University, Lafayette, Ind.

Winterberg A., Gerhards H. (1997) Langzeitergebnisse der Pars-plana-Vitrektomie bei equiner rezidivierender Uveitis. Pferdeheilkunde 13, 377–383; DOI 10.21836/PEM19970409

Witmer H. (1954) Periodic ophthalmia in horses. Am. J. Ophthalmol. 37, 243–253

Wollanke B. (2002) Die equine rezidivierende Uveitis (ERU) als intraokulare Leptospirose. Habil. Vet. Vet. Munich

Wollanke B., Geiger T., Gerhards H. (2018) Evaluation of "SNAP® Lepto"-ELISA and comparison with MAT and PCR results for diagnosis of leptospiral uveitis in horses using intraocular samples. Pferdeheilkunde 34, 508–516; DOI 10.21836/PEM20180601

Wollanke B., Gerhards H., Brem S., Gothe R., Wolf E., Herzog S., Kopp P., Meyer P. (1998a) Studies on vitreous and serum samples from horses with equine recurrent uveitis (ERU): the role of Leptospira, Borrelia burgdorferi, Borna disease virus and Toxoplasma in the etiology of ERU. Proceedings of the 29th Annual Meeting of the American College of Veterinary Ophthalmologists, Seattle, 31

Wollanke B., Gerhards H., Brem S., Kopp H., Meyer P. (1998b) Intraocular and serum antibody titers to Leptospira in 150 horses with equine recurrent uveitis (ERU) subjected to vitrectomy. Berl. Münch. Tierärztl. Wschr. 111, 134–139

Wollanke B., Gerhards H., Brem S., Meyer P., Kopp H. (2004) Ätiologie der equinen rezidivierenden Uveitis (ERU): Autoimmunkrankheit oder intraokulare Leptospireninfektion? Pferdeheilkunde 20, 327–340

Wollanke B., Gerhards H., Brem S., Wolf E., Kopp H., Meyer P. (2000) Zur Leptospirenätiologie der equinen rezidivierenden Uveitis (ERU). Tierärztl. Prax. G 28, 153–158

Wollanke B., Rohrbach B. W., Gerhards H. (2001) Serum and vitreous humor antibody titers in and isolation of Leptospira interrogans from horses with recurrent uveitis. J. Am. Vet. Med. Assoc. 219, 795–800